Acute and long-term effects of a single dose of psilocybin on neuroplasticity in mouse auditory cortex

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To be shaken out of the ruts of ordinary perception, to be shown for a few timeless hours the outer and the inner world, not as they appear to an animal obsessed with survival or to a human being obsessed with words and notions, but as they are apprehended, directly and unconditionally, by Mind at Large—this is an experience of inestimable value to everyone and especially to the intellectual.

— Aldous Huxley, The Doors of Perception

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Abstract

Psilocybin, a psychoactive compound found mostly in the *psilocybe* genus of mushroom, has long been employed by various peoples for spiritual, medicinal and recreational purposes. A number of promising clinical studies have created a surge of interest in the potential of psilocybin for the treatment of conditions involving maladaptive neuroplasticity, such as addiction, depression and tinnitus. It is now believed that the serotonergic receptor agonist exerts its prolonged effects through facilitating a burst of structural and functional neural plasticity. However, knowledge of how this affects the regulation of long-term plasticity in sensory cortices remains sparse. Moreover, despite profound acute changes in auditory perception, there has been very little study of psilocybin's effects in the auditory cortex (ACx), particularly with single-neuron resolution. My study had two primary hypotheses: First, that psilocybin's acute auditory hallucinatory effects may be exerted through modulation of sound-evoked responses in primary auditory cortex (A1). Second, that the burst of plasticity observed in other cortices would facilitate prolonged changes in ACx sound-evoked responses and the regulation of tonotopic organization in response to sound-exposure.

Using *in vivo* two-photon microscopy and wide field calcium imaging in mice, we found that acute administration of 1 mg/kg psilocybin prevented the habituation of sound-evoked responses to familiar stimuli, maintaining overall responsiveness, bandwidth tuning and sound-level response thresholds after repeated stimulation. A similar effect is observed chronically, with sound-evoked responses remaining unhabituated for up to two weeks following administration. Taken together, these data highlight that psilocybin impairs normal inhibitory habituation of A1 sound-evoked responses to stimuli, and that prolonged effects on ACx activity remain at least two weeks following administration. This may support models of psychedelic action in which acute perceptual effects are driven by disrupted sensory gating of familiar or irrelevant information. With further research, the direct effects of psilocybin on ACx processing could be used to treat conditions of maladaptive plasticity observed in this cortex, such as tinnitus.

Résumé

La psilocybine, un composé psychoactif que l'on trouve principalement dans les champignons de type psilocybe, est utilisée depuis longtemps par différents peuples à des fins spirituelles, médicinales et récréatives. Un certain nombre d'études cliniques prometteuses ont suscité un regain d'intérêt pour l'utilité de la psilocybine dans le traitement de pathologies impliquant une neuroplasticité inadaptée, telles que la dépendance, la dépression et les acouphènes. On pense aujourd'hui que cet agoniste des récepteurs sérotoninergiques exerce ses effets prolongés en facilitant une poussée de plasticité neuronale structurelle et fonctionnelle. Cependant, nos connaissances sur la manière dont cela affecte la régulation de la plasticité à long terme dans les cortex sensoriels demeurent limitées. Outre la démonstration de profonds changements aigus dans la perception auditive, les effets de la psilocybine dans le cortex auditif (ACx) ont été très peu étudiés, notamment avec une résolution au niveau du neurone individuel. Mon projet de recherche avait deux hypothèses principales : Premièrement, les effets hallucinatoires/ hallucinogènes auditifs aigus de la psilocybine peuvent être provoqués par la modulation des réponses évoquées par le son dans le cortex auditif primaire (A1)). Deuxièmement, la poussée de plasticité observée dans d'autres régions corticales faciliterait à la fois des changements prolongés dans les réponses évoquées par le son du ACx ainsi que la régulation de l'organisation tonotopique en réponse à l'exposition au son.

En utilisant la microscopie à deux photons *in vivo* et l'imagerie calcique à grand champ chez la souris, nous avons découvert que l'administration aiguë de 1 mg/kg de psilocybine empêchait l'habituation des réponses sonores à des stimuli familiers, en maintenant la réactivité globale, le réglage de la bande passante et les seuils des réponses évoquées par le son après une stimulation répétée. Ces résultats contrastent avec l'habituation marquée des réponses évoquées et le rétrécissement de la bande passante observés chez le groupe témoin. Un effet à long-terme a également a été observé, les réponses évoquées par les sons restant inchangées jusqu'à deux semaines après l'administration de la psilocybine. Dans l'ensemble, ces données soulignent que la psilocybine nuit à l'habituation inhibitrice normale des réponses évoquées par le son dans A1, et que les effets prolongés sur l'activité persistent au moins deux semaines après

l'administration. Cela pourrait étayer des modèles d'action psychédélique dans lesquels les effets perceptifs aigus sont induits par une perturbation du « gating sensoriel » des informations familières ou non pertinentes. Avec des recherches plus approfondies, les effets directs de la psilocybine sur le fonctionnement du ACx pourraient être utilisés pour traiter les conditions de plasticité inadaptée observées dans ce cortex, telles que les acouphènes.

Contribution of original knowledge

In this study, we identified an inhibition of normal auditory response habituation to familiar stimuli following psilocybin, which to our knowledge has not been characterized before with single-neuron resolution. We describe effects of psilocybin on the acute maintenance of response sensitivity and tuning bandwidths during repeated stimulation. This indicates a potential scenario where psilocybin acutely disrupts auditory sensory gating in A1, resulting in reduced filtering of irrelevant sensory inputs.

We are also, to our knowledge the first to examine the long-term effects of psilocybin administration in the mouse ACx, identifying a prolonged sensitization of responses to repeated auditory stimuli, for a period of multiple weeks following a single dose.

The completion of this study required us to construct an experimental paradigm in which we were able to longitudinally examine the effects of psilocybin on neuronal response properties in the awake animal, with single-neuron resolution. Moreover, we were able to chronically track changes in bulk cortical activity and tonotopic map structure over weeks following psilocybin administration. In future, the development of this paradigm and analysis pipeline will allow our group to further elucidate the effects of psychedelics on ACx neuronal activity and plasticity using two-photon microscopy and wide field calcium imaging.

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Contribution of Authors

Literature Review and Discussion:

All text and figures in chapters 1 and 4 were produced by Conor Lane.

Chapter 2: Lane P, Tarka V, Valentin O, Lehmann A, Hamel E, de Villers-Sidani E (2024). Psilocybin prevents adaptation to familiar stimuli and preserves sensitivity to sound following repeated stimulation in mouse A1. (preparation for submission)

The experiments and analysis pipeline were designed by Conor Lane, with support from Dr's Etienne de Villers-Sidani, Edith Hamel and Stuart Trenholm. All experiments were conducted by Conor Lane. Preprocessing code was written by Conor Lane and Veronica Tarka. Analysis and generation of figures were conducted by Conor Lane, as was production of the manuscript. Dr's Olivier Valentin and Alexandre Lehmann obtained psilocybin and the drug exemption license, and provided advice on presentation of findings.

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List of Abbreviations

ACx – Auditory cortex

A1 – Primary auditory cortex

LSD – Lysergic acid diethylamide

DOI - 2,5-Dimethoxy-4-iodoamphetamine

$5HT_{2A}$ - 5-hydroxytryptamine receptor 2A

DMT - N,N-Dimethyltryptamine

SERT – Serotonin transporter

GPCR – G-protein coupled receptor

BBB – blood brain barrier

DOM - 2,5-dimethoxy4-methylamphetamine

VTA – Ventral tegmental area

EPSP – Excitatory postsynaptic potential

fMRI – Functional magnetic resonance imaging

FC – Functional connectivity

PET – Positron emission tomography

DMN – Default mode network

CSTC – Cortico-striato-thalamocortical

REBUS – Relaxed belief under psychedelics and the anarchic brain

SP – Strong priors

SS – Synthetic surprise

SOM – Somatostatin

PV - Parvalbumin

AMPA - α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

BDNF – Brain-derived neurotrophic factor

TrkB – Tropomyosin related kinase B

mTOR – Mammalian target of rapamycin

ECM – Extracellular matrix

MDD – Major depressive disorder

AUD – Alcohol use disorder

TBI – Traumatic brain injury

CP – Critical period

PNN – Perineuronal net

BF – Best Frequency

SSA – Stimulus-specific adaptation

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General Introduction

Multiple models of psychedelic action posit a disruption of the balance between bottom-up flow of information from sensory cortices, and top-down sensory gating and contextual modulation. Previous work however has focused heavily on frontal regions (Riga et al., 2014; Shao et al., 2022; Wood et al., 2012), with less known about how psychedelics affect processing in primary sensory areas. Studies have identified changes in sensory drive and context modulation in primary visual cortex with psychedelics (Michaiel et al., 2019; Rose & Horn, 1977), but no substantial examination has been undertaken with single-neuron resolution to assess similar effects in primary auditory regions. As the two cortices exhibit differing patterns of behavior-dependent modulation of neuronal activity (Attinger et al., 2017; Henschke et al., 2021), it is possible that the effect of perception-altering drugs on sensory neuron activity may be different between them. In this project, we seek to ascertain how psilocybin affects information processing in the mouse auditory cortex, using a combined wide field and two-photon calcium imaging approach. This gives us the ability to examine effects in the awake animal and longitudinally track both macro-cortical changes in circuitry, and tuning properties of individual neurons over time.

Chapter 1: The first chapter gives a review of what is currently known about the acute and long-term effects of psychedelics, with a particular focus on psilocybin. It covers their action at different receptors in the brain, acute and long-term effects on neuronal activity in different sensory regions, and their effect on modulating neuroplasticity. It also discusses some of the promising therapeutic potential of these molecules and the results of recent clinical studies.

Finally, an explanation is presented of the value of using the mouse auditory cortex to study how psychedelics influence sensory information, both acutely and through long-term induction of plastogenic mechanisms.

Chapter 2: In the first study, we sought to understand the acute effects of psilocybin on sound-evoked activity in auditory-sensitive neurons. We placed a particular focus on the precise neuronal tuning to both preferred and non-preferred stimuli, control of which is vital for gating the flow of sensory information in response to changes in behavioral context, such as in attention. We also longitudinally tracked the tuning properties of individual neurons across manipulations, in order to ascertain whether observed effects were elicited by finely altering sound-evoked responses. We identified a marked habituation in overall responsiveness and tuning breadth to repeated stimuli in the awake state, which was inhibited by administration of psilocybin. We also discuss the remarkable amount of representational drift seen in response properties of neurons under both control and psilocybin conditions. Our findings highlight the potential of psilocybin to disrupt the sensory gating of familiar auditory stimuli, with potential implications for models of psychedelic actions that involve disruption of bottom-up vs top-down modulation of sensory information.

Chapter 3: We also sought to investigate whether the ability of psilocybin to rapidly induce significant structural and functional neural plasticity would result in prolonged changes to auditory cortex neuronal response properties at the macro-cortical level. As psilocybin has been

shown to reopen behavioral critical periods (CPs, periods of dynamic plasticity during development, in which neuronal circuitry reorganizes in response to passive sensory experience) (Cisneros-Franco et al., 2020) in adult mice for up to two weeks (Nardou et al., 2023), we hypothesized that this induction of a pro-plasticity state could also facilitate tonotopic reorganization in auditory cortex in response to passive sound exposure. We identified a similar effect on habituation of responses to that shown in Chapter 2. In control mice, repeated stimulation resulted in rapid habituation of responsive tonotopic area to tones, whereas psilocybin treated mice showed no significant habituation to the majority of frequencies. We did not identify significant tonotopic reorganization in response to passive sound exposure in either control or psilocybin conditions, with distribution of best frequencies (BFs) remaining very stable. We discuss whether this suggests psilocybin does not reopen CPs in auditory cortex, or whether a lack of effect is the result of factors in the experimental design and analysis pipeline. These findings identify a prolonged effect of psilocybin on neuronal activity in the auditory cortex, with a similar duration to CP reopening seen in previous studies.

Chapter 4: The final chapter gives a collective summary of this project's findings and discusses the potential mechanistic causes of the acute and chronic effects seen on response habituation. It proposes future experiments to directly probe the relative effects on neuronal subtypes within the cortical circuitry. It also discusses the similarity in habituation effect seen with acute vs chronic administration of psilocybin and whether this is likely to represent the same mechanism seen on different timescales.

Chapter 1: Literature Review

1.1 Introduction

For many around the world, April 19th is the annual unofficial celebration of 'Bicycle Day'. This little-known holiday commemorates the fateful 1943 journey of Swiss Chemist Albert Hofmann home from his lab after ingesting the recently synthesized compound lysergic acid diethylamide, or LSD. Over the course of two hours, Hofmann experienced what would later be described as a descent into madness, characterized by "an uninterrupted stream of fantastic pictures, extraordinary shapes with intense, kaleidoscopic play of colors" (Hofmann, 1980). Hofmann's experience would later be known as 'the first acid trip', kicking off a wave of scientific and cultural fascination with the profound perception-altering effects of LSD and similar serotonergic psychedelics such as psilocybin and mescaline. Though the term *psychedelic* or 'mind manifesting' was first coined by Humphry Osmond in 1957 (Osmond, 1957), evidence for the regular use of psychoactive compounds by human societies abounds. From bronze age Greece (Guerra-Doce et al., 2023) to pre-Colombian Mexico (Guzmán, 2008), it is clear that the mind-altering effects of these compounds have been employed throughout history for recreational, medicinal and religious purposes. Indeed, it is perhaps the late 20th Century culture of legally suppressing their usage that represents a historical outlier. Promising early clinical studies into the use of psychedelics to treat conditions such as alcohol dependence and depression suggested our ancestors may have been wise to employ them for therapeutic purposes. For a while, these findings led to widespread hope of new treatments for a variety of neuropsychiatric conditions, with better safety profiles than many existing medications at the time (Rucker et al., 2018).

Throughout his life, Hofmann would be a passionate advocate for responsible, limited use of psychedelic compounds in medical treatment. However, the strong associations of psychedelics with counter-cultural movements and high profile cases of their use in unethical experiments led to a powerfully negative public and media perception of all psychedelics. This backlash against their use culminated in 1967 with their classification under Schedule I of the United Nations convention on drugs, defining them as harmful and of no medical use (Rucker et al., 2018). The immediate effect of this shift was to drive the therapeutic use of psychedelics underground, and to place a chill over any subsequent scientific investigation into their action. This persisted for decades until in the 90s, a liberalization of attitudes towards drug use allowed a new generation of researchers to continue the work in healthy volunteers (Hermle et al., 1998; Strassman & Qualls, 1994).

The years since this thaw have seen a rapid expansion in our understanding of how serotonergic psychedelics exert both their acute effects on sensory processing, and the longer-term changes to mood and cognition that lend them promise as therapeutics. A consensus is emerging that these therapeutic effects are conferred through their roles as *psychoplastogens*, namely molecules that rapidly evoke rewiring of neuronal circuits, such as shifts in intrinsic excitability and dendritic growth (Olson, 2018). This facilitation of enhanced circuit reorganization in the adult brain makes them promising tools for a wide-range of conditions in which maladaptive plasticity plays a part in the etiology, such as major depression and tinnitus (Rădulescu et al., 2021; Shore et al., 2016a). This review focusses most closely on psilocybin, the psychoactive compound found in a number of species of mushrooms, and its metabolite psilocin. Here, I will outline what is known about the complex receptor pharmacology of classical psychedelics and

their acute effects on neuronal activity and information processing, as well as their persistent changes to brain function and plasticity. We will also cover the outcomes of clinical investigations into the effectiveness of psilocybin and other psychedelics for different neuropsychiatric conditions.

1.2 Receptor pharmacology of psilocybin and other psychedelics

1.2.1 Classification

Classical psychedelics can be divided into two broad categories based on their chemical structure. The phenethylamines (e.g. 2,5-Dimethoxy-4-iodoamphetamine (DOI) and mescaline) are characterized by a benzene ring with an attached amino group through two-carbon. They exhibit a high specificity for the 5-hydroxytryptamine type 2A ($5HT_{2A}$) and $5HT_{2C}$ subtypes of the 5-HT receptor family (Ray, 2010). In contrast, the tryptamines (e.g. psilocybin, N,N-Dimethyltryptamine (DMT)) exhibit substantial similarity to the neurotransmitter 5-HT, by their shared possession of an indole group (a 6-member benzene ring fused to a 5-member pyrrole ring with an ethylamine chain at the C3 position) (Kelmendi et al., 2022). They exhibit a more promiscuous binding with 5HT receptor subtypes, as well as other receptor classes entirely. For example, psilocybin and other tryptamines also display affinity for the serotonin transporter (SERT) (Cozzi et al., 2009) and non-serotonergic receptors such as muscarinic and histamine receptors (Ray, 2010). The ergolines, such as LSD are often referred to either as a third class, or a sub-class of tryptamines owing to the DMT pharmacophore being embedded in the ergoline structure (Kwan et al., 2022). Tryptamine psychedelics are found in a variety of natural forms

such as toads, fungi and plants, though many synthetic analogues have now been synthesized (Araújo et al., 2015). Psilocybin in particular is found in over 100 varieties of mushrooms, falling mostly in the genus *psilocybe*. The molecule psilocybin is in fact a pro-drug, which is rapidly dephosphorylated in the body into its active metabolite, psilocin (D. E. Nichols, 2020).

1.2.2 Action at serotonergic receptors

Of the 14 subtypes of the serotonin receptor family, 13 are G-protein coupled receptors (GPCRs), and are distributed widely throughout the periphery and CNS (McCorvy & Roth, 2015). This highly diversified family underlies both the variety of the systems in which serotonin is involved, and the complex effects seen with the administration of psychedelics. Psilocybin in particular exhibits affinity for a wide range of 5HT receptor subtypes with diverse physiological roles, with high affinity both for the excitatory $5HT_{2A}$ receptor, and inhibitory $5HT_{1A}$ (Kwan et al., 2022). Evidence points to $5HT_{2A}$ being a key mediator of psychedelic effects. In humans, pre-treatment with the $5HT_{2A/C}$ antagonist ketanserin blocks psilocybin-induced deficits in pre-pulse startle reflex (Quednow et al., 2012) and significantly reduces duration of acute subjective response to LSD (Becker et al., 2023). Similar results have been seen in animal studies where ketanserin pre-treatment abolishes head-twitch responses caused by psilocybin (Shao et al., 2022). There is also clear correlation between activation of $5HT_{2A}$ receptors and psychedelic effects. In humans, $5HT_{2A}$ occupancy and plasma psilocin levels both correlate with intensity of subjective effects (Madsen et al., 2019), and affinities of different psychedelics for $5HT_{2A}$ correlate well with intensity of their effects (Glennon et al., 1984). Importantly however, both human (Carter et al.,

2007) and animal (Shao et al., 2022) studies have shown that this ketanserin pre-treatment does not completely eradicate all acute perceptual and longer-term effects on neuronal circuits. This suggests that though $5HT_{2A}$ activation is central to many of the effects, it may not explain all of them.

Though psilocybin and other tryptamines share a great deal of structural similarity with 5-HT, they exert profoundly different physiological effects. There are multiple reasons for this, for example, the high polarity of the serotonin molecule severely restricts its passage across the blood-brain-barrier (BBB) into the CNS. In contrast, psilocin readily diffuses across the BBB, lending it a high bioavailability (MacCallum et al., 2022). The differing effects are also due to differences in action at the receptor-sites themselves. Site-directed mutagenesis and x-ray crystallography have identified both psychedelic and non-psychedelic binding sites on $5HT_{2A}$ receptors, binding to which results in biased agonism. This is the phenomenon where binding of different ligands induces specific conformational shifts in the receptor structure, which lead to changes in the activation of particular downstream pathways. Indeed, it is known that the $5\text{-}HT_{2A}$ receptor exhibits this ligand-dependent biased agonism depending on particular agonist-receptor interactions (Berg et al., 1998). Both serotonin and psychedelics have been shown to activate Gq-dependent signaling at $5\text{-}HT_{2A}$ receptors, leading to activation of multiple downstream signaling pathways such as protein kinase C (PKC), phospholipase C (PLC) and extracellular signal-regulated kinase (ERK) (Banks et al., 2021). Involvement of non-Gq pathways such as β-arrestin signaling have also been identified and head-twitch response to DOI administration in Gq-knockout mice is reduced but not abolished (Garcia et al., 2007), suggesting action via multiple signaling pathways.

1.2.3 Cellular distribution of $5HT_{2A}$ receptors

The powerful physiological effects of psychedelics come not just from the diversity of serotonergic signaling pathways they stimulate, but also from the wide-ranging, heterogeneous distribution of these receptors throughout the CNS. Immunohistochemical studies in rodent brains have identified $5HT_{2A}$ receptors in all layers of the neocortex (particularly in layers 1 and IV-V), in various hippocampal structures, globus pallidus, caudate putamen, and others (Xu & Pandey, 2000). The receptors have also been identified in sensory cortices, such as primary visual cortex (V1), primary somatosensory cortex (S1) and A1 (Weber & Andrade, 2010). Underlining their complex functional role, $5HT_{2A}$ receptors have been confirmed on pyramidal neurons, interneurons (Willins et al., 1997) and, both astrocytes (Xu & Pandey, 2000) and microglia (Glebov et al., 2015).

1.3 Effects of psychedelics on neuronal activity

1.3.1 Acute effects

The complex pharmacology of psychedelic action is clearly evident when considering acute effects on neuronal activity *in vivo*, in which neurons appear to exhibit mixed responses depending on brain region and prior firing properties. Multiple animal studies have shown complex effects in frontal cortices. In one study, low-dose administration of DOI drove sporadic increases in anterior cingulate cortex single-unit activity, whereas higher doses decreased activity. In orbitofrontal cortex however, activity was reduced at all dose levels and the overall effect on population activity in both regions was one of suppression (Wood et al., 2012). 5-

methoxy-N,N-dimethyltryptamine (5-MeO-DMT) administration both increased and decreased the firing rates of individual rat medial prefrontal cortex pyramidal neurons, with a net population increase (Riga et al., 2014).

Neocortical and particularly sensory regions such as primary visual cortex have also been examined, with similarly complex results. 5-MeO-DMT was found to reduce low frequency (<4 Hz) cortical oscillations in V1, S1 and A1 cortices of mice, with differential effect sizes between these cortical regions (Riga et al., 2016). A study in primary visual cortex found that DOI dramatically shifted temporal dynamics, with decreased visually evoked LFP power across V1 layers. They also observed differences on an inter-individual cell basis, with DOI altering transient responses in excitatory, but not inhibitory L2/3 neurons and cells with low initial firing rates being facilitated, while those with low firing rates were suppressed (Michaiel et al., 2019). Other studies have also shown particular effects on interneurons, for example, administration of both DOI and LSD excited cortical interneurons in rat piriform cortex slices (Marek & Aghajanian, 1996).

Significant effects have been observed in particular subcortical nuclei of the brain. In the locus coeruleus, which has widespread norepinephrine projections throughout the brain, multiple psychedelics (mescaline, 2,5-dimethoxy4-methylamphetamine (DOM), and LSD) had the effect of both decreasing spontaneous neuronal activity, and increasing evoked activity (Rasmussen & Aghajanian, 1986). As the region with the largest concentration of serotonergic neurons in the brain, the dorsal raphe nucleus has also been extensively studied. Administration of multiple psychedelics dramatically reduced activity in the dorsal raphe. Interestingly, this total effect was limited to compounds with seemingly higher activity at $5HT_{1A}$ receptors, such as LSD. Mescaline and DOM showed reductions in activity only in the ventral portion of the dorsal raphe. The

hallucinogenic anti-cholinergic drugs atropine, scopolamine and phencyclidine had no effect on raphe nucleus firing (G.K. Aghajanian et al., 1970; George K. Aghajanian et al., 1968). It is unlikely that these effects on the dorsal raphe are the direct cause of the acute hallucinogenic effects of serotonergic psychedelics, as LSD-induced behavioral changes in cats did not correlate closely with raphe suppression. Small doses of LSD produce minimal raphe suppression but large behavioral changes. These behavioral changes drastically outlasted raphe suppression, and suppression was just as pronounced in tolerant and non-tolerant scenarios (Trulson et al., 1981). A dose-dependent reduction in neuronal firing activity has also been observed in the rat ventral tegmental area (VTA), although with the suggestion of a more complex mechanism of action involving $5HT_{1A}$, dopamine 2 (D_2) and trace amine-associated receptor 1 ($TAAR_1$) receptors (De Gregorio et al., 2016).

