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Authors

Saeger, Hannah N
Olson, David E

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Psychedelic-Inspired Approaches for Treating Neurodegenerative Disorders

Hannah N. Saeger[1], **David E. Olson**[2,3,4,*]

[1]Pharmacology and Toxicology Graduate Group, University of California, Davis, Davis, CA, USA.

[2]Department of Chemistry, University of California, Davis, One Shields Avenue, Davis, CA 95616, USA

[3]Department of Biochemistry & Molecular Medicine, School of Medicine, University of California, Davis, 2700 Stockton Blvd, Suite 2102, Sacramento, CA 95817, USA

[4]Center for Neuroscience, University of California, Davis, 1544 Newton Ct, Davis, CA 95618, USA

Abstract

Psychedelics are increasingly being recognized for their potential to treat a wide range of brain disorders including depression, post-traumatic stress disorder (PTSD), and substance use disorder. Their broad therapeutic potential might result from an ability to rescue cortical atrophy common to many neuropsychiatric and neurodegenerative diseases by impacting neurotrophic factor gene expression, activating neuronal growth and survival mechanisms, and modulating the immune system. While the therapeutic potential of psychedelics has not yet been extended to neurodegenerative disorders, we provide evidence suggesting that approaches based on psychedelic science might prove useful for treating these diseases. The primary target of psychedelics, the 5-HT_{2A} receptor, plays key roles in cortical neuron health and is dysregulated in Alzheimer's disease. Moreover, evidence suggests that psychedelics and related compounds could prove useful for treating the behavioral and psychological symptoms of dementia (BPSD). While more research is needed to probe the effects of psychedelics in models of neurodegenerative diseases, the robust effects of these compounds on structural and functional neuroplasticity and inflammation clearly warrant further investigation.

Graphical Abstract

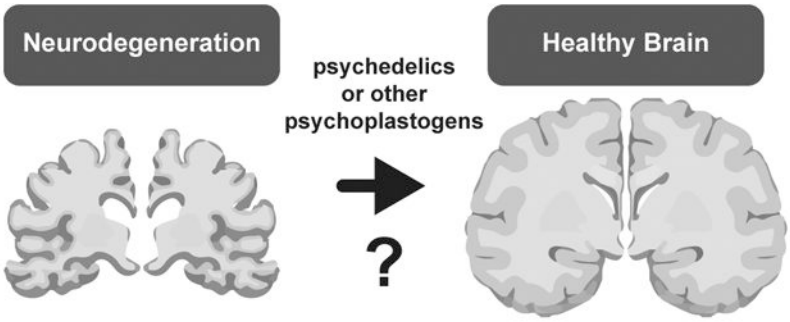
*Corresponding Author: David E. Olson, deolson@ucdavis.edu.

Author Contributions

DEO wrote the abstract, introduction, conclusion, and several sections in the body of this review. HNS wrote the section on the effects of psychedelics on inflammation. All authors were involved in editing the final version of the manuscript.

Disclosure

David E. Olson is a co-founder and chief innovation officer of Delix Therapeutics, Inc.



Increasing evidence suggests that psychedelics have potential for treating various neuropsychiatric disorders, but it is currently unclear if their therapeutic potential extends to neurodegenerative conditions like Alzheimer's disease. Here, we review the effects of psychedelics that might be relevant to treating neurodegenerative diseases including their abilities to promote cortical neuron growth and reduce inflammation. We also discuss how psychedelics might treat the cognitive, behavioral, and psychological symptoms of dementia. Finally, we describe the unique properties of ayahuasca and non-hallucinogenic psychoplastogens that make them attractive as potential treatments for neurodegenerative diseases.

