The Impact of Psychedelics on Active Olfaction in Mice

by

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DISSERTATION ABSTRACT

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Title: The Impact of Psychedelics on Active Olfaction in Mice

The olfactory system is critically important to the survival and well-being of animals. It is necessary for flavor perception, mate selection, and distinguishing safety from threat in the environment. In addition, olfactory hallucinations have been documented in various psychiatric and neurological disorders. Hallucinations may emerge as a disruption in typical brain activity or in response to the ingestion of psychedelic compounds. While neural correlates and cognitive processes of visual and auditory hallucinations have been extensively studied, olfactory hallucinations remain largely unexplored. In contrast, the neural circuits and behaviors of olfaction in mice provide an opportunity to better understand the neural mechanisms of psychedelic drug action. Thus, this dissertation focuses on characterizing changes to olfactory behavior and neural activity evoked by a psychedelic compound.

In this dissertation, I begin by reviewing scientific literature on active sensing, the olfactory system, olfactory hallucinations, and the use of psychedelics in human and animal research. Movement is inextricably linked to respiration and neural activity, thus studying psychedelics in the context of movement provides a naturalistic representation of hallucinations. Chapter II captures this, as I describe experiments and results after administration of a psychedelic in freely-moving mice during an olfactory search task. We recorded movement and sniffing during an olfactory search task to increase our understanding of how a psychedelic drug impacts olfactory behaviors during goal directed behavior. We found that search behavior and sniff rate are impacted by a psychedelic. In Chapter III, I describe how a psychedelic impacts

spontaneous, uninstructed behavior and neural activity in freely-moving mice. We recorded neural activity in the olfactory bulb, sniffing, and movement. We found that neural activity, sniffing, and the stereotypical head-twitch response of mice are correlated, linking olfaction and psychedelics together in a novel way.

Finally, in Chapter IV, I summarize the results from Chapters II and III within the broader context of olfaction and psychedelic research. I discuss the impact, limitations, and future directions of this work. Together, this dissertation advances our understanding of the impact of psychedelics on active olfaction in mice. This dissertation includes previously unpublished co-authored material.

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DEDICATION

This work is dedicated to Peggy and Tom. I wouldn't be here without you - literally! And lovingly.

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CHAPTER I

INTRODUCTION

This chapter was written by me. Dr. Avinash Singh Bala and Dr. Matthew Smear provided editorial suggestions.

Olfaction is an ancient sensory system, which evolved early and persisted, being crucial to the survival of various species. Sensation is key to navigating through space, avoiding danger, determining an appropriate mate, and extracting important information from the environment. While we humans primarily rely on our visual system to solve these problems, the olfactory sense was likely the first to evolve (Philpott et al., 2008) and used by many species such as insects and rodents as their primary sensory system. Due to its crucial role in survival, the significance of a properly functioning olfactory system cannot be understated. The focus of this dissertation is specifically on olfactory hallucinations. Olfactory hallucinations have been documented in various psychiatric and neurological disorders. They can occur after ingestion of a psychedelic substance as well. While the phenomenon is well documented, it is still poorly understood, with limited research in animal models to explore this sensory disturbance.

The objective of this dissertation is to elucidate alterations in the olfactory system in response to a psychedelic compound. Through changes in observable behavior, we can begin to understand how psychedelics impact active sensing through smell. Chapter II investigates how the psychedelic DOI (2,5-Dimethoxy-4-iodoamphetamine) affects sniffing as a form of active sensing, behavioral structure, and accuracy in reporting location of an odor in an olfactory navigation task. Chapter III investigates how DOI impacts spontaneous, uninstructed behavior

and activity in the olfactory bulb. Chapter IV is a general discussion of the findings from chapters II and III and the impact of those findings on the field of olfaction and psychedelic research. Chapter I as follows reviews the literature on active sensing, olfaction in rodents, the serotonin system, olfactory hallucinations, and the use of psychedelics in research.

ACTIVE SENSING AND THE OLFACTORY SYSTEM

Active Sensing

Biological systems are constantly seeking feedback from the environment to discern which direction to move, what to eat, where to hide, or with whom to mate. How animals interact with the world around them directly impacts their interpretation of internal and external stimuli. If a loud sound pops, we turn our heads to that location and actively scan the area with our eyes to solve the puzzle of where the sound came from, whether we are safe, and what to do next. Movements generated to receive more salient information from the environment are what we call active sensing. Active sensing is crucial for survival and varies in a species-specific way, for example: rodents whisk and sniff, humans foveate their eyes, bats echolocate, and insects move their antennae. Without active sensing, the environmental landscape would only be sensed passively, without intentionally informing the organism's conscious perception.

Active sensing is a closed-loop process, meaning that there is a feedback cycle between sensory information and movement (Ahissar & Assa, 2016; Yang et al., 2016). Movement modulates perception, as demonstrated by the interaction between an organism and its environment. This is supported by evidence of a stimulus that is actively controlled influencing perception, like sniffing faster to improve odor perception (Jones & Urban, 2018; Wachowiak,

2011), whisking and sniffing the environment for targeting an object in space (Deschênes et al., 2012), or using vision to localize and capture prey (Hoy et al., 2016). The importance of active sensing to test whether a perception is real then becomes clear as it pertains to hallucinations, since hallucinations are perceptions without sensations (James J. Gibson, 1970). Active sensing provides feedback about the environment; if a percept is not based on external sensory information, moving sensory organs will elucidate confounding evidence from the environment that a percept may not be real. An inability to actively sense the environment for feedback due to damaged sensory organs may lead to hallucinations. For example, individuals with vision loss due to Charles Bonnet syndrome experience vivid visual hallucinations (Pang, 2016). Similarly, amputees report perception of the amputated limb, often painfully so (Ramachandran & Hirstein, 1998). In the case of phantom limbs, providing missing feedback can be helpful. By using a mirror to provide visual feedback, patients feel relief from painful sensations (Ramachandran & Hirstein, 1998; Ramachandran & Rogers-Ramachandran, 2000). James Gibson (James J. Gibson, 1970) argued that through active sensing, one could distinguish between hallucination and true perception. During rapid eye movement of the sleep state, eye movement may be an attempt to find sensory input to make sense of our sleeping percept. Active sensing, therefore, can be key to differentiating hallucination from a stimulus driven percept.

The Olfactory System

The olfactory system evolved before any other sensory system and was preserved over time and across species because of its critical role in navigation, threat detection, identification of food sources and mates, and extraction of relevant information from the environment. Utilized by primates, rodents, birds, fish, and other vertebrates alike, the olfactory system remains of

utmost importance for wellness and survival. Even humans smell spoiled milk and know not to drink it. We smell smoke and detect potential danger in the environment. These olfactory cues drive behavior, planning, and execution of plans.

For rodents, the olfactory system is central to behavior. Rodents sniff to learn about their environment. In order to increase the number of odor molecules inhaled, rodents increase sniff rate and move their heads as a way to compare odor between nares for localization (Jones & Urban, 2018; Khan et al., 2012). Moreover, occluding a nostril is not necessary for localizing an odor, as mice strategically synchronize their sniff rate and head movement depending on their internal state of investigation or approach in relation to an odor stimulus (Findley et al., 2021). Sniffing is also temporally linked to other behaviors, such as vibrissae protraction and retraction, (Deschênes et al., 2012; Kleinfeld et al., 2014; Welker, 1964) which enhance perception of the environment. The link between sniffing, movement, and behavior justifies the mouse as an experimental subject for understanding active sensing and olfactory perception.

Each sniff triggers a cascade of neural events. How information is processed within the olfactory system is retained between both humans and rodents, which makes the use of rodents in research relevant to humans. Air is inhaled, bringing odor molecules to olfactory sensory neurons (OSNs) in the nasal epithelium, which generate action potentials to transmit into the olfactory bulb (Shipley & Ennis, 1996). These OSNs express specific odor receptors (Buck & Axel, 1991; Malnic et al., 1999), which then project to specific spherical structures called glomeruli within the olfactory bulb (OB) in a highly organized way. Glomeruli contain the termination point of sensory neurons of the same receptor type (Mombaerts et al., 1996; Treloar et al., 2002). Within each glomerulus are dendrites of the principal projection neurons, mitral and tufted cells, which send axons to the olfactory cortices (Mori & Sakano, 2011; Shepherd et al.,

2004). Additionally, within and adjacent to the glomerular layer are inhibitory interneurons, as well as granule cells in the deep layers of OB, which synapse back onto mitral and tufted cells via dendrodendritic connections (Shepherd et al., 2004). The OB is a region of high plasticity, with neurogenesis of OSNs, the glomerular layer, and granule cells (Graziadei & Monti Graziadei, 1985; Shepherd et al., 2004). The olfactory cortex is made up of several regions, including the piriform cortex, entorhinal cortex, and the amygdala (Neville & Haberly, 2004; Sicard, 2008). The olfactory circuit is intricate yet efficient in processing information to allow for real-time behavioral responses to the environment. Within each sniff cycle contains rich information processed by the brain. Activity of the OB is linked to the sniff cycle (Kepecs et al., 2006), where odors evoke specific firing patterns in the mitral and tufted cells that are in synch with the sniff cycle (Shusterman et al., 2011).

The complexity of the olfactory system is highlighted by the interactions between mitral and tufted cells with neurotransmitters. Neurotransmitters modulate signal transduction. For example, glutamate, an excitatory neurotransmitter, is released from mitral cells onto granule cells, which then synapse back onto mitral cells through GABAergic (inhibitory) cells in the dendrodendritic manner previously described (Isaacson, 2001). This demonstrates the importance of glutamate in the propagation of signal transmission, thus regulating the communication of sensory information. Serotonin is a neurotransmitter important in sensory perception and olfactory learning. Since serotonin is related to hallucinations and the primary neurotransmitter responsible for the action of psychedelic drugs, I will next discuss serotonin pathways in relation to the olfactory system.

Serotonin Expression in the Brain

Of high relevance to olfaction and hallucinations is the neurotransmitter serotonin (5-hydroxytryptamine, 5-HT). The 5-HT system is well known for its role in regulating mood, appetite, sleep, and various physiological processes. 5-HT is known to impact sensory perception by affecting how information is filtered and processed. The raphe nuclei are responsible for the major serotonergic nuclei (Hornung, 2003), and serotonergic neurons project to the forebrain as well as areas responsible for respiration (Morinaga et al., 2019). Interestingly, the OB receives some of the heaviest projections from the raphe nuclei (Dugué & Mainen, 2009), which is an important consideration for how serotonergic psychedelics could impact the OB. Stimulation of 5-HT neurons in dorsal raphe of mice decreases spontaneous firing in the piriform cortex, but not when odor is presented (Lottem et al., 2016). This finding illustrates the role of 5-HT in modulating neural activity in primary olfactory cortex, and likely on processing of olfactory information.

The 5-HT system is complex, with 14 known receptor types, including several specific receptor types known for their role in sensory processing. In primates, primary visual cortex has the highest expression of 5-HT_{1B} and 5-HT_{2A} receptors (Watakabe et al., 2009). Of these, 5-HT_{2A} contributes to the regulation and amplification of visual information in mice (Barzan et al., 2024), while hallucinogenic 5-HT_{2A} agonists reduce activity in visual cortex (Michaiel et al., 2019). Psychedelic drugs that target the 5-HT_{2A} receptor, such as LSD (lysergic acid diethylamide), mescaline, and psilocybin, induce hallucination through this mechanism (Nichols, 2018). In patients with schizophrenia, post-mortem analysis shows increased 5-HT_{2A} in prefrontal cortex, suggesting its involvement in hallucinations (Muguruza et al., 2013). Together,

these examples illustrate the 5-HT_{2A} receptor involvement in hallucination as induced by drug or psychiatric disorder.

The olfactory system is deeply influenced by the activity of 5-HT fibers, especially the 5-HT_{2C} and 5-HT_{2A} receptors. In contrast to primates where visual cortex receives the most abundant 5-HT projections, in rodents the olfactory system is their primary target. Antibody staining has shown highest levels of 5-HT_{2A} receptors within the mitral cell layer of the OB, piriform cortex, and neocortex (Hamada et al., 1998). The OB's glomerular layer and granule cell layers are heavily innervated with 5-HT projections from the raphe nuclei (J. H. McLean & Shipley, 1987; Steinfeld et al., 2015). Excitation of the external tufted cells and mitral cells in the OB are directly driven by 5-HT_{2A} receptor activation (Brill et al., 2016). Further, 5-HT_{2C} activation has been shown to control how odor signal is received by the OB from OSNs (Petzold et al., 2009). 5-HT is also critical for olfactory behavior, as odor preference requires 5-HT_2 activation in rats (John H. McLean et al., 1996). Overall, evidence shows that 5-HT, which modulates sensory perception, is known to impact visual perception in primates, but in rodents, it may have its largest impact in the olfactory system.

OLFACTORY HALLUCINATIONS AND PSYCHEDELIC RESEARCH

Olfactory Hallucinations in Humans

Olfactory hallucinations are known to occur in numerous disorders and diseases, including schizophrenia, Parkinson's disease, migraines, epilepsy, depression, and anorexia nervosa (C. Chen et al., 2003; Diamond et al., 1985; Fénelon et al., 2000; Hsu & Suh, 2018; Stevenson et al., 2011). The prevalence of olfactory hallucinations ranges depending on the

population studied. Up to 34.6% of schizophrenia patients reporting olfactory hallucinations (Kopala et al., 1994), whereas the non-clinical older population is seen in up to 4.9% (Sjölund et al., 2017). Further, women more frequently experience olfactory hallucinations compared to men in both clinical (C. Chen et al., 2003; Diamond et al., 1985; Fénelon et al., 2000; Hsu & Suh, 2018) and non-clinical populations (Bainbridge & Byrd-Clark, 2020; Sjölund et al., 2017; Wehling et al., 2021). These hallucinations are often unpleasant in nature, with smoky or burnt qualities reported most often (C. Chen et al., 2003; Coleman et al., 2011; Kulick et al., 2018; Kumar et al., 2012; Sjölund et al., 2017). While this phenomenon has been described across multiple population types, there are open questions regarding why they occur with little consensus on how to treat it.

Epilepsy

Epilepsy is one of the world's most prevalent neurological disorders, affecting approximately 50 million people according to the World Health Organization. The disorder is characterized by recurrent seizures precipitated by irregular neuronal activity (Fisher et al., 2014). Visual, auditory, or olfactory hallucinations may predict the onset of a seizure, and can be associated with the focus of a seizure (Bien et al., 2000; Furia et al., 2021). In the case of olfactory hallucinations, the focus may be in several regions of the brain, including the temporal lobe or orbitofrontal cortex (Hamasaki et al., 2014; Khurshid et al., 2019). Patients with a history of seizures and hallucinations are at an increased risk of suicidal behavior, marking a need for improved understanding and treatment of hallucination in epilepsy (Yates et al., 2020).

Temporal lobe epilepsy is the most common type of epilepsy. Regions within the temporal lobe such as the hippocampus and amygdala are known to be epileptogenic because of

their plasticity. Patients with temporal lobe or mixed frontal lobe type epilepsy also report the most olfactory dysfunction, in contrast to occipital lobe or other types (Khurshid et al., 2019; Türk et al., 2020). In temporal lobe epilepsy case studies, patients who underwent temporal lobectomy or amygdala resection to control seizures also eliminated their olfactory hallucinations (C. Chen et al., 2003; Hamasaki et al., 2014). The olfactory bulb and piriform cortex are regions known for their neural plasticity, with the piriform cortex also being a key site of epileptogenic activity. Despite this, both areas have been largely overlooked in research on epilepsy and olfactory hallucinations (Sarnat & Flores-Sarnat, 2016; Vaughan & Jackson, 2014). Since research in humans is often limited to surgical intervention for epileptic alleviation, only a handful of studies have been performed in epileptic patients in olfactory regions. For example, electrical stimulation of the olfactory bulb or tract, or stimulation of the orbitofrontal cortex, produced olfactory hallucinations (Bérard et al., 2021; Kumar et al., 2012; Penfield & Jasper, 1954) in patients undergoing primary surgery for epilepsy.

Parkinson's Disease

Parkinson's Disease (PD) is neurological disorder characterized by impairments in movement, coordination, and balance. Olfactory dysfunction is a common non-motor symptom in PD affecting 65% to 90% of patients and reported as the second most common reason for a decline in quality of life, second only to physical pain (Ercoli et al., 2023; Politis et al., 2010). Hallucination is also a common non-motor symptom in PD, with visual hallucinations reported by up to 75% of patients (Weil et al., 2020). Up to 18.2% of PD patients report olfactory hallucinations depending on methodology of study (Ercoli et al., 2023). In those who experience olfactory hallucinations, a history of visual or auditory hallucinations can predict olfactory

hallucination (Solla et al., 2021; Weil et al., 2020). Despite the occurrence of olfactory hallucinations and their negative effect on those with PD, their neurological underpinnings are not agreed upon.

The source of olfactory hallucinations in those with PD remains unclear. Loss of olfactory bulb volume and atrophy of olfactory cortex in those with PD has been reported in some studies (S. Chen et al., 2014), while other studies have found no difference in olfactory bulb size of patients (Mueller et al., 2005). PD is often treated with dopaminergic drugs, including rasagiline, which may increase olfactory hallucination (Haehner et al., 2013; Henkin et al., 2013). Further, patients with PD compared to controls show an increase of dopaminergic cells in the olfactory bulb, which may decrease communication between mitral cells and glomeruli leading to hyposmia (Huisman et al., 2004). However, due to the general dysfunction of the olfactory system in PD it is challenging to pinpoint the causation of hallucination.

