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Previews

The cranial windows of perception

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Psilocybin has emerged as a potentially rapidly acting antidepressant with enduring actions. In this issue of *Neuron*, Shao et al. (2021) show that psilocybin quickly induces dendritic spine formation in cortical layer V pyramidal neurons. These results provide a potential cellular substrate for psilocybin's therapeutic actions.

> If the doors of perception were cleansed, every thing would appear to man as it is, Infinite. For man has closed himself up, till he sees all things thro' narrow chinks of his cavern. –William Blake (*The Marriage of Heaven and Hell*)

Psychedelic drugs such as lysergic acid diethylamide (LSD), psilocybin, mescaline, and N,N'-dimethyltryptamine induce profound alterations in perception and have been used ritualistically by indigenous peoples for millennia (Nichols, 2016). Although psychedelic drugs were actively studied for their therapeutic potential in the 1950s and 1960s (Nichols, 2016), widespread recreational use of psychedelics in the 1960s led to their eventual criminalization. Psychedelics are experiencing a renaissance in psychiatry due to several clinical trials demonstrating the potential of one or two doses of psilocybin to cause rapid and enduring improvements in depression and anxiety (Reiff et al., 2020). Psilocybin, found in mushrooms of the genus *Psilocybe* and prodrug of the 5-HT_{2A} receptor (5-HT2AR) agonist psilocin, has gained particular clinical traction after being designated a "breakthrough therapy" for treatment-resistant depression by the United States Food and Drug Administration (hereafter, PSI will interchangeably refer to psilocybin and psilocin). Despite an atomic-level understanding of psychedelic drug actions (Kim et al., 2020) and a mushrooming body of literature maintaining psychedelics' therapeutic potential (Reiff et al., 2020), the neurobiological mechanisms by which psychedelic drugs exert their enduring therapeutic effects remain unknown.

Many prior studies have demonstrated that antidepressant drugs, including the rapidly acting antidepressant ketamine (Li et al., 2010) as well as conventional antidepressants (Benes and Vincent, 1991), can induce dendritic spine formation. Among many other compensatory alterations in neuronal function induced by antidepressants, spine formation has emerged as a potential final pathway (Moda-Sava et al., 2019). Some years ago, Jones et al. (2009) reported that the psychedelic drug 2,5-dimethoxy-4-iodoamphetamine rapidly induced spine formation in cortical pyramidal neurons. More recently, others have reported rapid spine formation of cortical neurons *in vitro* to be a common feature of psychedelic, but not of non-psychedelic, 5-HT2AR agonists (Ly et al., 2018). Collectively these findings have raised the intriguing possibility that psychedelic-drug-induced spine formation and synaptic plasticity might represent one way in which psychedelic drugs exert their therapeutic potential.

A key distinguishing feature of the putative therapeutic action of PSI is its enduring action after one dose. In this issue of *Neuron*, Shao et al. (2021) used two-photon microscopy to show, remarkably, that a single dose of PSI induced sustained alterations in cortical neuron spine formation and plasticity. For these studies, the authors chronically monitored cortical layer V pyramidal neuron apical dendrites, where 5-HT2AR expression is enriched, and quantified spine dynamics as well as the functional consequences of behaviorally relevant doses of PSI on spine structural remodeling in mice (Figure 1).

The authors began their study by establishing a behaviorally relevant dose of PSI to use for their experiments. First, they administered mice PSI or saline to determine what doses produce a head-twitch response, a behavioral phenotype in rodents evoked by psychedelics that is characterized by rapid side-to-side head movements. Finding that a 1 mg/kg dose of PSI robustly increases head twitches relative to saline or lower drug doses, the authors next show that this dose also ameliorates escape avoidance behavior in mice subjected to a learned helplessness paradigm.