Keywords

Psychedelic; psychoplastogen; psilocybin; neuroplasticity; ayahuasca; neurodegeneration; Alzheimer's disease; frontotemporal dementia; BPSD

INTRODUCTION

The atrophy of dendritic arbors, loss of dendritic spines, and reduction of synapse density in cortical regions controlling cognition, memory, and mood are hallmarks of Alzheimer's disease (AD), frontotemporal dementia (FTD), and related neurodegenerative disorders (Pini et al. 2016; Former et al. 2017; Scheff et al. 2014; Jack et al. 2010). In fact, progressive loss of spines and synapses is a strong correlate of the degree of dementia (Selkoe et al. 2014; Dorostkar et al. 2015; Pchitskaya et al. 2018; Terry et al. 1991). Moreover, neuroinflammation is increasingly being recognized as a critical component of AD pathophysiology (Hong et al. 2016). Neuropsychiatric disorders share many common features with AD and related dementias including cortical atrophy, synapse loss, and inflammation (Christoffel et al. 2011; Duman and Aghajanian 2012; Qiao et al 2016; Russo et al. 2009; Russo et al. 2013; Izquierdo et al. 2006; Autry and Monteggia 2012; Duman et al. 2016; Raison 2016). As in various depressive and anxiety disorders, atrophy of key neurons in the prefrontal cortex (PFC) that regulate motivation, fear, and reward is likely a contributing factor to the depression and anxiety experienced by many patients with dementia. Thus, compounds capable of both promoting cortical neuron growth and modulating neuroinflammation have enormous therapeutic potential.

Recent evidence suggests that psychedelics stimulate 5-HT_{2A} receptors to potently promote cortical neuron growth, activate neuronal survival mechanisms, and modulate the immune system (Ly et al. 2018; Aleksandrova and Phillips 2021; Savalia et al. 2021; Banks et

al. 2021; Inserra et al. 2021; Artin et al. 2021). These characteristics have made them attractive experimental treatments for neuropsychiatric disorders characterized by cortical atrophy such as depression, post-traumatic stress disorder (PTSD), and substance use disorder (SUD) (Mithoefer et al. 2016; Carhart-Harris and Goodwin 2017; Nichols et al. 2017; Vollenweider and Kometer 2010). In fact, psychedelics have distinguished themselves as promising medicines as they elicit therapeutic responses in multiple neuropsychiatric disorders (Dos Santos et al. 2016) and produce beneficial effects that can last for months following a single administration (Kyzar et al. 2017). Several large clinical trials in the neuropsychiatric disease space have demonstrated impressive effect sizes for psychedelic-assisted therapy (Mitchell et al. 2021; Davis et al. 2021; Carhart-Harris et al. 2021). The ability of psychedelics to promote cortical neuron growth and plasticity has been proposed as a potential mechanism explaining why psychedelics produce therapeutic effects across a variety of disparate diseases (Vargas et al. 2021; Kočárová et al. 2021). As cortical atrophy underlies many symptoms of neurodegenerative diseases related to mood, memory, and cognition, it is reasonable to hypothesize that psychedelics and related compounds might prove useful for treating these patients as well. Furthermore, 5-HT_{2A} receptor density has consistently been shown to be reduced in AD and related disorders (Blin et al. 1993; Hasselbalch et al. 2008; Santhosh et al. 2009; Marner et al. 2011; Huey et al. 2006) and this loss does not appear to be due to a loss of serotonergic innervation (Marner et al. 2012). Furthermore, postmortem and positron emission tomography (PET) imaging studies have shown that the loss of 5-HT_{2A} receptors in the cortex of AD and FTD patients correlates well with the rate of cognitive decline (Franceschi et al. 2005; Lai et al. 2005). In preparation for future clinical studies assessing the ability of LSD to treat and/or prevent AD, a phase 1 tolerability study was recently performed (Family et al. 2020). Though direct evidence supporting the use of psychedelics for treating neurodegenerative disorders is lacking, this review outlines reasons why the use of psychedelics or related plasticity-promoting molecules should be explored as potential treatments for AD and related dementias. For other perspectives, we point the reader to recent related reviews (Kozlowska et al. 2021; Vann Jones et al. 2020).