The array of studies performed into the effect of psychedelics on neuronal activity highlight the variability in observed responses depending on the specific drug employed, brain region, dosage and cell type under examination. This complicates efforts to settle on universal mechanisms of action, but may explain along with their broad binding profiles, why they seem to offer potential therapeutic benefits in many conditions with different etiologies.

1.3.2 Long-term effects

One of the traits of psychedelics that has garnered the most interest is their ability to exert effects on neuronal activity long after the drug's removal from the body. Despite the half-life of psilocin being roughly 30 minutes (N. T. Jones et al., 2023), studies in mice have shown enhanced

excitatory post-synaptic potentials (EPSPs) in medial pre-frontal cortex pyramidal cells 24 hours following administration (Shao et al., 2022). Similar effects have been observed with DMT in rat cortical pyramidal neurons, showing an increase in both spontaneous and evoked EPSP frequency and amplitude (Ly et al., 2018). These persistent effects on neuronal activity are accompanied by rapid increases in the expression of immediate early genes associated with neuroplasticity, such as *c-Fos, arc, egr-1* and *egr-2,* 90 minutes following a single dose of LSD in mice. Importantly, these effects were absent in $5HT_{2A}$ knockout mice (González-Maeso et al., 2007). Similar studies in both mice (Davoudian et al., 2023) and rats (Funk et al., 2024) found that a single dose of psilocybin produces elevations in *c-Fos* expression in several brain regions, such as anterior cingulate cortex, locus coeruleus, V1, amygdala and claustrum. Though psychedelics do not seem to upregulate a large number of genes, there is a preponderance of genes primarily involved in neuroplasticity (Nichols & Sanders-Bush, 2002). It is this ability to stimulate a rapid and pronounced reorganization of neuronal structure that underlies their ability to prolong functional plasticity long after leaving the body, making them targets of such intense interest as therapeutics.

1.4 Neural networks and models of psychedelic action

1.4.1 Effects of psychedelics on neuronal network function

In the last decade, whole-brain neuroimaging approaches have been extensively employed to study psychedelic effects, identifying a complex picture where broad global changes in activity are clearly visible, but with significant heterogeneity between studies when brain region and

network-specific effects are examined. A variety of functional magnetic imaging (fMRI) studies have led to a consensus that psychedelics broadly reduce functional integration within and increase integration between most major brain networks (Robin L. Carhart-Harris et al., 2012; McCulloch, Knudsen, et al., 2022; Siegel et al., 2024). Some network-specific consistencies have been observed, for example the reduction in activity and functional connectivity (FC) of association networks such as the default mode network (DMN) (Carhart-Harris et al., 2012; Gattuso et al., 2023), which is most active when people are focused on internally focused processes such as memory recall and 'daydreaming'. However, these effects have been observed with pharmacologically distinct drugs such as 3,4-Methylenedioxymethamphetamine (MDMA) (Felix Müller et al., 2021), creating difficulty linking them to specific actions of serotonergic psychedelics. Results are far less consistent for studies of between and within-network interactions, with different datasets often resulting in opposing findings. For example, groups have found psychedelic-induced increases in global FC in transmodal association cortices such as the DMN and frontoparietal networks (Girn et al., 2022; Tagliazucchi et al., 2016), whereas others have found minimal changes in transmodal regions (Preller et al., 2018, 2020).

One interesting trend that emerges from these many studies is the opposing effects on connectivity observed in distinct brain regions. For example, positron emission tomography (PET) studies have identified relative hyper-metabolism of glucose in prefrontal brain regions, and hypo-metabolism in sub-cortical and occipital regions (Vollenweider et al., 1997). Psilocybin and LSD have both been shown to induce increases in connectivity between sensory regions (Preller et al., 2018, 2020) in stark contrast to the hypo-connectivity in association cortices. Several studies have also identified increased FC between thalamic and sensorimotor cortices with

psychedelics (Müller et al., 2017, 2018; Preller et al., 2018). However, these effects are also not specific to serotonergic psychedelics (Avram et al., 2022), and a recent psilocybin study has cast doubt on these increases, citing artefact effects from averaging over various thalamic regions with their own distinct patterns of thalamocortical FC (Gaddis et al., 2022).

A recent psilocybin study employed a longitudinal precision functional mapping model (18 individual fMRI sessions per participant), to collect an impressive amount of data, providing enhanced ability to separate out inter-individual and per-session variability from psychedelic effects. They reported acute reductions in FC across the brain, most heavily in areas associated with the DMN, which were correlated with the strength of subjective experience. Importantly, they observed a powerful desynchronization of activity that was most pronounced in association cortex but fairly minimal in primary cortex, and correlated with the spatial distribution of $5HT_{2A}$ receptors (Siegel et al., 2024). They also identified a prolonged reduction in FC between the anterior hippocampus and DMN three weeks following administration, though whole brain FC change scores indicated a return to baseline. A small number of other studies have also detected prolonged changes in resting state FC from weeks to months following psilocybin administration (Barrett et al., 2020; McCulloch, Madsen, et al., 2022). This suggests that the prolonged effects of psychedelics may be detectable as persistent changes in neuronal networks, but comparisons are limited by inter-individual variability and varied analytical approaches between groups (McCulloch et al., 2022). It remains unknown whether induction of plastogenic mechanisms at the cellular level leads directly to these changes, and whether observed changes in network function are directly involved in the therapeutic efficacy seen in recent trials.

1.4.2 Theoretical models of psychedelic action

Several theoretical models have been proposed to explain how altered communication between various brain regions could lead to the perceptual effects of psychedelics. A few are only briefly outlined here, as they and others have been described in detail in a number of excellent reviews (Carhart-Harris & Friston, 2019; De Filippo & Schmitz, 2024; Doss et al., 2022; Kwan et al., 2022). We will cover the cortico-striato-thalamocortical (CSTC) model, the relaxed belief under psychedelics and the anarchic brain (REBUS) model, the strong prior (SP) model, and the recently proposed synthetic surprise (SS) model, though this is far from an exhaustive list of those proposed.

The CSTC model posits that through the stimulation of $5HT_{2A}$ receptors within cortico-striato-thalamo-cortical loops, thalamic gating of incoming sensory information is disrupted. This disinhibition results in an inundation of the cortex with sensory information, and an increase in feedforward information to higher regions, inducing cognitive fragmentation (Vollenweider & Geyer, 2001). There is evidence for this model from human studies, where disruptions of sensorimotor gating are observed following psilocybin and LSD (Schmid et al., 2015; Vollenweider et al., 2007). However, as previously stated, studies of thalamic disinhibition often did not parcellate the functionally distinct thalamic nuclei, and $5HT_{2A}$ expression is not particularly high in the thalamus relative to other regions (Beliveau et al., 2017).

In the REBUS model, enhanced bottom-up flow of sensory inputs is combined with a weakened precision of prior beliefs and expectation from higher areas. This results in an inability of higher regions to exert inhibitory control over sensory information (Carhart-Harris & Friston, 2019). The

model is based around the relatively consistent finding that psychedelics induce dissociation of higher order areas such as the DMN, in a more dramatic way than in sensory cortices (Gattuso et al., 2023; Siegel et al., 2024). The model remains controversial as studies in visual cortex seem to suggest overall reduced stimulus-evoked activity when an increase would be expected (Michaiel et al., 2019). However, the loss of context-modulated surround suppression seen in the study, and the broadening of visual tuning seen with DMT in humans (Pais et al., 2024) could still suggest loss of hierarchical control. The strong priors model argues effectively the opposite of this, that reduced bottom-up sensory drive leads to an over-dependence on prior beliefs and expectations (Corlett et al., 2019). This model is supported by observations that perceptual hallucinations can occur as a result of sensory deprivation rather than over-stimulation, for example resulting from visual loss (Silber et al., 2005) or perceiving music in white noise (Barber & Calverley, 1964).

The final model discussed here is the synthetic surprise model, in which psychedelics disrupt serotonergic involvement in the encoding of novelty and cognitive flexibility in dynamic environments (De Filippo & Schmitz, 2024). This is based on the idea that psychedelics may induce a 'partial' activation of the normal serotonergic circuit encoding novelty and prediction error, due to their selective activation of serotonergic receptor subtypes with varying potencies. The model focusses on the ability of layer II/III cortical neurons to compute prediction error responses, and the involvement of inhibitory somatostatin (SOM) interneurons to encode novelty and differential responses to familiar vs deviant stimuli (Hainmueller et al., 2024; Hamm & Yuste, 2016). These interneurons are also known to be involved in lateral inhibition of cortical neurons to familiar stimuli (Kato et al., 2015, 2017). Disruption of these prediction errors may lead to an imbalance between top-down predictions and sensory input. Supporting this model,

both LSD and psilocybin have been shown to produce aberrant mismatch negativity responses in humans (Duerler et al., 2022; Timmermann et al., 2018), and there is evidence that $5HT_{2A}$ receptor activation may directly drive activity of GABAergic interneurons, including SOM interneurons (de Filippo et al., 2021). However, the model remains speculative pending further experiments, as little is known about how psychedelics may directly affect the activity of SOM interneurons in the cortex, and their encoding of prediction error.

1.5 Effects of psychedelics on neuroplasticity

The ability of a compound to induce structural and functional neuronal plasticity (referred to as iPlasticity) has been identified in a variety of different drug classes (Castrén & Antila, 2017). This process is often slow, for example with drugs such as selective serotonin reuptake inhibitors (SSRI's), which can take weeks of chronic administration to see behavioral effects. What sets the group of small molecules known as 'psychoplastogens' apart is their ability to rapidly (around 24-72 hours) induce measurable changes in plasticity. These include classical psychedelics like psilocybin, as well as others such as ketamine, MDMA and the muscarinic-receptor antagonist scopolamine (Olson, 2018).

1.5.1 Structural plasticity

Several interesting *in vivo* and *ex vivo* studies have observed rapid and persistent remodeling of neuronal structure following a single psychedelic dose. One study used chronic two-photon

microscopy to track dendritic remodeling in mouse medial frontal cortex following a single dose of psilocybin. They observed significant increases in spine density and head width, driven by an increase in spine formation rate. These changes were rapid, visible within 24 hours, and in some cases persisting for up to a month (Shao et al., 2022). A similar study using 5-MeO-DMT found persistent (1 month) increases in spine density in the same region, but no changes in spine size (Jefferson et al., 2023). increases in spine density have been seen in rat prefrontal cortex (PFC), 24 hours following administration of DMT (Ly et al., 2018) and in mouse frontal cortex 24 hours following administration of DOI (de la Fuente Revenga et al., 2021) or 5-MeO-DMT (Vargas et al., 2023). Tracking with PET ligands in pig PFC/hippocampus has also identified increases in cortical density of the pre-synaptic marker synaptic vesicle glycoprotein 2A (SV2A) 1-7 days following a single administration of psilocybin. This may be reflective of prolonged synaptogenesis (Raval et al., 2021).

1.5.2 Signaling mechanisms inducing plasticity

Evidence suggests that this induction of plasticity is mediated primarily through $5HT_{2A}$ receptors (Figure 1.1). Changes in dendritic spine structure in mouse frontal cortex pyramidal neurons were not present in $5HT_{2A}$ knockout mice administered DOI (de la Fuente Revenga et al., 2021), nor was the expression of plasticity-related immediate early genes following LSD administration (González-Maeso et al., 2007). In primary cell cultures of rat cortical neurons, co-treatment with $5HT_{2A}$ receptor antagonist ketanserin completely blocked the ability of DOI, DMT and LSD to induce neuritogenesis and spinogenesis (Ly et al., 2018). However, *in vivo* administration of

ketanserin, while abolishing head-twitch responses, is not sufficient to abolish the induction of structural plasticity in mice (Hesselgrave et al., 2021; Shao et al., 2022). This may be due to the poor diffusion of ketanserin across non-polar membranes, with a 1mg/kg dose of ketanserin blocking only 30% of $5HT_{2A}$ receptors (Smith et al., 1995).

There is ample evidence that non-serotonergic psychedelics such as ketamine and scopolamine are also able to induce these changes in structural plasticity (Li et al., 2010; Voleti et al., 2013; Yao et al., 2018), pointing to a convergent mechanism of induction. Though the picture is still unclear, studies suggest that the different targets of these drugs result in a similar, glutamatergic mechanism of plasticity (Aleksandrova & Phillips, 2021). Both *in vitro* and *in vivo* LSD and DOI administration have been shown to increase glutamate release in frontal cortex (de Gregorio et al., 2021; Muschamp et al., 2004), leading to activation of post-synaptic AMPA receptors (AMPARs), which is also observed with ketamine (M. Wu et al., 2021). Repeated LSD treatment potentiated AMPAR and $5HT_{2A}$ synaptic responses of rodent PFC neurons, and their optogenetic inhibition blocked the pro-social effects of the drug (de Gregorio et al., 2021). These effects can be blocked by antagonists of $5HT_{2A}$ (Muschamp et al., 2004), AMPAR (Zhang & Marek, 2008), as well as $mGluR_2$ modulators. The latter has implicated a $5HT_{2A}$-$mGluR_2$ signaling complex in DOI drug action (González-Maeso et al., 2008). Several studies have suggested that psychedelics induce a hyper metabolic state mostly in frontal cortices, which correlates with their physiological effects (Carhart-Harris et al., 2016; Lambe & Aghajanian, 2006; Scruggs et al., 2003).

This increase in glutamate release and activation of AMPARs stimulates important signaling cascades for the induction of plasticity, such as production of brain-derived neurotrophic factor (BDNF) (Jourdi et al., 2009; Olson, 2022). BDNF then binds to tropomyosin related kinase B (TrkB) and stimulates mammalian target of rapamycin (mTOR) activation, which can upregulate BDNF production further (Jeon et al., 2015). Combined with non-exocytotic glutamate release stimulated by BDNF (Takei et al., 1998), this loop may keep the pathway open for some time. Administration of classical psychedelics has been directly linked to these increases in BDNF (Moliner et al., 2023) and mTOR (Ly et al., 2018) mobilization, and blocking AMPAR (Ly et al., 2021) or mTOR (de Gregorio et al., 2021) abolishes their plasticity-inducing and behavioral effects. Although less plentiful, human studies have identified a complex picture, in which increases in plasma BDNF levels may only occur at high doses (Holze et al., 2021; Hutten et al., 2021) following psychedelic administration. However, this variability may be due to demographic differences or in methodology, such as testing whole blood or serum, which show differing results (Trajkovska et al., 2007).

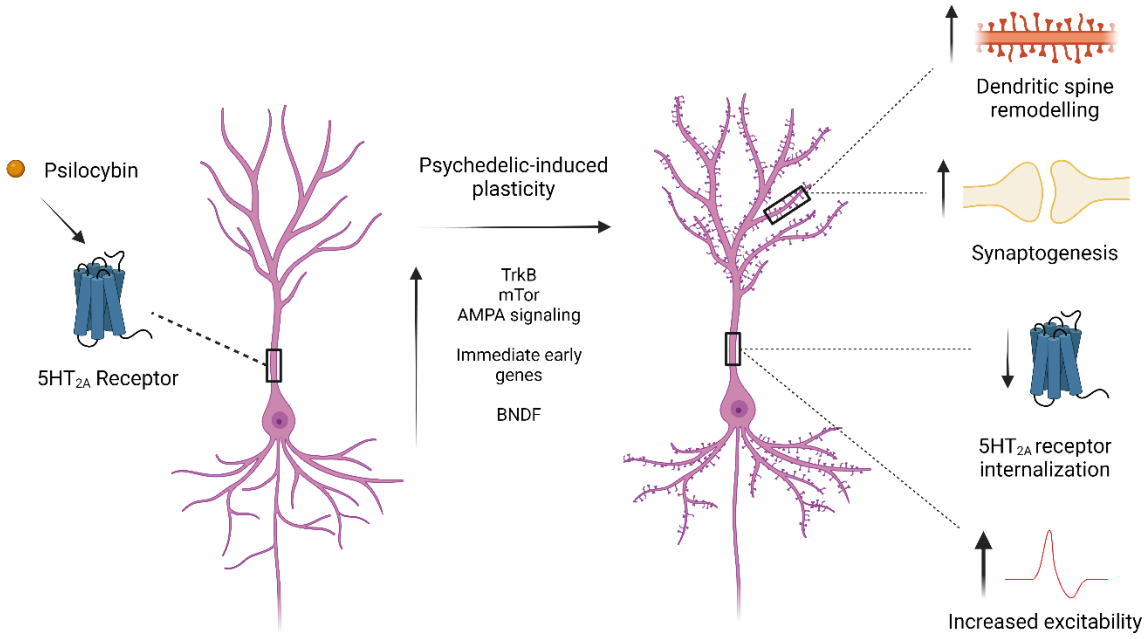

Figure 1.1: Psychedelics rapidly induce structural and functional neural plasticity.

Psychedelics including psilocybin are described as *psychoplastogens,* small molecules that rapidly induce measurable plasticity in the brain. Psychedelics rapidly stimulate a number of GPCR-mediated signaling pathways, such as mTor and TrkB, leading to upregulation of plasticity-associated immediate early genes such as c-*Fos, arc, egr-1* and *egr-2.* Increased glutamate release drives AMPA receptor activation, leading to upregulation of neurotrophic factors such as BDNF. Promotion of plasticity leads to increased dendritic spine formation and spine head size, as well as increased synapto- and neuritogenesis. Also observed are the internalization of $5HT_{2A}$ receptors, and increased spontaneous and evoked excitatory post-synaptic potentials. Shown in an example pyramidal neuron. Figure generated with *BioRender.com*.

1.5.3 Behavioral plasticity

Several pre-clinical studies have shown that the ability of psychedelics to act as psychoplastogens leads to long-lasting behavioral changes. A single dose of psilocybin has been found to facilitate fear extinction in mice (Du et al., 2023), reverse anhedonic responses to stress (Hesselgrave et al., 2021) and ameliorate maladaptive stress-induced behavioral deficits (Shao et al., 2022). In rats, LSD, psilocybin and DMT have all been shown to induce anti-depressant effects (Cameron et al., 2020; Hibicke et al., 2020), and DMT also produced them in a juvenile marmoset model of depression (Da Silva et al., 2019). A recent study found that several psychoplastogens are able to reopen the CP for social reward learning. Durations ranged from very short for ketamine (48 hours) to two weeks for psilocybin and MDMA or three for LSD. Interestingly, the length of CP reopening appears to correlate with the duration of subjective effects of each drug, and RNA sequencing of the nucleus accumbens detected upregulation of a number of genes involved in regulating extracellular matrix (ECM) structure, following administration (Nardou et al., 2023). It has also been shown that repeated ketamine administration is able to reopen the CP for ocular dominance plasticity by targeting the ECM (Grieco et al., 2020; Venturino et al., 2021). As the ECM is heavily involved in the regulation of CPs (Baroncelli et al., 2010; Cisneros-Franco et al., 2020; Reha et al., 2020), it may be that the facilitation of cognitive flexibility seen with psychedelics is partly due to a shared ability to reopen them by targeting ECM remodeling.

1.6 Psychedelics in the clinical context

1.6.1 Psychoplastogens and maladaptive plasticity

A consensus is now developing that it is the ability to rapidly induce a prolonged period of enhanced plasticity that confers the powerful therapeutic effects of psychedelics. Indeed, depressed patients administered ayahuasca (a plant-based psychedelic containing DMT) show elevated BDNF levels that correlate with their clinical improvement (de Almeida et al., 2019). It makes sense that the ability to facilitate plasticity could help with a variety of neuropsychiatric conditions, as many are conditions of reduced or maladaptive plasticity themselves. For example, patients with depression exhibit reduced cortical neuroplasticity (Player et al., 2013), cognitive flexibility (Murphy et al., 2012) and reductions in PFC synapse numbers (Kang et al., 2012). The aforementioned ability of psychedelics to induce spinogenesis and neuritogenesis may contribute to therapeutic benefits, as depression has been associated with prefrontal lesions (Ramezani et al., 2015; F. F. Zhang et al., 2018), as well as reductions in striatal grey matter intensity (Rădulescu et al., 2021), and in volume of the hippocampus (Geerlings & Gerritsen, 2017) and thalamus (Lu et al., 2016). Prolonged stress also results in elevation of glucocorticoid levels, which can reduce size and branching of PFC apical dendrites (Radley et al., 2004), cause neurotoxic effects on pyramidal neurons in the hippocampus (Woolley et al., 1990) and downregulate hippocampal neurogenesis (Masi & Brovedani, 2011). Importantly, chronic stress can lower the expression of AMPAR subunits (Kvarta et al., 2015) and lower AMPA-mediated excitation in hippocampal synapses (Kallarackal et al., 2013), effects which can be partially reversed with the antidepressant fluoxetine. This is a potential key link between the AMPAR-mediated effects of classical psychedelics and their observed therapeutic efficacy in humans.

1.6.2 Depression and anxiety

Much of the focus of psychedelic therapies has been on their potential to alleviate symptoms of depression and anxiety, and a number of recent clinical trials with different classical psychedelics (primarily psilocybin) have yielded promising results. One group found that a single dose of psilocybin (25 mg) resulted in clinically significant reduction in depressive symptoms and functional disability in patients with major depressive disorder (MDD), without adverse events, which was sustained for over a month (Davis et al., 2021; Raison et al., 2023). Another group found similar reductions in symptom severity in MDD patients at a dose of 15 mg (von Rotz et al., 2023). Other trials have been conducted with similar results for both depression and anxiety (Galvão-Coelho et al., 2021). However, a trial involving patients with treatment resistant depression found that though a 25 mg dose reduced depressive symptoms, it was also associated with adverse effects (Goodwin et al., 2022), suggesting that specific disease conditions and dosage should be considered when comparing results from these trials. Psilocybin has also been used to successfully reduce symptoms of anxiety and depression in patients with life-threatening cancer (Griffiths et al., 2016; Ross et al., 2016). A similar life-threatening disease study employing LSD found significant reductions in anxiety (Gasser et al., 2014), and studies have found improvements in depression and anxiety symptoms 7 days (Palhano-Fontes et al., 2019) and three weeks (Sanches et al., 2016) following administration.

1.6.3 Substance abuse and addiction

Substance abuse issues are a massive and growing health problem, yet effective treatment options remain scarce. The resurgence of psychedelics research has therefore brought with it a major focus on exploring their use as adjuncts to addiction treatment, driven by promising findings during their first age of study (Krebs & Johansen, 2012; Rydzyński & Gruszczyński, 1978; Savage & McCabe, 1973). Though prohibition stalled any new clinical trials, retrospective observational analyses of psychedelics in addiction continued to be performed. These studies have suggested classical psychedelics may be effective in combatting opioid dependence (Argento et al., 2022; G. Jones et al., 2022; Pisano et al., 2017), other recreational drug addictions (Calleja-Conde et al., 2022; Garcia-Romeu et al., 2019; G. M. Jones & Nock, 2022; Nunes et al., 2016), and aiding smoking cessation (Johnson, Garcia-Romeu, Johnson, et al., 2017).

In the wake of increased tolerance of their study, a small number of clinical trials have been completed in recent years to actively try to use classical psychedelics as an adjunct to traditional psychotherapy. Psilocybin was employed and seems to show real promise in a long-term smoking cessation (Johnson et al., 2014; Johnson, Garcia-Romeu, & Griffiths, 2017) study, in which participants had previously attempted to quit a mean of six times. 80% of participants remained abstinent 6-months later, a far higher proportion than is observed with existing interventions, at less than 35% (Zafar et al., 2023). On the back of these data, a larger phase II trial is now underway (NCT05452772). A similar pilot study into alcohol use disorder (AUD) showed a significant reduction in drinking and heavy drinking days (Bogenschutz et al., 2015). This was since replicated in a phase II trial (NCT02061293), which found a 14% reduction in heavy drinking days compared to diphenhydramine control (Bogenschutz et al., 2022). At least 12 other trials

are now underway at various locations to further assess the use of psilocybin-assisted therapy for AUD.