Schizophrenia

Schizophrenia is a chronic, long-term condition impacting thought, perception, and behavior. Hallucinations are one of the most common symptoms in schizophrenia, along with disordered thoughts and delusions. Odor identification is worse in patients, where pleasant odors are identified as unpleasant, demonstrating a dysfunction in the olfactory system (Urban-Kowalczyk et al., 2019). Though auditory hallucinations are the most common, impacting 60 to 80% of patients, up to 53% of patients experience multiple sensory type hallucinations, including olfactory (Lim et al., 2016). Women with schizophrenia are more likely to report olfactory hallucinations than men, with up to 52.6% of women patients reporting olfactory hallucinations compared to 27.2% of men (Kopala et al., 1994). In congruence with other disorders, the nature

of olfactory hallucinations are generally negative, although patients often report body odors as the perception, as opposed to smoke (Langdon et al., 2011). In schizophrenia, the understanding of olfactory hallucinations remains inconsistent with modeling and treatment of other sensory hallucinations (Stevenson et al., 2011).

Although data on the topic of olfactory hallucinations in schizophrenia is limited, researchers have developed theories through clinical case studies and reviews. There are competing theories, such that olfactory hallucinations occur through reduced brain activity or hyperactivity in regions involved in sensory processing (Stevenson, 2008). Other models implicate neurotransmitter function, such as the opioid system in schizophrenia and its localization to the olfactory bulb (Mansour et al., 1988; Urban-Kowalczyk et al., 2019).

Migraines

Migraines occur in roughly 14-15% of people globally (Steiner & Stovner, 2023), with women affected more than men (Stewart et al., 1996). The prevalence of olfactory hallucinations with migraine is unknown, yet few case studies have estimated the number between 0.66% and 3.9% (Coleman et al., 2011; Mainardi et al., 2017). Migraines with aura occur in about one third of migraine patients (Lucas, 2021), yet auras do not include olfactory hallucinations. The majority of patients who report olfactory hallucinations report unpleasant odors, such as burning or rotting as with other disorders and diseases (Coleman et al., 2011; Mainardi et al., 2017). Case studies of olfactory hallucinations with migraines are increasing (Partovi & Tolebeyan, 2022; Wolberg & Ziegler, 1982), yet the neurological basis for why they occur is not understood.

Next Steps

Given the various diseases and neurological disorders that are associated with olfactory hallucinations, a clearer understanding of the neural basis and behavioral manifestation would be beneficial. To date, there is no animal model for olfactory hallucinations, since the question poses many inherent challenges. However, with advanced tools in data acquisition and behavioral analysis available today, we can finally examine hallucinogen[1] induced changes in olfactory behavior and function.

Psychedelics in Human and Rodent Research

Psychedelics have been used in both human and animal research for decades. Drugs such as LSD (lysergic acid diethylamide), psilocybin (magic mushrooms), DMT (dimethyltryptamine), and DOI (2,5-Dimethoxy-4-iodoamphetamine) are strong agonists for the 5-HT_{2A} receptor, which mediates their hallucinogenic effects (González-Maeso et al., 2007, 2003; Halberstadt, 2015; López-Giménez & González-Maeso, 2018). Initially these compounds were used to better understand neuropsychiatric disorders, neural circuits involved in hallucination and perception, altered consciousness, and the human psyche. While research with psychedelic compounds was quite active through the 1960s, their use ceased after 1970 primarily

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[1] I use the term *psychedelic* and *hallucinogen* interchangeably throughout this dissertation. The term "hallucinogen" is generally used more broadly today to include substances such as MDMA (3-4methylenedioxymethamphetamine), cannabis, and others that may induce different levels of alteration in consciousness or hallucination. Described well by David E. Nichols (Nichols, 2004), the term "hallucinogen" may be inappropriate for these drugs as they have different mechanisms of action compared to 5-HT agonists. The term "psychedelic" is generally used more specifically to mean LSD, psilocybin, or other compounds that act on 5-HT_{2A} receptors and alter consciousness, perception, and cognition. Thus, the term hallucinogen in this dissertation will refer to 5-HT_{2A} agonists. I will use hallucinogen more when discussing animal research since cognitive state, perception, and consciousness may only be inferred. I will use psychedelic more when discussing human research, as these states can be verbally confirmed by participants.

due to changes in US drug laws and schedules which limited their availability and use. The continued relevance of psychedelics to psychiatry, neuroscience, psychology, and other disciplines has motivated a recent resurgence in the use of these drugs in medicine and research. One critical reason is that psychedelics may offer unique insights into understanding neural and behavioral bases of perception in addition to their therapeutic utility.

Human Research

Early psychedelic research used drugs such as mescaline and psilocybin to study psychosis because psychedelics provided insights into mental disorders in otherwise neurotypical populations. In an interesting juxtaposition, the same psychedelics used to model psychosis and mental health problems were also being studied as potential treatments for the same disorders. Recent history of psychedelic research in humans has primarily focused on therapeutic use for various disorders, such as post-traumatic stress disorder, anxiety, addiction, and depression. Due to the regulated status of psychedelics as a schedule I substance, which classifies these chemicals as having no accepted medical use and high potential for abuse, research over the last several decades has been limited. Despite this limitation on access, researchers have demonstrated that psilocybin and LSD reduce anxiety induced by terminal diagnoses such as cancer (Gasser et al., 2014; Grob et al., 2011). In addiction studies, psilocybin and LSD have been shown to reduce alcohol and tobacco consumption (Garcia-Romeu et al., 2014; Johnson et al., 2014, 2017; Krebs & Johansen, 2012). Evidence now shows that psychedelics have a place in therapeutic medicine.

Research examining brain states after psychedelic administration has increased in recent years but is limited in scope and tools accessible. Like any other pharmacological agent, understanding the mechanism of action and effect on brain and behavior is necessary to have

informed consent when considering treatment for patients. How do psychedelics produce such profound cognitive, emotional, perceptual, and long-lasting effects? What brain mechanism drives these effects and what are the expected behavioral readouts? Early research with psychedelics described stereotypical patterns of behavior, such as increased eye saccades that correlate to the intensity of visual hallucination (Hebbard & Fischer, 1966). Recently, researchers have focused on the experiences of participants and where those experiences could originate in the brain. For example, the psychedelic psilocybin modulates blood-oxygen level-dependent (BOLD) signal and desynchronizes activity within the default mode network (DMN), a network within the brain that includes the thalamus, anterior cingulate cortex, and posterior cingulate cortex (Carhart-Harris et al., 2012; Siegel et al., 2024). When active, the DMN is associated with introspection and mind wandering, while when focused on external stimuli, the DMN is quiet (Menon, 2023). This change in DMN activity is thought to drive both the mystical experience and therapeutic benefit of psychedelics.

When it comes to sensory processing regions and psychedelic research, the visual system has been prioritized since humans most frequently report visual hallucinations compared to all other sensory modalities. Electroencephalogram (EEG) recordings after psilocybin administration found decreased amplitude of the N170 component, increased amplitude of P1 over occipital lobe after exposure to visual stimuli, and decreased activity in the extrastriate cortex (Kometer et al., 2011). The decrease of activity in extrastriate cortex, which is involved in visual perception and higher order processing, also correlated with the intensity of visual hallucinations. Experiments using fMRI, magnetoencephalography (MEG), and arterial spin labeling (ASL) show visual hallucination is correlated with increased blood flow in visual cortex, decreased alpha power in visual cortex, and increased functional connectivity between primary

visual cortex and other regions such as hippocampus (Carhart-Harris et al., 2016; Kaelen et al., 2016). Taken together, these findings demonstrate the impact of psychedelics on visual processing. Reduced activity in the extrastriate suggests structured perception may be impacted, while increased activity in primary visual cortex without visual stimulus may suggest top-down processes lead to hallucinations. While research into olfactory hallucinations remains limited, findings in the visual system suggest that the OB or piriform cortex may be hyperactive while higher order areas may be quieter during olfactory hallucination. Interestingly, multiple case studies report that patients with olfactory dysfunction related to COVID-19 and depression showed marked improvement of symptoms following recreational use of psychedelics (Kovacevich et al., 2023). This anecdotal link between olfactory performance and psychedelic use thus indicates that psychedelics may target mechanisms in the olfactory system (Lizbinski & Dacks, 2017). Although these recent studies in human research have advanced our understanding of psychedelics and their impact on the nervous system, much remains unknown.

Animal Research

The use of animals in research has contributed greatly to our understanding of psychedelics, for example, in elucidating their biological underpinnings and therapeutic potential. When research on humans diminished in the 1970s, animal research forged on, although at a decreased pace. Various animal models of psychiatric and neurological disorders have been developed and used to assess the therapeutic and safety potential of psychedelics, yielding insights into the neural mechanisms of action, and expected behavioral outcomes.

Hallucinogens have been used in animals to examine spontaneous behaviors. In patients with schizophrenia and obsessive compulsive disorder, sensorimotor gating dysfunction reflects

sensory processing deficits (Braff et al., 1978; Halberstadt & Geyer, 2016; Swerdlow et al., 1994). Thus, to model sensorimotor gating deficits in rodents, prepulse inhibition (PPI) is used to test startle response. In the PPI paradigm, a small stimulus followed by a loud stimulus prevents a large startle response in control subjects. Rats administered a hallucinogen have impaired PPI, suggesting hallucinogens impact sensorimotor gating like those with schizophrenia (Halberstadt & Geyer, 2016; Ouagazzal et al., 2001). Investigative behaviors in rodents, such as locomotion and hole pokes, have been used to assess how hallucinogens impact behaviors without a task. Hallucinogens dose-dependently decrease rearing, hole pokes, and locomotion (Adams & Geyer, 1985; Halberstadt & Geyer, 2016). While these metrics have been useful to understand basic behavioral changes, we are missing the rich repertoire of behaviors that animals use when actively sensing.

The visual system has been of primary interest to researchers due to its translational relevance to humans, with few studies examining olfactory behaviors or brain regions. Rodent studies have looked at changes in brain regions relevant to visual processing, for example, rats given DOI and 5-MeO-DMT have decreased oscillations in mPFC and decreased BOLD signal in visual cortex and mPFC, respectively (Riga et al., 2018). Mice given DOI also show decreased activity in visual cortex during passive viewing (Michaiel et al., 2019). Within these paradigms, there has been little interest in recording sniff behavior, although rodents rely heavily on sniff to navigate and understand their environment. In a social interaction study, chronic LSD exposure increased sniff behavior in rats, although sniff was recorded via hand scoring of a video and not with a biometric calculation tool (Marona-Lewicka et al., 2011). The changes in olfactory cortices and sniffing frequency in freely moving mice after hallucinogen administration remain unknown.

Psychedelics produce a reliable behavioral effect in mice and rats known as the head-twitch response (HTR) by primarily targeting the 5-HT_{2A} receptors. The HTR has been well described as a rapid, rotational head shake, twisting from side to side much like a wet dog shaking its head (Halberstadt & Geyer, 2013). This behavior in rodents is used as a behavioral proxy for hallucination in humans, where a higher dose produces increased HTR events over time (Clint E. Canal & Morgan, 2012; Hanks & González-Maeso, 2013). The rodent HTR has become the predominant behavioral readout for whether a hallucinogen is a 5-HT_{2A} agonist and predictive for hallucinogenic effects in humans (Halberstadt et al., 2020). The 5-HT_{2A} receptor is required for the HTR, as genetically modified mice without these receptors do not experience a HTR nor do mice pre-treated with a 5-HT_{2A} antagonist (González-Maeso et al., 2007; Halberstadt, 2015; Titeler et al., 1988; Franz X. Vollenweider & Preller, 2020). Drugs that are non-hallucinogenic in humans but target the 5-HT_{2A} receptor do not elicit an HTR in rodents (González-Maeso et al., 2007). The 5-HT_{2C} receptor is yet another receptor targeted by hallucinogens, which modulates the HTR. Mice with the 5-HT_{2C} receptor genetically knocked out have reduced HTRs after hallucinogen administration (Clinton E. Canal et al., 2010) and treatment with a 5-HT_{2C} agonist a decreases the HTR, while antagonists leave the HTR unaffected (Fantegrossi et al., 2010). Additionally, the metabotropic glutamate receptor 2 (mGluR2) when knocked out in mice, eliminates the HTR as induced by LSD or DOI (Moreno et al., 2011). Another neurotransmitter important to the OB and olfactory system is glutamate. The mGluR2 is in the granule cells of the OB (Shepherd et al., 2004) and modulates signal from the mitral cells (Hayashi et al., 1993). The elimination of the HTR when signal within the OB and olfactory system is simultaneously blunted by the knockout of those genes raises questions regarding the role of the olfactory system in the effects of hallucinogens in mice.

The HTR has been an incredibly useful behavior in gaining insight into the neural underpinnings of psychedelics, as illustrated by the findings that 5-HT_{2A} and mGluR2 receptor activation are necessary for the HTR. How does this behavior fit into the larger picture of hallucinogenic effects? While much insight has been gained from studying the HTR, how the HTR relates to the olfactory system and olfactory behaviors is an open question. While most researchers believe the HTR is involuntary, it cannot be ruled out that it occurs in response to perceived state. These are the questions that motivate chapters II and III of this dissertation.

SPECIFIC AIMS

The goal of this dissertation is to examine how the hallucinogen DOI impacts behaviors related to olfaction. The olfactory system is well developed and heavily relied on by mice, but the impact of psychedelics on the olfactory system represents a gap in the field that warrants further investigation. Considering the established use of psychedelics in animal models of psychiatric disorders and their treatment, employing DOI to explore olfactory related perturbations of behavior and neural activity constitutes an innovative and scientifically sound strategy.

Chapter II of this dissertation will address how the hallucinogen DOI impacts conditioned behavior. This chapter will address how DOI effects odor search strategy in an olfactory navigation task, in addition to sniffing and behavioral structure and strategy. In particular, little is known about how psychedelics impact sniffing behavior. Introducing the measurement of sniffing behavior into psychedelic research may yield novel insights into how mice actively sense the environment when exposed to a hallucinogen. Using a 2-alternative force choice task to

report the location of an odor is a novel paradigm we introduce into the world of psychedelic research which will provide unique perspectives in how mice report odor perception. By investigating odor perception in mice, we for the first time illustrate how DOI impacts the report of odor in a task through sniffing and movement.

Chapter III will examine how DOI impacts uninstructed, spontaneous behavior in the mouse. The primary goal is to establish an understanding of changes in neural activity in the OB and breathing rhythms in mice after hallucinogen administration. Movement and exploratory behaviors will also be studied using video tracking techniques that allow for a more robust and rich understanding of behavior. Furthermore, the HTR will be examined as it pertains to sniffing behavior and neural activity, examining the most utilized behavior in rodent psychedelic research through a novel lens. Together, chapters II and III will provide unique insights into the impact of psychedelics on active olfaction in mice, which can be related to how humans actively sense during hallucination.

CHAPTER II

THE IMPACT OF A PSYCHEDELIC DRUG ON OLFACTORY SEARCH BEHAVIOR BY MICE

This chapter includes material in preparation for publication in *eLife Sciences Journal*, co-authored by Nate Gonzales-Hess, Takisha Tarvin, Jessica Connor, and Matthew C. Smear. I conceptualized the study, designed the experiments, collected all data, analyzed data, and wrote the manuscript. Nate Gonzales-Hess contributed to hardware and software creation and maintenance for data collection. Takisha Tarvin contributed to data collection. Jessica Connor contributed greatly to labeling videos. Dr. Matthew Smear contributed to design, data analysis, writing, and editing.

Introduction

Animals use their sense of smell for survival, reproductive guidance, and navigation, so a properly functioning olfactory system is vital for animal well-being and life expectancy. The interaction between the environment and an animal's sensory organs to investigate around it is crucial. In active sensing, animals expend energy to acquire information and interpret external sensory cues (Nelson & MacIver, 2006). Movement and behavior modulate perception, where this feedback updates an animal's perception of its world. In a hallucination, the ability to differentiate between reality or hallucination may depend on this intentional, active sensing exist (J. J. Gibson, 1962; James J. Gibson, 1970). Capturing active sensing as a behavioral output can give insight into perception in an animal model of hallucination.

Olfactory disturbances are experienced and well documented in numerous psychiatric and neurological disorders, including schizophrenia, Parkinson's disease, depression, epilepsy, and migraines (Bannier et al., 2012; Kopala et al., 1994; Mainardi et al., 2017; Sarnat & Flores-Sarnat, 2016). Patients with these diagnoses may experience olfactory hallucinations, where prevalence varies, with some reports as high as 34.6% (Kopala et al., 1994) and a sex difference showing women more frequently affected than men (Bainbridge & Byrd-Clark, 2020; Sjölund et al., 2017). Olfactory hallucinations are predominantly unpleasant, with patients most often reporting smoke, waste, decaying matter, and mold (Sjölund et al., 2017). The impact of olfactory hallucinations on the population is largely negative, calling for a model of research to explore them. While hallucinations occur in psychiatric and neurological disorders, they may also be induced by the consumption of psychedelics. Here, we introduce a mouse model of behavior for exploring psychedelics and their impact on olfaction.

Psychedelics induce stereotypical behaviors in both humans and animals. In rodents, administration of a serotonergic psychedelic reliably produces a rotational head shake known as the head-twitch response (HTR; (González-Maeso et al., 2007; Halberstadt et al., 2020; Halberstadt & Geyer, 2013). The quantity of HTRs correlates with the potency of hallucinations in humans. This correlation has motivated the idea that HTRs are a behavioral analog to the human experience (Hanks & González-Maeso, 2013). In humans, erratic, high-rate eye saccades occur after administration of a classic hallucinogen (Hebbard & Fischer, 1966). In schizophrenia, auditory hallucinations can be predicted by subtle lip movement (Rapin et al., 2013), and humming can decrease the rate of auditory hallucinations (M. F. Green & Kinsbourne, 1990). Behavior is linked to perception, and how olfactory behaviors interact with psychedelics remains unclear.

Considering the importance of olfaction in rodents and the large gap in understanding how psychedelics impact the olfactory system, we sought to establish an understanding of respiration and behavior of mice after the administration of the hallucinogen DOI (2,5-Dimethoxy-4-iodoamphetamine). Here, we show the changes in active sampling, movement, and olfactory search behavior after the administration of the psychedelic DOI.