Effects of psychedelics on neuronal growth and survival signaling

To promote neuronal growth and survival, nature utilizes growth factors that bind to receptor kinases, which activate signaling cascades ultimately leading to the production of cytoskeletal proteins and ion channels necessary for changes in neuronal morphology and excitability (Switon et al. 2017). Of these growth factors, brain-derived neurotrophic factor (BDNF) plays a preeminent role in plasticity due to the ubiquitous expression of its high affinity receptor TrkB in the brain (Yan et al. 1997). Levels of BDNF and TrkB are reduced in Alzheimer's disease (Phillips et al. 1991; Connor et al. 1997; Ferrer et al. 1999), and deficiencies in BDNF/TrkB signaling can exacerbate AD phenotypes (Wu et al. 2021; Xia et al. 2020; Wang et al. 2019).

While BDNF is known to produce positive effects in various models of AD (Nagahara et al. 2009; Jiao et al. 2016; Nigam et al. 2017; Arancibia et al. 2008), its proteinaceous nature prevents it from crossing the blood-brain barrier, rendering it of little use as a therapeutic. Thus, several groups have endeavored to identify small molecule TrkB agonists (Longo

et al. 2013). The putative TrkB agonist 7,8-dihydroxyflavone (7,8-DHF) and the related optimized compound CF_3CN have both been shown to improve spatial memory in mouse models of AD (Castello et al. 2014; Chen et al. 2021). While this approach is promising, it suffers from a lack of specificity given that TrkB is widely expressed across the brain. In fact, induced neuroplasticity can lead to drastically different behavioral effects depending on the brain regions and circuits involved. For example, infusion of BDNF into the medial prefrontal cortex (PFC) reduces drug-seeking behavior and the expression of fear, while direct injections into the nucleus accumbens or amygdala tend to have the opposite effects (Peters et al. 2010; Whitfield et al. 2011; McGinty et al. 2010; Penzo et al. 2015). This lack of anatomical restriction has plagued the development of brain-penetrant small-molecule agonists of TrkB receptors due to the potential for serious on-target side effects such as epilepsy, pain, and tumor formation (Longo et al. 2013).

Like BDNF and TrkB agonists, psychedelics share the ability to activate the mammalian target of rapamycin (mTOR)—a key kinase involved in neuronal growth and survival. However, psychedelic-induced mTOR activation is dependent on 5-HT_2 receptors (Ly et al. 2018; De La Fuente Revenga et al. 2021; De Gregorio et al. 2021), which are expressed in multiple brain regions involved in sensory processing and cognition with particularly high expression in layer V pyramidal neurons of the cerebral cortex—the same neurons that undergo atrophy in AD and FTD. The expression pattern of 5-HT_{2A} receptors has been confirmed using immunohistochemistry (Cornea-Hébert et al. 1999; Xu et al. 2000; Willins et al. 1997; Miner et al. 2003), light and electron microscope immunocytochemistry (Cornea-Hébert et al. 1999), in situ hybridization (Amargós-Bosch et al. 2004; Santana et al. 2004; Burnet et al. 1995), receptor autoradiography (Quirion et al. 1985; Pazos et al. 1987), and transgenic mice expressing GFP under control of the 5-HT_{2A} receptor promoter (Weber and Andrade 2010).

The mechanisms by which psychedelics promote neuronal growth have not been fully elucidated. Although classic psychedelics exhibit complex receptor pharmacology, they exert their primary effects through activation of 5-HT_{2A} receptors (Nichols 2004; Nichols 2016). The affinities of psychedelics for the 5-HT_{2A} receptor correlate well with both their human hallucinogenic potencies (Glennon et al. 1984) and their effects in the mouse head-twitch response (HTR) assay (Halberstadt et al. 2020)—a behavioral proxy for hallucinations with high predictive validity (Hanks and González-Maeso 2013). Moreover, genetic knockout (KO) of 5-HT_{2A} receptors eliminates psychedelic-induced HTR in mice (González-Maeso et al. 2007), and blocking 5-HT_2 receptors using ketanserin abolishes the subjective effects of both psilocybin (Vollenweider et al. 1998) and LSD (Preller et al. 2018; Holze et al. 2021) in humans.