1.6.4 Other neuropsychiatric conditions and broader applications

Though the clear focus of clinical study has been targeted towards using psychedelics to treat depression, anxiety and substance abuse conditions, work is also being done on a variety of other neurological conditions such as anorexia nervosa (Calder et al., 2023), headache and chronic pain (Schindler, 2022), dementias, and traumatic brain injury (Khan et al., 2021). While some of this variety may simply be the optimism that comes with a new class of drugs, one guiding idea behind much of the work is the ability of classical psychedelics to rapidly induce a period of enhanced neuronal plasticity, which can then be harnessed to alleviate functional deficits. Observed structural changes in dendrites (Shao et al., 2022) offer a tantalizing prospect of restoring healthy neuronal architecture in neurodegeneration by boosting new connections. Similarly, the ability to reopen CPs (Nardou et al., 2023) could facilitate reorganization of cortical circuits where maladaptive plastic changes have become fixed, such as in post-traumatic stress disorder (PTSD) (Ressler et al., 2022) or tinnitus (Shore et al., 2016b). Though studies remain very limited, there is pre-clinical evidence highlighting psychedelic-induced plasticity ameliorating functional deficits following injury. One study identified a neuroprotective effect of DMT in rats following stroke, with lower ischemic lesion volume and better functional recovery (Nardai et al., 2020). In a mouse model of traumatic brain injury (TBI), acute treatment with TrkB agonist LM22A-4 conferred a neuroprotective effect and preserved myelin integrity (Fletcher et al., 2021), suggesting that the

TrkB-mediated effects of psychoplastogens could have similar benefits. A recent study in veterans suffering from TBI found that administration of the tryptamine psychedelic ibogaine caused rapid reductions in disability and improved measures such as executive function, persisting for up to a month (Cherian et al., 2024).

One of the most common conditions of maladaptive plasticity is tinnitus. Most cases are caused by loss of sensory input to central auditory pathways, which triggers plastic reorganization, leading to increased spontaneous activity and neuronal synchrony (Shore et al., 2016b). A number of approaches to treating tinnitus that have shown some effect involve trying to induce reorganization of the neuronal circuit through auditory stimulation. Playing 'notched' music to patients (self-chosen music, edited to contain no energy in the frequency range surrounding the tinnitus frequency) is thought to distribute lateral inhibition into the notched frequency region, significantly reducing subjective tinnitus loudness and cortical activity corresponding to the tinnitus frequency (Okamoto et al., 2010). A more active training approach involves pairing vagus nerve stimulation with tones tailored to activate auditory neurons around but not within the tinnitus frequency. This promotes plasticity targeted to the paired experience by triggering a timed neurotransmitter burst (Tyler et al., 2017). Though it remains untested, pairing these kind of plasticity-targeting therapies with a psychoplastogen such as psilocybin may enhance the reversal of maladaptive plasticity, in a way similar to the enhanced extinction of fear conditioning in animal studies.

1.7 Excitatory-inhibitory balance and regulation of acute and long-term plasticity in the auditory cortex.

The juvenile brain is characterized by a state of heightened plasticity, in which the formation of cortical sensory representations is driven by passive sensory input (Cisneros-Franco et al., 2020). CPs in the developing brain overlap in different regions and for different forms of sensory information (De Villers-Sidani & Merzenich, 2011). As the brain develops, the stabilization of cortical sensory representations (De Villers-Sidani et al., 2007; Rice & Van Der Loos, 1977) is driven by maturation of inhibitory networks of GABAergic interneurons, such as parvalbumin (PV) and somatostatin (SOM)-positive cells (Hensch, 2005).

Increasing inhibitory tone in the cortex leads to the closure of these CP's, with subsequent plastic reorganization possible only by targeting a number of 'molecular brakes', which work to inhibit plasticity (Bavelier et al., 2010) (Figure 1.2A). Adult experience-dependent plasticity is driven by targeted modulation of these structural and functional regulators including PV and SOM interneurons (Cisneros-Franco & De Villers-Sidani, 2019a), extracellular matrix proteins such as perineuronal nets (PNN's) (Reichelt et al., 2019), myelin-associated proteins (Kaller et al., 2017), and glial cells such as astrocytes and microglia (Dzyubenko & Hermann, 2023) (Figure 1.2A). Indeed, active disruption of PNN's or targeted downregulation of interneuron inhibition has been shown to restore CP-like plasticity (Fagiolini & Hensch, 2000; Reichelt et al., 2019). Stable cortical representations are also driven by maintenance of sensory inputs, and loss of sensory salience such as with noise exposure (Thomas et al., 2018) or loss of vision (Van Brussel et al., 2011) can also reinstate CP-like plasticity (Figure 1.2B). This highlights that stable cortical representations

in the adult brain are maintained not just through static maintenance of structure with molecular brakes, but through continued input from an enriched sensory environment.

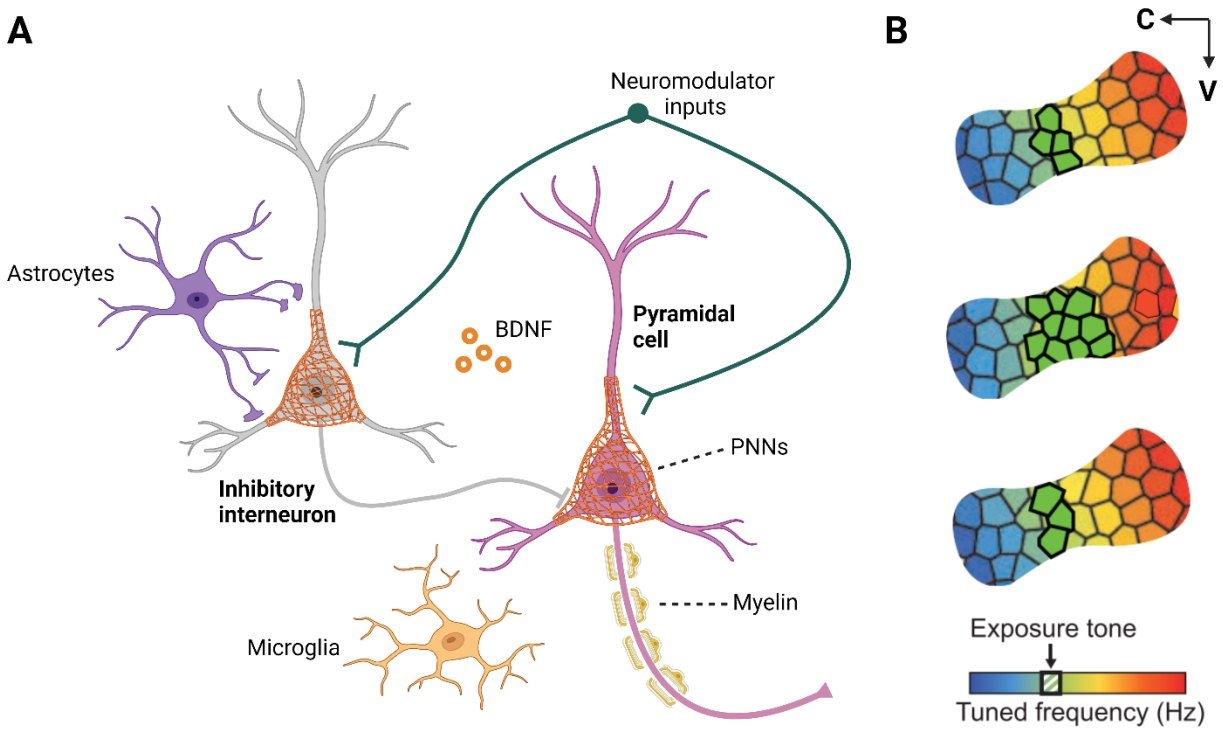

Figure 1.2: Molecular brakes and regulators of neuroplasticity in the adult brain

A) In the adult brain, induction of plasticity is mostly stimulated by goal-directed behavior such as task learning. This involves the interplay of a number of interacting mediators, which modulate excitatory-inhibitory balance, and physically maintain synaptic architecture. Inhibitory interneurons: GABAergic interneurons such as those expressing PV, SOM and vasoactive intestinal peptide (VIP) regulate the excitatory-inhibitory balance through targeted inhibition. Perineuronal nets (PNNs) are extracellular matrix components, which surround neurons and their synapses, to physically restrict structural reorganization. Glial cells: Astrocytes and microglia are

able to induce structural remodeling through targeted lysis of extracellular matrix proteins such as PNN's, in response to both local neuronal activity and from projecting inputs. Myelin: Through restricting axonal growth and regeneration, myelin and myelin-associated proteins prevent large-scale plasticity, and myelin-remodeling is a key part of experience-dependent plasticity. BDNF: Neurotrophins such as BDNF promote neuronal survival, dendritic remodeling and synaptogenesis, and also regulate excitatory-inhibitory balance through suppression of GABAergic signaling. Neuromodulator inputs: Projecting neuronal inputs from other brain regions and subcortical nuclei are important for facilitation of goal-directed plasticity in behavioral states such as attention. Neuromodulator stimulation from regions such as the nucleus basalis is important for facilitation of goal-directed plasticity. B) Representative mouse A1 tonotopic map responses to sound exposure. Top: Naïve animal map. Middle: Sound exposure pre CP closure. Bottom: Sound exposure post CP closure. During the CP, passive exposure to sound drives reorganization of A1 cortical representations. Once the CP has closed, representations remain stable without a plasticity-inducing stimulus such as task-learning. Adapted with permission from (Cisneros-Franco et al., 2020). Figure generated with *BioRender.com.*

These cortical inhibitory networks are also involved in much more rapidly evolving forms of plasticity, such as the modulation of neuronal representations in response to sensory context and changes in behavioral state. A finely timed balance of excitation and inhibition takes place even with the simplest auditory stimuli. A single tone-pip generates a co-occurring increase in both synaptic excitation and inhibition, with the latter appearing within a couple of milliseconds

of the sound-evoked response (Wehr & Zador, 2003; Wu et al., 2008). This balance appears to be relatively proportional, with increases in the intensity of sensory stimuli leading to similar changes in the strength of both excitatory and inhibitory activity. The proportionality is driven by the reciprocal nature of inhibitory circuits, in which pyramidal cells form excitatory synaptic connections with inhibitory cells, which then form inhibitory synapses with the pyramidal population, known as feedback inhibition. Excitatory inputs from other cortical layers, subcortical nuclei and other brain regions also synapse with both pyramidal cells and local interneurons, providing feedforward inhibition (Isaacson & Scanziani, 2011). This facilitates both local regulation of cortical excitability and the top-down control over cortical state that is vital for mechanisms such as attention (Buszaki, 1984; Cruikshank et al., 2007). Different subtypes of inhibitory cells also target one-another and synapse with particular segments of pyramidal cells (Isaacson & Scanziani, 2011), significantly increasing the complexity of these excitatory-inhibitory circuits.

Not limited to the homeostatic maintenance of cortical excitability, inhibition also acts with high temporal precision to modulate the tuning characteristics of sensory neurons. Auditory neurons exhibit preferences for particular frequencies of auditory stimuli, evidenced as variation in the spike output of the cell, a feature seen across sensory modalities. Individual neuron tuning to preferred stimuli is sharpened by inhibition of responses to non-preferred stimuli (Priebe & Ferster, 2008). This effect may be facilitated through tuning curves of inhibition being broader than that of excitation (Wu et al., 2008), so that non-preferred stimuli tip the excitatory-inhibitory balance in favor of inhibition, relative to a preferred stimulus. SOM interneurons have been shown to have broader tuning curves than their surrounding excitatory neurons and their

activation drives narrowing of tuning selectivity, suggesting they may integrate the frequency tuning information of surrounding neurons to provide lateral inhibition of sound-evoked responses (Kato et al., 2017). Indeed, pharmacological blockade of $GABA_A$ receptors reduces the stimulus selectivity of neurons both in the auditory (Wang et al., 2000) and other sensory cortices (Katzner et al., 2011; Poo & Isaacson, 2009), highlighting the important role these inhibitory inputs play in maintaining cortical sensory representations.

These inhibitory networks have also been shown to be involved in the processing of perceived novelty and behavioral relevance of stimuli. Auditory neurons habituate over time to the repeated presentation of a stimulus. This reduction in response amplitude is driven by increasing activity of SOM interneurons, an effect which is rapidly reversed by presentation of unexpected stimuli (Kato et al., 2015). When taken together, it is clear that much of the acute plasticity of sensory representation seen in auditory cortical processing is made possible by dynamic regulation of cortical excitability by these finely tuned inhibitory circuits. More prolonged perturbations in inhibitory circuit activity can also drive long-term restructuring of these sensory representations.

1.8 The auditory cortex as a model to study psychedelic-induced plasticity

Most of the work with psychedelics so far has focused on how they affect information processing in frontal regions, with fewer studies in primary sensory areas. What examination there has been in sensory areas has focused primarily on the visual cortex (Michaiel et al., 2019), with very little focus placed on studying the effects on auditory regions. This is despite the well-documented

auditory hallucinations produced by psilocybin and other classical psychedelics (Studerus et al., 2011), as well as the preponderance of auditory hallucinations in neuropsychiatric conditions such as schizophrenia (Romeo & Spironelli, 2022). The effects of sensory gating are often different in certain behavioral conditions between visual and auditory cortices. For example, locomotion generally increases sensory-evoked activity in primary visual cortex (Niell & Stryker, 2010), but decreases it in primary auditory cortex (Henschke et al., 2021). It is therefore important to consider potential diverging effects of psychedelics on neuronal activity in auditory vs other sensory cortices. A small number of human neuroimaging studies have examined how psychedelics affect auditory processing and sensory gating (Timmermann et al., 2018; Vollenweider et al., 2007), but very little examination has been undertaken directly in primary auditory cortex, particularly with single-cell resolution.

In addition to the need to examine how psychedelics affect auditory cortex neuronal activity, this cortex itself presents an excellent model for the study of psychedelic-induced changes in information processing and plasticity. The simplicity of presenting free-field sound stimuli in both head-restrained and freely moving conditions readily allows for the assessment of various manipulations on experience-dependent plasticity. The same free-field design allows for sound stimuli to be presented continuously for several weeks, making it ideal for study of long-term gating of plasticity, such as the regulation of CPs (Cisneros-Franco et al., 2020).

Indeed, our group has already utilized *in vivo* electrophysiology in the auditory cortex as a model to study how certain interventions can facilitate cortical reorganization, such as with chronic noise exposure (Thomas et al., 2018, 2020), or reopening CPs (Figure 1.2B) by manipulating PV-positive interneurons (Cisneros-Franco & De Villers-Sidani, 2019b). As the effects of psilocybin

involve significant perceptual disturbances, it was clear that in order to examine how the drug affects auditory sensory processing and plasticity, we needed a model in which neuronal activity could be directly imaged in the awake animal as opposed to under anesthesia. There are often major differences between the stable balance of tuning at the overall cortical level, and constant representational drift within individual neurons. With this in mind, we decided that we required the ability to longitudinally track individual neurons across interventions, in order to assess whether psilocybin either influenced this drift, or produced subtler changes in response properties not detected with population averages.

In order to achieve all of these requirements, we shifted our focus early in the study, away from using *in vivo* multi-channel electrophysiology in anaesthetized rats. Instead, we have employed a constitutively active calcium indicator mouse model with a chronic cranial window placed over the auditory cortex (adapted from Romero et al., 2020). Using this, we established a longitudinal paradigm for head-fixed, two-photon and wide field calcium imaging in the intact, awake mouse. The findings shown here are the result of the construction and optimization of this imaging set-up and surgical procedure, as well as establishment of an analysis pipeline to extract the tuning properties of individual neurons across recordings. We also established a wide field imaging paradigm and analysis pipeline to reconstruct wide field auditory tonotopic maps, and examine changes in structure and response properties with chronic sound exposure.

1.9 References

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Chapter 2: Psilocybin prevents adaptation to familiar stimuli and preserves sensitivity to sound following repeated stimulation in mouse A1.

2.1 Abstract

Psilocybin is a psychoactive compound found mostly in the *psilocybe* genus of mushroom, which has been used by various peoples recreationally, medically and spiritually for centuries. The drug rapidly induces profound perceptual disturbances, such as visual and auditory hallucinations. Promising results from recent clinical studies have generated a wave of interest in employing psilocybin as a treatment for conditions of maladaptive plasticity such as depression, PTSD and substance abuse disorders. Despite this interest, exactly how psychedelics alter neuronal circuit function to cause acute perceptual effects, and how these may relate to longer term psychological changes is still debated. Moreover, though it is thought that perceptual disturbances may be caused by disruption of the flow of information between sensory and higher order areas, *in* vivo studies have been focused mostly in the latter. In particular, there has been very little study of how psilocybin affects neuronal activity and sensory representations in the auditory cortex. In this study, we used a combination of two-photon microscopy and wide field imaging to examine how psilocybin affects A1 neuron response properties in the mouse. We found that acute administration of 1 mg/kg psilocybin prevented the habituation of sound-evoked responses to repeated stimuli, maintaining overall responsiveness, bandwidth tuning and sound-level response thresholds after repeated stimulation. This was in contrast to a marked habituation of responses and narrowing of tuning observed in controls. We observed no effect on the overall distribution of best frequencies at the cortical level, suggesting that the effects of psilocybin in A1 involve disruption of normal sensory gating, rather than overall tonotopic organization. This may support models of psychedelic action in which acute perceptual effects are driven by disrupted sensory gating of familiar or irrelevant information.

2.2 Introduction

Serotonergic psychedelics such as psilocybin have been employed for centuries by various communities, for recreational, spiritual and medicinal purposes (Nichols, 2020). These drugs share a common ability to induce profound alterations in sensory perception and cognition, coupled with longer term changes in mood and social interaction (Erritzoe et al., 2018). Recently, a resurgence in clinical interest in psychedelics, including psilocybin, has opened up a number of promising avenues for the treatment of conditions such as depression (Griffiths et al., 2016; Raison et al., 2023) , addiction (Garcia-Romeu et al., 2019; Johnson et al., 2014) and anxiety (Griffiths et al., 2016; Yu et al., 2021).

Psilocybin's metabolite psilocin belongs to the tryptamine class of psychedelics, which possess a high affinity both for the primarily excitatory serotonin receptor subtype $5HT_{2A}$ and its inhibitory cousin $5HT_{1A}$, among other targets (Kwan et al., 2022). This reflects psilocin's complex pharmacological profile, in which effects on neuronal excitability may differ depending on brain region and receptor density in certain neuronal subtypes (Burnet et al., 1995). Indeed, this class of drugs has been shown to exert mixed excitatory effects in frontal cortices (Shao et al., 2022; Wood et al., 2012), as well as primarily suppressive effects in primary sensory cortices (Michaiel et al., 2019). Prior work in human primary auditory cortex has found that $5HT_{2A}$ agonists induce acute changes in cortical responses to sensory stimuli, such as neuronal adaptation and connectivity (Timmermann et al., 2018). Complex, layer-specific effects on temporal processing and surround-suppression of responses have also been found in mouse V1 (Michaiel et al., 2019). These data suggest that the effects of serotonergic psychedelics may involve changes to neuronal tuning and adaptation in sensory cortices, disrupting bottom-up sensory gating.

The effect of psilocybin on activity in the auditory cortex remains understudied relative to other sensory cortices, and to date no study has been undertaken with single-neuron resolution, particularly tracking a single cell population. Here, we used a combination of wide field calcium imaging and two-photon microscopy in awake, head fixed mice to assess the effects of psilocybin on primary auditory cortex neuronal activity. We also tracked a subset of cells between recordings to longitudinally measure changes in tuning properties with psilocybin. We found that 1 mg/kg psilocybin prevented the reduction in excitatory neuronal activity occurring with prolonged exposure to auditory stimuli. Psilocybin also preserved baseline response thresholds and tuning bandwidths of neurons, in contrast to observed narrowing of both with repeated stimulation under control conditions. This study suggests that psilocybin alters inhibitory sensory gating and filtering of familiar stimuli in the primary auditory cortex, which supports models of psychedelic action in which bottom-up sensory inputs are disrupted.

2.3. Materials and Methods

Animals and Drugs: All experimental procedures were approved by the Montreal Neurological Institute Animal Care Committee and follow the guidelines of the Canadian Council on Animal Care. All experiments were performed on male and female adult mice (no older than 24 weeks) of the Thy1-GCaMP6s strain (Jackson labs, stock number 024275), crossed with CBA/CaJ, a strain that retains good hearing thresholds (Zheng et al., 1999). GCaMP6s-positive offspring retain good hearing thresholds well into adulthood (Romero et al., 2020). Mice were maintained on a 12-hour light/dark cycle with *ad libitum* access to food and water and were group-housed until

cranial window surgery, from which point they were single-housed. Psilocybin was supplied by Psygen Inc. (Calgary, AB) and use of psilocybin for research purposes was approved by Health Canada, April 2022.

Cranial Window Surgery: Cranial window procedure was adapted from (Romero et al., 2020). Briefly, animals are anaesthetized with isoflurane in oxygen (5% induction, 1-2% maintenance). An incision was made to expose the skull, periosteum removed from the skull and an etchant (C&B Metabond, Parkell, Inc. NY) applied for 30 s to increase surface area for adhesion. Custom head-fixation hardware (iMaterialise, Belgium) was attached to the skull using dental cement (C&B Metabond) mixed with black ink. Left auditory cortex was localized using the skull anatomical landmarks (rostral to lambdoid suture and dorsal to zygomatic arch extension) and a 3 mm craniotomy drilled. A 3 mm glass coverslip (#0 thickness, Warner Instruments, MA) was cleaned with 70% ethanol and rinsed with sterile saline. The coverslip was then inserted into the craniotomy and affixed with dental cement. Animals were allowed to recover in a warmed chamber and administered 20 mg/kg carprofen for three days post-operatively. Imaging began a minimum of 5 days following surgery.

Two-photon Imaging: Imaging of calcium activity was performed using an Ultima Investigator two-photon microscope (Bruker, MA) with a Cambridge Technology 8 kHz CRS resonant scanner (Novanta Photonics, MA) and 350-80LA pockels cell (Conoptics, CT). Excitation light was provided using a Mai-Tai eHP laser (SpectraPhysics, UK) tuned to 920 nm. System was controlled and images collected with PrairieView software (Version 5.4, Bruker). Microscope and animal fixation set-up were enclosed in a light-attenuating box. Resonant scanner was used at a resolution of

512 x 512 pixels, collecting images at 10 Hz. A 16X/0.80 LWD immersion objective (Nikon, UK) was employed. Neuronal activity was imaged at 175 µm below the pial surface (layer 2/3).

Wide field Imaging: Wide field calcium activity was collected using a PCO Panda 4.2 scMOS camera (Excelitas Technologies, MA), recording at 10 Hz framerate. A UPlanFL N 4X, 0.13 numerical aperture lens (Olympus, Japan) was used. Excitation light was provided by an X-Cite Series 120 Q lamp (Excelitas Technologies) and passed through a 470-10 nm band pass filter (Thorlabs, NJ). Light was focused at a depth of 200 µm. Images were collected using PCO Camware software (version 4.12, Excelitas) at a resolution of 512x512 pixels.

Imaging procedure: Prior to imaging, animals were acclimatized to head fixation for three days by securing them in the set-up for progressively longer periods (15, 30, 45 minutes) with wide field excitation light. On imaging day 1, a wide field tonotopic map was taken to ascertain the location of left primary auditory cortex (A1) and the two-photon field of view fixed in this region. Animals underwent two imaging sessions separated by 5 days. In the first session, a battery of stimuli was presented while recording from A1, immediately followed by intraperitoneal (IP) injection of saline and a 15-minute incubation period. A second battery of stimuli were then presented and second recording taken. Animals underwent the same imaging protocol in session 2, and were injected with 1 mg/kg psilocybin instead of saline. To avoid potential long-term effects of psilocybin on saline controls, all animals were administered saline on session 1 and psilocybin on day 2.

Sound Presentation:

For both two-photon and wide field imaging, stimuli were designed with OpenEx software (Tucker-Davis Technologies (TDT), FL) and generated using a TDT RZ6 multi I/O processor (TDT). Sounds were presented with an MF1 free-field speaker (TDT) placed 10 cm from the contralateral (right) ear.

Two-photon: Neuronal receptive fields were reconstructed using responses to a range of frequency-intensity combinations of pure tones. For two-photon imaging, 12 sound frequencies (100 ms tones, 5 ms on/off ramps, ranging from 4-45 kHz in 0.5 octave increments) were presented at four intensities (35-80 dB SPL, 15 dB increments), with a 1.5s inter-stimulus interval (ISI). Stimuli were presented in random order, with each of the 48 total frequency-intensity conditions repeating 10 times.

Wide field: To reconstruct wide field tonotopic maps, 12 frequencies were presented at 65 dB SPL (100 ms tones, 5 ms on/off ramps, ranging from 4-45 kHz in 0.5 octave increments), each repeating ten times.