Results

DOI alters olfactory search behavior

To study the impact of psychedelics on active olfactory behavior we administered DOI to mice and tested them in an olfactory search paradigm. Mice can reliably report the source of a noisy, turbulent odor gradient in an olfactory search paradigm (Findley et al., 2021). In the search paradigm, mice poked into an initiation port to start a trial. Odor was pseudo-randomly delivered from the left or right side of the end of the arena. To receive a water reward, mice had to navigate toward higher odor concentration. To investigate task performance in the absence of a stimulus, we omitted odor on 10% of trials. Mice were trained until they performed at 85% accuracy for 1 week, which varied per mouse but took less than 2 weeks total. Mice were then administered 3 mg/kg DOI or saline IP then placed into the task 5 min later (Figure 1A). Mice were crossed over into the opposite condition 1 week later.

Given that psychedelics disrupt perception in humans, we hypothesized that mice would perform less accurately in olfactory search. Indeed, mice more often navigated to the incorrect side of the arena in the DOI condition (Figure 1B; Wilcoxon signed rank test, $p = 0.024$, $n = 22$). DOI was administered 5 min before the session began, so we wondered whether its effect would become larger as the session proceeded. To ask how DOI impacted performance as a function of

Figure 1

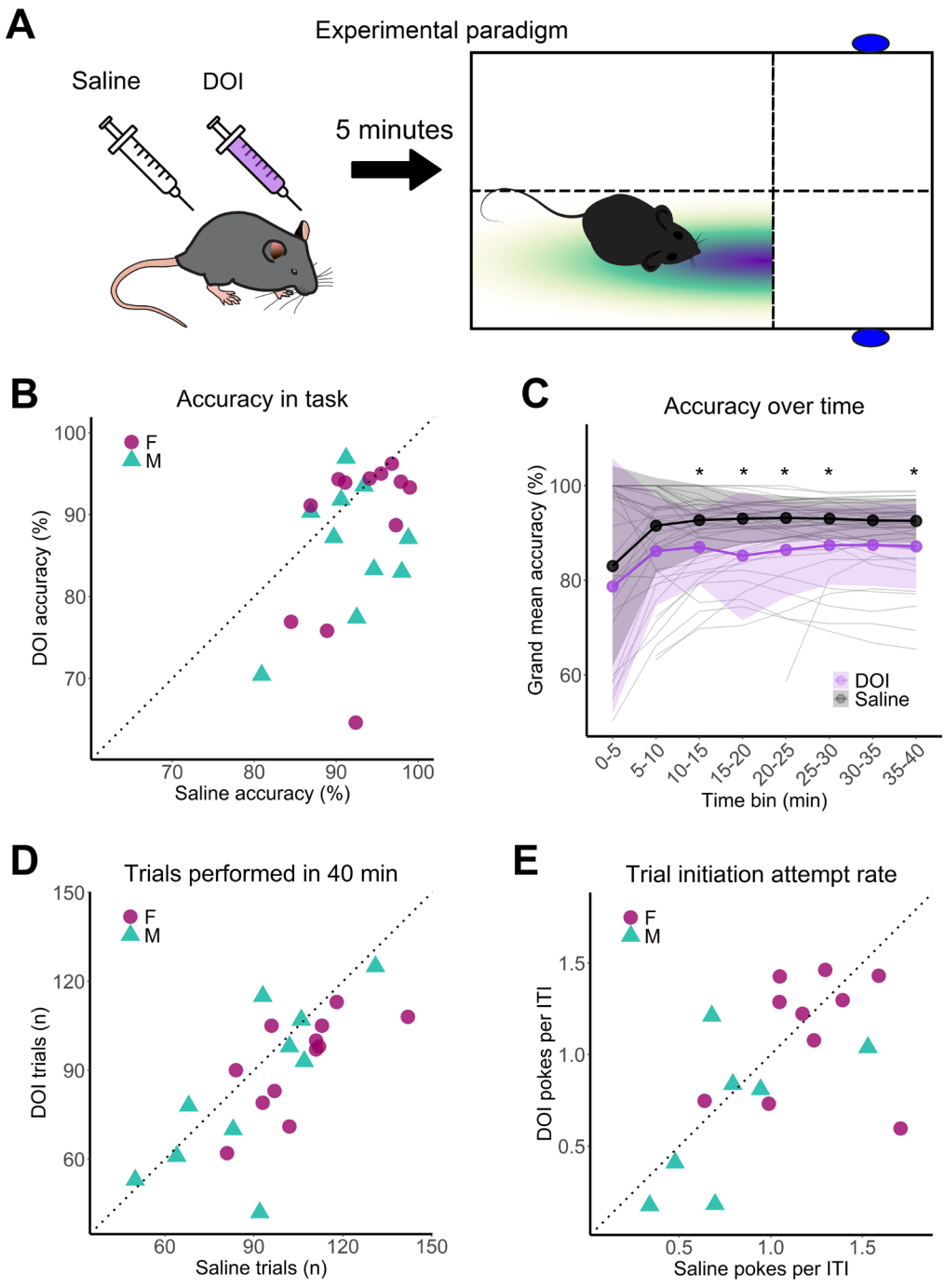

Figure 1. Mice performance in the olfactory search paradigm. (A) Diagram of experimental paradigm. Mice were injected with 3 mg/kg DOI or saline then placed into the task 5 min later. **(B)** Scatter plot of accuracy in the task for each mouse in DOI and saline conditions. Color and shape denote mouse sex. **(C)** Line graph of grand mean accuracy in the task binned in 5 min intervals. Shaded areas are standard deviation. **(D)** Scatter plot of number of trials performed for each mouse. Sessions were at a fixed duration of 40 min. **(E)** Scatter plot of trial initiation attempts during the ITI for each mouse. Rate was normalized as the number of pokes into the initiation port by the number of ITIs.

time in the session, we quantified accuracy in 5 min time bins. In odor trials, accuracy was higher in the saline condition after the first 10 min, except for the 30 – 35 min bin (Figure 1C; Wilcoxon rank-sum test, $p < 0.01$ for time points within 10 – 25 min, $p = 0.039$ for 35 – 40 min). Thus, the change in performance is overall uniformly distributed across the duration of behavioral sessions.

Since high doses of DOI can decrease locomotor activity in an open field test (Halberstadt et al., 2009), we next assessed task adherence after DOI administration. Mice completed fewer trials in the DOI condition (Figure 1D; Wilcoxon signed rank test, $p = 0.011$, $n = 22$). This effect was driven by female mice; female mice performed fewer trials on DOI compared to saline (Figure 1D; Wilcoxon signed rank test, $p = 0.011$, $n = 12$), whereas male mice did not show a significant difference (Figure 1D; Wilcoxon signed rank test, $p = 0.39$, $n = 10$). We further assessed whether mice repeatedly poked into the initiation port during the ITI to start a new trial. We found that mice poked into the initiation port, but there was not a significant difference between conditions (Figure 1E; Wilcoxon signed rank test, $p = 0.27$, $n = 17$). In an auditory detection task, mice false alarmed at a higher rate both when a signal was expected and when administered the drug ketamine compared to vehicle (Schmack et al., 2021). Similar to how mice would false alarm, we hypothesized that mice in the DOI condition would report an odor stimulus during the ITI of a session, especially during a longer ITI, but this was not the case. Mice rarely reported an odor during the ITI after trial initiation attempt (Wilcoxon rank sum test, $p = 1$).

DOI impacts speed and timing

When given the drug ketamine to induce hallucination-like percepts, mice wait longer for a reward when they are confident they experienced a stimulus, even when one did not occur (Schmack et al., 2021). This has been speculated to be due to confidence as a function of time invested awaiting a variably scheduled reward. Since mice cannot report confidence in a percept, this metric allows for a measurable output that they were correct in their decision. If mice similarly show confidence in our olfactory search task, we would predict that they spend longer in the reward port in the DOI condition. Reward port duration was increased in the DOI odor trial condition compared to both saline odor and saline odor omission trials (Figure 2A; Wilcoxon rank sum test, $p < 0.001$, $n = 17$). We did not find a sex effect of condition (Figure 2A supplemental, $p = 1$). When comparing the median duration between conditions, mice in the DOI condition spent longer in the reward port compared to saline (Figure 2B; Wilcoxon signed rank test, $p = 0.002$). This effect was driven by the odor trial (Figure 2B supplemental; Wilcoxon signed rank test, $p = 0.001$), as we did not see a difference between median duration after an omission trial (Wilcoxon signed rank test, $p = 0.60$).

In incorrectly performed trials, when mice did not receive a reward, mice spent the longest duration in the reward port after the DOI odor trial and the least amount of time in the reward port after a saline odor omission trial. We found an increased duration in DOI odor trials compared to DOI odor omission trials (Figure 2C; Wilcoxon rank sum test for all comparisons, $p < 0.001$), saline odor trials ($p = 0.030$), and saline odor omission trials ($p < 0.001$). Additionally, there was an increased reward port duration for the saline odor trial compared to the saline odor omission trial ($p < 0.001$). Sex differences within each condition were not significant (Figure 2C supplemental, Wilcoxon rank sum, $p = 1$). When comparing the median duration between

Figure 2

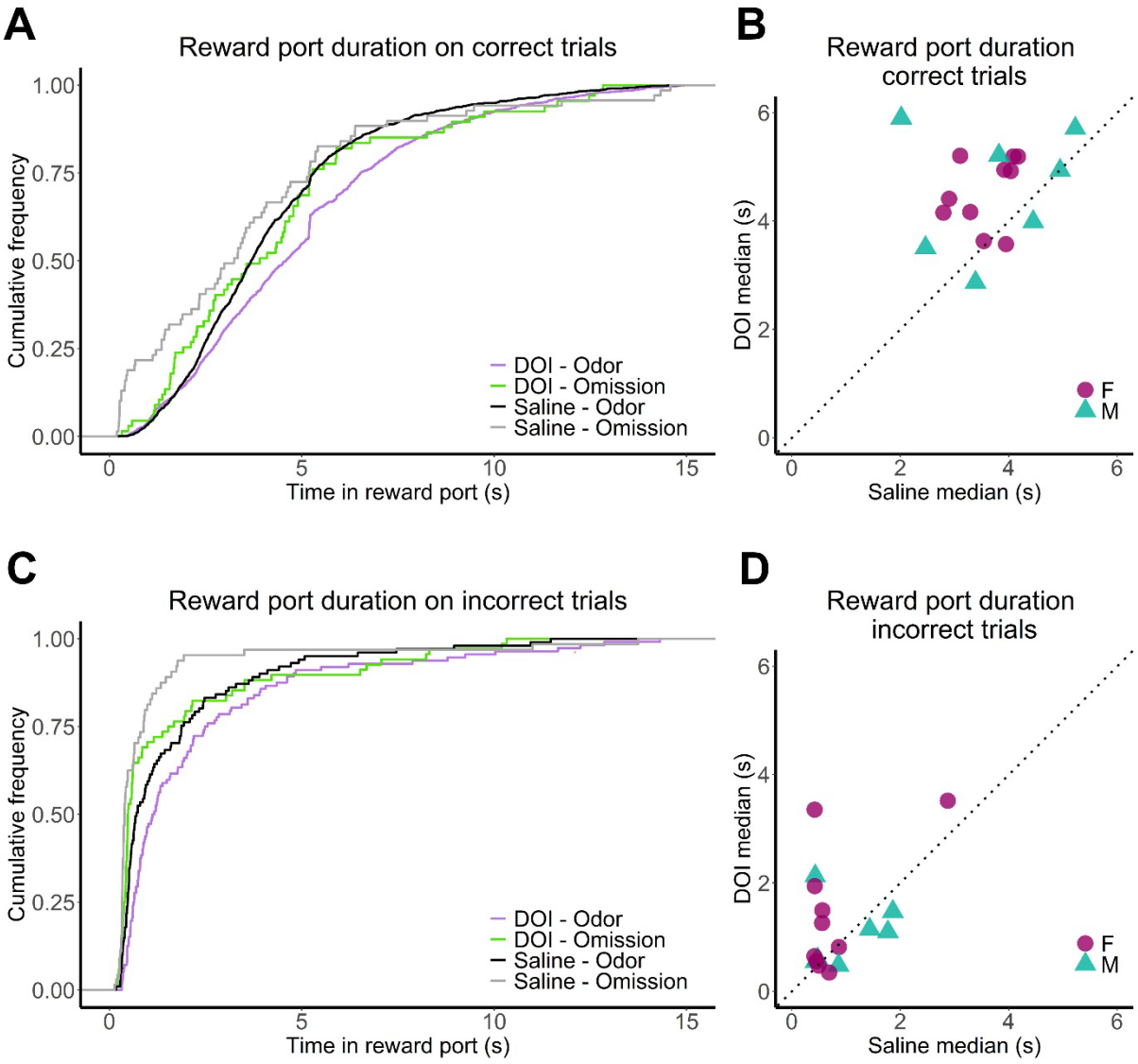

Figure 2. Duration in reward ports increased in the DOI condition. (A) Cumulative histogram of duration in a reward port after a correct response in a trial. Colored lines show DOI odor and omission trials. Black and grey lines show saline odor and omission trials. **(B)** Scatter plot of median duration in a reward port after a correct trial per mouse in DOI and saline conditions. **(C)** Cumulative histogram of duration in a reward port after an incorrect response in a trial. Color as in A. **(D)** Scatter plot of median drinking duration after an incorrect trial per mouse in DOI and saline conditions.

conditions, there was no difference between DOI and saline (Figure 2D; Wilcoxon signed rank test, $p = 0.21$). However, after an odor omission trial, mice spent longer in the reward port in the DOI condition (Figure 2D supplemental, Wilcoxon signed rank test, $p = 0.049$). Taken together,

we show that mice spend longer in the reward port under the influence of DOI. Our results are thus consistent with previous work suggesting that psychedelics may increase perceptual confidence (Schmack et al., 2021). However, we cannot rule out a general impact of psychedelics on task adherence. An increased reward port duration could also be due to a decreased ability or desire to move out of the reward port. DOI can increase dopamine signaling and reward salience (Martin et al., 2024), thus the increased duration in the reward port may be driven by an increased valuation of water.

Since mice show decreased locomotion at high doses of DOI (10 mg/kg) (Halberstsadt & Geyer, 2018), we asked whether trial duration and movement speed varied between conditions. In odor trials, mice took longer to complete a trial in the DOI condition compared to the saline condition (Figure 3A; Wilcoxon signed rank test, $p < 0.001$, $n = 22$). In contrast, there was no difference in trial duration in omission trials between DOI and saline (Wilcoxon signed rank test, $p = 0.26$, $n = 22$). Next, we wanted to know if mice took longer to initiate a new trial and thereby increased time in the ITI. However, there was no difference in ITI duration between conditions (Figure 3B; Wilcoxon signed rank test, $p = 0.19$, $n = 22$).

Using DeepLabCut (DLC; (A. Mathis et al., 2018), the nose, head, and center of mass were tracked to triangulate the position of mice per frame from video. We found that DOI decreased movement speed both within trial (Figure 3C; Wilcoxon rank sum test, $p = 0.011$, pooled trial type) and during the ITI (Figure 3D; Wilcoxon rank sum test, $p = 0.036$) compared to saline. In odor trials specifically, the speed between DOI and saline sessions were not different (Figure 3 supplemental; Wilcoxon rank sum test, $p = 0.059$). Within the DOI condition, speed was decreased in the ITI compared to an odor trial (Figure 3 supplemental; Wilcoxon signed

Figure 3

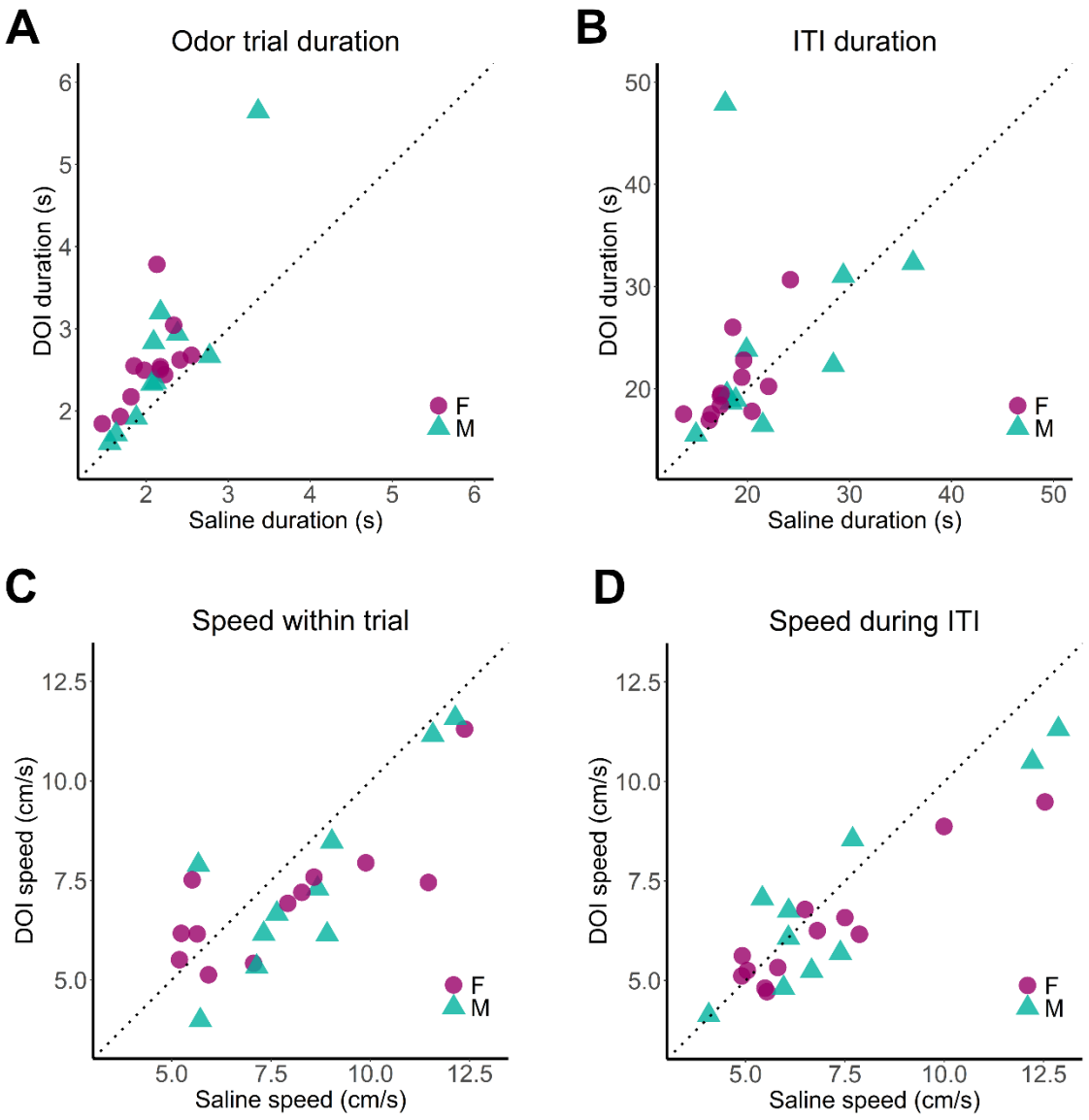

Figure 3. Trial duration increased and speed decreased in the DOI condition. (A) Scatter plot of mean odor trial duration for each mouse in the DOI and saline condition. **(B)** Scatter plot of mean ITI duration. **(C)** Scatter plot of mean speed within trial for each mouse in the DOI and saline condition. **(D)** Scatter plot of mean speed during the ITI.

rank test, $p < 0.001$). However, there was no difference in speed between the odor and odor omission trials in the DOI condition (Wilcoxon rank sum test, $p = 0.21$), nor the ITI and odor

omission trials (Wilcoxon rank sum, $p = 0.068$). In comparison, in saline sessions the ITI speed was slower compared to odor ($p = 0.002$) and odor omission trials ($p = 0.017$). Speed within the odor and odor omission trials were not different in the saline condition (Wilcoxon rank sum, $p = 0.54$).