In addition to mediating the hallucinogenic effects of psychedelics, the 5-HT_{2A} receptor also seems to play a critical role in their plasticity-promoting properties. Psychedelics induce immediate early gene (IEG) expression through activation of 5-HT_{2A} receptors, and many of these IEGs have been implicated in neuroplasticity (Martin and Nichols 2018). One of the most consistent findings is that psychedelics like 2,5-dimethoxy-4-iodoamphetamine (DOI) and lysergic acid diethylamide (LSD) increase *c-Fos* expression in the cortex (Leslie et al. 1993; Frankel et al. 2002; Erdtmann-Vourliotis et al. 1999), and that this effect can

be blocked by 5-HT_2 antagonists (Leslie et al. 1993; Gresch et al. 2002). Most 5-HT_2 antagonists cannot reliably distinguish between 5-HT_{2A} and 5-HT_{2C} receptors, which are both widely expressed in the brain. However, studies using 5-HT_{2A} receptor KO mice suggest that psychedelic-induced immediate early gene expression is primarily dependent on activation of 5-HT_{2A} receptors (González-Maeso et al. 2003; González-Maeso et al. 2007).

Psychedelic-induced IEG expression is restricted to specific brain regions. For example, *c-Fos* expression in the cortex, but not the hippocampus is commonly observed following administration of psychedelics such as DOI and psilocybin (Leslie et al. 1993; Jefsen et al. 2021). This expression pattern likely reflects the fact that 5-HT_{2A} receptors are highly expressed in excitatory pyramidal neurons in the cortex, but in the hippocampus, their expression is primarily localized to inhibitory interneurons (Cornea-Hébert et al. 1999; Wright et al. 1995). In the cortex of animals administered DOI, *Fos* positive cells exhibited higher expression of 5-HT_{2A} receptors (but not 5-HT_{2C} receptors) as compared to *Fos* negative cells (Martin and Nichols 2016). Other psychedelic-induced IEGs, such as *arc*, exhibit a similar cortical expression pattern as *c-Fos* (Pei et al. 2000; Pei et al. 2004). Additional IEGs induced by psychedelics that are implicated in plasticity mechanisms include *egr-1*, *egr-2, MKP-1*, and *C/EBP-β* (Gonzalez-Maeso et al. 2003; Nichols and Sanders-Bush 2002; Nichols et al. 2003; Nichols and Sanders-Bush 2004).

While IEGs have been indirectly linked to plasticity mechanisms, a more direct link between psychedelics and neuroplasticity was established when Duman and co-workers reported that DOI can modulate *BDNF* gene expression (Vaidya et al. 1997). As with studies of psychedelic-induced IEG expression, they found that *BDNF* transcript levels increased in the cortex, but decreased in the hippocampus, following administration of DOI. Both effects were blocked by the 5-HT_2 antagonist ketanserin (Vaidya et al. 1997). DOI-induced upregulation of cortical *BDNF* can be enhanced and inhibited by mGlu2R antagonists and agonists, respectively (Gewirtz et al. 2002). Thus, it has been proposed that psychedelics increase glutamate release via a presynaptic mechanism (Aghajanian and Marek 1997; Marek and Aghajanian 1999), potentially involving a putative 5-HT_{2A}-mGlu2R heterodimer (González-Maeso et al. 2008; Fribourg et al. 2011; Shah et al. 2020). Presumably, this increase in glutamate stimulates AMPA receptors leading to upregulation of *BDNF* transcription. By stimulating cell survival and growth mechanisms, BDNF is believed to positively impact outcomes of neurodegenerative disorders (Zuccato and Cattaneo 2009). The fact that psychedelics induce *BDNF* transcription in the cortex, but not the hippocampus, suggests that psychedelics might be particularly useful for treating neurodegenerative disorders characterized by cortical atrophy such as FTD.