Data analysis – Two-photon:

Extracting neuronal calcium responses from two-photon recordings: Recordings were exported from PrairieView software and imported into Suite2p (https://github.com/MouseLand/suite2p) (Pachitariu et al., 2017), an open source package providing a full pipeline for the extraction of calcium signals from neuronal ROI's. Briefly, Suite2p performs motion correction, extraction of calcium traces from neuronal ROI's and deconvolution to infer spike activity from raw calcium traces. Half-decay kernel for the GCaMP6s calcium indicator was set at $\tau = 1.5$. Detected neuronal

ROI's were manually confirmed as healthy neurons by the presence of a clearly demarcated ROI, a ring of fluorescence and a dark center. The neuronal calcium trace (ΔF/F0) and deconvolved spike activity were then exported for further analysis in Python.

Identification of sound-sensitive neurons: The total trial length was 1.5s (-0.5 seconds from stimulus onset to 1s post-onset) and the response period was stimulus onset to 1s post-onset. Evoked activity was defined as the mean activity of the trace during the response period. We determined whether a cell was sound-responsive using a two-way ANOVA, using tone frequency and sound intensity of the stimulus as predictors. Cells significantly modulated by frequency or intensity ($p = <0.05$ main effect for either frequency, or frequency/intensity interaction) were labelled as sound responsive and taken forward for further analysis.

Matching neurons across recordings*:* In order to directly examine changes of tuning with single-cell resolution, a subset of identified neurons was tracked across the pre- and post-recordings. The cell coordinates and mean image Suite2p output for each recording were imported to the open source MATLAB package ROIMatchPub (https://github.com/ransona/ROIMatchPub), which then displayed aligned ROI's for manual confirmation. We matched a total of 1071 cells in the saline session, and 1831 cells in the psilocybin session, across 8 animals.

Calculating individual neuron tuning properties: Frequency-intensity tuning curves were reconstructed from the peak of the baseline-corrected response to stimulation, averaged across trials. *Best frequency (BF):* BF was calculated as the frequency of stimulation that elicited the maximal trial-averaged peak response, collapsed across intensities. *Bandwidth:* Tuning bandwidth was defined as the continuous range of frequencies around the BF at which a

response above half of the maximum was observed. *Lowest Response Intensity:* For sensitivity to intensity analyses, the lowest response intensity was defined as the lowest intensity at which an above threshold (4 SD from baseline) peak response was elicited. *Trial-Trial Variability:* In order to examine how psilocybin may impact the variability of responses to sound stimulation across trials, we used a response quality index (QI), described in detail in (Baden et al., 2016) to compute the signal-to-noise ratio

$$QI = \frac{Var[\langle C \rangle_r]_t}{\langle Var[C]_t \rangle_r}$$

where *C* is the *T* by *R* response matrix (time samples by stimulus repetitions) and ⟨ ⟩x and Var[ ]x denote the mean and variance across the indicated dimension, respectively. A higher QI denotes that the mean response is a closer representation of the variance across trials, with a QI of 1 being a perfect representation.

Data Analysis – wide field:

Image pre-processing: Recordings were first motion corrected by aligning all frames to a mean reference image, constructed from the 20 most correlated of a random selection of frames. Recordings were then down-sampled from their native resolution of 512 x 512 pixels to 256 x 256. Global fluctuations in the signal were removed by fitting a linear regression model, which predicts the pixel intensities of each frame based on global average intensity, and subtracts predicted global fluctuations from the activity of each pixel. The total trial length was 2.5s (-0.5s from stimulus onset to 2s post-onset). Pixel traces were then baseline corrected by subtracting the mean of the five pre-stimulus baseline frames from the mean of the response period, which

was taken as the 0.8s immediately following the stimulus. Pixel responses were then expressed as z-scores from local pre-stimulus baseline.

Tonotopic map reconstruction: Best Frequency (BF) tonotopic maps were reconstructed first by z-scoring median responses to a given frequency relative to every other pixel response at that frequency. This corrects for general biases in response amplitude in the cortex for particular frequency ranges. Only pixels with a z-score greater than 1 for the given frequency were included in analyses. The frequency at which the maximal trial-averaged median response was elicited was defined as the BF and each pixel was labelled accordingly.

Quantification and statistical analysis: Analyses were performed using Python 3.12. All data are reported as mean ± SEM unless stated otherwise. For categorization of cell sensitivity to sound, two-way ANOVA was used. For comparison between saline and psilocybin groups, Mann Whitney U or Kolmogorov-Smirnov tests were used, and false discovery rate (FDR) was controlled with a Benjamini Hochberg correction. Statistical significance was defined as $p < 0.05$.

2.4 Results

Imaging neuronal calcium responses to sound in A1 neurons.

Prior to 2-photon imaging, wide field calcium imaging was performed and A1 identified by the presence of a large, rostro-caudal high-to-low frequency tonotopic gradient, and from pial vessel positions (Figure 2.1A). Recordings were focused at 150-175 µm below the pial surface, with a field of view of 794 x 794 µm (Figure 2.1B). Mice were exposed to randomly presented pure tones

(4-45 kHz, 30 – 80 dB SPL) and neuronal ROIs were extracted based on calcium activity (Figure 2.1C) and categorized as 'responsive' if their activity was significantly modulated by either frequency or intensity ($p < 0.05$ Two-Way ANOVA) (Figure 2.1D) of sound stimulation. In total, 3886 neurons were identified in the pre-saline recording and 3593 in the post-saline condition. Tuning curves were reconstructed for all responsive cells in order to quantify tuning properties (Figure 2.1E).

Sensitivity to low sound intensities following repeated stimulation is preserved with psilocybin.

We examined the effects of psilocybin on the response magnitudes and tuning properties of individual neurons, both at the whole population level, and longitudinally in a subset of cell ROI's that were manually tracked between recordings. Briefly, each mouse underwent two imaging sessions (session refers to a full imaging day, containing two recordings per mouse) separated by 5 days (N = 8 mice). In the first session, animals were exposed to an initial randomized stimulus battery (see Methods) while recording A1 activity. Immediately following this, mice were injected with 0.1 ml/10 g saline and a second recording was taken following a 15-minute wait period. The second session proceeded in the same way, with a 1 mg/kg dose of psilocybin between recordings (Figure 2.2A). We observed a significant difference in the change in the overall amount of activity (using the deconvolved activity trace, the number of evoked events per frame) between saline and psilocybin conditions ($p = 0.004$, $U = 22850$, p, Mann Whitney U and FDR correction) with the saline condition showing a median reduction of -0.211 and psilocybin condition, -0.133 (Figure 2.2B). However, when examining the trial-averaged mean response

amplitude at best frequency (BF) of the same cells, we observed no significant difference between saline and psilocybin conditions (Figure 2.2C) ($p = 0.133$, $U = 30525$), despite saline showing a median change of -0.327 and psilocybin, -0.148 (z-score). This suggested that the change in overall response activity was not due to an increase in the amplitude of responses at BF, but instead may be due to shifts in the off-BF shape of the tuning curves. To investigate this further, we examined changes in the response thresholds (lowest sound intensity eliciting an above threshold response) of neurons with repeated stimulation (Figure 2.2D). Across all responsive cells, those in the saline condition exhibited a lower cumulative probability of responding to lower intensity stimuli (Figure 2.2E, left). A significant difference in the distribution of sensitivities between the post-saline and post-psilocybin recording was observed ($p = 4.12 \times 10^{-5}$, $U = 316620$, Mann Whitney U and FDR correction) (Figure 2.2E, right). However, no significant difference in lowest response intensity was observed between the baseline recordings for saline and psilocybin conditions ($p = 0.12$, $U = 348502$) (Figure Supplementary 2A). The same lower sensitivity following saline administration was observed in the matched cell subset (Figure 2.2F) ($p = 0.04$, $U = 36103$, Mann Whitney U and FDR correction), with baseline recordings showing no significant difference ($p = 0.86$, $U = 33323$, Mann Whitney U) (Figure Supplementary 2B). These findings suggest that administration of 1 mg/kg psilocybin prevents the reduction in overall responsiveness and raising of response thresholds that normally occurs with repeated exposure to the stimulus. This may indicate that instead of the stimulus becoming familiar and being filtered out as background noise, psilocybin disrupts normal sensory gating, ensuring the stimulus continues to be processed as novel.

Narrowing of tuning bandwidths with repeated stimulation is prevented by psilocybin.

To further examine how psilocybin affects changes in the tuning properties of neurons with repeated stimulation, we measured changes in the bandwidth tuning (the continuous range of frequencies from the BF, at which a neuron exhibits a response above half the maximal response) of neurons, at a range of sound intensities. At 80 dB, we observed no significant difference in the distribution of response bandwidths pre- and post-intervention in either the saline ($p = 0.671$, $U = 112753$, Mann Whitney U and FDR correction) or psilocybin ($p = 0.574$, $U = 69531$) conditions, although data suggest a trend towards a reduction in the saline condition (Figure 2.3B). At 65 dB, however we observed a significant reduction in response bandwidths in the saline condition ($p = 0.006$, $U = 135108$) that was not present in the psilocybin condition ($p = 0.947$, $U = 83546$) (Figure 2.3C). A similar reduction was also observed at 50 dB with saline ($p = 0.015$, $U = 70360$) but not with psilocybin ($p = 0.574$, $U = 57703$) (Figure 2.3D). Finally, no difference was found at 35 dB between the saline ($p = 0.300$, $U = 41186$) and psilocybin ($p = 0.794$, $U = 42284$) conditions, although a trend towards a reduction was observed with saline (Figure 2.3E). Lack of significance here may be due to lesser statistical power as fewer neurons have their lowest response intensity at 35 dB than higher intensities. At intensities 80, 65, 50 and 35 dB, no significant difference was observed in the baseline distributions of bandwidths between saline and psilocybin conditions (data not shown, $p = 0.384$, 0.393, 0.328 and 0.187, respectively). These data suggest a similar effect to that observed in Figure 2.2, that the narrowing of tuning occurring with repeated stimulation is prevented by psilocybin administration, maintaining a state in A1 as if responses are to a novel and not a familiar stimulus.

Rapid drift in neuronal response properties is observed, and is unaffected by psilocybin.

A subset of neurons was matched across recordings, in order to longitudinally examine changes in their tuning properties with single-cell resolution. We tracked 1071 neurons across the two saline session recordings, and 1831 with psilocybin. We observed significant variability in distribution of responsive to non-responsive neurons between recordings. For the saline condition, 49.2 % ± 4.75 of matched cells were non-responsive and 55.7 % ± 4.87 for psilocybin. 13.6 % ± 1.24 were active only in the first saline recording, and 12.7 ± 1.12 for psilocybin. 14.9% ± 1.86 were active only in the second saline recording, and 12.7 ± 1.34 for psilocybin. 23.2% ± 3.07 were responsive in both saline recordings, and 17.9% ± for psilocybin (Figure 2.4A). No significant differences in saline or psilocybin conditions were observed across any of the response categories (Mann Whitney U and FDR correction), (Figure Supplementary 1). This highlights that those cells responsive in both recordings are actually a relatively small proportion (20-25% of total cells) and that far more cells either become responsive or lose responsiveness to sound over a short time period of around 20 minutes.

In cells responsive in both recordings, we observed a shift in preferred intensity (PI, intensity at which the maximal trial-averaged response was elicited) between recordings for both conditions (Figure 2.4B). In the saline condition, we observed that 64% of total cells showed no shift in PI, 22% shifted by 15 dB, 10% by 30 dB and 2.5% by 45 dB. Results for the psilocybin condition were similar, with 61.3% showing no shift, 26.2% shifting by 15 dB, 8.6% by 30 dB, and 3.9% by 45 dB. For the distributions of both the absolute magnitude of the PI shifts (data not shown) and the signed change, no significant difference was observed between saline and psilocybin sessions ($p = 0.446$, $U = 32290$, $p = 0.700$, $U = 25660$, respectively, Mann Whitney U and FDR correction).

Similarly, a sizeable proportion of cells showed a shift in BF between recordings, for both conditions (Figure 2.4C). In the saline condition, we observed that 71.3% of cells either maintained their initial BF or shifted by 0.5 octaves. 15.6% shifted by one octave, 9.7% by two, 2.5% by three and 1.4% by four. For the psilocybin condition, 71.3% of cells either maintained their initial BF or shifted by 0.5 octaves. 9.7% shifted by one octave, 8.9% by two, 6.1% by three, 2.5% by four and 1.4% by five. For the distributions of both the absolute magnitude of the BF shifts (data not shown) and the signed change, no significant difference was observed between saline and psilocybin sessions ($p = 0.374$, $U = 32909$, $p = 0.110$, $U = 21566$, Mann Whitney U and FDR correction).

To ensure that the observed changes were not due to degradation in the signal-to-noise ratio across recordings, we computed the trial-trial reliability (Quality Index, see Methods). We found no difference in the shift in reliability between pre- and post-recordings for saline and psilocybin groups ($p = 0.120$, Kolmogorov-Smirnov), with a median change of -0.008 for saline and -0.004 for psilocybin (Figure 2.4D). Plotting the distributions of pre- and post-intervention reliability showed similar distributions with no clear clustering of groups of neurons around certain reliability values (Fig 2.4E). Taking the whole cell population, we observed no change in the distribution of response reliabilities in either the saline or psilocybin conditions ($p = 0.414$, $p = 0.339$, respectively, Kolmogorov-Smirnov). Using the unmatched cell populations, we also looked at the distribution of BFs at the whole-population level (Figure 2.4F). Distributions are represented as the mean of the population percentage of each BF within mice ($N = 8$). Here, we identified no significant changes in BF's between pre- and post-recordings, for either the saline or psilocybin condition (Mann Whitney U and FDR correction). Taken together, these data

suggest a significant degree of representational drift in single-cell tuning properties over a short period of time, while maintaining stable representation at the cortical level. This observed drift is not due to a worsening of the signal-to-noise ratio. The magnitude of drift, however appears to be unaffected by psilocybin.

2.5 Discussion

This study used two-photon microscopy combined with neuronal calcium imaging (Figure 2.1) to examine the effects of a 1 mg/kg dose of psilocybin on A1 sensory processing both on the overall population, and on response properties of individual cells. We observed a number of key findings: 1) Psilocybin prevents habituation of overall neuronal response activity, but does not affect response amplitude at BF. 2) Psilocybin preserves neuronal response thresholds at low sound levels. 3) Narrowing of neuronal frequency tuning with habituation is also prevented by psilocybin. 4) Rapid representational drift occurs in A1 on the order of minutes, which is unaffected by psilocybin. Our results indicate a clear effect of psilocybin on sensory gating in A1, preventing the habituation of neuronal responses to familiar stimuli.

Habituation of neural responses to auditory stimuli

In the control condition, we observed a marked habituation of responses across the presentation of the two stimulus batteries, both in terms of the overall firing activity of neurons and the broadness of tuning (Figure 2.2B, Figure 2.3C, D). This is in line with previous two-photon studies in A1 of awake mice, where habituation was observed across days (Kato et al., 2015). This adaptation to repetitive stimuli is a vital part of the neural computations that allow for the

detection of novel and behaviorally relevant information, while filtering out irrelevant background noise (Benda, 2021). Specific groups of interneurons are heavily involved in neuronal habituation to repetitive stimuli. For example, habituation in A1 involves increased inhibitory activity of cortical SOM expressing interneurons (Kato et al., 2015). These interneurons also facilitate lateral inhibition of responses in both A1 and V1 by integrating horizontal inputs across extensive cortical space and suppressing recurrent excitation, narrowing frequency selectivity in A1 (Kato et al., 2017) and orientation selectivity in V1 (Song et al., 2020). This habituation effect has been found to be far more detectable with two-photon relative to classical electrophysiological studies, which suggest that A1 sound responses remain more stable following repeated tone exposure. However, electrophysiological detection of neuronal activity can be biased towards cells with high firing rates, and anesthesia may cause significant changes in the processing of sensory representations. Indeed, even with two-photon, Kato and colleagues identified a significant shift in response kinetics under anesthesia, towards more transient responses, and a complete loss of inhibitory responses (Kato et al., 2015). Interestingly, anesthesia also drastically reduces activity of SOM interneurons, suggesting their involvement in the lack of observed habituation in this state (Adesnik et al., 2012). However, the direct involvement of SOM+ cells remains speculative as the cellular expression of the calcium indicator in this study does not allow us to differentiate pyramidal cells and interneurons.

Psilocybin prevents habituation of neural firing activity to repeated stimulation

Our findings indicate that psilocybin administration prevents this inhibition-driven habituation in A1. We observed a significant reduction in overall response activity in the saline condition, which did not occur with psilocybin (Figure 2.2B). We did not observe an effect on amplitude of responses at BF, in either control or psilocybin conditions (Figure 2.2C). This may reflect our stimulus design, in which frequency-intensity combinations were randomly presented in order to actively reduce the rate of habituation. It may also be that recordings were close together in time, as Kato and colleagues also report that habituation of response amplitudes in day 1 was initially modest, and accumulated across days (Kato et al., 2015). A recent study in visual cortex suggested a complex effect on response amplitude upon DOI administration, where low firing rate neurons were facilitated whereas high firing rate were suppressed, resulting in a net suppression of amplitude (Michaiel et al., 2019). We did not observe this suppression in A1, though this may simply reflect regional differences in regulation of sensory gating, for example the opposing excitatory and suppressive effects of locomotion in visual and auditory cortices, respectively (Henschke et al., 2021; Niell & Stryker, 2010). As we did not observe changes in the amplitude at BF in either condition but did see an overall reduction of activity in control, this suggests we were not simply observing an additive change in neuronal response gain, reflecting instead a shift primarily in the shape of the tuning curve.

Psilocybin preserves neural response thresholds at low sound intensities

In line with this, we observed a significant difference between the distribution of intensity-response thresholds between control and psilocybin conditions, with the latter exhibiting a

significantly greater maintenance of responses to low sound intensities. This effect was observed both at the level of the whole population (Figure 2.2E), and in the subset of consistently responsive cells tracked across both recordings (Figure 2.2F). No difference between control and psilocybin groups was observed for response thresholds before intervention (Figure Supplementary 2A-B). The difference in habituating effect was most pronounced at lower sound intensities. This may be explained by the increased stimulus-specific adaptation (SSA) observed at lower sound intensities in both primary and secondary auditory fields (Nieto-Diego & Malmierca, 2016), and in the inferior colliculus of the rat (Duque et al., 2012). These data indicate that psilocybin preserves sensitivity of A1 neurons to low sound levels, counteracting increased adaptation at these levels. It is interesting to speculate here that this may reflect the commonly reported feature of psychedelic experiences where seemingly mundane stimuli become far more salient. This loss of sensory gating of irrelevant information we see in the human experience could present in our experimental model as a lack of habituation to repetitive stimuli.

Psilocybin prevents the narrowing of tuning bandwidth with habituation to auditory stimuli

The narrowing of frequency tuning bandwidths with prolonged stimulation is a well-established phenomenon in auditory cortex. Previous studies have shown that increased lateral inhibition of responses driven by enhanced SOM interneuron activity narrows frequency tuning of neurons in primary auditory cortex (Kato et al., 2017). We observed this narrowing of tuning with prolonged stimulation as significant at the mid-range of presented sound levels, namely 65 and 50 dB (Figure 2.3C, D) but not at the lowest and highest levels, 35 and 80 dB (Figure 2.3B, E), although a trend

towards a narrowing of tuning was present. Importantly, this narrowing was not observed at any sound level following psilocybin administration, suggesting that it somehow prevents this inhibition-induced narrowing of tuning.

Rapid representational drift is observed in A1, which is unaffected by psilocybin

Far from being a static system, at the individual neuron level, cortical representations of sensory input are highly unstable. Recent studies have highlighted that underlying the relatively stable tonotopic representations in macro-cortical space is a constantly shifting network (Driscoll et al., 2022). The shape of tuning curves, and even a neuron's ability to respond to sound represent only a snap shot of the network at the time of measurement, and not permanent properties of individual cells. We hypothesized that its acute effects on neuronal activity may result in psilocybin affecting the rate of representational drift. We found a significant degree of drift in BF and PI between the pre- and post-recordings in both the control and psilocybin conditions, but the rate of this drift was unaffected by psilocybin (Figure 2.4 B-C). We also found that in both conditions, less than half of sound-responsive neurons were so across both recordings (Figure 2.4A), again with no differences between control or psilocybin conditions (Figure Supplementary 1). The scale of representational drift we observe is similar to that found in previous studies in A1 (Chambers et al., 2022), but the time scale is of note. Where it was previously measured on the order of days, our data show that this instability is pronounced even on the order of tens of minutes, in line with findings in the visual cortex (Deitch et al., 2021). Importantly, we observed no change in the reliability of individual neuronal responses across trials, suggesting that the

observed drift represents a genuine change in neuronal tuning, and is not the result of a technical confound such as change in image quality. We observed no change in the mean BF tuning of the overall population with saline or psilocybin, supporting previous findings that representational drift in A1 preserves a stable macro-cortical tonotopy, and suggests that the effects of psilocybin on A1 involve disruption of normal sensory gating, rather than overall tonotopic organization.

A recent study (Brockett & Francis, 2024) reported an increase in mean response amplitude in A1 5 minutes following administration, but that amplitudes were not significantly different from baseline roughly 30-minutes post-administration. As our post-psilocybin recording period includes 30 minutes post-administration, these findings do not contradict one another. The study reports no changes in neuronal tuning selectivity at a single sound level, and we note that selectivity changes we observed were also not statistically significant in controls at our highest presented sound-level, with effects being present at lower intensities. Our data concurs with their finding that there is no overall shift in the mean distribution of neuronal BFs with psilocybin. Previous studies have reported similar findings to ours, with other classical psychedelics. For example a magnetoencephalography study in humans found that LSD reduces response adaptation in A1 (Timmermann et al., 2018). The habituation of responses to familiar stimuli and narrowing of tuning in auditory cortex are driven by increased activity of SOM interneurons (Kato et al., 2015, 2017), and SOM neuron activation in visual cortex narrows tuning selectivity. It is tempting therefore to suggest that psilocybin may exert this effect through disruption of SOM interneuron-driven inhibition in the cortex. Indeed, a recent study found that DOI reduces surround suppression in V1 (Michaiel et al., 2019), which has been shown to be modulated by

SOM interneurons (Adesnik et al., 2012), and DMT has been shown to broaden visual tuning selectivity in humans (Pais et al., 2024). GABAergic interneurons are also known to express $5HT_{2A}$ receptors (Willins et al., 1997), and their activity is directly modulated by tryptamine psychedelics (Marek & Aghajanian, 1996; Tang et al., 2023). An interesting future experiment would be to examine more directly the effect of psilocybin on A1 SOM interneurons, to ascertain whether psychedelic-induced blocking of habituation is coupled with a disruption of their normal signaling.

SOM interneurons are also closely involved in the regulation of prediction error responses, providing inhibition to excitatory mismatch neurons (Attinger et al., 2017; Green et al., 2023). Multiple studies have previously implicated disruption of the normal balance between top-down predictions and sensory input as a potential cause for the perceptual effects of psychedelics. As previous brain imaging studies have found effects on neural 'surprise' responses with psychedelics (Timmermann et al., 2018), it would be interesting to examine more closely how psilocybin affects the processing of familiar vs unexpected stimuli in A1, with a particular focus on the modulation of SOM interneuron activity.

2.6 Conclusions

Taken together, our findings demonstrate that psilocybin prevents the habituation of A1 neurons to repeated sensory stimulation, preserving response thresholds at low intensities and preventing narrowing of frequency tuning. Importantly, our study tracked neurons longitudinally across recordings, highlighting that the effect of psilocybin is present both at the level of

individual cells and as a circuit-level phenomenon. Additionally, we observed a rapid drift in tuning properties of individual neurons, occurring on the order of minutes. This supports previous findings that this drift occurs in A1 over days, but suggests a much faster timescale. Further studies are required to more directly ascertain whether the effect of psilocybin is due to disrupted modulation by local groups of interneurons. We hypothesize an effect on SOM interneurons due to their influence over habituation and modulation of tuning selectivity in A1, as well as their involvement in generation of prediction-error signals in sensory cortices. As we increasingly explore the treatment of a variety of conditions with psychedelics, it becomes of particular importance to understand how they exert their profound effects on sensory perception. Understanding how psychedelics influence neuronal circuits to modulate sensory gating may also help to elucidate new targets to counteract maladaptive disruptions to auditory sensory processing as seen with tinnitus or in neuropsychiatric conditions.