DOI increases sniff frequency

Active sensing is crucial to investigating the environment. Rodents increase sniff rate when investigating a novel odor or in an olfactory task (Findley et al., 2021; Kepecs et al., 2007; Verhagen et al., 2007; Youngentob et al., 1987). In humans, administration of LSD increases eye movements (Hebbard & Fischer, 1966), but does not alter respiration rate (Sokoloff et al., 1957). Since mice primarily use their olfactory system to interpret their environment, in contrast to humans that use the visual system we expected the sniff frequency to increase in the mouse after DOI administration. When all sessions with sniff measurement were combined, we found that the sniff frequency was higher in DOI sessions (Figure 4A – C; Fisher-Pitman Permutation test, $Z = 24.9$, $p < 0.001$). In 13 mice with a matched DOI and saline session, all of them had a higher sniff frequency in the DOI condition (Figure 4 supplemental; Kolmogorov-Smirnov test, $p < 0.001$ for 13 of 13 mice). When comparing sniff frequency by trial type, mice sniffed faster in the DOI condition for each trial type and during the ITI (Figure 4D; Fisher-Pitman Permutation test for all trial types; Odor trials: $Z = 3.38$, $p < 0.001$; Omission trials: $Z = 2.71$, $p= 0.007$; ITI: $Z = 18.4$, $p < 0.001$). We did not observe a difference in median sniff frequencies between conditions (Figure 4E; Wilcoxon signed rank test; $p = 0.11$).

Figure 4

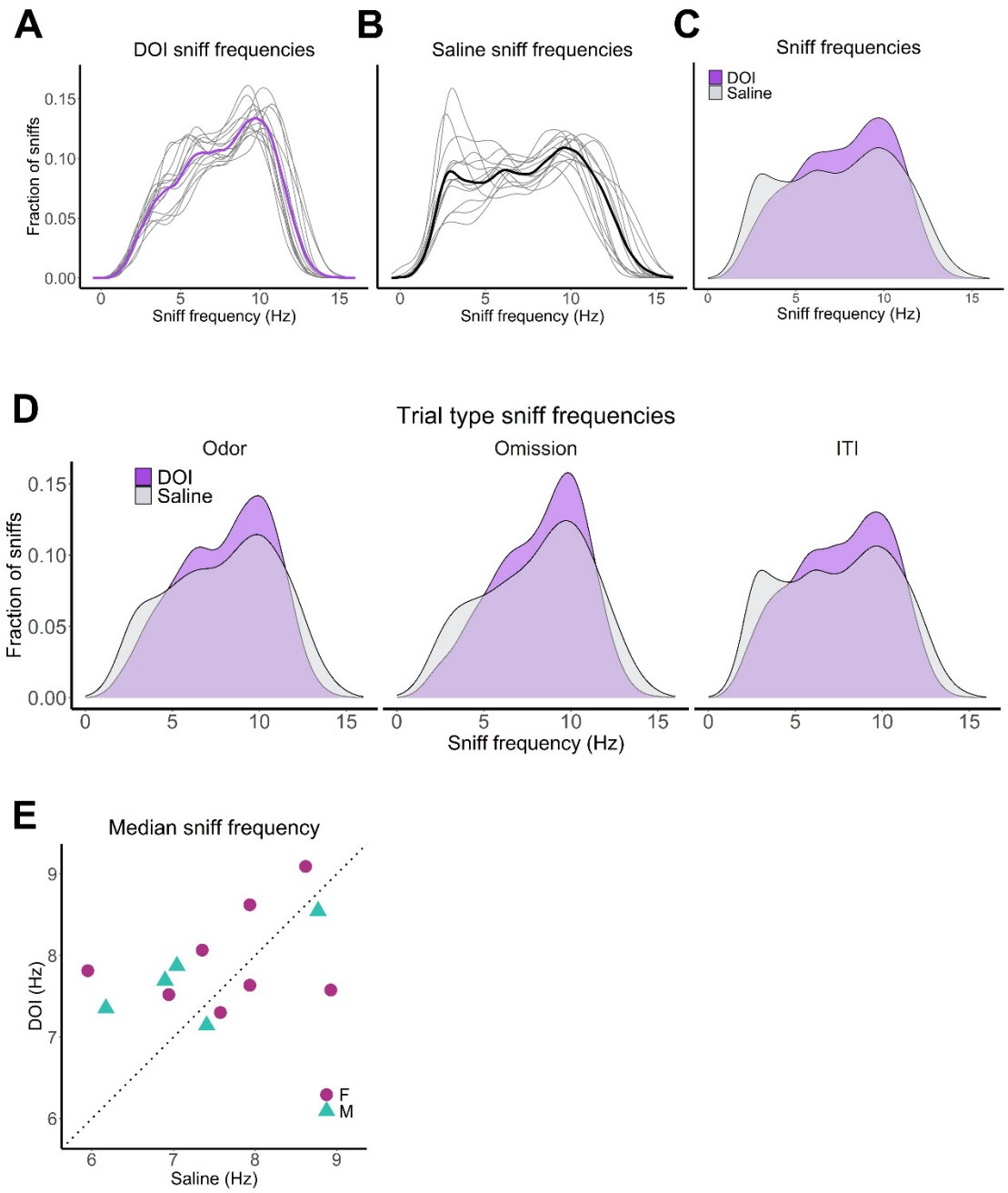

Figure 4. Sniffing frequency increased in the DOI condition. (A) Histogram of sniff frequencies across all mice with signal in the DOI condition (n = 14). The thick purple line represents all mice, thin grey lines are individual mice. **(B)** Histogram of sniff frequencies across all mice with signal in the saline condition (n = 13). The thick black line represents all mice, thin grey lines are individual mice. **(C)** Histogram of all DOI and saline sniff frequencies overlaid. Purple is the DOI session, grey is the saline session. **(D)** Histograms of sniff frequencies for an odor trial, odor omission trial, and during the ITI. Purple is DOI, grey is saline. **(E)** Scatter plot of median sniff frequency per mouse in the DOI and saline condition.

Mice occupy allocentric space similarly but head twitch preferentially in proximity to odor ports

To investigate where mice structured their behavior allocentrically, we quantified occupancy across all mice. As we predicted mice would perform worse in the task in the DOI condition, we expected their arena occupancy to display increased duration outside of the path towards the reward ports and around the initiation port. We expected in the DOI condition they would spend more time in areas irrelevant to the task such as corners of the arena, with a more even distribution across the arena, however, we did not see this. Between DOI and saline conditions, mice were generally uniform in occupancy (Figure 5A, B). In contrast, the saline condition revealed increased duration near the odor ports.

The head-twitch response (HTR) is a reliable observed behavior when mice are administered a hallucinogen. Next, we assessed where in the arena mice in the DOI condition emitted a HTR. We expected to see HTRs during the task with an equal distribution of events across the arena. We plotted the nose location at the onset of a HTR (Figure 5C) then spatially binned the arena in ~ 2.5 cm^2 to quantify HTR location counts (Figure 5D). We normalized the rate of HTR based on occupancy per mouse, as some areas of the arena had disproportionate levels of occupancy. During a trial, HTR rate occurred throughout the arena without spatial predictability on the Y-coordinate (Figure 5 supplemental; Permutation test, $p = 0.92$), but with preference for the X-coordinate (Figure 5 supplemental; Permutation test, $p = 0.002$). Similarly, during the ITI, we found that mice HTR more frequently closer to the end of the arena after crossing the decision line (as X- coordinate increases), but not immediately next to the reward ports (on the Y-coordinate) (Figure 5 supplemental) and when conditions were combined (Figure 5E; Permutation test, $p < 0.001$ for X-coordinates). Hallucinations that occur in Parkinson's

Figure 5

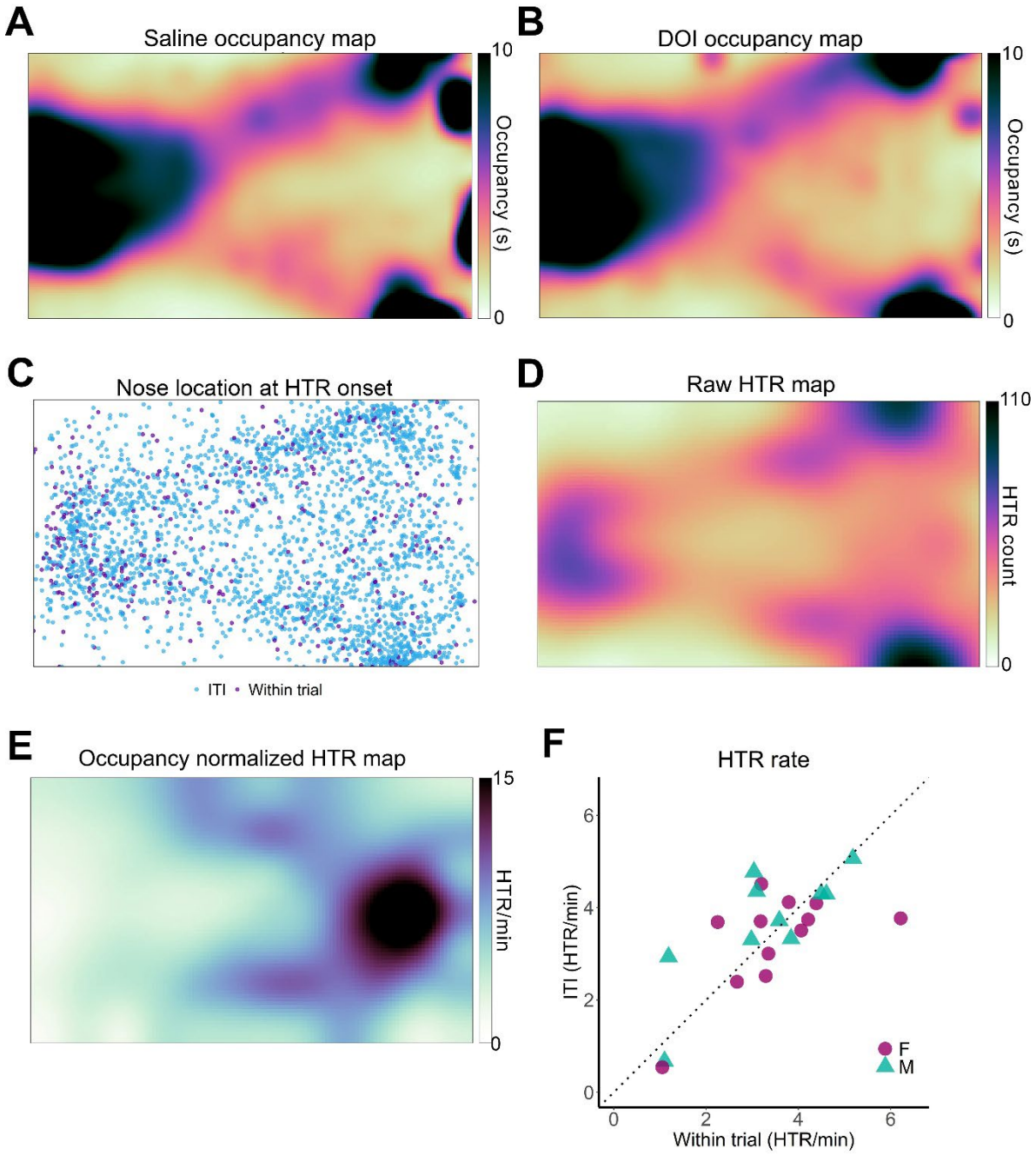

Figure 5. Mice similarly occupied the arena between conditions, but head twitched more frequently near odor ports. (A) Two-dimensional histogram of occupancy (fraction of frames spent in each 1 cm^2 bin) in the saline session. Color is mean across all mice (n = 22). **(B)** Same as in A, but for the DOI session. **(C)** Scatter plot of nose location at the onset of a HTR across all mice. **(D)** Two-dimensional histogram of HTR location and Gaussian smoothed. **(E)** Two-dimensional histogram of HTR rate during a DOI session based on ~2.5 cm^2 bin location. HTR was normalized based on occupancy per mouse, then averaged across all mice (n = 22). Color bar represents the HTR rate per min. **(F)** Scatter plot of HTR rate per mouse in the ITI versus within a trial.

disease have impairment of the Dorsal Attention Network and Default Mode Network coupled with sensory regions (Shine et al., 2015), suggesting hallucinations occur more due to attention disruption. Thus, in the search phase of a task, we expected HTR frequency to be lower. We normalized HTR rate based on within trial and ITI duration and found no difference in HTR rate based on whether the mouse was in a trial or ITI (Figure 5F; Wilcoxon signed rank, $p = 1$). Additionally, we did not see a sex difference in HTR rate over the 40 m session (Figure 5 supplemental; Wilcoxon rank sum, $p = 0.31$).

Mice differentially use subsets of behaviors between DOI and saline

Behavior is rich with movements and structures not observed in occupancy or speed analyses, thus we wanted to assess if mice use sub second behavioral motifs called "syllables" more or less frequently (Lin et al., 2024; Wiltschko et al., 2020). Labeled points from DeepLabCut (DLC) were used to capture behavioral syllables (Figure 6A). Syllables were more likely to be used in the DOI session and one more likely to be used in saline (Figure 6B). We found that between DOI and saline, specific syllables were used more in DOI and others used more in saline (Figure 6C; Permutation test, $p < 0.01$). This analysis shows that DOI influences the kinematic structure of behavior.