Having established a dose of PSI that produces psychedelic drug-like actions and ameliorates a model stress-coping behavior, the authors next investigated how PSI might alter dendritic spine morphology *in vivo*. Shao et al. installed cranial windows above the cingulate/premotor cortex of *Thy1GFP* mice, in which cortical layer V and VI pyramidal neurons were fluorescently labeled. Following a single administration of PSI, the authors quantified thousands of dendritic spines at various time points over the course of about 1 month. They found that PSI modestly, but significantly, increases spine morphological parameters including spine density, head width, and protrusion length. Notably, the formation of new spines occurred rapidly after drug treatment, with the rates of spine protrusion and retraction returning to baseline levels after several days. Of the new spines that form in cingulate/premotor cortex dendrites, about half remained morphologically stable after 1 week, and about one-third remained so after 1 month.

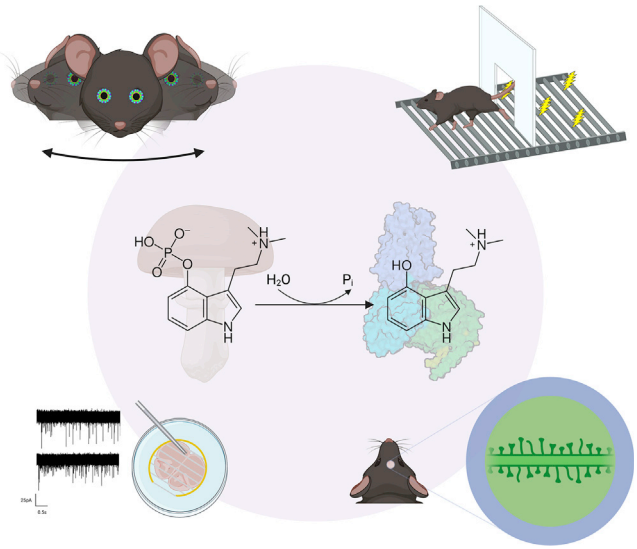

Figure 1. Figure 1. Psilocybin alters behavior and neuronal properties after a single administration

Psilocybin, found in mushrooms of the genus *Psilocybe*, is dephosphorylated *in vivo* into the 5-HT2AR agonist psilocin (center). At sufficient doses, systemic administration of psilocybin produces a hallucinogenic-like head-twitch response (top left) and promotes stress-related escape avoidance behaviors (top right) in mice. Additionally, psilocybin treatment remodels apical dendrite spines in cortical layer V pyramidal neurons, which can be monitored *in vivo* by two-photon microscopy (bottom right), and results in elevated glutamatergic synaptic function (bottom left). This figure was created with BioRender.com. Protein Data Bank entry 6WHA was used to create the 5-HT2AR icon.

Shao et al. next demonstrated that the morphological changes in these regions were correlated with elevated synaptic function. Since cortical layer V neurons receive dense glutamatergic innervation, the authors used whole-cell electrophysiology to record miniature excitatory postsynaptic currents (mEPSCs) in these cells. At 24 h after drug administration, they observed a significant increase in mEPSC frequency and a moderate increase in mEPSC amplitude in neurons from PSI- versus saline-treated mice. Given that many PSI-induced dendrites persist 1 month following treatment, it would be of interest to determine the extent to which this increased excitability is maintained over a longer period of time.

Shao et al. also examined infralimbic/prelimbic and motor cortex to determine if PSI's effects generalize across cortical areas. Using confocal microscopy, they again compared spine characteristics between PSI- versus saline-treated mice 24 h after drug administration. Although the changes they observed in these regions were less pronounced and inconsistent in the morphological parameters effected (e.g., protrusion length), the authors concluded that PSI broadly alters spines in cortical layer V pyramidal neurons. If spine remodeling is related to PSI's therapeutic effects, the heterogeneity across cortical areas observed in this study could provide clues to the locus or loci for PSI's potential therapeutic actions.

A particularly intriguing finding from this study is that pretreatment of mice with 1 mg/kg ketanserin, a 5-HT2A/CR antagonist, completely blocks PSI-evoked head twitches without significantly affecting spine remodeling in the cingulate/premotor cortex. A recent study by Hesselgrave et al. conducted in rats similarly found that 2 mg/kg ketanserin reduces PSI's ability to evoke head twitches but not its antidepressant-like behavioral effects in the forced-swim test (Hesselgrave et al., 2021). Shao et al. note, however, that ketanserin has poor brain penetration and that results could be different with more potent and selective 5-HT2AR antagonists. An alternative is that although 5-HT2ARs are necessary for psychedelics' hallucinogenic and hallucinogenic-like effects in humans and rodents, because PSI and other psychedelics activate many other serotonin receptors (Kim et al., 2020, Nichols, 2016), these "off-target" actions of PSI might be therapeutically important. As suggested by Hesselgrave et al. (2021), PSI and other psychedelics may exert their therapeutic actions by virtue of their robust polypharmacology.