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2.9 Figures

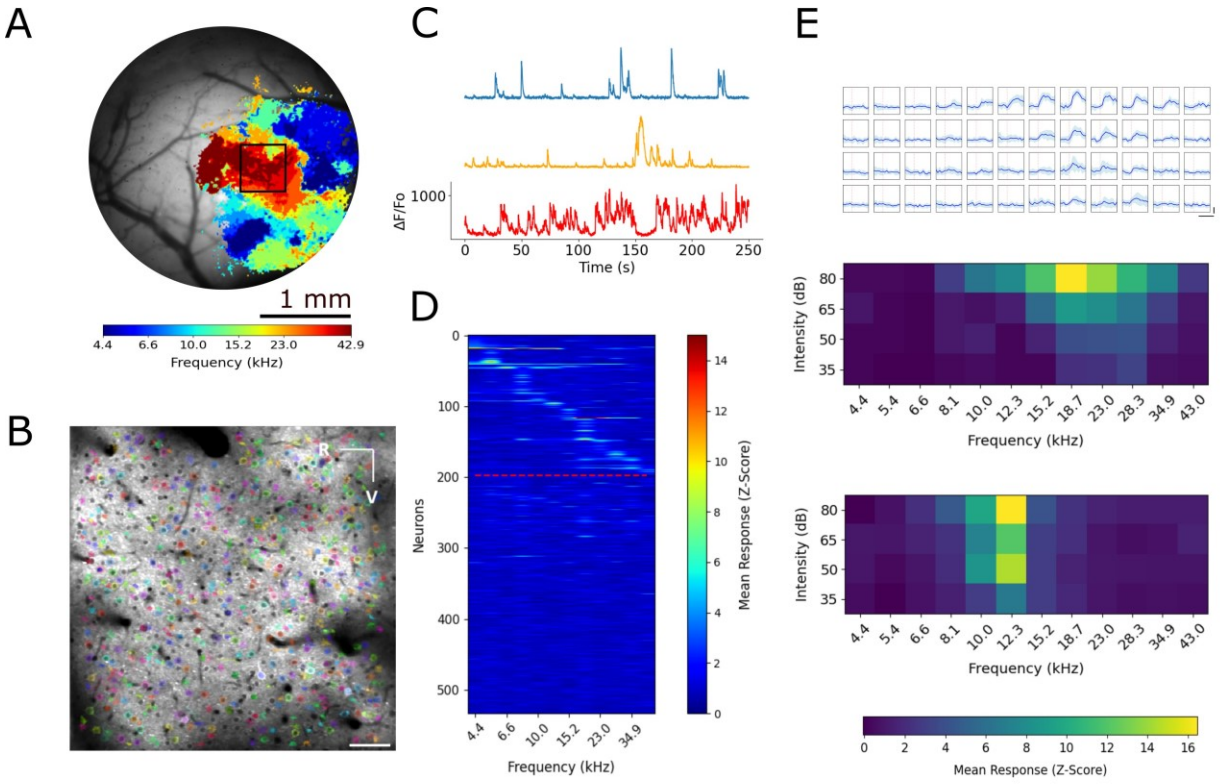
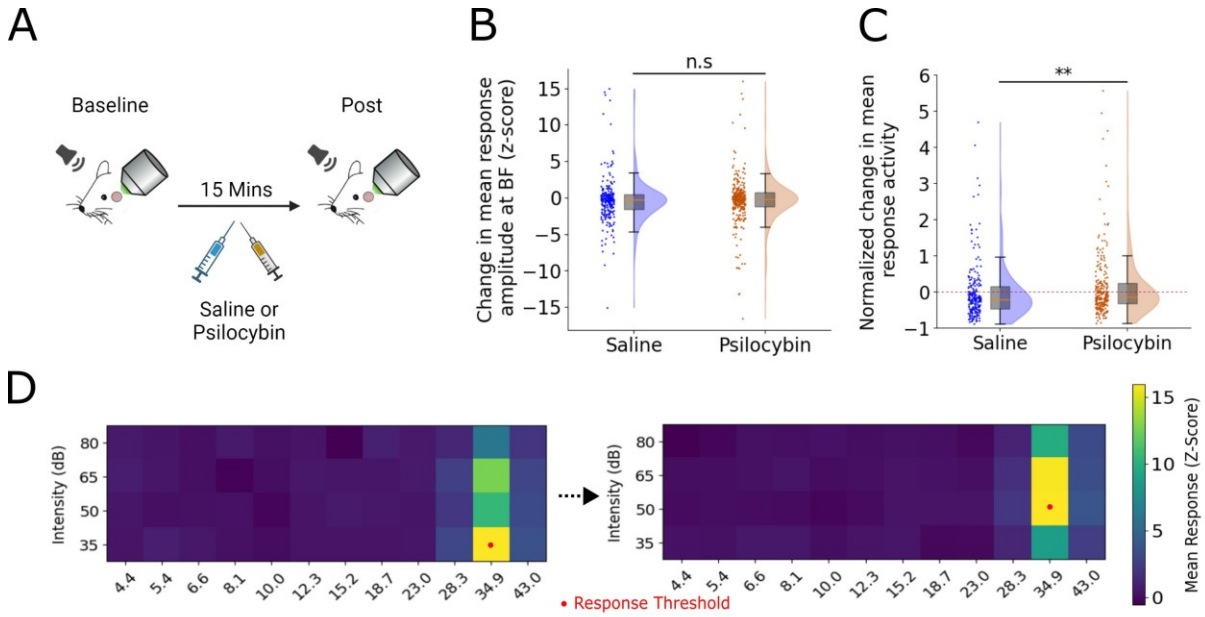

A
1 mm
4.4 6.6 10.0 15.2 23.0 42.9
Frequency (kHz)
B
R
V
C
ΔF/Fo
1000
0 50 100 150 200 250
Time (s)
D
Neurons
0 100 200 300 400 500
4.4 6.6 10.0 15.2 23.0 34.9
Frequency (kHz)
Mean Response (Z-Score)
0 2 4 6 8 10 12 14
E
Intensity (dB)
80 65 50 35
4.4 5.4 6.6 8.1 10.0 12.3 15.2 18.7 23.0 28.3 34.9 43.0
Frequency (kHz)
Intensity (dB)
80 65 50 35
4.4 5.4 6.6 8.1 10.0 12.3 15.2 18.7 23.0 28.3 34.9 43.0
Frequency (kHz)
0 2 4 6 8 10 12 14 16
Mean Response (Z-Score)

Figure 2.1: Imaging auditory cortex neuronal activity in awake mice.

A) Representative best frequency tonotopic map used to locate left A1, by the presence of a large, rostro-caudal high to low frequency tonotopic gradient and position of pial vessels. Inset: two-photon field of view seen in B. B) Representative frame-averaged image of mouse A1 overlaid with suite2P neuronal cell body identification. FOV is 794 x 794 µm, 175 µm below pial surface (layer 2/3). R and V represent rostral and ventral directions. ROI coloration is random. C) Three example activity traces during sound stimulation, from ROI's identified in B. y-axis is fractional fold-change in fluorescence from baseline ($\Delta F/F_0$), corrected for neuropil contamination. D) Trial-averaged responses of all identified neurons in B to pure tones. Cells above the red line showed activity significantly modulated by frequency or intensity ($p < 0.05$, two-way ANOVA), and are sorted by BF, cells below line are unsorted. E) Representative frequency-intensity tuning curves of two neurons identified in B. Above: Trial averaged ($\Delta F/F_0$) neuronal response traces. Blue line represents the mean response across trials, shading represents standard deviation. Horizontal scale bar is 1 second, vertical is $\Delta F/F_0$ of 100. Below: Trial-averaged Frequency-intensity tuning maps. The top map is the tuning map of raw traces shown above. Constructed from the deconvolved neuronal activity (see Methods) and smoothed with Gaussian kernel for visualization.


A
Baseline
Post
15 Mins
Saline or
Psilocybin
B
n.s
Change in mean response amplitude at BF (z-score)
Saline
Psilocybin
C
**
Normalized change in mean response activity
Saline
Psilocybin
D
Intensity (dB)
Response Threshold
Mean Response (Z-Score)

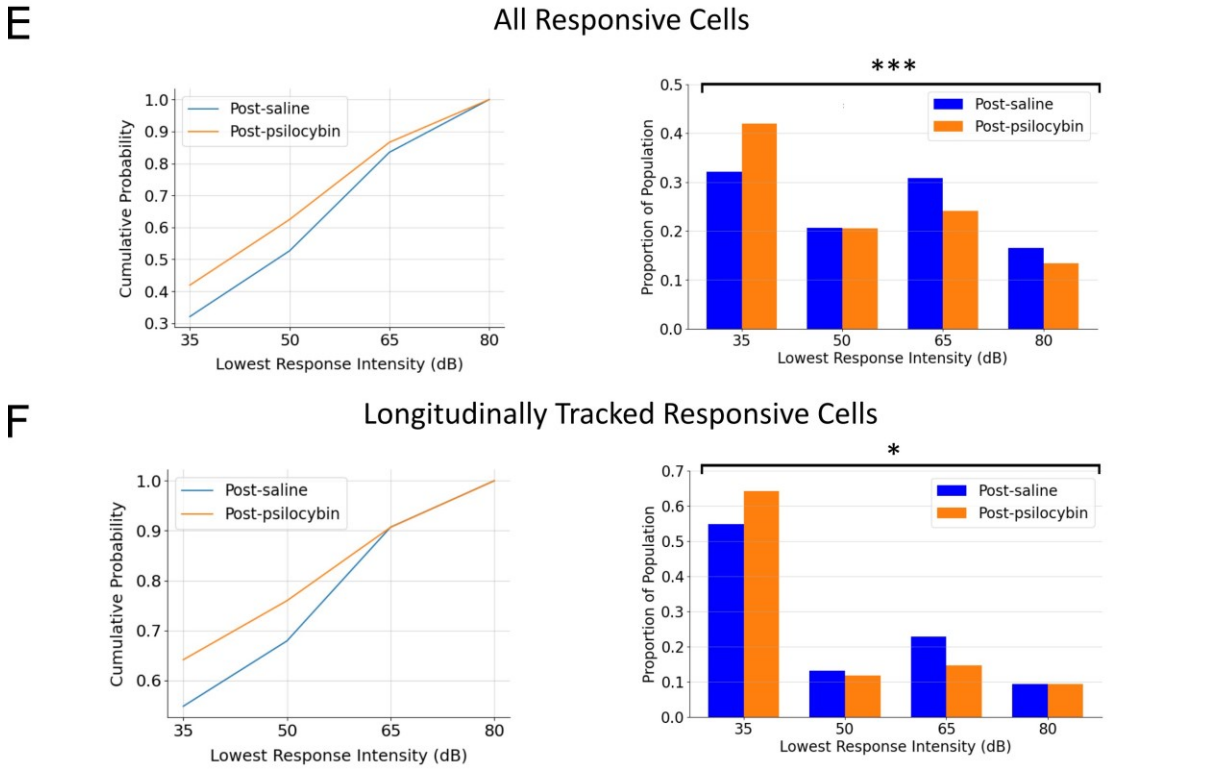

E
All Responsive Cells
Post-saline
Post-psilocybin
Cumulative Probability
Lowest Response Intensity (dB)
***
Proportion of Population
F
Longitudinally Tracked Responsive Cells
*

Figure 2.2: Overall response activity and sound-level response thresholds are preserved by psilocybin.

A) Each mouse has two recording days. An initial stimulus battery (see Methods) is presented, animal is then given saline IP (session 1) or 1 mg/kg psilocybin (session 2) and a second recording taken following 15 min incubation. 5 days are left between saline and psilocybin recording sessions and the same cell population is recorded from across all four recordings. B) Change in trial-averaged peak response amplitude at BF, for matched, consistently responsive cells. n.s, p = 0.120, (Mann Whitney U + FDR correction). Shaded area represents kernel density estimate of distribution. Boxplot, orange line is median, grey shading is interquartile range, whiskers are SEM. C) Change in mean firing activity (deconvolved activity, see Methods) across all frequency intensity combinations, between pre- and post-recordings, for matched, consistently responsive cells. Relative change is normalized to baseline response values for each neuron. **, p = 0.006, Mann Whitney U + FDR correction. Dotted line represents zero change in amplitude. D) Representative cell tuning matched across recordings, illustrating a shift in lowest response threshold. E) Left: Cumulative distribution plots of lowest sound intensity eliciting an above threshold response, for all responsive neurons. Distributions show the post-drug intervention recording for saline and psilocybin conditions. Right: Distribution of lowest response threshold for post-saline and post-psilocybin conditions, for all responsive neurons. Normalized according to total cell number in each group. ***, $p = 4.12 \times 10^{-5}$ (Mann Whitney U + FDR correction). N Post saline = 1222 cells, post psilocybin = 1194 cells. F) Left: lowest sound intensity, for cells matched and consistently responsive across pre- and post-recordings. Right: Distribution of lowest response intensity for matched, consistently responsive cells. *, p = 0.040 (Mann Whitney U + FDR correction). B, C, F) N post saline = 237 cells, post-psilocybin = 328.

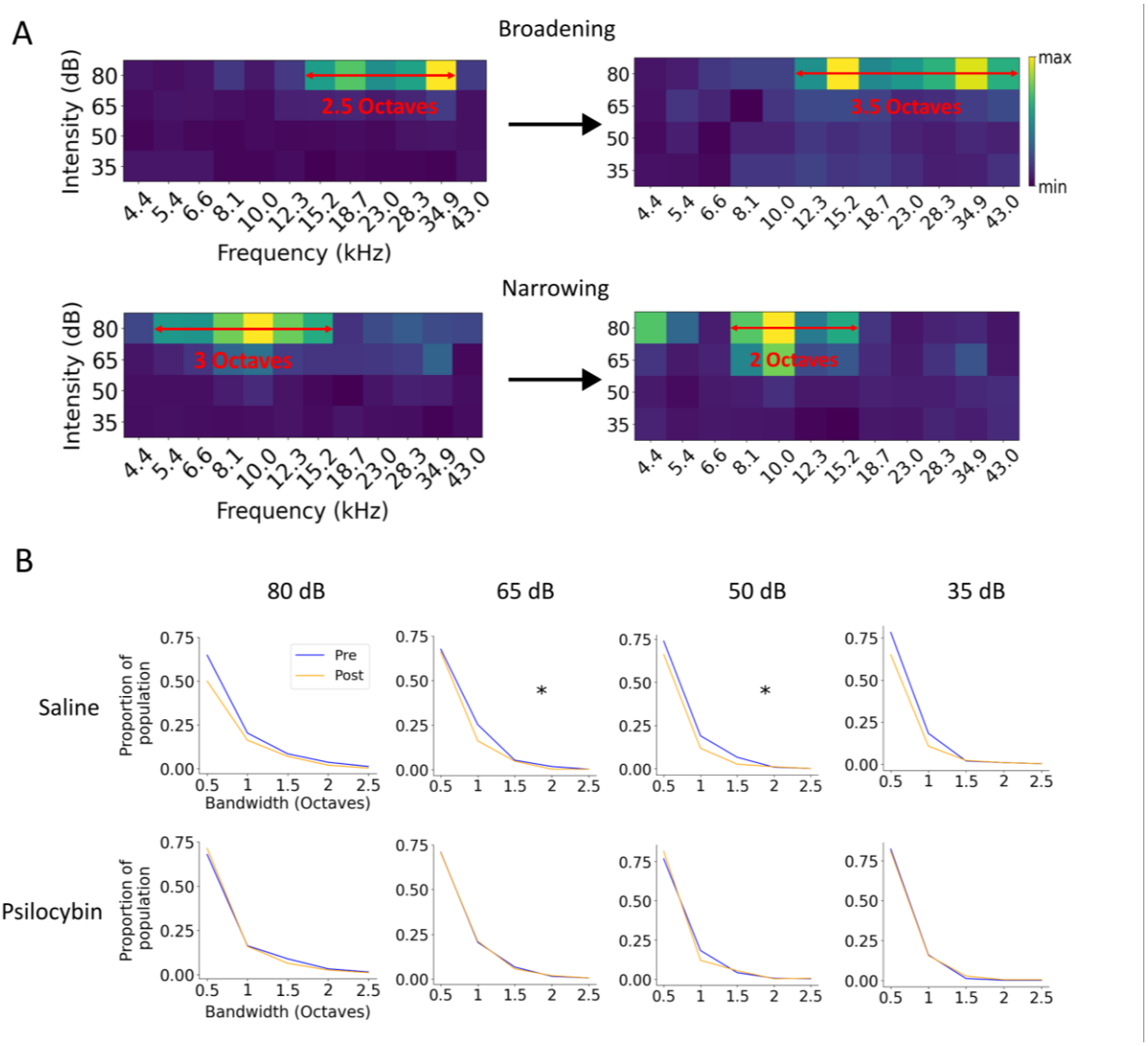

A
Broadening
Intensity (dB)
80
65
50
35
2.5 Octaves
3.5 Octaves
max
min
4.4
5.4
6.6
8.1
10.0
12.3
15.2
18.7
23.0
28.3
34.9
43.0
Frequency (kHz)
Narrowing
3 Octaves
2 Octaves
B
80 dB
65 dB
50 dB
35 dB
Saline
Psilocybin
Proportion of population
Pre
Post
0.75
0.50
0.25
0.00
0.5
1
1.5
2
2.5
Bandwidth (Octaves)
*

Figure 2.3: Narrowing of tuning bandwidths with habituation is prevented by psilocybin

A) Representative tuning curves from matched cells pre- and post-psilocybin (above) and post-saline (below), illustrating an increase in bandwidth with repeated stimulation following psilocybin, and reduction in bandwidth in control. B) Change in bandwidth at 80, 65, 50 and 35 dB SPL between pre- and post-intervention recordings, for saline condition (above) and psilocybin condition (below). Data are normalized as relative frequency of each bandwidth within that group. n.s = $p > 0.05$, * = $p < 0.05$. (Mann Whitney U + FDR correction) Top, left to right: N Saline pre = 540, 536, 401, 317 cells, respectively. Post = 412, 467, 326, 251. Bottom, left to right: N Psilocybin pre = 391, 425, 334, 283 cells. Psilocybin post = 343, 394, 332, 304.

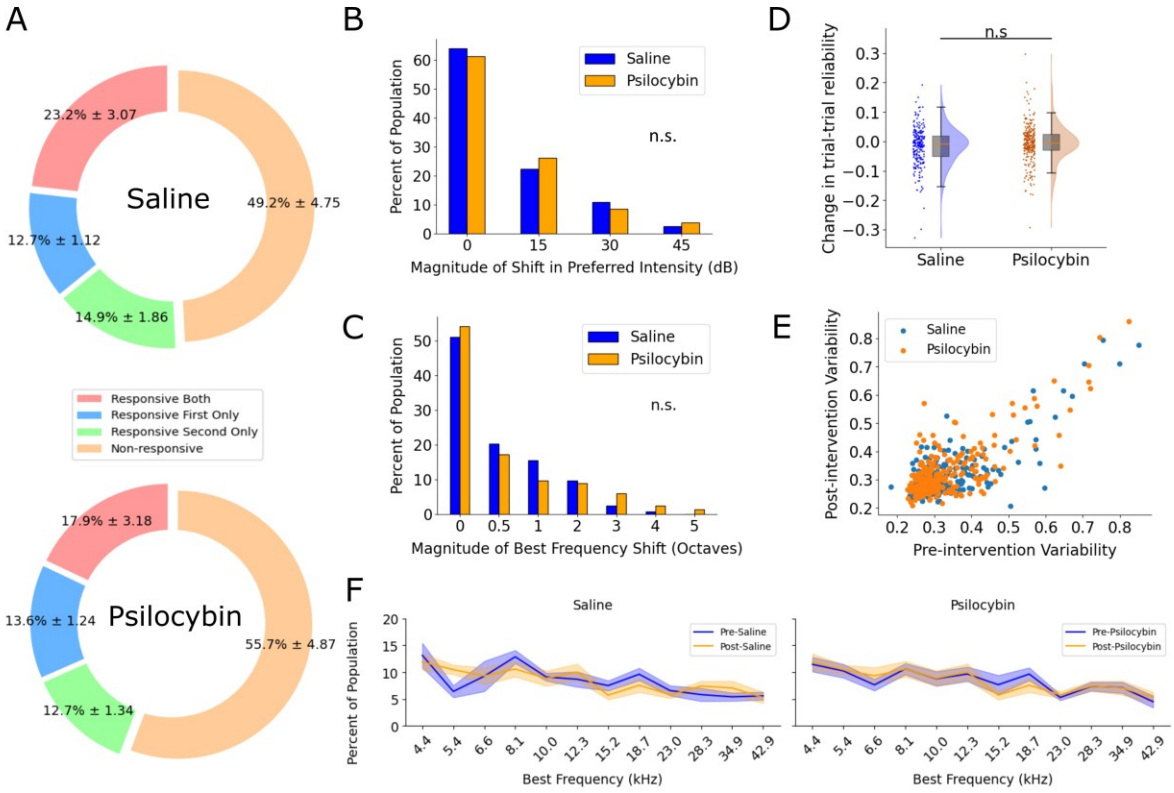
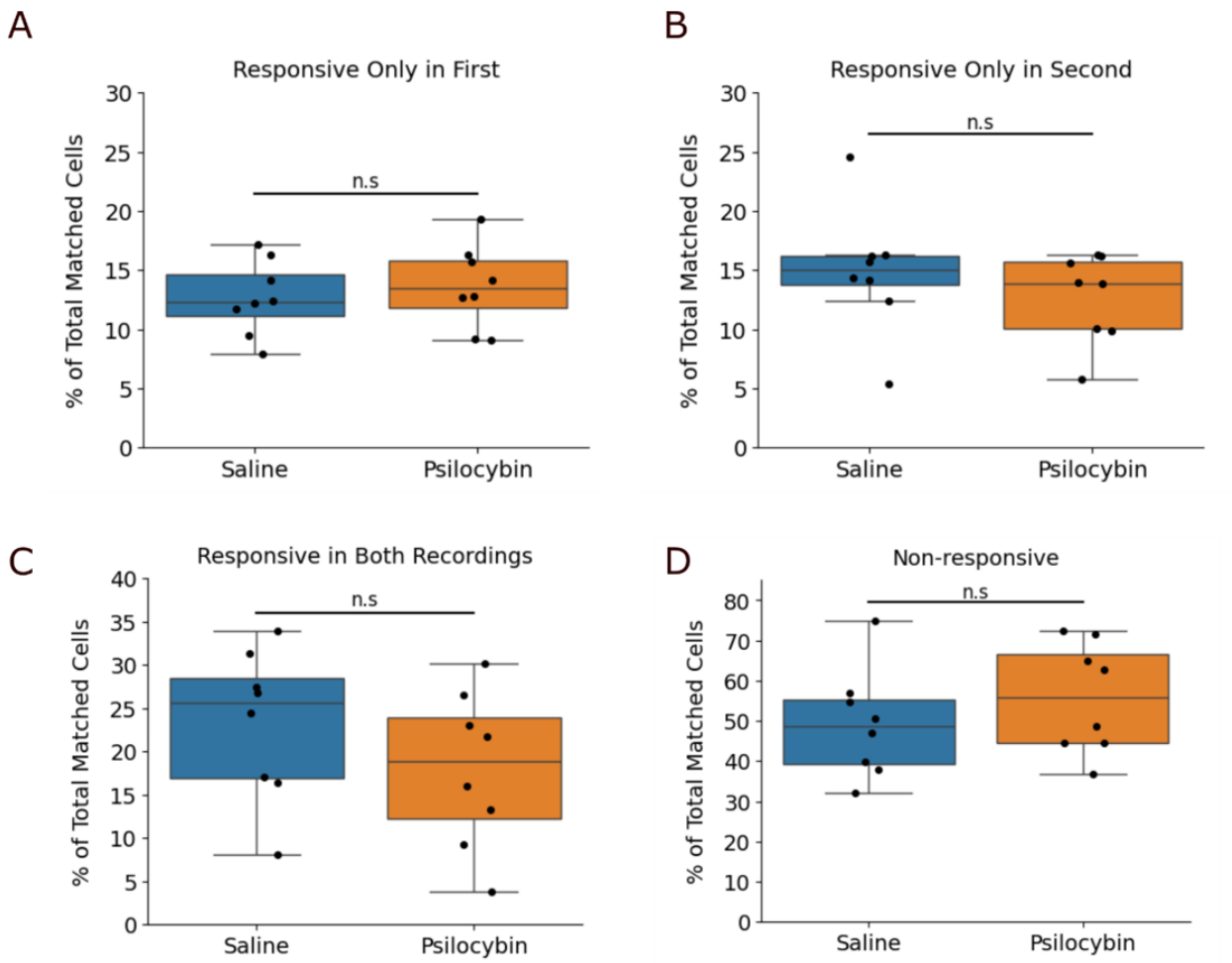