Discussion

In this study, we demonstrate that the psychedelic DOI impacts olfactory navigation and breathing rhythms in mice. Mice quickly learn the olfactory navigation task, but their performance statistics demonstrate a decreased ability to correctly report the side an odor is released from. Within the first 10 minutes of the task, accuracy is not different between the DOI

Figure 6

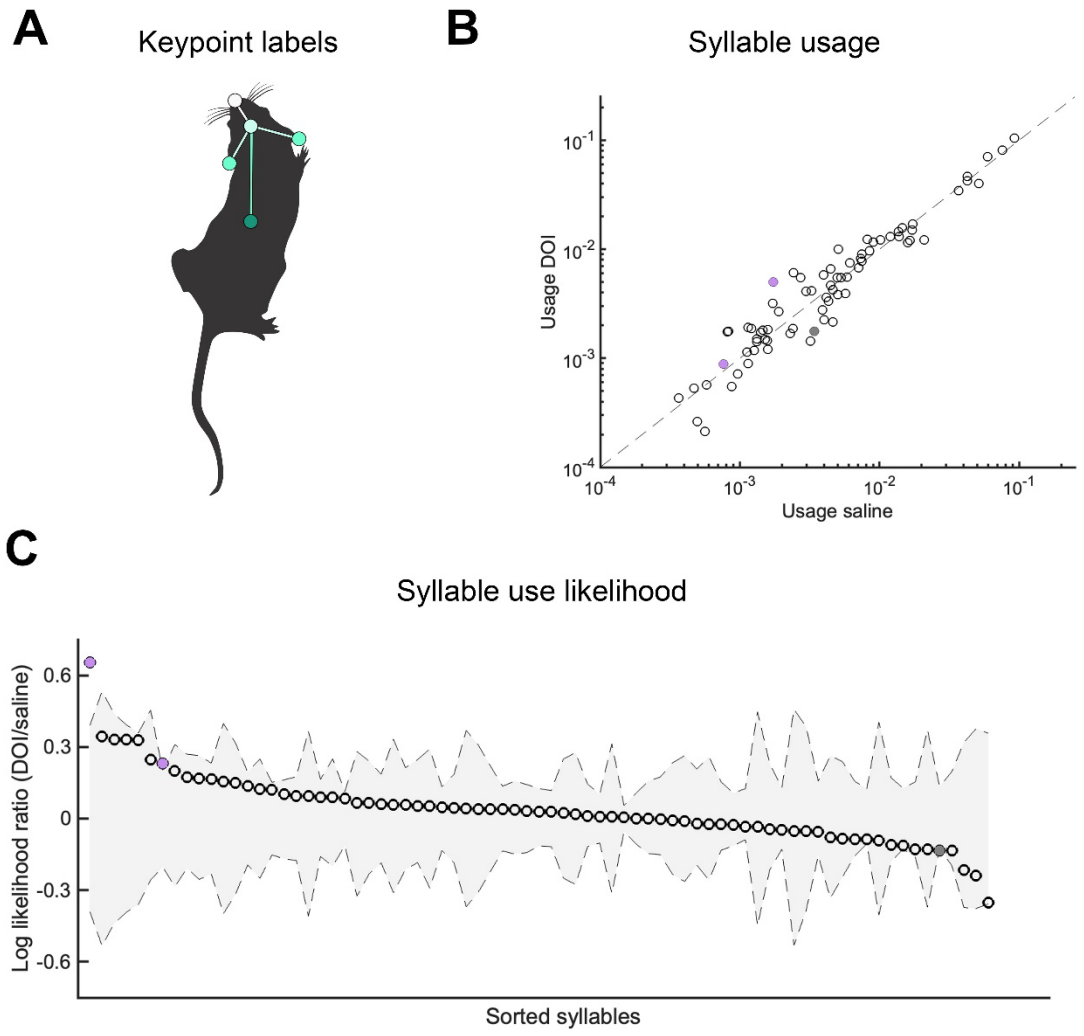

Figure 6 (next page). DOI induced different behavioral patterns at sub second scale. (A) Diagram of keypoint labels. **(B)** Scatter plot of syllable usage between DOI and saline. Purple circles signify significant use in DOI. Grey circles signify significant use in saline. Empty circles are non-significant. **(C)** Syllables sorted by likelihood of use with the most commonly used DOI syllables on the left in descending order of likelihood use. Dots are colored as in B. Shaded regions show the 99% confidence intervals of the permutation test null distributions.

and saline conditions, but after that their accuracy drops. As expected, report of an odor within the omission trials were at chance demonstrating no contamination within the experimental

paradigm. We expected about 50% reporting on the left and right side which is what we found. We found that female mice, but not male mice, in the DOI condition perform fewer trials. We do see a sex difference in trials performed in females. On average, female mice perform slightly more trials than males in both conditions (though not significant), however, DOI selectively decreases trial numbers in females in paired comparison. The number of trials performed was more widely distributed in the males in both conditions. Taken together, mice perform worse in the odor navigation task but remain motivated to do the task and do not falsely report an odor stimulus during the ITI. These findings give additional insight into how DOI impacts females differently than males.

In the ITI of a session, mice poke into the initiation port repeatedly to initiate a new trial. During the ITI after an initiation poke, mice do not navigate to the opposite end of the arena to report an odor and retrieve a reward. We reasoned that mice would report an odor in the absence of one. Although DOI decreased olfactory search accuracy, it did not instigate an entirely new repertoire of behavior. They waited to report an odor until an odorant was released, suggesting that DOI does not completely eliminate task adherence and perceptual capacity.

Timing in the task is skewed slower in the DOI condition. Mice take more time to complete an odor trial in the DOI condition, as demonstrated by trial duration. In an odor omission trial, there is no difference within subject. Additionally, there is no difference in the amount of time in the ITI. The average speed within trial was faster for mice in the saline condition. When looking at trial type specifically, we found that mice are slower in odor trials in the DOI condition, but the odor omission trials do not have a difference in speed. The speed during the ITI was faster for the saline condition compared to DOI as well. The slower speed and longer trial duration in an odor trial taken together indicate that DOI slows the process in

reporting which side of the arena the odor is coming from. The decreased speed during ITI for DOI sessions suggests a reduced motivation to perform the task. Since we are tracking the nose, it may also indicate a slower process in trying to reinitiate trials in the ITI. In the DOI condition, mice do not differ in speed between ITI and omission trials.

Timing is further disrupted in the DOI condition when retrieving a reward. We looked at how long a mouse spent in the reward port on correct trials and found that mice spend the longest amount of time in a reward port after an odor trial in the DOI condition. They spend longer in the reward port compared to the saline odor and odor omission trials. Interestingly, mice that complete an odor omission trial in the DOI condition do not spend more time in the reward port compared to any other condition. This effect is unique to odor trials in DOI. On incorrect trials when there is no water reward delivered, mice still spend a significant amount of time in the reward port after a DOI odor trial. This is also the case for mice in the saline condition. On incorrect odor trials they spend more time in the reward port compared to odor omission trials.

Psychedelics interfere with the perception of time in mice (Halberstadt et al., 2016) and reduce reaction time in humans (Yousefi et al., 2025). Additionally, mice that are confident they experienced a stimulus wait longer in a reward port for a reward (Schmack et al., 2021). Considering the several metrics regarding timing in which mice are different in DOI compared to saline, their sense of time may be altered by DOI. The increased duration in the reward port on incorrect odor trials could be a sign of increased confidence in an incorrect decision. Additionally, the sense of timing may be interrupted in that under both response outcomes, there is a lost sense of how much time has been spent in the reward port. The salience of a reward may also be increased during the DOI condition, as DOI increases dopamine signaling for predictable rewards (Martin et al., 2024). Thus the increased duration in the reward ports could be an

increase of the value of water during the task. An alternative interpretation is that the introduction of an odor stimulus in combination with DOI may lead to an intensified perception of odor. By moving more slowly in the task, when in non-task paradigms they move more quickly (Halberstadt & Geyer, 2018) in addition to a longer trial duration in odor trials, more time investigating the odor is required to report its location.

Mice rely on sniffing to investigate their environment. In this study, we demonstrate that the sniff rate is altered with DOI in a way that suggests increased active sensing to discern the odor landscape. Sniffing is highly synchronized to movement and investigation (Findley et al., 2021), however, in the DOI condition we see that mice sniff faster throughout the session and lose sniff rate structure, despite moving more slowly in the task. This increase in sniff rate is evident in both trial conditions and during the ITI. The increase in sniff rate taken with the decrease in movement speed suggests that sniffing the environment in the absence of an external stimulus could be due to a hallucination-like perception. Mice investigate and sniff novel and attractive odors at a higher rate than neutral or familiar odors (Li et al., 2023; Qiu et al., 2021; Wesson et al., 2008), yet we see a sustained elevated sniff rate in the absence of novel or attractive odors.

The HTR is a reliable behavior observed in rodent psychedelic research. Serotonergic psychedelics induce a HTR rate that varies with dose (Clint E. Canal & Morgan, 2012). In this study, we expected to observe the HTR at a higher rate during the ITI without location dependency. However, we found that the HTR is location dependent after occupancy normalization but not trial dependent. Hallucinations are argued as a top-down process, where prior assumptions and internal state can influence perception (Grossberg, 2000; Kowalski et al., 2024; Powers et al., 2016). The proximity to the location of the odor source may thus contribute

to the increased HTR rate. As mice approach the decision line in a trial, odor concentration in the air becomes higher, suggesting the prior knowledge of an odor source could influence perception. However, there is uncertainty in what brain regions are directly responsible for the HTR. The HTR can be induced by infusion of a psychedelic into the prefrontal cortex (Willins & Meltzer, 1997), while transection of the brain at the posterior commissure eliminates the HTR (Bedard & Pycock, 1977). Whether the HTR is purely a motor tic or a behavior in response to perceptual experience is unknown. However, if the HTR were happening randomly as a tic might do, we would not expect to see spatial preference for this behavior.

Overall, this work advances our understanding of how the psychedelic DOI alters olfactory search behavior and sniff in freely-moving mice. We are the first group to identify changes in sniff frequency in mice in response to a psychedelic. We are also the first to implement an olfactory task with psychedelics. Our findings demonstrate that psychedelics impact the olfactory system and thus establish a framework for studying hallucination-like percepts in olfaction. More work is needed to synchronize movement with sniffing and to better understand how DOI would impact a dynamic, changing odor space.

Materials and methods

Animal housing and care

All experimental procedures were approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Oregon and in accordance with the ethical guidelines of the National Institutes of Health. Animals were group housed on a reverse 12:12 h light cycle. All behavioral testing was performed during the dark cycle. Food and water were given ad libitum unless otherwise specified for water restriction. Mice were given a minimum of 1 mL

water daily and maintained above 80% pre-water restriction weight. Health was monitored daily and removed from water restriction if weight dropped below 80% baseline as approved by the IACUC. All mice used were C57Bl6/J and at least 12 weeks of age, but no more than 5 months, at the time of surgery.

Surgical procedure

Animals were deeply anesthetized with isoflurane (3% concentration during induction, then maintained at 1-2%) for the procedure. The incision site was topically anesthetized with lidocaine (8 mg/kg) SQ prior to incision. Meloxicam-ER (4 mg/kg) and buprenorphine (0.1 mg/kg) were given SQ peri-operatively. Supplemental lactated ringers (LRS, 1 mL) were given SQ post-operatively to improve recovery and surgical outcome. Health was monitored daily for 3 days post-operatively.

Thermistors were implanted between the nasal bone and inner nasal epithelium to measure respiration (Findley et al., 2021). A custom titanium head bar was secured to the skull. Prior to surgery, the thermistor (TE Connectivity, #GAG22K7MCD419) wires were minimally stripped then soldered into pins (JST Sales America, # A02KR02DS28W305B) for signal conduction. The wire was fixed in place using cyanoacrylate. Exposed tissue was sealed using Vetbond tissue adhesive. Exposed skull was sealed using cyanoacrylate. A small dot of orange tempera paint (Pro Art, #4435-2) was stamped onto the headbar for live tracking in Bonsai.

Drugs

Drugs were administered IP 5 min prior to behavioral testing. (±)-DOI hydrochloride (DOI) (Sigma-Aldrich, #D101) was dissolved in sterile physiological saline and injected at a

fixed volume of 5 mL/kg at a dose of 3 mg/kg. Prior to administration, freshly mixed drugs were sterilized through a 0.2-micron filter. Sterile physiological saline was used as the control (Hospira, #NDC 0409-4888-02).

Behavioral testing

For full documentation on rig software and use protocols, see: https://nghess.github.io/fmon-docs/

Water association

Mice were water restricted and trained to associate 3 pokes in the behavioral arena with water. Each poke was calibrated daily to dispense 6-8 µL water, each within 0.1 µL of the other. Water was made available in an alternating fashion: initiation, left, initiation, right, repeat. Each session lasted 30 min. Mice were moved to the odor navigation task after completing 50 pokes.

Odor navigation task

Mice were water restricted and maintained at a minimum of 80% baseline weight for training and experiments. They were trained first to associate an initiation port, left reward port, and right reward port in an alternating pattern with a water reward. When mice received a minimum of 50 water rewards in a 30-min session by poking into these ports, they graduated onto the odor navigation task. In the two-alternative choice odor navigation task, no water was awarded by initiating a trial, only when correctly navigating to the left or right side of the arena where the odor was produced. A correct response was registered when the mouse entered the corresponding quadrant where odor was released. An overhead camera tracked movement in

real-time and provided live feedback to the system. Upon correctly navigating to the left or right, mice had 5 seconds to poke into the reward port to receive their reward. The left and right sides were calibrated each day to ensure equivalent volumes for each reward, ranging from 1.2 to 1.8 μL. We pseudo-randomly assigned left or right-side trials with a maximum of 5 consecutive trials on one side. The odorant 2-Phenylethanol (2-PE) (Sigma-Aldrich, #77861) was diluted in deionized water to a final concentration of 0.001%. Control trials without odor administration occurred at a rate of 10% total trials. We also imposed a variable inter-trial interval (ITI) of 1 to 15 s regardless of correct response. Mice were able to complete as many trials as possible within 40 min. When mice were able to complete 5 consecutive sessions with an accuracy of 85% or higher to ensure task comprehension, mice were assigned to start in the DOI or saline condition then crossed over into the other condition at least 1 week later.

Pose estimation and behavioral syllables

The location of the nose, head, left and right ears, body, left and right hips, and tail base were tracked via DeepLabCut (A. Mathis et al., 2018). A limit was placed on tracking data so the likelihood of < 0.95 and points that moved faster than 8 pix/frame were smoothed by linear interpolation. Movement speed was calculated as the distance traveled (difference in position) over time elapsed (s). Tracked videos were analyzed in Keypoint Motion Sequencing (KP-MoSeq; (Wiltschko et al., 2020) to obtain behavioral syllables.

Head-twitch response

Raw video of behaving mice was played at 50% speed in Adobe Premiere Pro. The HTR was manually marked by an observer when at least 3 paroxysmal rotations of the head occurred.

The onset of the HTR (+/- 2 frames) was when the time stamp was marked. Time stamps were exported to csv for alignment with tracked pose estimations and further analysis.

Data analysis

Analysis of sniff signals were cleaned in MATLAB and visualized in R. Inhalation and exhalation times were extracted by finding peaks and troughs in the temperature signal after smoothing with a 25 ms moving window. Any sniffs with dropped out exhalation times were excluded. Analyses of DLC tracking, performance statistics, and sniff frequencies were performed in R. KP-Moseq analyses were performed in MATLAB.

Figure 1

Accuracy (percent correct) was calculated by dividing the correct odor trials by total odor trials in both the DOI and saline conditions. Accuracy for odor omission trials was calculated with the same method. Rolling accuracy was calculated by dividing the current number of correct trials by the current iteration of trials for each trial for each mouse. Sessions were separated into sequential 5 min time bins. The mean accuracy for trials within each time bin was calculated for each mouse in the odor, odor omission, DOI, and saline conditions. The grand mean was calculated taking the mean of all the means from each mouse at each time bin. Trials completed were calculated by taking the sum of all trials in a session per mouse. Repokes were calculated by taking the sum of initiation port beam breaks during the ITI. A false odor report was calculated as the occurrence of an initiation port beam break followed by crossing the decision line during the ITI. The number of mice used in repoke and false report analyses was 17 due to data acquisition updates that were not in place for the first cohort of mice.

Statistical tests were performed using R Statistical Software (v 4.4.1). Graphs were made using package ggplot2 (Wilkinson, 2011). The Wilcoxon signed rank test was used for paired samples and group comparisons. The Wilcoxon rank-sum test was used for rolling accuracy data since some mice did not perform during a time bin, creating unmatched data. Paradigm figure was created using images from https://scidraw.io/ and https://stock.adobe.com using Adobe Photoshop.

Figure 2

We used 17 mice in our drinking duration calculation due to our initial system not capturing beam breaks in the reward ports. All mice after our first cohort of 5 had reward port breaks recorded. For correct trials, reward port duration was calculated as time poking into the reward port until exiting the reward port. Re-entries into the reward port after exit did not add time to the calculation. For incorrect trials, duration in the reward port was calculated with the same method although no water reward was delivered.

Statistical tests were performed in R. For the reward port duration cumulative frequencies, normality was checked using the Shapiro-Wilk test. One or more groups violated normality assumptions. The Kruskal-Wallis was used to test for a difference in drinking duration groups. Post-hoc pairwise comparisons were performed using the Wilcoxon rank sum test with Bonferroni adjustment for multiple comparisons to reduce Type I error. Wilcoxon signed rank tests were used for paired comparison of median durations.

Figure 3

Trial duration was calculated by subtracting trial start time from trial end time for DOI and saline conditions. Trials were grouped by odor or odor omission trials. The mean duration was taken for trial type and condition for each mouse. Actual ITI duration was calculated as the difference between the current trial start time and previous trial end time. The mean ITI duration was taken for each condition and mouse. Task speed was determined using DLC keypoints. Tracking data was imported and points with likelihood < 0.95 or delta > 8 pixels were interpolated. Interpolation and speed calculations were used with modified functions from the collection DLC Analyzer (Sturman et al., 2020). Any speed that was > 160 cm/s was excluded from analysis. Using the nose keypoint, mean speed for each condition per mouse was calculated by taking the distance traveled over time elapsed.

Statistical tests were performed in R. For trial durations, ITI duration, and overall task speed, Wilcoxon signed rank tests were used for paired comparison.

Figure 4

Initial pre-processing of sniff was performed in MATLAB. Inhalation and exhalation times were extracted by finding peaks and troughs in the temperature signal after smoothing with a 25 ms moving window. Sniffs with duration less than the 5^{th} percentile and greater than the 95^{th} percentile were excluded from analysis. Exported sniff signals with inhalation and exhalation time stamps in ms were imported into R using the R.matlab package (Bengtsson, 2022). Sniff duration was calculated by taking the difference between inhalation start times of successive sniffs. Any sniff event with missing inhalation or exhalation time stamps were excluded from analysis. Any sniffs below 10 s or above 1000 s were excluded from analysis. Sniff frequency

was calculated as 1000/difference in consecutive inhalation time stamps. Trial summary files that stored trial start and trial end time stamps were imported into R. Sniff inhalation and exhalation times were converted to sec and categorized as within trial or ITI sniffs based on trial start and end time stamps.

Not all sessions recorded had usable sniff signals due to variable levels of noise, signal drop out, or signal loss. For mice with a usable sniff recording in both DOI and saline sessions, sniff frequencies were compared between conditions within subject using the Kolmogorov-Smirnov test in R. Since some mice had usable sniff in one condition but not the other, we ran a two-sample Fisher-Pitman Permutation test with 10,000 permutations on all usable sniff frequencies between DOI and saline conditions. We ran the same test for all trial types: odor trial, omission trial, and ITI. Permutation tests were performed using the coin package in R (Hothorn et al., 2008).