This study by Shao et al. is the first to demonstrate an enduring action of a psychedelic drug on spine morphology *in vivo*. Indeed, a similar phenomenon has been observed in response to another rapid-acting antidepressant, the dissociative drug ketamine (Li et al., 2010). These convergent biological consequences to drugs diverging in their pharmacological sites of action merit further investigation, as the signaling pathways responsible for them may elucidate alternative drug targets with more direct action and greater clinical efficacy. While the behavioral consequences of psychedelic spine remodeling were not directly assessed by Shao et al., Moda-Sava et al. used a photoactivable, synapse-targeted Rac1 to optogenetically reverse ketamine-induced spine remodeling, blocking its lasting but not initial antidepressant-like effects (Moda-Sava et al., 2019). A similar approach may be useful for future studies to understand the necessity of psychedelic-induced spine remodeling to elicit and maintain a therapeutic response.

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Data-driven computational modeling predicts "superhubs" play key role in epileptic dynamics

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How individual neurons influence epileptic networks remains an open question. In this issue of *Neuron*, Hadjiabadi et al. (2021) use data-driven, computational models to predict the presence of "superhubs": highly connected neurons that drive network activity through feedforward motifs.

Computational models have become increasingly prominent in neuroscience research because of their ability to simulate highly complex interactions between elements of brain networks, provide a platform to make predictions about experimental outcomes, and perform computational experiments that might not be possible *in vivo* (Bansal et al., 2018). With the availability of experimental data that probe brain networks at high levels of spatial and temporal resolution, researchers can now incorporate these data into models to build increasingly specialized and/or personalized models of brain structure and function. While much work has focused on building brain network models at the macroscopic level and studying regional brain dynamics (Sanz-Leon et al., 2015), other recent work has involved microscopic models studying networks of neurons to probe how individual neurons impact network dynamics (Sadeh and Clopath, 2020). A key benefit of these brain network models is their ability to explore the link between brain structure and function in a controlled environment, which also makes them particularly appealing to study the role of network structure in pathological conditions such as epilepsy.

Epilepsy is one of the most common neurological disorders and is characterized by recurrent seizures that represent the abnormal activity of neurons. Seizures are generally observed at the macroscopic scale through electroencephalogram (EEG) or local field potential (LFP) signals and have been traditionally described as "hypersynchronous" activity of neurons. However, in the past decade as it has become possible to record the activity of individual neurons, it has become increasingly clear that neurons play a heterogenous role in seizure dynamics (Truccolo et al., 2011), and current research now strives to understand how the activity of individual neurons combines to give rise to seizure states (Wenzel et al., 2019). In this issue of *Neuron*, Hadjiabadi et al. (2021) take a data-driven, computational approach to this question and build models of epileptic circuits to explore the role of individual neurons in driving epileptiform dynamics. Importantly, the structure of these networks is constructed from and constrained by experimental data from two-photon imaging of neuronal activity, providing a further link between experimental and computational work.

Hadjiabadi et al. (2021) first study a model of acute seizures in zebrafish. Neuronal activity from both baseline and preseizure states is used to fit models of effective connectivity (directed network structure) between neurons for each state. Importantly, during the fitting process, the known regional connectivity of zebrafish is used as a constraint in order to encourage models that reflect the actual anatomy of the system. The authors then study the topology of the connectivity of the models, specifically looking for the presence of hub neurons—neurons with an unusually high number of connections.

Hub neurons have previously been shown to play a driving role in healthy synchronous brain activity in developing networks (Bonifazi et al., 2009), and computational modeling work has also predicted that the presence of hub neurons would