A
Saline
23.2% ± 3.07
49.2% ± 4.75
12.7% ± 1.12
14.9% ± 1.86
Responsive Both
Responsive First Only
Responsive Second Only
Non-responsive
Psilocybin
17.9% ± 3.18
55.7% ± 4.87
13.6% ± 1.24
12.7% ± 1.34
B
Percent of Population
Saline
Psilocybin
n.s.
Magnitude of Shift in Preferred Intensity (dB)
C
Percent of Population
Saline
Psilocybin
n.s.
Magnitude of Best Frequency Shift (Octaves)
D
n.s
Change in trial-trial reliability
Saline
Psilocybin
E
Saline
Psilocybin
Post-intervention Variability
Pre-intervention Variability
F
Saline
Psilocybin
Pre-Saline
Post-Saline
Pre-Psilocybin
Post-Psilocybin
Percent of Population
Best Frequency (kHz)

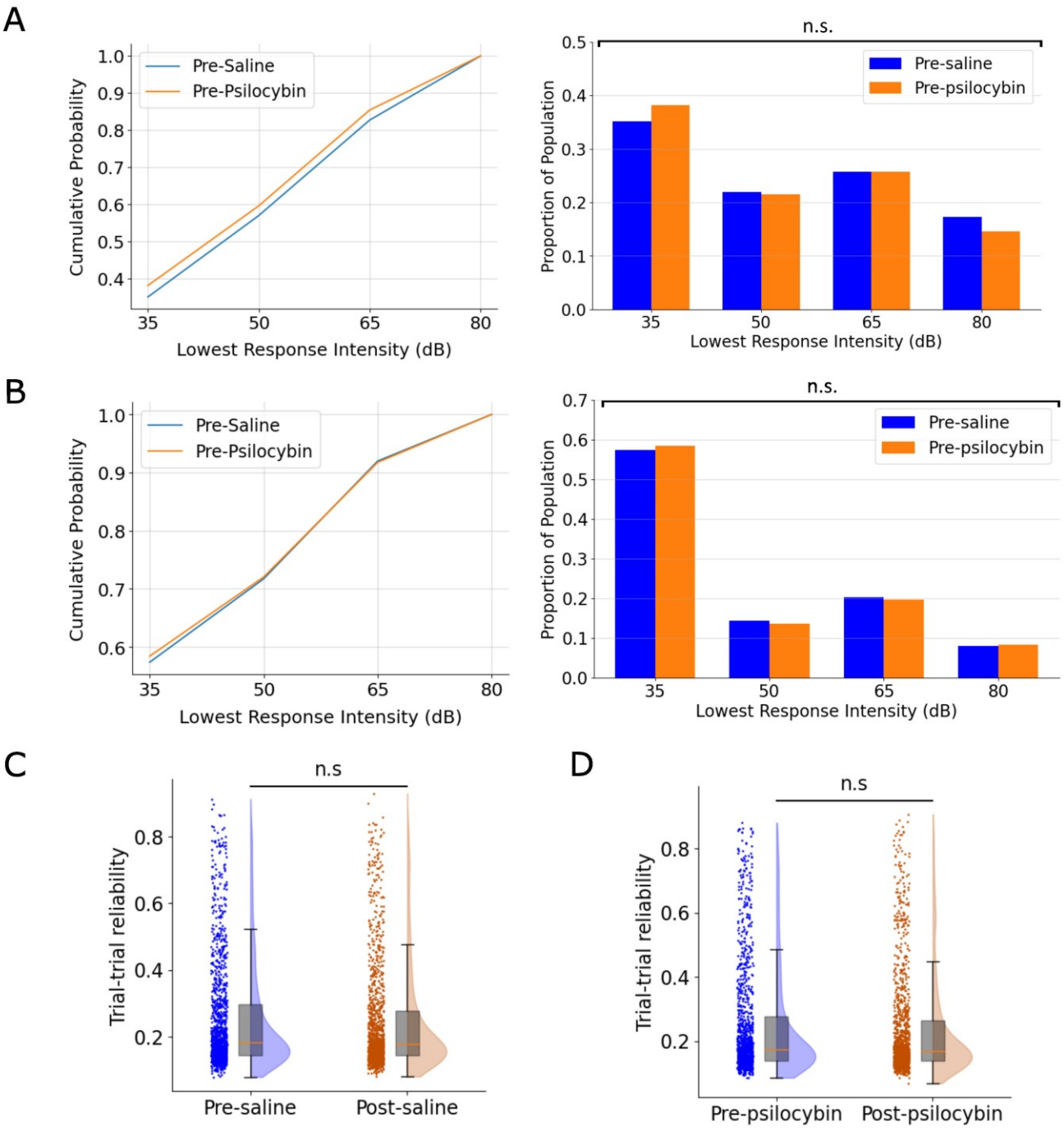
Figure 2.4: Rapid drift in neuronal tuning properties is observed and is unaffected by psilocybin.

A) Categorization of neuron responsiveness as a percentage of the overall population (% ±, SEM), when tracked across recordings. Cells were categorized as either responsive in both recordings, responsive only in the first recording, responsive only in the second, or non-responsive in either recording. No significant differences in proportion between saline and psilocybin conditions were observed (Mann Whitney U + FDR correction). N = 8 mice. B) Change in preferred intensity (intensity at which the maximum trial-averaged response was elicited) across cells responsive in both recordings. Difference between the two distributions is non-significant (Mann Whitney U + FDR correction, p = 0.70). C) Magnitude of shift in neuronal best frequency, across matched cells responsive in both recordings. Difference between the two distributions is non-significant (Mann Whitney U + FDR correction, p = 0.10). B, C) N Saline = 237, N Psilocybin = 328 cells from 8 mice. D) Shift in trial-trial reliability for matched, consistently responsive cells. n.s, p = 0.120, Mann Whitney U. Orange line = median, saline = -0.008, psilocybin = -0.004. E) Distribution of pre- and post-intervention trial-trial reliability for matched, consistently responsive cells. A-E) N Saline = 237, N psilocybin = 328 cells from 8 mice. F) Distribution of BFs in the neuronal population, as a percentage of total responsive cells (unmatched). Shaded areas are mean ± SEM. No significant difference was observed between pre- and post-recordings for any BF, in either saline or psilocybin conditions. No significant difference was observed in the overall distribution in the post-recording, between saline or psilocybin (Mann Whitney U + FDR correction). N Pre-saline = 1307 cells, N post = 1222. N Pre-psilocybin = 1194 cells, N post = 1214.



Supplementary Figure 1: No difference in distributions of frequency/intensity sensitive vs insensitive cells with psilocybin administration.

Response characterization of cells tracked across pre- and post-intervention recordings, as a percentage of the total number of tracked cells. A) Cells responsive to changes in frequency/intensity only in the first recording. B) Cells responsive only in the second recording. C) Cells consistently responsive in both recordings. D) Cells responsive in neither of the two recordings. n.s = $p > 0.05$, (Mann Whitney U + FDR correction).


A
Cumulative Probability
Pre-Saline
Pre-Psilocybin
Lowest Response Intensity (dB)
n.s.
Proportion of Population
Pre-saline
Pre-psilocybin
Lowest Response Intensity (dB)
B
Cumulative Probability
Pre-Saline
Pre-Psilocybin
Lowest Response Intensity (dB)
n.s.
Proportion of Population
Pre-saline
Pre-psilocybin
Lowest Response Intensity (dB)
C
n.s
Trial-trial reliability
Pre-saline
Post-saline
D
n.s
Trial-trial reliability
Pre-psilocybin
Post-psilocybin

Supplementary Figure 2: No difference in baseline response threshold and reliability between saline and psilocybin conditions

A) Left: Cumulative distribution comparing the baseline lowest response threshold values for the saline and psilocybin conditions, for all responsive cells in the population. Right: Distribution of lowest response threshold values. B) Left: Cumulative distribution comparing the baseline lowest response threshold values for the saline and psilocybin conditions, for matched cells responsive in both recordings. Right: Distribution of lowest response threshold values C) Trial-trial reliability across all responsive cells, for the pre- and post-saline conditions. D) Trial-trial reliability for cells tracked across recordings, for the pre- and post-psilocybin conditions. n.s. = $p > 0.05$ (Mann Whitney U + FDR correction).

Preface to Chapter 3

In the previous chapter, we identified an acute effect of psilocybin on ACx neuronal activity, in which the habituation of responses as they become familiar or irrelevant was attenuated. Through the maintenance of responses to low sound levels and preservation of broader tuning bandwidths, it appears that psilocybin is able to acutely negate the sensory gating that leads to narrower filtering of auditory stimuli, potentially resulting in enhanced flow of bottom-up sensory information.

Previous studies have shown both prolonged changes to neuronal activity following drug washout, and the induction of structural and functional plasticity that persists at least for weeks (Ly et al., 2018; Shao et al., 2022). We therefore hypothesized that the effect seen in the first study may persist in some form for a number of weeks, and the plasticity-inducing effects could facilitate an enhanced predisposition towards reorganization of ACx tonotopy. In chapter 3, we used chronic wide field calcium imaging to track neuronal response properties to repeated auditory stimuli, and investigate whether chronic sound exposure following psilocybin results in CP opening and subsequent tonotopic reorganization. This project utilizes a different technique to the two-photon approach in Chapter 2. The larger imaging field with wide field calcium imaging allows for analysis of macro-scale cortical tonotopic organization, which normally remains stable in response to passive sound exposure in adult animals (De Villers-Sidani et al., 2007; Voss et al., 2017). The exception is with learning in goal-directed behaviours or critical period reopening, meaning we can use macro-scale tonotopic reorganization in response to tone exposure as a readout of critical period state (Thomas et al., 2018).

Using this technique, we identify a similar preservation across auditory cortex, of response sensitivity to repeated stimuli following psilocybin administration, persisting for at least two weeks. Interestingly, this time window suggests a similar period of prolonged psilocybin action identified by Nardou and colleagues (Nardou et al., 2023). These data suggest that psilocybin induces functional plasticity in the normal responses of auditory cortex to sound-stimulation, which persists over a number of weeks.

Chapter 3: A single dose of psilocybin chronically inhibits habituation of sound-evoked responses in auditory cortex to repeated stimuli.

3.1 Abstract

Various cultures throughout history have employed psychedelics such as psilocybin for spiritual, medicinal and recreational purposes. These compounds acutely cause profound perceptual alterations, coupled with long-term effects on mood and cognition. Results from a number of recent clinical trials have shown that psilocybin is able to rapidly improve functional disability and general wellbeing in people suffering from conditions of maladaptive plasticity, such as major depression and substance abuse issues. A consensus has developed that psychedelics are able to exert these therapeutic effects by rapidly inducing a burst of enhanced plasticity, producing increased dendritic remodeling, synaptogenesis and reopening critical periods for behavioral plasticity. However, despite the clear auditory perceptual effects of psilocybin, little is known about whether this burst of plasticity is also seen in sensory cortices such as auditory cortex, and whether it can trigger functionally significant cortical reorganization in primary sensory areas. In the adult auditory cortex, tonotopic maps remain stable in response to passive sound experience. We hypothesized that due to this burst of plasticity, psilocybin may exert long-term effects on sound-evoked responses in auditory cortex, and potentially allow tonotopic reorganization in response to passive sound exposure. We exposed mice to chronic 12 kHz tone pips for two weeks following a single dose of psilocybin, and tracked cortical response properties and tonotopic map structure. We observed that a single 1 mg/kg dose of psilocybin prevented habituation of sound-evoked responses to repeated stimulation, in contrast to a marked habituation observed in control. This lack of habituation persisted for at least two weeks, but did not appear to be coupled with a reorganization of tonotopic map structure averaged across all auditory regions. These data suggest that psilocybin exerts direct effects on auditory cortex responses to sound long after the acute perceptual effects have faded. With further research, these prolonged effects of psilocybin on auditory cortical processing could be used to treat conditions of maladaptive plasticity and aberrant processing of sound observed in this cortex, such as tinnitus.

3.2 Introduction

Promising clinical trial results have highlighted the ability of psilocybin and other psychedelics to produce fast-acting, long-lasting improvements in functional disability, mood and general feelings of wellbeing in patients with depression and anxiety disorders (Davis et al., 2021; Raison et al., 2023; von Rotz et al., 2023). They also show great promise as adjuncts for the treatment of substance use disorders (Bogenschutz et al., 2022; Johnson et al., 2014; Johnson, Garcia-Romeu, & Griffiths, 2017). A number of recent studies have strengthened the idea that psychedelics produce these effects by inducing an enhanced state of neuroplasticity, classifying them as 'psychoplastogens'. This facilitates a prolonged burst of increased dendritic growth and complexity, that can lead to behaviorally relevant reorganizations in neuronal circuits, such as the extinction of fear conditioning (Du et al., 2023; Funk et al., 2024; Jefferson et al., 2023; Shao et al., 2022). Though tryptamine psychedelics such as psilocybin have actions at a number of receptors, their action at serotonin type 1A and 2A ($5HT_{1A}$, $5HT_{2A}$) receptors is thought to drive much of this plasticity. Glutamate-driven activation of AMPA receptors activates important signaling cascades for the induction of plasticity, resulting in upregulation of plasticity-associated immediate early genes and increased production of brain-derived neurotrophic factor (BDNF).

During brain development, there are periods of maximal plasticity referred to as CPs in which normal sensory experience leads to significant cortical reorganization, in order to establish cortical representations of the sensory environment (Cisneros-Franco et al., 2020). The closure of CPs presages a shift in the brain to a much more restrained form of plasticity, during which goal-directed behavior such as task learning is required to induce circuit reorganization. Interesting recent work from Nardou and colleagues has found that psychedelics including

psilocybin act to reopen the behavioral CP for social reward learning, mediated by modulation of the extracellular matrix proteins that maintain structural neuronal architecture (Nardou et al., 2023). Interestingly, the length of these changes correlates with the length of psychedelic experience, suggesting a link between the cause of the profound perceptual alterations with acute psychedelic action, and their longer-term effects. For psilocybin in particular, they identified around two weeks as the duration of CP reopening.

The ability to reopen CPs in a targeted manner would be a powerful tool for the treatment of conditions in which a maladaptive circuit reorganization leads to deleterious outcomes. In tinnitus, loss of sensory input to central auditory pathways triggers plastic reorganization, leading to increased spontaneous activity and neuronal synchrony (Shore et al., 2016a) that can cause aberrant perception of sound without corresponding sensory input. This ranges from annoying to severely disabling, causing issues such as loss of concentration and impaired sleep (Trochidis et al., 2021). Current treatments often rely on promoting auditory cortical plasticity, such as enhancing lateral inhibition of the tinnitus frequency (Okamoto et al., 2010; Tyler et al., 2017). However, this only mildly reduces symptom severity in many cases. Inducing CP plasticity with psychedelics to improve the efficacy of training-based therapies that rely on cortical plasticity could significantly improve treatment outcomes.

It remains to be seen whether psychedelic-induced CP reopening is specific to frontal regions, or is also present in primary sensory cortices. The dense presence of $5HT_{2A}$ receptors on layer V cortical pyramidal neurons and interneurons (Weber & Andrade, 2010; Xu & Pandey, 2000), and upregulation of plasticity-associated immediate early genes in sensory cortices (Davoudian et al., 2023) suggest that it may also be possible to reopen CPs in sensory cortices. The ability to induce

changes in adult auditory cortex tonotopic map structure through plasticity-promoting interventions such as noise exposure (Thomas et al., 2018, 2020) and the modulation of specific interneuron subgroups (Cisneros-Franco & De Villers-Sidani, 2019b) is well documented. The model therefore represents an excellent candidate to examine whether psychedelics can induce CP reopening in primary sensory regions, and may hold promise for the treatment of conditions of maladaptive auditory plasticity such as tinnitus.

In this study, we employed wide field calcium imaging in awake, head-fixed mice to reconstruct auditory tonotopic maps and longitudinally track changes in map structure following 1 mg/kg psilocybin. In the CP open-state, passive sound experience drives reorganization of tonotopy in auditory cortex, providing a clear readout of whether psychedelic action can drive CP-like plasticity in the region. We predicted that the long-term, plasticity-inducing effects of psilocybin may facilitate a pro-plastic state in the auditory cortex akin to critical period reopening. This would be evidenced as a reorganization of best frequency tonotopic maps in response to passive sound exposure. To examine this, we exposed mice to chronic tone pips for two weeks, to examine how a single dose of psilocybin affects auditory cortex neuronal activity and tonotopic map stability over prolonged periods. Following psilocybin, we identified a clear lack of adaptation to auditory stimuli across the auditory cortex, over a broad frequency range. This effect persisted for at least two weeks, suggesting that psilocybin induces long-lasting changes to auditory processing at the macro-cortical level.

3.3 Materials and Methods

Animals and Drugs: All experimental procedures were approved by the Montreal Neurological Institute Animal Care Committee and follow the guidelines of the Canadian Council on Animal Care. Approval for the use of psilocybin for research purposes was granted by Health Canada (April 2022), and supplied by Psygen Labs Inc., (Calgary, Alberta). All experiments were performed on male and female adult mice (no older than 24 weeks) of the Thy1-GCaMP6s strain (Jackson labs, stock number 024275), crossed with CBA/CaJ, a strain that retains good hearing thresholds (Zheng et al., 1999). GCaMP6s-positive offspring also retain good hearing thresholds well into adulthood (Romero et al., 2020). Mice were maintained on a 12-hour light/dark cycle with *ad libitum* access to food and water and were group-housed until cranial window surgery, from which point they were single-housed. Group sizes were N = 9 mice for each of the saline and psilocybin cohorts.

Cranial Window Surgery: Cranial window procedure was adapted from (Romero et al., 2020). Briefly, animals are anaesthetized with isoflurane in oxygen (5% induction, 1-2% maintenance). An incision was made to expose the skull, periosteum removed from the skull and an etchant (C&B Metabond, Parkell, Inc. NY) applied for 30 s to increase surface area for adhesion. Custom head-fixation hardware (iMaterialise, Belgium) was attached to the skull using dental cement (C&B Metabond) mixed with black ink. Auditory cortex was localized using the skull anatomical landmarks (rostral to lambdoid suture and dorsal to zygomatic arch extension) and a 3 mm craniotomy drilled. A 3 mm glass coverslip (#0 thickness, Warner Instruments) was cleaned with 70% ethanol and rinsed with sterile saline. The coverslip was then inserted into the craniotomy and affixed with dental cement. Animals were allowed to recover in a warmed

chamber and administered 20 mg/kg carprofen for three days post-operatively. Imaging began a minimum of 5 days following surgery.

Wide Field Imaging: Wide field calcium activity was collected using a PCO Panda 4.2 scMOS camera (Excelitas Technologies, MA), recording at 10 Hz framerate. A UPlanFL N 4X, 0.13 numerical aperture lens (Olympus, Japan) was used. Excitation light was provided by an X-Cite Series 120 Q lamp, passed through a 470 - 10 nm band pass filter (Thorlabs). Images were collected and camera controlled using pco.camware software (version 4.16, Excelitas Technologies).

Sound Presentation: Stimuli were designed with OpenEx software (version 2.32, Tucker-Davis Technologies, TDT, FL) and generated using a TDT RZ6 multi I/O processor (TDT). Sounds were presented with an MF1 free-field speaker (TDT) placed 10 cm from the contralateral (right) ear. 12 frequencies were presented at 65 dB SPL (100 ms tones, 5 ms on/off ramps, ranging from 4-45 kHz in 0.5 octave increments), each repeating ten times, with a 2 s inter-stimulus interval.

Chronic Exposure: Mice were housed in sound-attenuated chambers under a 12-hour light/dark cycle, with *ad libitum* access to food and water. Both saline control and psilocybin groups were exposed for two weeks to trains of 65 dB SPL, 12.3 kHz tone-pips, followed by one week with no acoustic manipulation of the environment (background sound level, 40 dB SPL). Tone pips were generated using custom MATLAB scripts (The MathWorks, Inc., MA) and played through an Ultralite-mk3 Hybrid Interface (MOTU Inc., MA) with sampling at 192 kHz. Tones were 50 ms in duration (5 ms onset and offset ramps), delivered in trains of 5 pulses per second. To minimize adaptation effects, the interval between each train of tones was a random duration generated

from a normal distribution with a mean of 2.5 s. The tone pips were amplified to an intensity of 65 dB SPL measured in the center of the chamber. All stimuli were played 24 h per day for the duration of the exposure period.

Imaging Procedure: Prior to imaging, animals were acclimatized to head fixation for three days by securing them in the set-up for progressively longer periods (15, 30, 45 minutes) with wide field excitation light. A baseline stimulus protocol was presented on day 1 to reconstruct a tonotopic map, immediately followed by injection of either 1 mg/kg psilocybin or sterile saline (0.1 ml/10 g). Animals were then placed in sound-exposure cages (see, *chronic exposure)* and further recordings (using the same mapping stimulus protocol) were taken at days 7, 14 (during sound-exposure) and 21 (one-week post-cessation of exposure).

Data Analysis

Pre-processing: Recordings were first motion corrected by aligning all frames to a mean reference image, constructed from the 20 most correlated of a random selection of frames. Recordings were then down-sampled from their native resolution of 1024 x 1024 pixels to 256 x 256. Global fluctuations in the signal were removed by fitting a linear regression model, which predicts the pixel intensities of each frame based on global average intensity, and subtracts predicted global fluctuations from the activity of each pixel. The total trial length was 2.5s (-0.5s from stimulus onset to 2s post-onset). Pixel traces were then baseline corrected by subtracting the mean of the five pre-stimulus baseline frames from the mean of the response period, which was taken as the 0.8s immediately following the stimulus. Pixel responses were then expressed as z-scores from local pre-stimulus baseline.

Tonotopic map reconstruction: Best Frequency (BF) tonotopic maps were reconstructed first by z-scoring median responses to a given frequency relative to every other pixel response at that frequency. This corrects for general biases in response amplitude in the cortex for particular frequency ranges. Only pixels with a z-score greater than 1 for the given frequency were included in analyses. The frequency at which the maximal trial-averaged median response was elicited was defined as the BF and each pixel was labelled accordingly. All analyses were conducted on the original unsmoothed data, and maps used only for visualization purposes were smoothed with a median filter (size=3). Tuning bandwidth for each pixel was calculated as the continuous range of frequencies from the BF, at which a median response greater than 50% of the maximal response was observed.

Quantification and statistical analysis: Analyses were performed using Python 3.12. All data are reported as mean ± SEM unless stated otherwise. For comparison with baseline recordings, Wilcoxon Signed Rank Test was used (Wilcoxon test statistic reported as W). For comparison between saline and psilocybin groups, Mann Whitney U was used (Mann Whitney test statistic reported as U). For longitudinal analyses of habituation, linear mixed models were used, with time-point, frequency and treatment group as fixed effects, and animal ID as a random effect. Wherever applicable, multiple comparisons were corrected for with Benjamini Hochberg false discovery rate (FDR) correction. Statistical significance was defined as $p < 0.05$.

3.4 Results

Chronic recording of auditory cortex neuronal activity with wide field calcium imaging,

Using individual frequency responses (Figure 3.1A, we were able to reconstruct best frequency (BF) tonotopic maps, which were structurally consistent between animals and with previous wide field mapping studies (Fig 3.1B). A baseline mapping stimulus was first presented for each mouse, followed immediately by an IP injection of either 1 mg/kg psilocybin, or 0.1 ml/10g saline. Animals were placed in sound-attenuated chambers and exposed to trains of 12 kHz tone pips, for two weeks. Further mapping stimuli were presented at days 7 and 14, during sound exposure, and at day 21, one week following the end of exposure (Figure 3.1C).

Psilocybin preserves response thresholds to sound-stimulation across multiple weeks.