Figure 5

Occupancy was calculated by binning the arena into 1 cm^2 bins, then mean duration in each bin for each mouse. Grand mean was calculated for occupancy in both conditions. HTR rate was calculated by binning the arena into 2.5 cm^2 bins. HTR was normalized to occupancy by counting HTR occurrences in each bin, then diving that number by occupancy for each mouse. The final normalized HTR map was calculated as the grand mean of normalized occupancy. Plots were upscaled then Gaussian smoothed in MATLAB and colored using the Cubehelix package (D. A. Green, 2011). Statistical testing was performed in R. Coordinate bin labels were permuted 10,000 times and HTR rate compared between the original observed values and permuted values.

Figure 6

Keypoint labeled mouse was made with image sourced from https://scidraw.io in Adobe Photoshop. All syllable plots were calculated with tracked location from DLC in MATLAB. We calculated usage differences as a log likelihood ratio between DOI and saline. To test statistical significance of usage differences between conditions, we formed a null distribution by permuting the session labels 10,000 times. This produces a distribution of log likelihood ratios for each syllable. Syllables that fell outside the 99% confidence interval are considered significantly different in usage.

Figure 2 supplemental

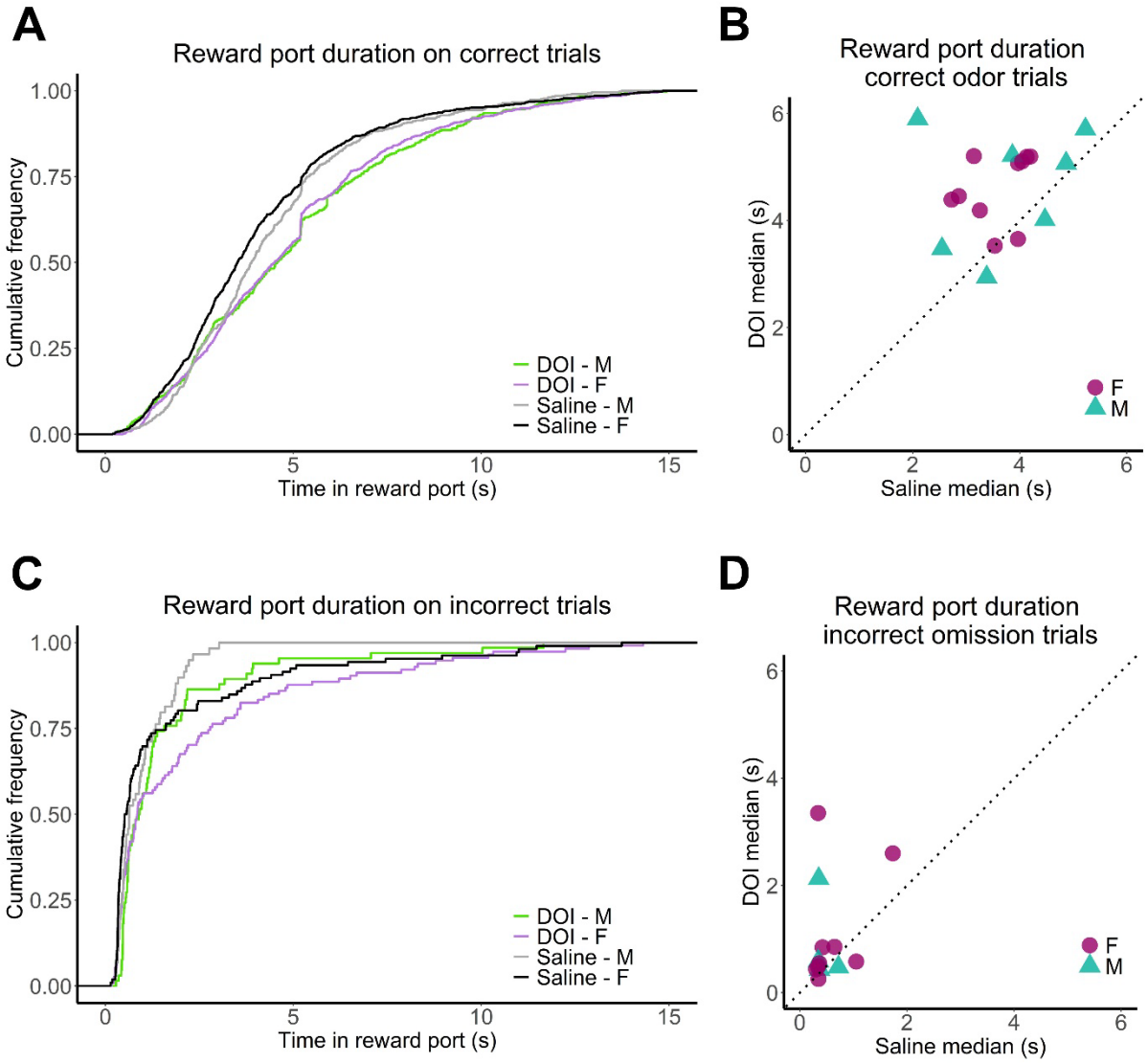

Figure 2 supplemental. Reward port duration was not sex dependent. (A) Cumulative histogram of duration in a reward port after a correct response in a trial. Colored lines show DOI trials separated by mouse sex. Black and grey lines show saline trials by sex. **(B)** Scatter plot of median duration in a reward port after a correct odor trial per mouse in DOI and saline conditions. **(C)** Cumulative histogram of duration in a reward port after an incorrect response in a trial. Color as in A. **(D)** Scatter plot of median drinking duration after an incorrect odor omission trial per mouse in DOI and saline conditions.

Figure 3 supplemental

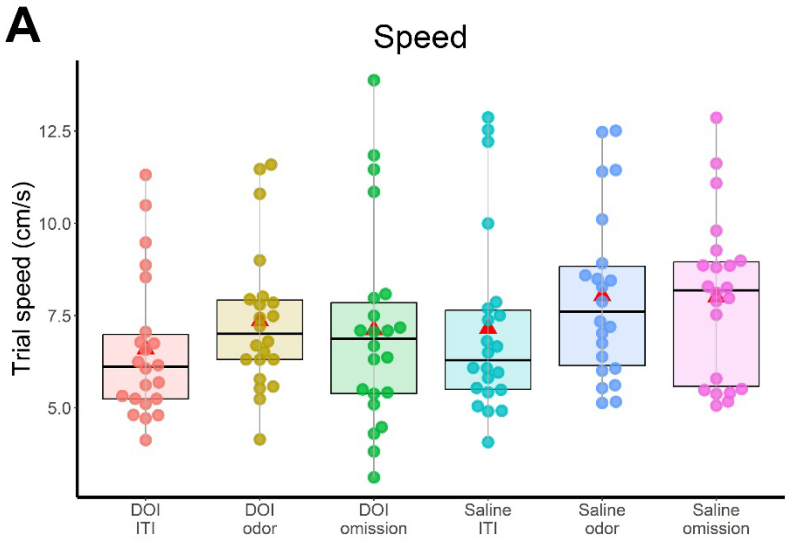

Figure 3 supplemental. Speed across all conditions and trials. Whisker plots of speed for each mouse in each drug condition and trial type.

Table 1 supplemental. Speed comparisons for all conditions and trial types.

Speed comparisons			
Comparison	V	P-value	Sig.
DOI ITI vs Saline odor	13.0000	0.0000	***
DOI odor vs DOI ITI	236.0000	0.0001	***
DOI ITI vs Saline omission	35.0000	0.0019	**
Saline odor vs Saline ITI	218.0000	0.0019	**
Saline omission vs Saline ITI	199.0000	0.0172	*
DOI omission vs Saline odor	61.0000	0.0329	*
DOI ITI vs Saline ITI	62.0000	0.0359	*
DOI odor vs Saline odor	68.0000	0.0587	ns
DOI omission vs Saline omission	68.0000	0.0587	ns
DOI omission vs DOI ITI	183.0000	0.0684	ns
DOI odor vs Saline omission	78.0000	0.1207	ns
DOI odor vs DOI omission	166.0000	0.2099	ns
Saline odor vs Saline omission	107.0000	0.5446	ns
DOI odor vs Saline ITI	145.0000	0.5661	ns
DOI omission vs Saline ITI	120.0000	0.8486	ns

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Figure 4 supplemental

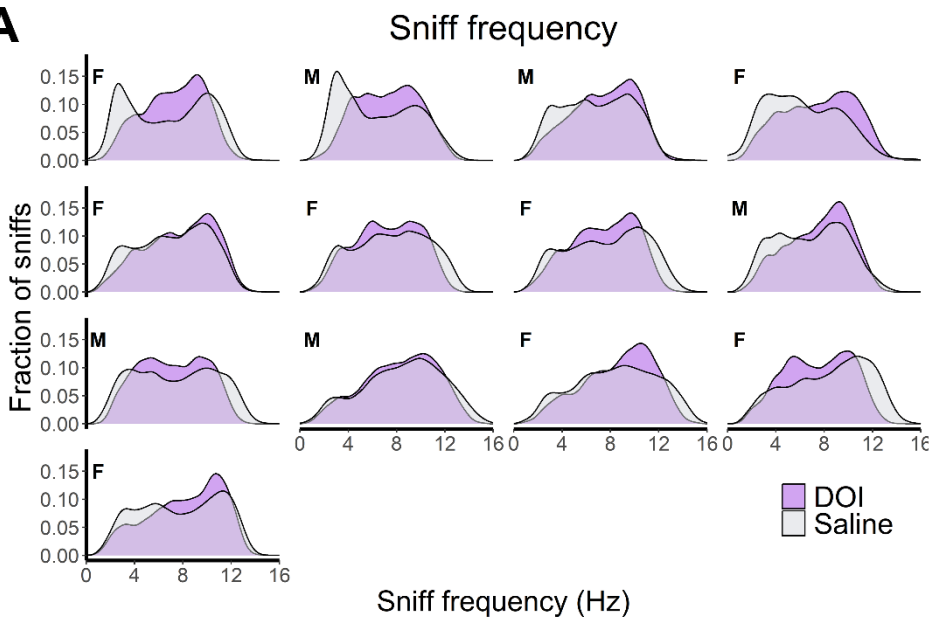

Figure 4 supplemental. Sniff frequencies per mouse. Histograms of sniff frequency for each mouse with a DOI and saline condition.

Figure 5 supplemental

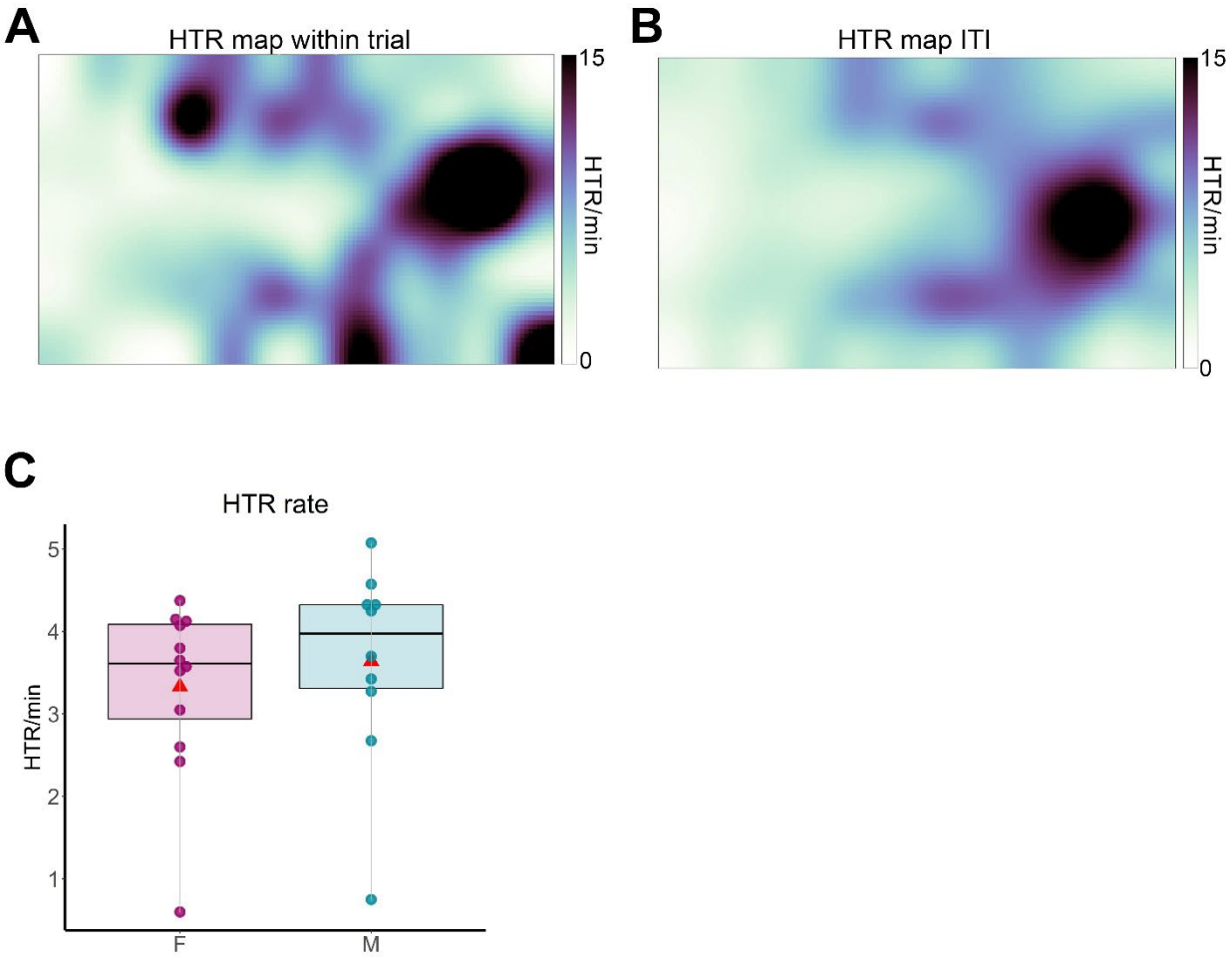

Figure 5 supplemental. Head-twitch response during the trial and inter-trial interval. (A) Two-dimensional histogram of HTR rate within a trial in the DOI session based on ~2.5 cm^2 bin location. HTR was normalized based on occupancy per mouse, then averaged across all mice (n = 22). Colorbar represents the HTR rate per min. **(B)** Same as in A, but for the ITI. **(C)** Whisker plot of HTR rate between male and female mice. Red square represents the mean rate.

CHAPTER III

THE IMPACT OF THE PSYCHEDELIC DOI ON SPONTANEOUS BEHAVIOR AND THE OLFACTORY BULB

This chapter includes unpublished material, co-authored by Sidney E. Rafilson, Aldis P. Weible, and Matthew C. Smear. I conceptualized the study, collected all data, analyzed behavioral data, and wrote the manuscript. Sidney E. Rafilson contributed to electrophysiology data analysis. Aldis P. Weible contributed to surgical procedures for data collection. Dr. Matthew Smear contributed to design, data analysis, writing, and editing.

Introduction

Sensory perception is driven by the interaction between an organism with external and internal stimuli. Movement is the pivotal component of active sensing and perception, where movement contributes to the interpretation of the environment. Moreso, movement and behavior drive neural activity (Musall et al., 2019). In the case of a hallucination, perception occurs in the absence of external stimuli. Hallucinations may be caused by neurological or psychiatric disorders, or the ingestion of a psychedelic compound. This chapter focuses on movement and neural activity in the olfactory bulb (OB) after psychedelic administration.

Psychedelics have long been used to study the nature of hallucinations and their impact on behavior and brain activity in both humans and animals. These drugs include psilocybin, mescaline, DOI (2,5-Dimethoxy-4-iodoamphetamine), DMT (dimethyltryptamine), and LSD (lysergic acid diethylamide). Classic psychedelics have an affinity for the serotonin-2A receptor (5-HT_{2A}R) with weak affinity for other subtypes, including the serotonin-2C receptor (5-HT_{2C}R)

(Halberstadt & Nichols, 2020; Nichols, 2004; F. X. Vollenweider et al., 1998). The 5-HT_{2A}R is widely distributed in the brain, with high concentrations in regions responsible for sensory processing (López-Giménez & González-Maeso, 2017). Human studies utilizing functional magnetic resonance imaging (fMRI) have demonstrated decreased blood flow in regions such as the anterior and posterior cingulate cortex and medial prefrontal cortex (mPFC) after administration of psilocybin, where decreased activity in these regions were associated with enhanced subjective changes in participants (Carhart-Harris et al., 2012). Recent research with psilocybin has found that with eyes closed, activity in early and high visual areas in the brain have decreased activity, suggesting a top-down increased level of activity for visual imagery (Stoliker et al., 2025).

Although few human studies examine olfactory regions, limited studies in animal models have investigated olfactory regions after psychedelic administration. Research in mice has documented the effects of psychedelics in visual cortices and in regions responsible for complex processing. In mice, researchers found decreased response to visual stimuli in visual cortex after administration of DOI (Michaiel et al., 2019). Administration of DOI in rats similarly decreased oscillations in mPFC, while 5-MeO-DMT (O-methylbufotenin) decreased blood-oxygen-level-dependent (BOLD) response in visual cortex and mPFC (Riga et al., 2014). In rabbits however, administration of DMT produced prolonged activity in the olfactory bulb (OB) but nowhere else in the brain (Vitale et al., 2011). While visual regions have been well documented to have decreased neural activity, the very limited research that discusses olfactory regions has shown increased activity in the OB.

The impact of psychedelics on the olfactory system of mice is not well understood, despite the OB as a primary sensory region with strong centrifugal input from serotoninergic

pathways. The OB of the mouse is dense with serotonin fibers (J. H. McLean & Shipley, 1987; Steinfeld et al., 2015). The 5-HT_{2A}R drives the excitation of external tufted cells (ETC) and the depolarization of some mitral cells (MC), the major projection neurons of the OB (Brill et al., 2016). The 5-HT_{2C}R has been shown to attenuate glomerular response to odor stimuli (Petzold et al., 2009). Further, input from the OB is integrated in olfactory cortex and signal is projected back onto the OB (Boyd et al., 2012; Markopoulos et al., 2012; Rothermel & Wachowiak, 2014). This reciprocal relationship demonstrates that signals are modulated bi-directionally in the olfactory system. Previously we described how mouse olfactory behavior in an olfactory search task is impacted by psychedelics (Chapter II), but how neural activity and spontaneous behavior is impacted is unknown. Here, we show preliminary data on how the psychedelic DOI impacts the OB during spontaneous behavior.

Motivated by the strong serotonergic input to the olfactory bulb and cortex, we speculate that psychedelics cause olfactory hallucinations in mice. The canonical head-twitch response (HTR), which is pervasive in psychedelic research, is well described but its trigger is not well understood. The HTR, sometimes known as a wet-dog shake, gives the impression that it is an attempt to clear the nose. We speculate that the mice head twitch when they experience the sensation of an unpleasant odor percept. Because mice are non-verbal subjects, they cannot describe the subjective effects of the drug so it may not be possible to test whether they experience hallucinations. However, our speculation motivates testable hypotheses based on observables: 1) the sniffing behavior of the mice will be altered before and after a HTR. 2) OB neural activity will increase as if to emulate the signal of an odor stimulus in the absence of one.

Results

DOI increases speed and distributes occupancy across the arena

To study how DOI impacts spontaneous behavior and neural activity, we recorded sniffing behavior, OB neural dynamics, and spontaneous movement in freely-moving mice in an arena (Figure 1A). Mice were implanted with a tetrode array and thermistor and allowed to recover from surgery for a minimum of 3 days. In experimental sessions, mice were injected with either saline or DOI (3 mg/kg) IP then placed into the arena 5 min later for 1 hr. Mice were crossed over into the opposite condition the next day. Tetrodes were not advanced between sessions.

We initially recorded movement without probe implants in a separate cohort of mice. In the combined behavior recordings, for mice with and without probe implants, we found that mice in the DOI condition moved at a faster rate compared to saline (Figure 1B; Wilcoxon signed rank test, $p = 0.007$, $n = 15$). This is consistent with previous studies that have demonstrated mice on moderate doses of DOI have increased locomotion (Halberstadt & Geyer, 2018). Next, we looked at where in the arena mice occupied space. Here we only looked at the mice without probe implants, as they were placed in a different arena with smaller dimensions. We found that when mice were in the saline condition, there were several areas with high occupancy duration (Figure 1C). In contrast, mice in the DOI condition stopped in few spaces in the arena (Figure 1D).

DOI synchronizes sniff, neural activity, and the head-twitch response

The HTR is a well-documented behavior in rodents that reliably occurs in response to the administration of a serotonergic psychedelic

Figure 1

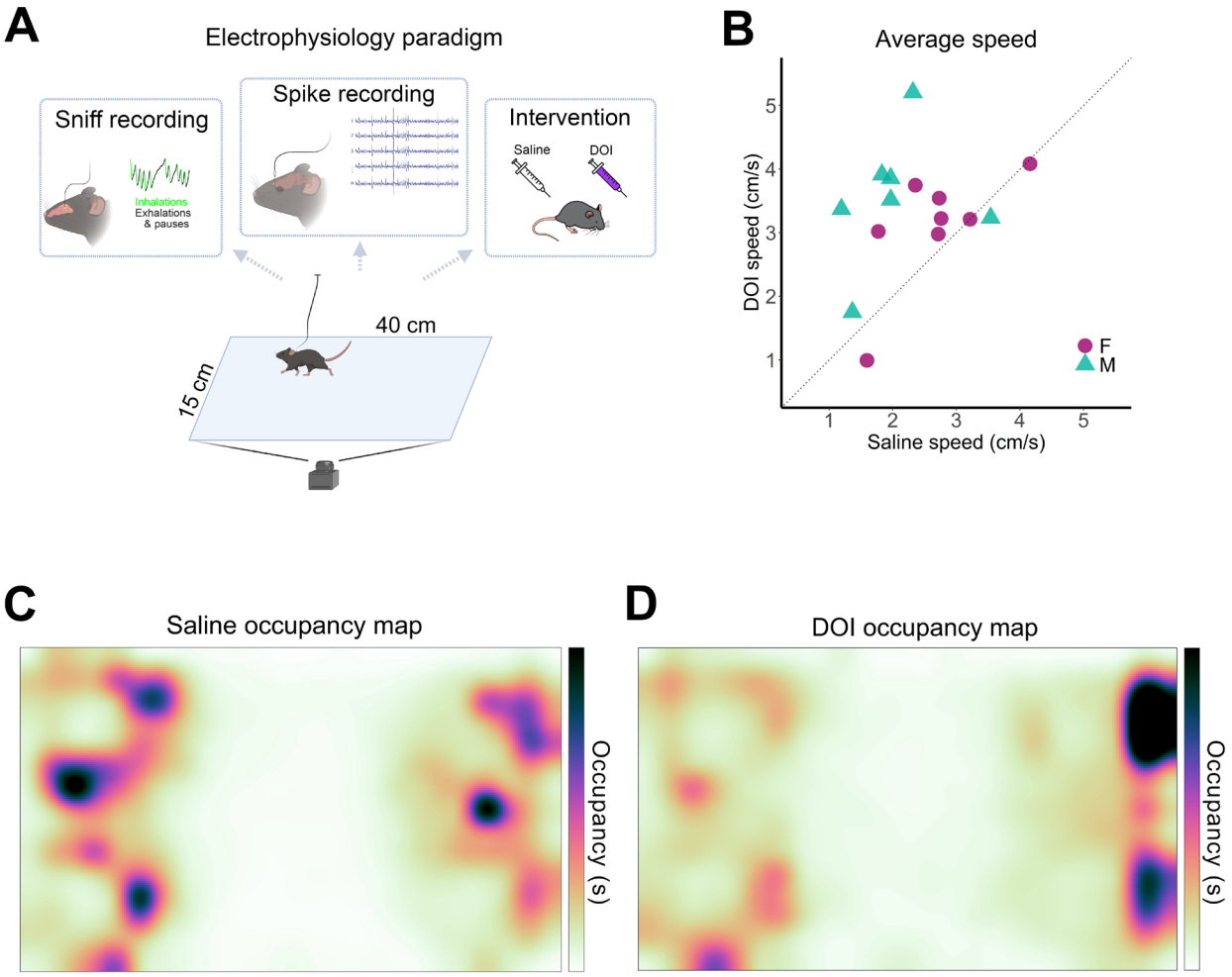

Figure 1. Mice moved faster and stopped in fewer spaces in the arena. (A) Diagram of electrophysiology experiment. **(B)** Scatter plot of speed across all mice. **(C)** Two-dimensional histogram of occupancy (fraction of frames spent in each 1 cm^2 bin) in the saline session. Color represents the mean across all mice (n = 15). **(D)** Same as in C, but for the DOI session.

(Halberstadt & Geyer, 2018; Hanks & González-Maeso, 2013). This behavior is considered analogous to the human psychedelic experience, where a higher dose induces more frequent twitches, as humans report more frequent visual hallucinations (Clint E. Canal & Morgan, 2012). We hand-labeled all HTR events and found that the HTR synchronized to inhalation time (Figures 2A, C). When HTR was aligned to time 0, inhalations paused for approximately 200 ms

Figure 2

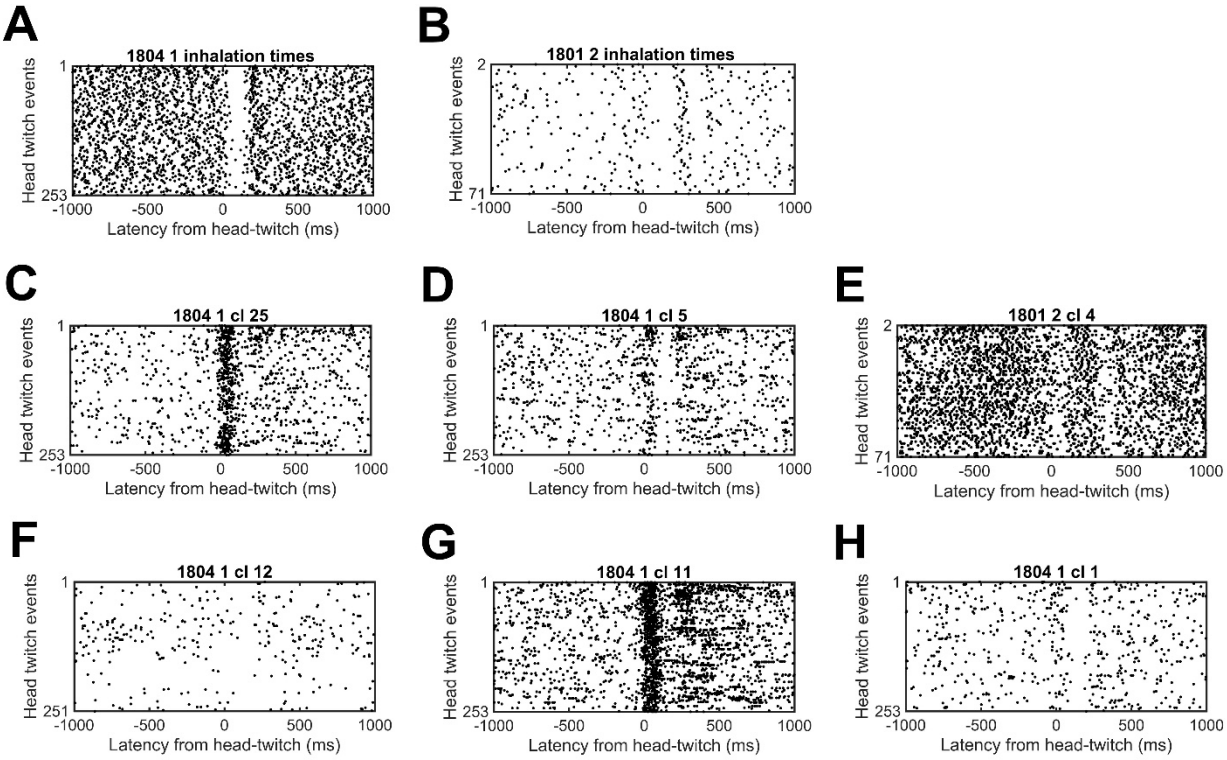

Figure 2. The HTR correlated with inhalation and neural activity. (A) Raster plot of inhalation times aligned to the onset of HTR for mouse 1804. **(B)** Same as A, but for mouse 1801. **(C-H)** Raster plot of neural population activity for a cluster aligned to HTR onset.

following the HTR. Similarly, we found that population activity in the OB synchronized to the HTR (Figure 2B, D-H). The onset of the HTR in most populations is followed by a rapid burst of activity. In some populations, the onset of the HTR is followed by decreased activity. In single units, we found a distinct pattern of firing in relation to the onset of a HTR (Figure 3A-B). Some units fired preferentially before onset, at onset, or shortly after the HTR.

Traditionally experiments with psychedelics in rodents quantify exploratory behavior by measurements such as hole poke entries, locomotion, and rearing (Halberstadt et al., 2009; Hanks & González-Maeso, 2013; Krebs-Thomson et al., 1998). With recent advancements in data analysis tools, we can dissect behavioral into its brief constituent parts, called “syllables”

Figure 3

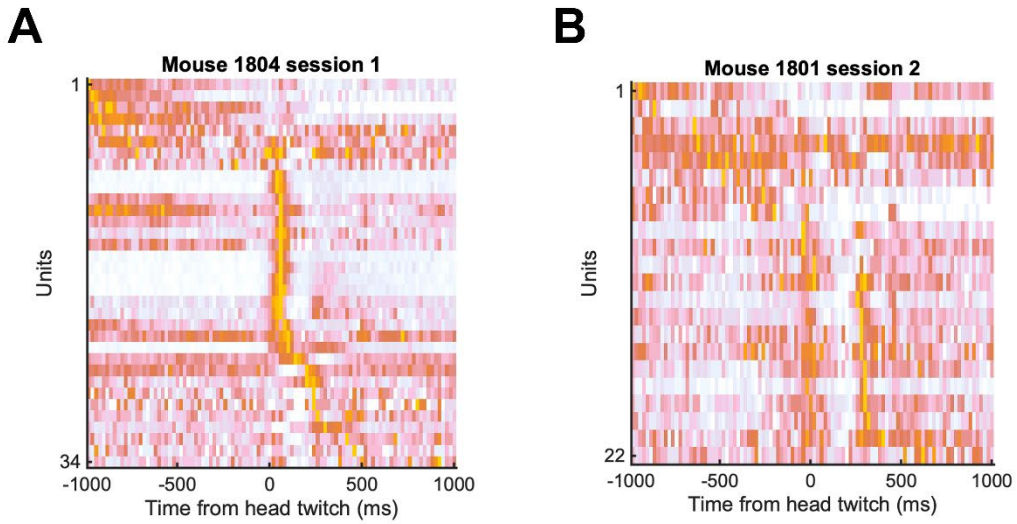

Figure 3. The HTR correlated with neural activity. (A) Raster plot of neural activity aligned to onset of HTR for mouse 1804. **(B)** Same as in A, but for mouse 1801

using Keypoint-MotionSequencing (KP-MoSeq; (Weinreb et al., 2024). We tracked the nose, neck, front paws, center of mass, back paws, and tail base using DeepLabCut (DLC; (A. Mathis et al., 2018; M. W. Mathis & Mathis, 2020)) then from these positions used KP-MoSeq to extract behavioral syllables using in the DOI and saline conditions. We found that there is a subset of syllables used more frequently in DOI and a subset used more in saline (Figure 4A). Syllable duration ranged from 100 ms to 2.5 s, with the median syllable duration lasting approximately 400 ms (Figure 4B). The most commonly used syllables in saline were larger, faster movements across space, whereas syllables in DOI were smaller movements of the nose and face (Figure 4C, D).

Figure 4

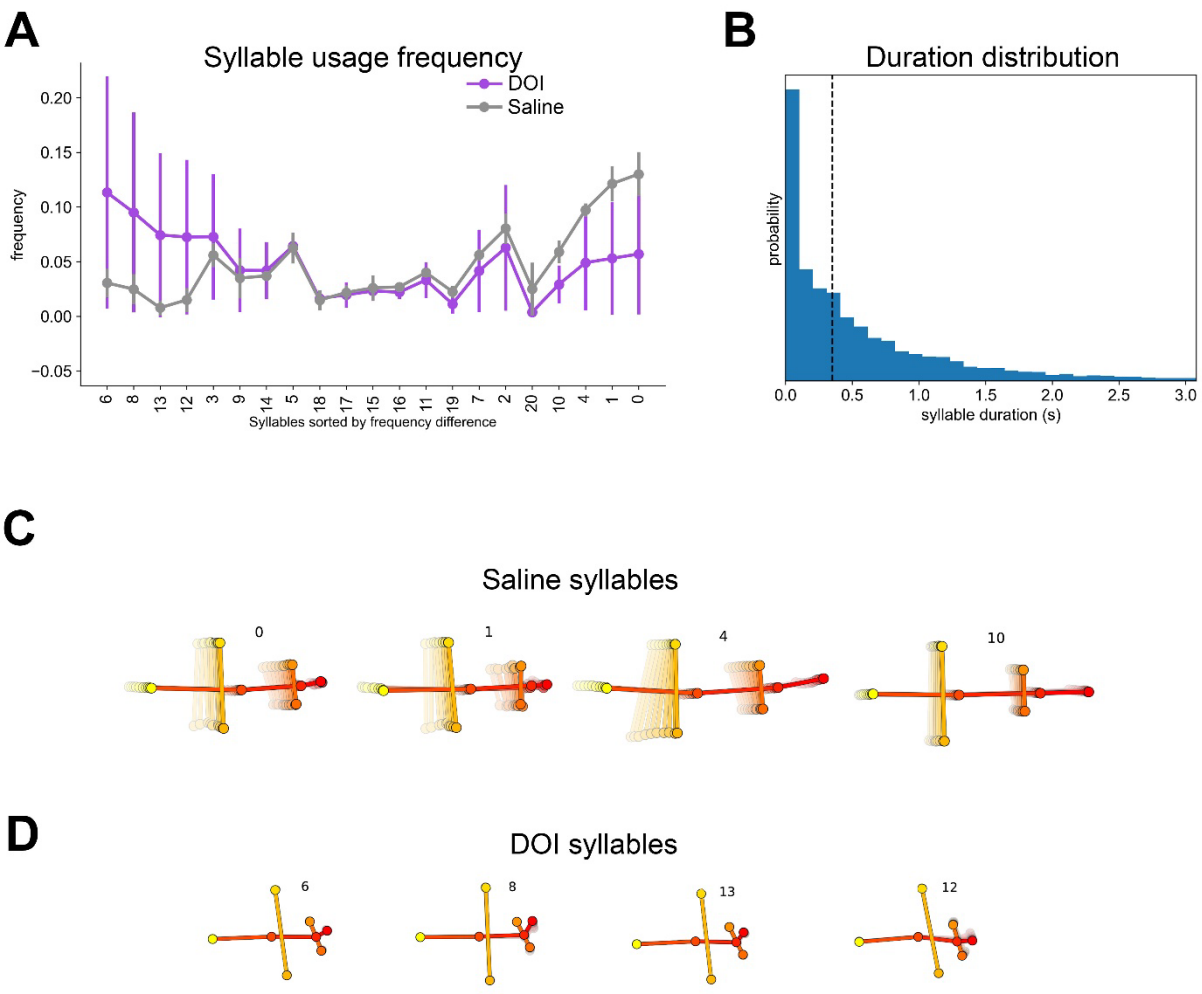

Figure 4. Mice behaved differently between DOI and saline. (A) Line graph with SEM of syllable usage frequency, sorted by degree of difference between DOI and saline. Most used DOI syllables are toward the left. Most used saline syllables are toward the right. Purple denotes DOI and grey is saline. **(B)** Bar plot probability distribution of syllable duration, where total area = 1. **(C)** Saline trajectory plots. **(D)** DOI trajectory plots.