We examined the effect across days of psilocybin on the overall responsiveness of pixels to each individual frequency, as a proportion of the total number of responsive pixels. In the saline condition we observed a significant reduction from baseline to day 7 in the proportion of pixels responsive at 8 of 12 of presented frequencies (Figure 3.2A). $W < 5$ and $P < 0.050$ at 4364, 5371, 8140, 10020, 15184, 23009, 28324 and 34867 Hz. (Wilcoxon signed-rank test + FDR multiple comparisons correction). We observed no significant reduction in responsive pixels at four presented frequencies (6612, 12335, 18691 and 42922 Hz, all $W > 9$, $P > 0.060$), including the target exposure tone. In contrast, mice injected with psilocybin showed no significant reduction at any of the 12 presented frequencies ($W > 12$, $P > 0.130$ for all frequencies). When plotted directly against one another, we observed a trend towards a greater drop in the saline condition

than psilocybin (Figure 3.2B), but this did not reach statistical significance at any frequency ($t > 15$, $P > 0.06$ for all. Mann Whitney U + FDR multiple comparisons correction). A similar trend was observed between baseline and day 14, with a significant reduction at 7 of 12 presented frequencies in the saline condition ($W < 6$, $P < 0.05$ at 4364, 5371, 15184, 23009 and 34867 Hz. $P < 0.01$ at 8140 and 28324 Hz). No significant reduction from baseline was observed at the other five frequencies (6612, 10020, 12335, 18691 and 42922 Hz. $W > 11$, $P > 0.130$ for all). Again, we observed no significant reductions from baseline with psilocybin across all frequencies ($W > 5$, $P > 0.117$ for all frequencies). Finally, at day 21 we observed the largest reduction in response activity, with a significant reduction across all frequencies in the saline condition (All $W < 4$, $P < 0.05$ at 4364, 5371, 6612, 8140, 12335, 15184, 23009 and 34867 Hz. $P < 0.01$ at 10020, 18691, 28324 and 42922 Hz) (Fig 3.2E). For both days 14 and 21, plotting the change in response directly between saline and psilocybin yielded no significant difference (Day 14: $t > 19$, $P > 0.092$ for all frequencies, Day 21: $t > 21$, $P > 0.210$ for all frequencies) between any pairs of frequency values (Figure 3.2B, D, F).

Separate linear mixed model (LMM) fits of saline and psilocybin conditions found a significant effect of time point on responsive area (averaged across frequencies) in both groups ($p < 0.0001$ for both) with a coefficient of -2.965% ± 0.269 for saline and -2.319% ± 0.266 for psilocybin. This suggested that the decrease in responsive across each time point was greater in the saline condition, though fitting a single LLM with both treatment groups included found only a non-significant trend ($p = 0.075$) towards an effect of treatment group on time point (Figure 3.2G). These data suggest that a single dose of psilocybin facilitates the maintenance of response thresholds generally across auditory cortex for a minimum of two weeks, but that by three weeks,

the majority of frequencies show a significant reduction in responsiveness with repetitive stimulation.

Post-psilocybin distribution of best frequencies (BFs) remains constant during chronic sound-exposure

The successful reopening by psilocybin of the critical period for tonotopic sensory representations would be evidenced here as a shift in the normally stable distribution of BFs, producing an over-representation of the 12 kHz exposure tone. In order to examine this, we mapped the distribution of BFs of all responsive pixels across each recording day. We observed a high degree of similarity in the distribution of BFs between saline and psilocybin conditions, at baseline (Figure 3.3A) ($U > 27$, $P > 0.273$ for all, Mann Whitney U + FDR multiple comparisons correction), day 7 (Figure 3.3B) ($U > 15$, $P > 0.110$ for all), day 14 (Figure 3.3C) ($U > 20$, $P > 0.251$ for all) and day 21 (Fig 3D) ($U > 22$, $P > 0.133$ for all). We also observed no change in the distribution across days, from baseline to day 7 (Figure 3.3E) ($W > 15$, $P > 0.225$ for all psilocybin cohort frequencies, $W > 9$, $P > 0.09$ for all saline. Wilcoxon signed-rank test + FDR multiple comparisons correction), baseline to day 14 (Figure 3.3F) ($W > 12$, $P > 0.110$ for all psilocybin cohort frequencies, $W > 16$, $P > 0.140$ for all saline), or to day 21 ($W > 17$, $P > 0.162$ for all psilocybin cohort frequencies, $W > 21$, $P > 0.180$ for all saline). The findings suggest that when averaging the distributions of BF's across all auditory regions, psilocybin does not induce tonotopic reorganization in response to passive sound exposure.

Narrowing of tuning bandwidths with repeated stimulation is unaffected by psilocybin.

We next examined whether psilocybin administration results in long-term alterations to the distributions of tuning bandwidths across responsive auditory regions (Figure 3.4A). Considering the effect observed on long-term habituation with psilocybin, it is possible that this would also be expressed as an increased maintenance of baseline response bandwidths. We observed a trend towards a successive reduction in bandwidth across all days, for both saline (Figure 3.4B) and psilocybin (Figure 3.4C) conditions. When plotting the change in the distribution of specific response bandwidths across responsive fields, we observed a similar trend, suggesting an increase in the lowest bandwidth (0.5 octaves) and decrease in broader bandwidths (1.0, 1.5 octaves). However, the increase in the 0.5 octave bandwidth was non-significant between baseline and day 7, as were the changes across broader bandwidths (At 0.5 octaves, saline $W = 34$, $P = 0.918$, psilocybin $W = 32$, $P = 0.875$. $W > 15$, $P > 0.125$ for all other bandwidths. Wilcoxon signed-rank test + FDR multiple comparisons correction). Similarly, differences were non-significant between baseline and day 14 (P at 0.5 octaves, saline $W = 36$, $P = 0.936$, psilocybin $W = 40$, $P= 0.986$, $P > 0.073$ for all others) and at day 21 (P at 0.5 octaves, saline $W = 25$, $P = 0.410$, psilocybin $W = 40$, $P = 0.994$, $W > 15$, $P > 0.0744$ for all others). At each time point, we also observed no differences in the distribution of any given bandwidth, between saline and psilocybin conditions (day 1-7: $U > 15$, $P > 0.157$ for all bandwidths, day 1-14: $U > 14$, $P > 0.185$, day 1-21: $U > 12$ $P > 0.094$). These data suggest that when taking the average activity across all auditory fields, psilocybin does not significantly affect the change in the distribution towards lower response bandwidths with repeated stimulation across time.

3.5 Discussion

Using wide field calcium imaging in awake mouse auditory cortex, we investigated how a single 1 mg/kg dose of psilocybin would affect long-term auditory processing, and whether the plastogenic effects were sufficient to induce CP reopening in sensory cortices. We identified a clear prevention of long-term adaptation to auditory stimuli across the auditory cortex as a whole. Given that studies looking at the long-term structural effects of psychedelics show changes across brain regions (Ly et al., 2018; Raval et al., 2021; Shao et al., 2022), we predicted that we would see this expressed as increased propensity for tonotopic reorganization across the whole auditory cortex. However, at this level we did not observe tonotopic map reorganization in response to chronic tone exposure. Multiple considerations must be applied when considering this finding in the context of CP reopening, which are discussed in detail below.

Chronic imaging of tonotopy in auditory cortex with wide field calcium imaging.

Similar to previous studies (Romero et al., 2020), we were able to reconstruct tonotopic maps of left auditory cortex that bore a high degree of structural similarity between mice (Figure 3.1B), and between recordings in the same mouse. A1 was clearly identifiable as the largest sub field, by the presence of a large rostro-caudal high to low frequency tonotopic gradient, and proximity to the low frequency core of the anterior auditory field (AAF) in a rostro-dorsal position within the window.

Psilocybin prevents habituation to repeated stimulation for up to three weeks.

The phenomenon of habituation to repeated stimuli has been clearly characterized in awake mice, driven by SOM interneuron inhibition of pyramidal neurons in layer II/III (Kato et al., 2015). Under control conditions, we observed a marked habituation of responses from days 1 to 7 in terms to the proportion of the tonotopic area that was responsive to a given frequency. This habituation was not present following psilocybin, with none of the presented frequencies showing significant reduction in responsive area from baseline (Figure 3.2A). The same effect was present at day 14 (Figure 3.2C). By day 21, though a larger proportion of frequencies exhibited a reduction from baseline in saline, the majority of frequencies in the psilocybin condition now also showed a trend towards a habituated response area, although still non-significant. A linear mixed model fit on the data showed similar results, with a significant negative coefficient across each time point seen in both groups, which appeared larger in the saline condition. However, direct comparison between groups indicated only a non-significant trend on the interaction between treatment group and time point. Importantly, this effect on response area was seen across the full frequency range, rather than specifically at the 12 kHz exposure tone. This suggests that the habituation effect may be related to repeated exposure to the mapping stimulus, and not the chronic single tones presented to the animals. These data indicate that psilocybin prevents a habituation in the response to passive stimuli that is observable up to three weeks from a single dose. It is interesting to note that the psilocybin group's trend towards habituation in the third week suggests this effect may last for around two weeks, a similar timescale of psilocybin's long-term effects on critical period reopening reported by Nardou and colleagues (Nardou et al., 2023). A useful further study could be to only expose the animals to mapping stimuli two weeks

following the psilocybin dose. If the effect indeed only lasts for two weeks, we may see habituation proceed in the same fashion in both psilocybin and control conditions. Other studies with tryptamine psychedelics have found also found a reduction in adaptation to repeated auditory stimuli in the acute phase of the drug, but these data suggest the effect is much more prolonged (Timmermann et al., 2018).

Averaged across whole auditory cortex, psilocybin does not trigger BF tonotopic map reorganization in response to passive tone exposure.

Previous studies have identified that a CP open state can be identified by the expansion of the tonotopic map's BF representation of a particular frequency, in response to prolonged passive exposure to that frequency. In this context, BF refers to the maximum trial-averaged response at a given intensity (65 dB). Here we sought to identify whether the plasticity-inducing effects of psilocybin could induce a CP open state, evidenced by this map expansion. On all mapping days, we identified no differences in the distribution of BFs between the saline and psilocybin conditions (Figure 3.3A-D). At no point were BFs significantly different from baseline distribution, suggesting that these remained very stable over the period in both conditions. No increase in representation of the exposure tone was observed. This would suggest that the effect of 1 mg/kg psilocybin seen on habituation may not be paired with CP reopening capable of facilitating cortical reorganization in response to sound exposure. As previous studies have reported dose-dependence of the effects of psychedelics (Wood et al., 2012), it is possible that this effect may

only be observed at higher doses. Future experiments should examine dose-response relationships to investigate this further.

Changes in tuning bandwidth with repeated stimulation are unaffected by psilocybin.

In both the control condition and with psilocybin, we observed a trend towards a reduction in pixel tuning bandwidth with repeated stimulation (Figure 3.4D-F). However, this was non-significant in all cases likely due to sizeable variability and multiple comparisons correction. We did not observe a difference in bandwidth distribution between saline and psilocybin conditions, suggesting that when averaging across the whole auditory cortex, psilocybin does not affect bandwidth tuning in a prolonged way.

It is important to note that in the current scope of this study, only changes averaged across the whole auditory cortex are examined. Previous studies looking at cortical map expansion focused particularly on A1 (Cisneros-Franco & De Villers-Sidani, 2019b; Thomas et al., 2020; Zhou et al., 2011), and it is likely that effects may be more pronounced in different regions. Future analysis should identify the A1 region in a data-driven manner, for example by projecting radial vectors out from low frequency cores, tracking BFs along these vectors and drawing field boundaries at BF reversals. Electrophysiological studies of map expansion have also been layer specific, focusing often on layer IV/V, whereas wide field imaging takes a bulk average across all layers. CP map expansion has been observed not to occur in all cortical layers, for example layer 1 preserves a stable tonotopic map when reorganization occurs in other layers (Takesian et al., 2018). Wide field calcium signals are also dominated by activity from superficial layers, particularly layer 1 and

II/III, due to strong scattering of excitation and emission light in brain tissue. It is possible that a bulk average may therefore mask tonotopic reorganization in particular layers.

3.6 Conclusions

Taken together, the data in this study suggest that 1 mg/kg psilocybin exerts prolonged effects on auditory cortical activity for at least two weeks following administration, in particular, preventing habituation to repeated stimuli. Data may also suggest that effects on CP reopening in sensory cortices are limited, however we caution that as these effects would likely differ by sub-field, taking an average of all fields may mask changes. Further analyses should focus on data-driven parcellation of auditory fields to isolate A1, as in classical electrophysiological studies investigating tonotopic map expansion in CP plasticity.

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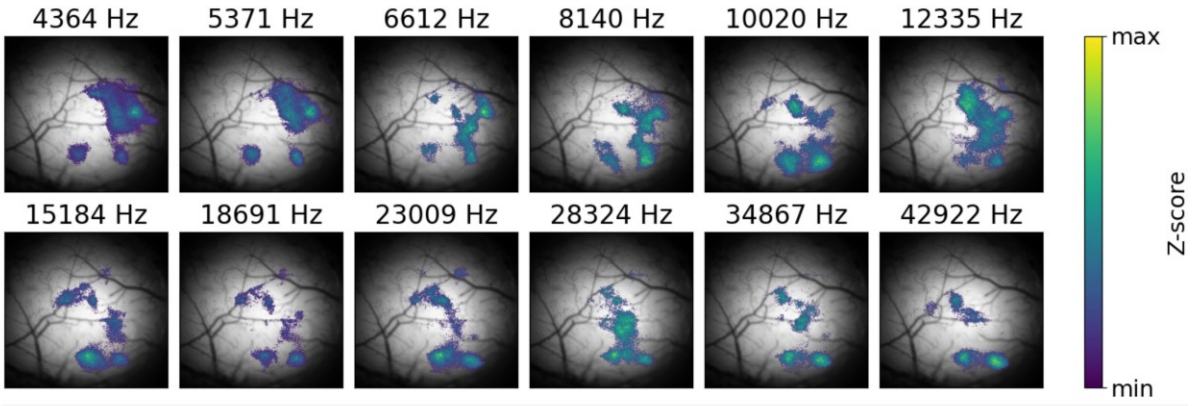
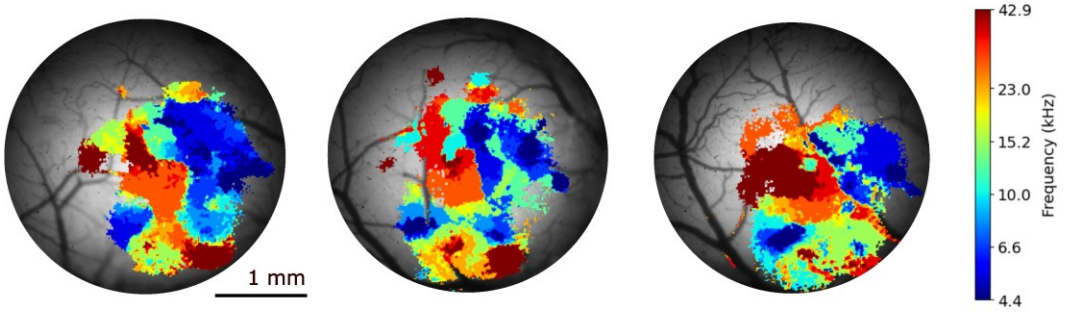
3.9 Figures

A



B



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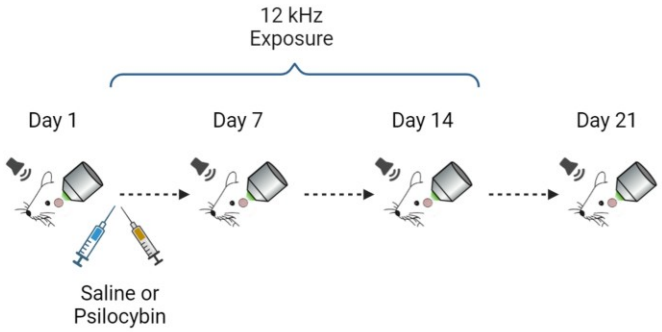

Figure 3.1: Chronic recording of auditory cortex neuronal activity in awake mice, with wide field calcium imaging.

A) Representative wide field response maps from a single mouse, showing trial-averaged median responses to each presented sound frequency at 65 dB, overlaid on the cortical surface. B) Best frequency (BF) tonotopic maps from three mice (left map is the same mouse as in A), where BF is defined as the frequency at which maximal trial-averaged median response was elicited. Responses one z-score above baseline are shown. C) Schematic illustrating chronic imaging. A baseline map is first taken for each mouse, followed by IP injection of saline or psilocybin and exposure to 12 kHz tone pips for two weeks in sound-attenuated chambers. Further maps are taken at days 7 and 14, and a final map one week following the end of tone exposure, at day 21.

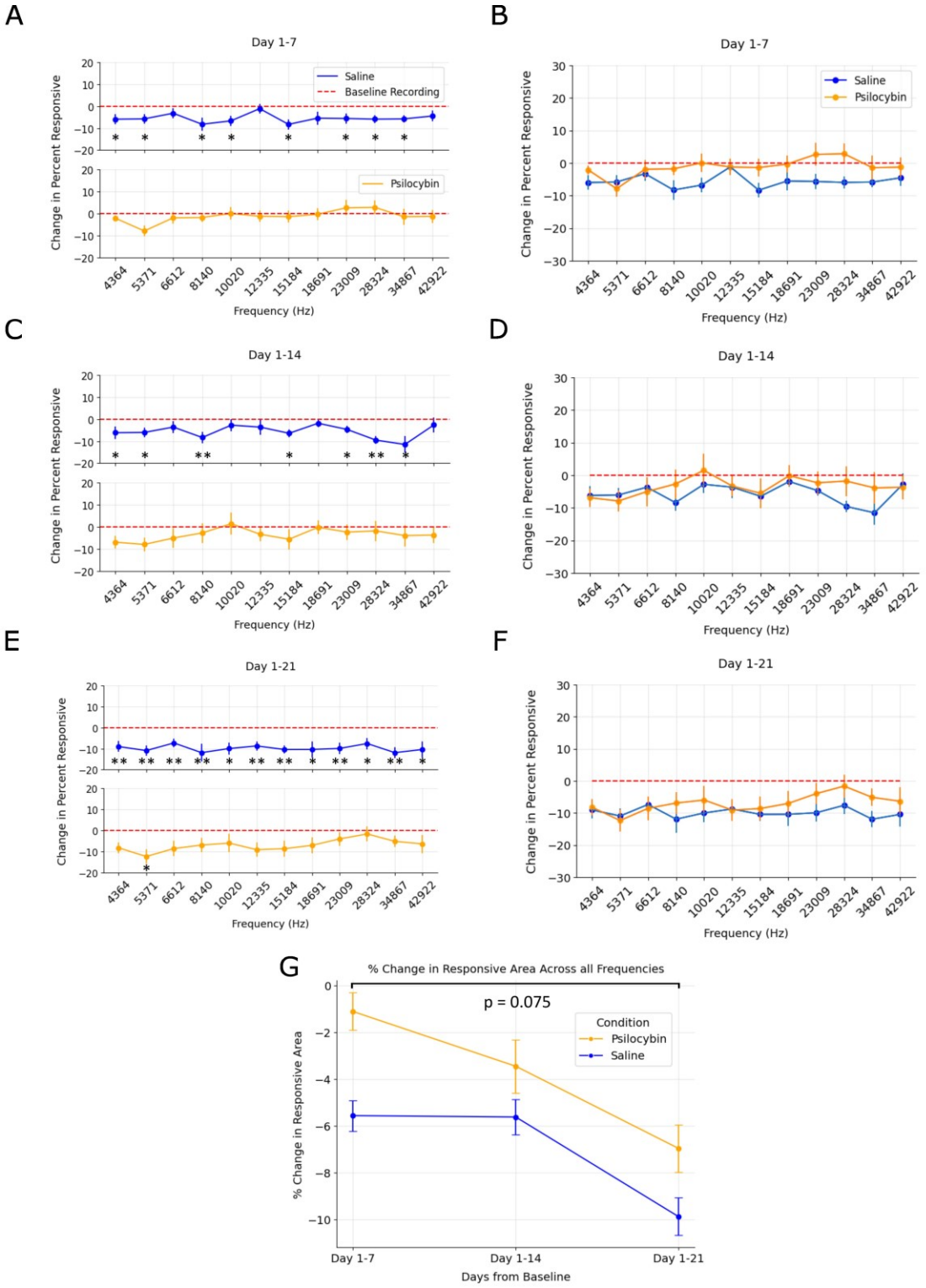
A
Day 1-7
Saline
Baseline Recording
Psilocybin
Change in Percent Responsive
Frequency (Hz)
B
Day 1-7
Saline
Psilocybin
Change in Percent Responsive
Frequency (Hz)
C
Day 1-14
Change in Percent Responsive
Frequency (Hz)
D
Day 1-14
Change in Percent Responsive
Frequency (Hz)
E
Day 1-21
Change in Percent Responsive
Frequency (Hz)
F
Day 1-21
Change in Percent Responsive
Frequency (Hz)
G
% Change in Responsive Area Across all Frequencies
p = 0.075
Condition
Psilocybin
Saline
% Change in Responsive Area
Day 1-7
Day 1-14
Day 1-21
Days from Baseline

Figure 3.2: Psilocybin preserves response sensitivity to sound-stimulation for at least two weeks.

A, C, E) Change in the proportion of the responsive tonotopic area sensitive to each presented sound frequency at 65 dB, as a percentage of total responsive pixels. Change is from day 1 to days 7, 14 and 21, respectively. *, $p < 0.05$, **, $p < 0.01$ (Wilcoxon Signed Rank Test with FDR correction for multiple comparisons). B, D, F) Comparison of change in responsive area for each frequency, between saline and psilocybin cohorts. Differences between saline and psilocybin were not significantly different from one-another for any frequency (Mann Whitney U + FDR correction, $p > 0.05$ for all). G) Linear mixed model fit of change in percent responsive area, averaged across all frequencies. Treatment group, timepoint and frequency are included as fixed effects and animal ID as a random effect. $p = 0.075$ represents interaction effect between timepoint and experimental group. N = 18 mice, 9 for each of saline and psilocybin cohorts.

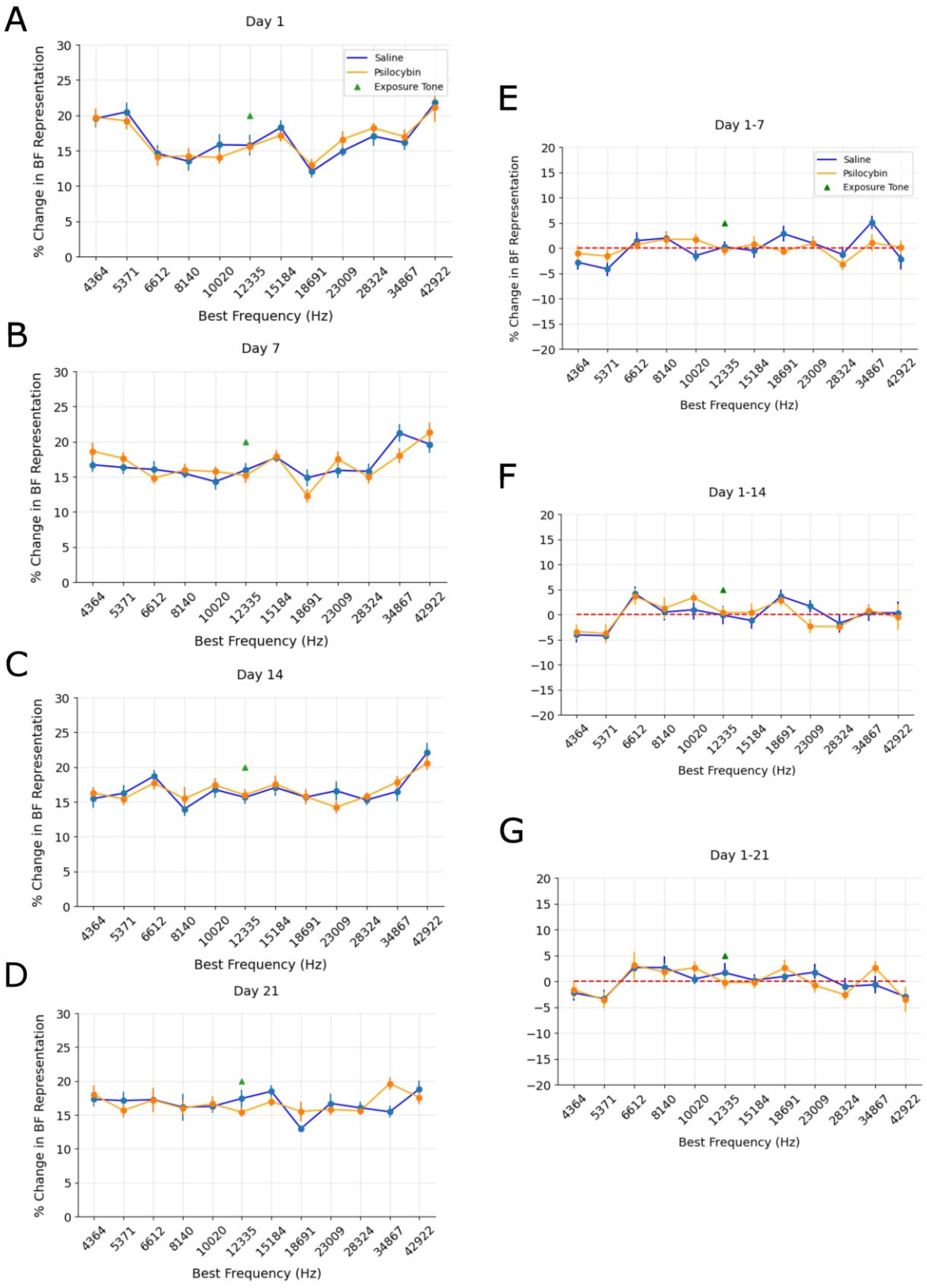
A
Day 1
Saline
Psilocybin
Exposure Tone
% Change in BF Representation
Best Frequency (Hz)
B
Day 7
C
Day 14
D
Day 21
E
Day 1-7
F
Day 1-14
G
Day 1-21
4364
5371
6612
8140
10020
12335
15184
18691
23009
28324
34867
42922

Figure 3.3: Post-psilocybin distribution of best frequency remains constant during chronic sound-exposure

A, B, C, D) Distribution of pixel best frequencies in responsive tonotopic area across days, as a percentage of total responsive area. Difference between saline and psilocybin groups was non-significant across all days, $p < 0.05$ (Mann Whitney U with FDR correction). E, F, G) Change in distribution of pixel best frequencies from day one baseline, across days. Changes were neither significantly different between saline and psilocybin groups across frequencies (Mann Whitney U + FDR correction) or significantly different from zero, within either group (Wilcoxon signed-rank + FDR correction). Green triangle represents the tone of chronic exposure. N = 18 mice, 9 for each of saline and psilocybin cohorts.