Discussion

In this study, we demonstrate that the psychedelic DOI impacts spontaneous, uninstructed behavior in mice. We found that mice move more quickly in the arena in the DOI condition

compared to saline. Additionally, we found that mice stop in fewer areas in the arena. We show in agreement with previous research (Halberstadt & Geyer, 2018), that movement is impacted by DOI. The limited areas of high occupancy in the DOI condition, compared to several areas of high occupancy in saline, illustrate that mice pause less in DOI. Mice remain in proximity to the arena edges in the saline condition whereas in the DOI condition there is higher occupancy throughout the arena.

We found that the HTR synchronized to both inhalation and neural activity. The onset of a HTR was followed by a pause in the initiation of an inhalation. Whether this is an extended exhalation or an intentional delay in inhalation is unclear. However, this nuanced detail does not overshadow the finding that inhalation initiation is delayed in correlation with the HTR. After inhaling an unpleasant odorant, exhalation is increased and inhalation decreased in humans (Arzi et al., 2010). Since olfactory hallucinations in humans are more often unpleasant than pleasant (Sjölund et al., 2017), this is consistent with our hypothesis that the HTR is linked to an unpleasant olfactory experience. Additionally, we found neural activity that increased in some populations and decreased in others in correlation with the HTR. Movement is tied to neural activity. Whether the HTR leads to changes in neural activity or the change in neural activity leads to the HTR is unclear. Despite this uncertainty of cause and effect, this finding connects the HTR to olfaction for the first time.

Using DLC and KP-MoSeq, we found that mice behaved differently in the DOI and saline conditions. While most syllables were used in both conditions, few syllables were used more frequently in DOI and saline. In the saline condition, we found syllables that were interpreted as fast moving and walking movements. In the DOI condition, we found syllables that we interpreted as small movements of the face. While these syllables did not look like a

HTR, they suggest that mice are moving their noses more frequently in the DOI condition. The increased nose movement could be increased active sensing to disambiguate the environment. This is consistent with the evidence that humans saccade their eyes more frequently when experiencing visual hallucination after psychedelic administration (Hebbard & Fischer, 1966).

These promising preliminary results bring together the field of psychedelic research and olfactory neuroscience in mice for the first time. This work will motivate future studies of the impact of psychedelics on the olfactory system. Given our small sample size, repeating these experiments so we are not underpowered would provide additional confidence in the effect of DOI on neural activity, sniff, and behavior. Follow up experiments that incorporate neural recording before and after presentation of odor stimuli in tandem with DOI administration could provide insight into how psychedelics impact odor processing in the OB. Manipulating the odor valence could provide additional insight into how DOI impacts odor processing. Specific odorants and their concentration activate glomeruli in a stereotyped way in the OB (Rubin & Katz, 1999), so would DOI alter expected odor-evoked activation in the OB? What patterns would be seen? Answering these questions would help develop a basic understanding of how psychedelics impact odor processing.

Materials and methods

Animal housing and care

All experimental procedures were approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Oregon and in accordance with the ethical guidelines of the National Institutes of Health. Animals were housed on a reverse 12:12 h light cycle. All behavioral testing was performed during the dark cycle. Food and water were given ad libitum.

All mice used were C57Bl6/J and at least 12 weeks of age, but no more than 5 months, at the time of surgery. Mice were single housed after surgery.

Experimental drugs

The drug (±)-DOI hydrochloride (Sigma-Aldrich, #D101) was dissolved in sterile physiological saline and injected at a fixed volume of 5 mL/kg at a dose of 3 mg/kg. Prior to administration, freshly mixed drugs were sterilized through a 0.2-micron filter. Sterile physiological saline was used as the control (Hospira, #NDC 0409-4888-02).

Surgical procedures

Tetrode implants

For olfactory bulb array implantation, we administered atropine (0.03 mg/kg) preoperatively to reduce inflammation and respiratory irregularities. Surgical anesthesia was induced and maintained with isoflurane (1.25–2.0%). The skin overlying the skull between the lambdoid and frontonasal sutures was removed. A rectangular window was cut through the skull overlying the lateral half of the left bulb for insertion of the recording array. The array was lowered to a depth of 1 mm and cemented in place with Grip Cement. To minimize postoperative discomfort, carprofen (10 mg/kg) was administered 45 minutes prior to the end of surgery. Mice were housed individually after the surgery and allowed 7 days of post-operative recovery.

Thermistor implants

Animals were deeply anesthetized with isoflurane (3% concentration during induction, then maintained at 1-2%) for the procedure. The incision site was topically anesthetized with

lidocaine (8 mg/kg) SQ prior to incision. Meloxicam-ER (4 mg/kg) and buprenorphine (0.1 mg/kg) were given SQ peri-operatively. Supplemental lactated ringers (LRS, 1 mL) was given SQ to improve recovery and surgical outcome. Health was monitored daily for 3 days post-operatively.

Thermistors were implanted between the right side nasal bone and inner nasal epithelium to measure respiration (Findley et al., 2021). Prior to surgery, the thermistor (TE Connectivity, #GAG22K7MCD419) wires were minimally stripped then soldered into pins (JST Sales America, # A02KR02DS28W305B) for signal conduction. The wire was fixed in place using cyanoacrylate. Exposed tissue was sealed to the skull using Vetbond tissue adhesive.

Electrophysiology recordings

Following the recovery period, the custom microdrive was advanced to the regions of interest (ROI) while recording. Tetrodes were made of 18 μm (25 μm coated) tungsten wire (California Fine Wire). Once the ROI was reached, a minimum of 24 hours was allowed prior to data collection to increase recording stability. Between DOI and saline injections, tetrodes were not advanced.

Data were acquired via a 128-channel data acquisition system (RHD2000; Intan Technologies) at a 30 kHz sampling frequency and Open Ephys software (http://open-ephys.org). A camera positioned 90 cm below the arena floor was used to record movement around the arena with Bonsai video acquisition software (http://bonsai-rx.org).
Custom Bonsai code was used to align the TTL triggers from the camera frames, the sniff, and the electrophysiology recording captured with no filters applied in the OpenEphys software.

Behavior recordings

Mice were injected with sterile 3 mg/kg DOI IP then placed back in a holding cage for 5 min then placed into the arena. For our recordings without electrophysiology, mice were placed into a custom built 15 by 25 cm arena for 1 h. Video was captured from above at 80 frames/sec. For our electrophysiology recordings, mice were placed in a custom built 15 by 40 cm arena for 1 h. Video was captured from below at 100 frames/sec.

We record sniff using intranasally implanted thermistors (TE Connectivity, #GAG22K7MCD419), amplified initially with custom-built op amp (Texas Instruments, TLV2460, circuit available upon request) and then a CYGNAS, FLA 01 amplifier fed into the analog input of an OpenEphys box.

Pose estimation and behavioral syllables

In video from below, the location of the nose, throat, sternum, center of mass, front left and right paws, back left and right paws, and tail base were labeled with DeepLabCut (A. Mathis et al., 2018). In video from above, nose, head, and center of mass was labeled. A limit was placed on tracking data so the likelihood of < 0.95 and points that moved faster than 8 pix/frame were smoothed by linear interpolation. Movement speed was calculated as the distance traveled (difference in position) over time elapsed (s). Tracked videos were analyzed using Keypoint Motion Sequencing (KP-MoSeq; (Wiltschko et al., 2015) to obtain behavioral syllables.

Head-twitch response

Raw video of behaving mice was played at 50% speed in Adobe Premiere Pro. The HTR was manually marked at onset (+/- 2 frames) by an observer when at least 3 paroxysmal rotations

of the head occurred. Time stamps and frame numbers were exported to csv for alignment with tracked pose estimations, neural data, and sniff for further analysis.

Spike and sniff data preprocessing and inclusion criteria

Analysis of spikes and sniffing were performed in MATLAB. Electrophysiological data were preprocessed via Kilosort, Phy2, and custom software in Python. Inhalation and exhalation times were extracted by finding peaks and troughs in the temperature signal after down sampling to 1000 samples per s and smoothing with a 25 ms moving window. All sniffs' instantaneous frequencies are inverse intersniff intervals. Sniffs with instantaneous frequencies greater than 17 and less than 0.5 sniffs per s were excluded from the analysis. Autocorrelations of sniff frequency and speed and their cross correlation were calculated after mean subtraction and de-trending.

Single units were curated with criteria of 5% refractory period violations (refractory period = 1.5 ms) and an amplitude loss cutoff of 10%. Amplitudes were calculated by first calculating the mean spike waveform on the channel giving the largest spike amplitude and finding its peak and trough times. Then, for each spike time, amplitude was calculated as the difference between the peak and trough times of the mean. The cutoff criterion was this amplitude being less than or equal to zero, so that the fraction of lost spikes can be estimated. This criterion greatly reduces the potential of significant electrode drift over the recording.

Figure 1

Speed was determined using DLC keypoints. Tracking data was imported and points with likelihood < 0.95 or delta > 8 pixels were interpolated. Interpolation and speed calculations were

used with modified functions from the collection DLC Analyzer (Sturman et al., 2020). Any speed that was > 160 cm/s was excluded from analysis. Using the nose keypoint, mean speed for each condition per mouse was calculated by taking the distance traveled over time elapsed. Occupancy was calculated by binning the arena into 1 cm^2 bins then mean duration in each bin for each mouse was calculated. Grand mean occupancy was calculated for overall sessions. Plots were upscaled then Gaussian smoothed in MATLAB and colored using the Cubehelix package (D. A. Green, 2011).

Statistical tests were performed in R. Wilcoxon signed rank tests were used for paired comparison for speed.

Figure 2

Raster and color peri-event time histograms (PETH): where the event is a HTR plotted in MATLAB as previously (Sterrett et al., 2025).

Figure 3

Same as in Figure 2.

Figure 4

Statistical tests were performed in Python using the KP-MoSeq package (Weinreb et al., 2024; Wiltschko et al., 2015). Syllable usage frequency was determined first by training DLC (A. Mathis et al., 2018; M. W. Mathis & Mathis, 2020) on video from below to track the nose, throat, sternum, front paws, center of mass, back paws, and tail base. KP-MoSeq was trained on all points except sternum. For model fitting, kappas of 1e2, 1e3, 1e4, and 1e5 were used, and

ultimately 1e3 was used in statistical analysis due to fit and interpretability. For syllable usage, the minimum frequency included in analysis was 0.5%, meaning the syllable made up 0.5% of all syllable instances. Probability distribution of all syllable durations was plotted and the median duration plotted. Syllables with durations outside of the 95^{th} percentile were excluded. Trajectory plots were generated without modification.

CHAPTER IV

GENERAL DISCUSSION

The goal of this dissertation was to assess the impact of psychedelics on olfactory behaviors and neural activity in the olfactory bulb of the mouse. Given the review of prior research (Chapter I) which highlighted the importance of olfaction and our limited understanding of psychedelics on the olfactory system and olfactory hallucinations, this work has greatly improved what is known in the field on these topics. Results from Chapter II identified changes in respiratory patterns, navigation behavior, reward duration, and psychedelic-induced behavioral structure. Results from Chapter III found changes in neural activity in the olfactory bulb and sniffing as they relate to stereotypical behavior used in rodent models of psychedelic research. This chapter discusses novel findings in psychedelic research on the olfactory system, demonstrating an increased understanding between serotonin agonists and how odor navigation, behavior, and neural correlates are impacted. Additionally, this chapter discusses limitations and future directions.

Impacts

In Chapter II of this dissertation, we significantly advanced our understanding of olfactory behaviors after psychedelic administration. Active sensing is critical to perception, as described in Chapter I, and here we demonstrate the alterations on movement, sniffing, and task performance. In task performance, mice navigate less accurately to the correct side of an arena where odor is delivered. This is not due to an inability to move or motivate in males, as they are able to complete trials in the DOI condition. Female mice show fewer trial attempts, which

demonstrates a sex effect of DOI. Most rodent research in psychedelics has been performed in males, so this research describes sex differences in how psychedelics impact female mice in an olfactory task. During reward acquisition, mice spend a longer duration in the reward port both when they were correct and incorrect in a trial. Additionally, mice spend more time completing odor trials and are slower in the task. This task is the first of its kind to examine how mice navigate olfactory scenes and make decisions in an olfactory paradigm after the administration of a psychedelic drug. This study suggests that DOI impacts behavior related to the olfactory system. Further, the sniff rate of mice is increased compared to saline. This is especially interesting considering the decreased movement speed of mice. While sniffing generally increases as movement speed increases in a naturalistic setting, here we find that sniffing does not cycle between low and high frequencies but maintains a higher frequency through the duration of the session. We show that active sniffing in mice is impacted by a psychedelic drug, a novel result that is relevant to a sensory neuroscience. Additionally, the localization of the stereotypical head-twitch response (HTR) to the side of the arena closest to the odor ports demonstrates the non-randomness of the behavior. If the HTR were truly a random muscle glitch, we would expect to see it occur in an even distribution pattern across the arena when normalized to occupancy. Its occurrence in proximity to the odor ports raises the question of prior experience inducing the behavior as an expectation of a stimulus. The HTR may therefore be tied to internal state and odor expectation, which provides unique insight into the behavior. Overall, these findings elucidate how psychedelics impact olfactory behaviors and sniffing as a form of active sensing.

Chapter III of this dissertation provided evidence of the impact of psychedelics on an olfactory brain region and the HTR in mice. Historically, animal and human research has focused

on the visual system and cognitive processes in response to psychedelics. Here we demonstrate that the olfactory bulb (OB) fires in temporal relation to the HTR and sniffing. The correlation between HTR, sniff onset, and OB activity is a novel finding that for the first time relates the HTR to olfaction. These results greatly improve our understanding of how DOI impacts the brain and sensory system, as these experiments are the first to characterize neural dynamics in the OB in response to psychedelic administration. This study has meaningful implications in how we understand neural circuits by determining that psychedelics impact the olfactory system in rodents, not just the visual system.

Taking the results from Chapter II and III into consideration, we found that some behaviors such as speed are not consistent between experimental conditions. When mice are performing the olfactory search task as in Chapter II, speed is low in DOI compared to saline. When naïve mice are placed in an arena without a task or stimulus as in Chapter III, speed is high in DOI compared to saline. In humans, stronger external stimuli, such as a video or music, disrupt brain changes and weaken the subjective psychedelic experience (Mediano et al., 2024). The contrast in mouse speed is interesting in that the effect of the psychedelic may be competing with the perception of an odor stimulus, much like external stimuli for humans.

Limitations and Future Directions

While the findings in this dissertation are impactful in the field of psychedelics and olfactory research, they are not without their limitations. In Chapter II, mice were trained to perform an olfactory search task for a water reward. While the results are compelling that there is a perceptual change, there is an inherent challenge to performing psychedelic research in animals as they cannot verbally communicate their experience. While we can infer internal state based on

behavioral outputs using advanced analysis tools, extreme confidence that an animal is hallucinating must be suspended. More work is necessary here to examine how movement and sniff are precisely synchronized after DOI administration. Although it was our goal to assess sniff and movement, due to unforeseen technical data acquisition anomalies in our video time stamps, we were unable to perform these analyses. Future work would allow for synchronization of all components of data. More work is also needed to better understand how mice use odor gradients in the DOI condition. Introducing variable odor gradients and different odorants could elucidate how mice strategize and behave when the odor landscape changes in complexity and in valence.

Additionally, we cannot rule out the possibility that mice are impacted by DOI in a non-specific way. DOI is likely to impact other sensory regions like vision (Michaiel et al., 2019) and locomotion (Halberstadt & Geyer, 2018), thus a global effect of DOI may contribute to performance. In future approaches, locally infusing DOI or another psychedelic directly into the OB would provide insight into the drug's impact on olfactory search when specifically targeting olfactory brain regions.

In Chapter III, mice were administered DOI and their neural activity and spontaneous behaviors recorded. This was the first experiment of its kind, looking at the olfactory system's response to a psychedelic compound. The link between HTR, OB activity, and sniff are exciting, but we are limited in our ability to interpret these findings. Although activity and behavior are correlated here the directionality of effect is uncertain. Whether the HTR drives OB activity and sniff or vice versa is unclear. The fundamental challenge in studying a behavior that emerges in response to psychedelic administration is that it is difficult to find an appropriate control condition to test that behavior. Since the HTR happens rarely in all other states and cannot be

generated by a different class of drugs, designing a study to see neural dynamics in response to the HTR outside of psychedelic administration remains an open problem.

Other questions regarding OB activity and psychedelic administration remain unresolved, especially as they pertain to odor stimuli. While recording and determining baseline, spontaneous activity is beneficial to our understanding of neural activity and behavior, the depth and richness of behavior and neural activity in response to odor stimuli is lacking in the current framework. Sensory systems evolved to interact with the environment, thus introducing odorants into the current paradigm would provide insight into changing neural dynamics. Recording sniff, OB activity, and movement for a baseline period followed by psychedelic administration could elucidate brain modulation in real time. Additionally, recording neural dynamics in response to different odor types could provide a foundation for understanding how psychedelics are represented at the neural level compared to odor.

Conclusions

Overall, this dissertation makes an important contribution to the field of olfactory neuroscience and psychedelic research. The studies and analyses presented provide evidence that psychedelics impact olfactory behaviors and neural dynamics in the olfactory bulb. This research could lay the groundwork for future approaches in sensory neuroscience and olfactory hallucination research. Although animal models of psychedelics can be challenging to interpret, they provide unique opportunities to examine neural underpinnings of drug and behavioral effects. It is my hope that research continues in the field of olfaction and psychedelics. Advancements in neuroscience tools and variations in genetic mouse models of disease and

disorders could provide additional insight into olfactory dysfunction and how to alleviate the negative effects of olfactory hallucinations.

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