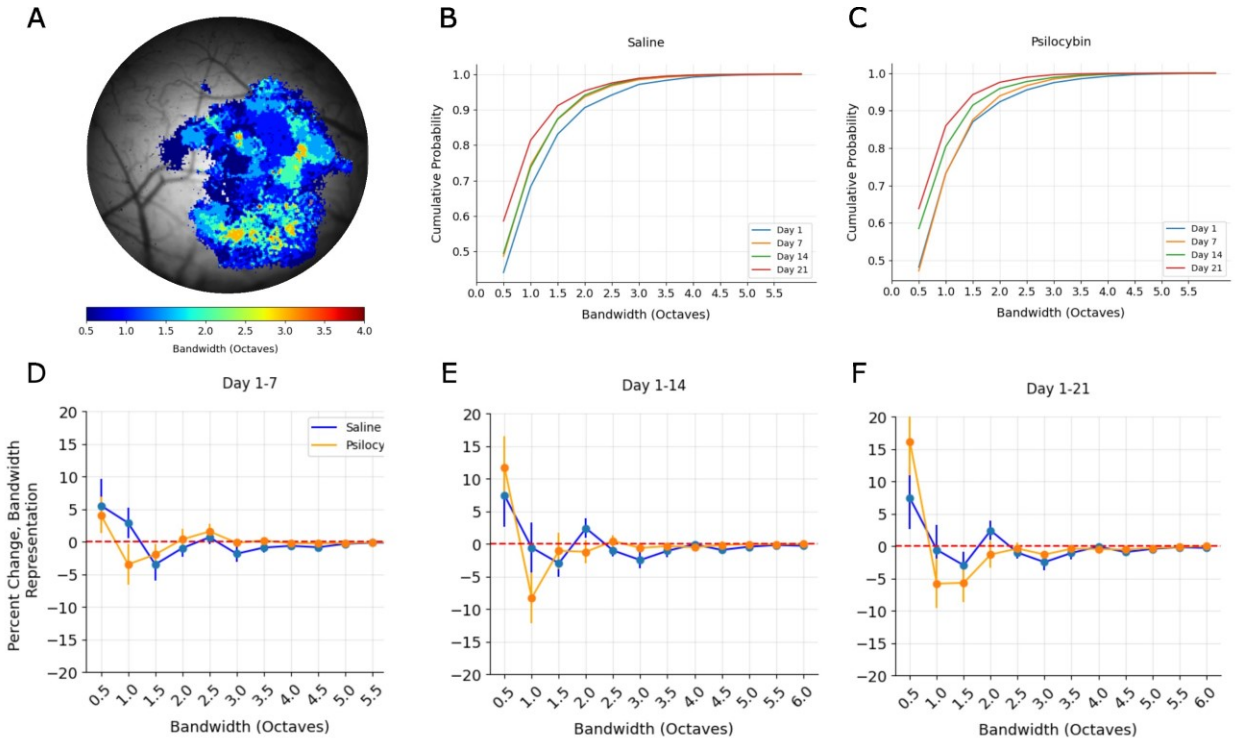

Figure 3.4: Narrowing of tuning bandwidths with repeated stimulation is unaffected by psilocybin.

A) Representative tonotopic map from one mouse, showing distribution of pixel bandwidths i.e. the range of continuous frequencies at which a pixel showed an above threshold (1 Z-score from baseline) trial-averaged response. B, C) Cumulative probability distributions of bandwidths for all responsive pixels, across days, for saline (left) and psilocybin (right) groups. All responsive pixels are collapsed together across mice for each group. D, E, F) Change in distribution of pixel response bandwidths, as a percentage of total responsive pixels, for saline and psilocybin groups. No differences between and psilocybin were significant (Mann Whitney U + FDR correction) for any bandwidths. N = 18 mice, 9 for each of saline and psilocybin cohorts.

Chapter 4: General Discussion

4.1 Two-photon microscopy for the study of psychedelic action

Most *in vivo* research into the effects of psilocybin on neuronal activity has focused on regions such as the prefrontal cortex and hippocampus. However, as multiple proposed models of psychedelic action involve shifts in the balance between sensory input and top down modulation of incoming sensory information, it is important to understand how processing is affected in primary sensory areas. Interesting work has been done in the visual cortex (Grieco et al., 2020; Michaiel et al., 2019; Riga et al., 2016), but very little has been conducted in the auditory cortex, particularly with single-neuron resolution. As modulation of activity based on factors such as behavioral context often differentially effects auditory and visual processing (Henschke et al., 2021), it is likely that differing effects of psilocybin may be observed in auditory regions, which could help to further elucidate its mechanisms of action. The auditory cortex also provides an excellent model for the study of long-term plastogenic effects of psychedelics, due to the ease of presenting constant, controllable sound exposure to animals.

The successful achievement of the aims of this study depended on the development of an experimental paradigm to track the activity of individual neurons in the awake animal. Several studies have shown that anesthesia can drastically change the temporal dynamics of sound-evoked auditory neuron responses (Kato et al., 2015), induce shifts in tuning (Gaese & Ostwald, 2001) and dull the contrast between processing of familiar vs unfamiliar stimuli (Kato et al., 2015). Investigation of how psilocybin affects sensory gating and its influence on behavioral relevance of stimuli could therefore be heavily confounded by anesthesia. Of great importance

also is the ability to resolve single neurons, and to longitudinally track them over the course of a manipulation. Traditional extracellular electrophysiological recordings can be biased towards the detection of neurons with higher firing rates (Siegle et al., 2021), meaning that changes in neuronal response properties can be missed if they are not within this sub-sample. Neurons that become non-responsive are also simply lost from analysis, whereas the detection of cells based on baseline fluorescence and matching of spatial location allows for these cells to be tracked longitudinally (Crowe & Ellis-Davies, 2014) with two-photon, even if they are no longer sound-sensitive.

One caveat of the technique that must be considered is the comparatively lower temporal resolution with two-photon imaging when compared to electrophysiology. With most two-photon studies recording at sampling rates of 10-30 Hz and the slower rise and fall times of calcium indicators (themselves an indirect measure of action potentials), two-photon imaging usually lacks the temporal resolution to detect changes in response latency of individual neurons (Robbins et al., 2021). Spike deconvolution methods also cannot accurately describe single spike events from calcium data, but are instead very useful for denoising periods of burst firing from the slow dynamics of the calcium indicator (Shen et al., 2022). As normal auditory processing depends heavily on the integration of neural inputs with millisecond timing (Kayser et al., 2010), it is very possible that psilocybin exerts temporal effects on processing that we cannot resolve with the scope of this study. Advances in *in vivo* electrophysiology in awake, behaving animals will therefore be useful going forward in elucidating how effects on factors such as neuronal response latency may modulate auditory processing with psychedelics.

In this study, we successfully constructed an experimental set-up that fulfills our requirements, with the ability to identify subtle changes in tuning and response properties of auditory neurons, and track these longitudinally across recordings. To our knowledge, this is the first study to use two-photon to longitudinally track the same population of A1 neurons before and after psilocybin administration, as well as to identify changes in directly matched cells.

4.2 How does psilocybin affect neuronal excitation in the auditory cortex?

In our first study, we recorded from A1 neurons both immediately before and 15 minutes following a 1 mg/kg IP injection of psilocybin. This time point was chosen to still be well within the period where mouse head-twitch response is observed (Shao et al., 2022; Sherwood et al., 2020), whilst allowing time to position the imaging plane at the exact coordinates of the first recording. Using the deconvolved spike-train output of the raw calcium activity (Pachitariu et al., 2017), we identified a reduction in the overall response of control neurons (Figure 2.1B), as the mean of response amplitudes from all stimulus periods in the recording. This was not coupled with a decrease in response amplitude measured either at BF (Figure 2.1C), or when including the two frequencies adjacent to the BF (data not shown).

As the data regarding the effects of tryptamine psychedelics on neuronal response amplitude are region-specific and use a number of different compounds, it is somewhat complex to contextualize this finding in the literature. Near complete cessation of firing has been observed in the dorsal raphe (George K. Aghajanian et al., 1968), heterogeneous excitatory or inhibitory effects have been seen in frontal regions (Tang et al., 2023) and have also reported different

effects depending on dosage (Wood et al., 2012), making it hard to directly compare. A recent DOI study in the visual cortex found an overall reduction in activity, disguising a more complex picture at the level of individual cells, where they were either facilitated or inhibited depending on baseline firing rates (Michaiel et al., 2019). Our data would suggest that this net suppression is not observed in layer II/III auditory cortex with psilocybin, though we did not segment neurons by baseline firing rate to examine whether the same heterogeneity is seen. A recent two-photon study examined the effect of a larger dose (2 mg/kg) of psilocybin in auditory cortex, reporting a short-lived increase in response amplitude at 5 minutes, followed by a decrease at 30 (Brockett & Francis, 2024). However, their reported data show no significant reduction from baseline at 30 minutes, indicating there is in fact not a net decrease in response amplitude. As our post-psilocybin recording covers the 30-minute time-point, our data would concur with this. They also observed a different neuronal population at each time-point, whereas we longitudinally tracked individual neurons that were consistently responsive across recordings. This may explain differing conclusions, along with the different dosages used.

Importantly, the suppression of responsiveness we observed in controls was not present in the psilocybin condition, either at the whole population level, or when tracking changes in the subgroup of directly matched neurons. Habituation to repeated auditory stimuli has been observed in terms of changes in response amplitude measured over days (Gillet et al., 2018; Kato et al., 2015) and on the order of minutes following repetitive stimulation in V1 (Chaloner & Cooke, 2022). This effect has been under-reported until fairly recently as it is effectively neutralized by anesthesia and is far more visible in awake animals (Kato et al., 2015). The fact that amplitude of responses at BF was unaffected suggests that the reduction in the overall response activity in

control animals came from loss of responses to off-BF frequencies or at lower intensities. This could reflect a narrowing of the tuning curve and increase in response threshold, rather than an additive loss of response gain (Arandia-Romero et al., 2016). Our data therefore highlight the interesting prospect that rather than simply increasing or decreasing gain of neuronal responses, psilocybin may affect modulation of the shape of the frequency-intensity response curve as stimuli become familiar.

4.3 Effects of psilocybin on neuronal tuning properties in the auditory cortex.

Similar to the other studies that have examined changes in overall population tuning in auditory (Brockett & Francis, 2024) and visual cortices (Michaiel et al., 2019), we found that the distribution of BF's at the population level did not change. This suggests that involvement of sensory cortices in acute psychedelic effects does not involve major shifts in cortical representations, but rather a disrupted modulation of neuronal activity by context of sensory input or behavioral state.

Our findings supported the hypothesis that the reduction in overall response activity in control conditions resulted from changes to the shape of the frequency-intensity tuning curve. Across the saline and psilocybin conditions, we observed that at baseline there was no difference between the distribution of intensity response thresholds of neurons (Figure Supplementary 2 A, B). Following repeated stimulation, post-psilocybin cells exhibited a significantly greater maintenance of responses to low sound intensities than in control. This effect was seen both at the level of the overall population and in the subset of matched neurons (Figure 2.2 E, F).

This was coupled to a significant reduction in frequency response bandwidth at 65 and 50 dB sound levels, a trend towards reduction at 80 and 35 dB in the saline condition, and no change in bandwidth at any intensity with psilocybin. Our data collectively suggested that psilocybin acts to prevent the habituation of responses to repeated, familiar stimuli in A1. It is important to contextualize this finding with the proposed methods of psychedelic action described in Chapter 1. We find that our data fit most closely with the REBUS model (Carhart-Harris & Friston, 2019), in which perceptual disturbances are driven by loss of top-down inhibitory modulation, and subsequent increased bottom up sensory drive. While we do not report an increase in sensory drive in A1 here, the findings do suggest a loss of the top-down inhibition that is usually responsible for conferring habituation to familiar or behaviourally irrelevant stimuli (Isaacson & Scanziani, 2011). This lack of habituation could contribute to perceptual disturbances by impairing features such as selective attention by inundating higher order regions with sensory information and reducing the encoding contrast between familiar and novel stimuli.

One feature this study does not directly examine is the effect of psilocybin on acute cortical connectivity at the single-neuron level. Though there are a range of whole-brain imaging studies that examine effects on connectivity at the level of millions of neurons (described in detail in 1.4.1), little is known about how local connectivity of smaller ensembles is affected. We can predict that effects would likely be seen, as studies have highlighted changes to contextual modulation of sensory information such as surround-suppression (Michaiel et al., 2019), requiring coordinated activity of neuronal ensembles (Miller et al., 2014; Yuste et al., 2024). An interesting further analysis would be to examine the effect of psilocybin on neuronal synchrony in response to sound exposure, and how this synchrony changes with repeated stimulation.

4.4 A potential interneuron-driven mechanism for psilocybin inhibition of habituation

There is some pre-existing evidence that tryptamine psychedelics may act to prevent response habituation in auditory cortex, with one MEG study finding that LSD reduced response adaptation in human A1 (Timmermann et al., 2018). Psilocybin has also been shown to impair pre-pulse inhibition of the startle reflex in humans, suggesting disrupted sensorimotor gating (Quednow et al., 2012). To our knowledge, we are the first to identify this effect on reduced response adaptation in A1, with single neuron resolution. Habituation observed with two-photon has been studied previously in A1, identifying both a modest habituation within the first recording day and a more prolonged habituation, which persists over multiple days (Gillet et al., 2018; Kato et al., 2015). It is far more pronounced in Layer II/III pyramidal cells than in thalamorecipient Layer IV cells, and is driven by a progressive increase in inhibitory activity in the cortex, mediated by increased activity of SOM interneurons (Kato et al., 2015). Several studies across multiple sensory cortices have identified the role of inhibitory activity in sharpening tuning of sensory neuron responses (Isaacson & Scanziani, 2011; Priebe & Ferster, 2008), and habituation has been shown to narrow auditory neuron receptive fields (Condon & Weinberger, 1991). Importantly, increased SOM interneuron activity has been shown to drive the narrowing of tuning in A1 by triggering network suppression that leads to increased lateral inhibition of neuronal responses (Kato et al., 2017).

It is possible therefore that the loss of response habituation and maintenance of broader tuning seen with psilocybin may be due to disruption of this inhibitory, SOM-mediated network suppression. Indeed, it is known that GABAergic interneurons express $5HT_{2A}$ receptors (Willins et al., 1997), that SOM interneurons show enrichment of $5HT_{2A}$ mRNA in cortex (De Filippo &

Schmitz, 2024; Z. Yao et al., 2023), and that 5HT activates these interneurons in entorhinal cortex, via $5HT_{2A}$ receptors (de Filippo et al., 2021). Evidence from psychedelic studies may also point to a SOM-driven mechanism involving loss of inhibitory control, as administration of DOI has been shown to reduce center-surround suppression in V1 of mice (Michaiel et al., 2019), and DMT broadens visual tuning selectivity in humans (Pais et al., 2024). Photo-inactivation of SOM interneurons results in a similar broadening of tuning in A1 (Kato et al., 2017), and integration of horizontal inputs across Layer II/III V1 cortical space by SOM interneurons has been shown to underlie visual surround suppression (Adesnik & Scanziani, 2010).

These studies, along with the loss of A1 response adaptation with LSD (Timmermann et al., 2018) support our findings that psilocybin prevents inhibitory narrowing of frequency and intensity selectivity with repeated stimulation, though further studies are required to ascertain the circuit mechanism. It is also possible that these effects are heterogeneous depending on dosage. The investigation of a dose-response relationship between psilocybin dose and the degree to which habituation and tuning properties are affected would therefore be interesting. Further investigations should focus specifically on how psilocybin administration affects the activity of inhibitory interneurons in A1, for example through the targeting of the GCaMP6s calcium indicator to specific interneuron subgroups including SOM expressing cells (Che & De Marco Garcia, 2021). A coupling of acute psilocybin action to reductions in SOM interneuron activity would more closely implicate these interneurons in driving the loss of inhibitory modulation of tuning curve shape.

A role for psychedelic-induced modulation of habituation and inhibitory control in A1 could be reasonably taken as evidence for the synthetic surprise model of psychedelic action, and it's

stressing of SOM interneuron activity (De Filippo & Schmitz, 2024). While this is indeed an interesting proposition, it requires further investigation to reconcile differences in our data and the proposed model. Namely, that the model posits an increase in the activity of SOM interneurons driving psychedelic effects, whereas a loss of habituation and lateral inhibition would suggest a decrease (Kato et al., 2015, 2017). As this process is governed not only by direct action of SOM interneurons but also by inhibition of PV interneurons, and by blocking recurrent excitation of pyramidal cells. It is possible that over-activation of SOM interneuron activity by psychedelics could upset the temporal dynamics of the circuit, resulting in a loss of precisely timed stimulus-evoked inhibition. An experiment that could further clarify this would be to examine the effects of psilocybin both on A1 pyramidal and SOM interneurons, in an auditory oddball paradigm, to assess whether the drug alters responses to familiar vs unexpected stimuli (De Villers-Sidani et al., 2010).

4.5 The effects of psilocybin on long-term A1 cortical activity and plasticity.

The recent study by Nardou and colleagues showed that a number of psychedelics including psilocybin are capable of reopening the CP for social reward learning, with a duration proportional to that of their acute subjective action (Nardou et al., 2023). In our second study, we investigated whether a single dose of psilocybin was able to induce long-term shifts in auditory cortex sound-evoked activity, and facilitate tonotopic reorganization in response to passive exposure. Across the majority of presented frequencies in control animals, we identified a progressive reduction in responsive pixel number as a proportion of the overall responsive area,

which persisted for three weeks without a restoration of responsiveness between imaging sessions. This parallels long-term, stable habituations in responsiveness to familiar stimuli across days, previously seen with two-photon in A1 (Kato et al., 2015). This was not observed in the psilocybin group, with the majority of frequencies showing no significant drop up to two weeks following administration, the same duration Nardou and colleagues identified for CP reopening with psilocybin. This supports the idea that ongoing effects on neuronal response properties in sensory cortices may parallel the effects seen with behavioral plasticity studies.

In contrast to this, we observed little sign of tonotopic reorganization in response to chronic sound exposure in either condition, evidenced by a stable distribution of pixel BF's across days. As discussed, this lack of an effect may be due to our analysis pipeline and experimental design, in which changes in activity were averaged across all auditory-responsive regions, in contrast to electrophysiological studies of CP reopening, which focus on regional changes (Cisneros-Franco & De Villers-Sidani, 2019b; Thomas et al., 2020). Further analysis with this dataset should parcel auditory regions in an objective manner based on reversal of tonotopic gradients, to ascertain effects specific to A1. We also recorded at only one sound intensity for the purpose of rapidly obtaining tonotopic maps. As the effects of psilocybin that we observed in our first study were often sound-level specific, it would be better for further studies to construct frequency-intensity tuning curves covering a range of low to high sound levels.

Our study sought to identify an effect of psilocybin on juvenile-like tonotopic reorganization in response to passive sound (Cisneros-Franco et al., 2020), but it may be that effects are more visible in a paradigm in which goal-directed plasticity is targeted. Nardou and colleagues argue that psychedelics enhance 'metaplasticity', i.e. dynamic regulation of the extent to which

synaptic plasticity can be triggered by other stimuli (Abraham & Bear, 1996). An interesting further study would be to examine whether a single dose of psilocybin enhances an animal's performance in, for example a rewarded auditory discrimination task (Voss et al., 2016), with associated tonotopic reorganization of A1 to the reward stimulus. It may be that persistent effect of psilocybin on sensory cortices is to enhance the plastogenic effect of a further goal-directed stimulus, such as in human clinical studies where psychedelics are used to enhance the effect of psychotherapy (Bogenschutz et al., 2022; Johnson, Garcia-Romeu, & Griffiths, 2017).

4.6 Integrating adaptation effects observed in acute and long-term studies. Is this the same mechanism?

We identified a similar effect in both studies, in that there was an observed loss of adaptation to repeatedly presented stimuli following psilocybin administration. It may seem that this is driven by the same mechanism, though there is important context that suggests otherwise. First, our controls in the first study found that 5 days following the saline session recordings, neuronal tuning properties of both bandwidth and sound-level response thresholds had returned to baseline, allowing us to perform the psilocybin sessions in the same animal. This was not the case in the chronic study, as response to tones was reduced in controls one week following the first mapping sessions. Previous studies have found similar results, in that rapid habituation within a recording day appears transient (Condon & Weinberger, 1991; Kato et al., 2015) and reverses with time, whereas over days, a more refractory habituation seems to develop (Kato et al., 2015).

Another factor to consider is that two-photon and wide field calcium are recording activity from two very different neuronal populations. While our two-photon recordings are specific to single neurons in layers II/III, wide field recording represent a bulk signal, including heavy neuropil activity from other layers and weighted towards the superficial layers. It is possible that the prolonged sensitivity of neurons we observed with wide field imaging is particular to a layer other than II/III. Further studies should examine this by including two-photon recording of populations in multiple layers, across the time course of wide field mapping days. It is therefore possible that we are witnessing a similar effect with two different mechanisms. Psilocybin could influence habituation to familiar stimuli via an acute mechanism potentially targeting interneuron-guided inhibition. Simultaneously, longer term impairment of response adaptation may reflect increased spine density and excitability (Ly et al., 2018; Shao et al., 2022), driven by rapid induction of psychoplastogenic mechanisms that persist long after the end of acute perceptual effects.

Conclusions

The first aim of this project was to expand the knowledge of how psilocybin acutely affects sound-evoked neural response properties in the auditory cortex. We sought also to ascertain whether psychoplastogenic effects of psilocybin induce prolonged functional shifts in auditory cortical circuits. We identified that psilocybin impairs A1 habituation to pure tones, preventing a reduction in sound-evoked activity with repeated stimulation. Psilocybin also prevented narrowing of frequency and intensity receptive fields observed during habituation. Impaired habituation of responses was observed both at the overall population level, and identified

directly as shifts in the tuning properties of individual neurons. This suggests psilocybin preserves a cortical state in which auditory sensory inputs are perceived as novel, potentially by targeting context-dependent modulation of neural responses. We also found a prolonged effect of psilocybin on long-term adaptation to repeated stimuli, persisting for up to two weeks. Further investigation is required to know whether this represents a reopening of the CP for A1 sound representation.

Our work adds context from the auditory system to the evolving understanding of how interplay between sensory and higher order regions is disrupted by psychedelics, and how plastogenic effects produce long-term alterations in sensory processing. These data support models of psychedelic action in which disrupted sensory gating creates imbalances between top-down predictions and sensory input. The establishment and optimization of this experimental paradigm lays the groundwork for our group to investigate how psilocybin-induced loss of habituation may be caused by disruption of the surrounding interneuron circuitry that governs cortical adaptation.

With further research, the psychoplastogenic effects of psilocybin could be a useful tool to target conditions of maladaptive auditory plasticity such as tinnitus.

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