While psychedelics reliably increase cortical *BDNF* transcription in vivo, similar increases in BDNF protein levels have not been observed (Ly et al. 2018; Marton et al. 2019), likely due to the known issues with quantifying BDNF from cortical tissue. In contrast, BDNF quantification in serum is much more reliable (Elfving et al. 2010; Naegelin et al. 2018; Polacchini et al. 2015), and several groups have demonstrated that psychedelics increase serum levels of mature (Holze et al. 2021; Hutten et al. 2021) or total BDNF (De Almeida et al. 2019). While the origin of serum BDNF is likely outside the brain (Chacón-Fernández et al. 2016), serum levels of BDNF may correlate with changes observed in the brain

(Molendijk et al. 2014). It is also important to consider that several isoforms of BDNF have been identified, with pro-BDNF being cleaved by intracellular and extracellular proteases to produce mature BDNF (Foltran and Diaz 2016). In contrast to mature BDNF, pro-BDNF acts through the p75 neurotrophin receptor and exerts opposing effects on neuronal function and structure (Foltran and Diaz 2016; Mizui et al. 2014; Woo et al. 2005). Studies to date have largely focused on the quantification of mature or total BDNF following the acute administration of psychedelics (Holze et al. 2021; De Almeida et al. 2019), leaving little known about the direct effects of psychedelics on pro-BDNF levels.

Most studies to date have focused on psychedelic-induced changes in BDNF expression. However, it is possible that psychedelics may impact the expression of other neurotrophic factors as well. For example, Ron and co-workers demonstrated that ibogaine, a psychoactive drug with effects similar to serotonergic psychedelics, increases *glial-derived neurotrophic factor (GDNF)* expression in the midbrain (He et al. 2005), and Carrera and co-workers extended this finding by demonstrating that GDNF proteins levels are elevated as well (Marton et al. 2019). Given the importance of GDNF for the survival and health of dopaminergic neurons of the midbrain (Lin et al. 1993; Granholm et al. 2000), compounds like ibogaine could prove useful for the treatment of Parkinson's disease (PD) in addition to addiction. A large number of ibogaine analogs have been developed (Iyer et al. 2020); however, relatively few have been tested for their effects on GDNF (Gassaway et al. 2016).

Links between the serotonergic system and neurotrophic factor signaling are well established (Mattson et al. 2004; Popova et al. 2017), but changes in the expression of neurotrophic factors only provides indirect evidence that psychedelics may impact neuronal structure and/or survival. Penzes and co-workers provided the first piece of evidence directly suggesting that psychedelics could impact structural plasticity. They showed that in cortical cultures, DOI transiently increased pyramidal neuron dendritic spine size during the first 30 mins of treatment, but spine size returned to normal within an hour (Jones et al. 2009). This increase in dendritic spine size was later found to be dependent on 5-HT_{2A}/5-HT_{2C}-mediated activation of transglutaminase, Rac1, and Cdc42 (Mi et al. 2017). Shiga and co-workers later demonstrated that treatment of embryonic rat cortical cultures with DOI for 24 h led to an increase in spine density (Yoshida et al. 2011).

In 2018, our group provided the first direct evidence that psychedelics produce long-lasting changes in neuronal structure not only in vitro, but also in vivo and across species (Ly et al. 2018). These long-lasting changes in neuronal structure could possibly explain their sustained therapeutic effects after a single administration (Barrett et al. 2020). Treatment with psychedelics from a variety of distinct chemical scaffolds (e.g. tryptamine, amphetamine, ergoline) led to robust increases in neuritogenesis, spinogenesis, and synaptogenesis in culture, and these effects were dependent on activation of 5-HT_2 receptors. Moreover, a single administration of *N,N*-dimethyltryptamine (DMT) increased dendritic spine density in vivo and also increased both the amplitude and frequency of spontaneous excitatory postsynaptic currents (sEPSCs) in the PFC of rats (Ly et al. 2018). Importantly, these structural and functional changes lasted long after the drug had been cleared from the body. Using two-photon imaging in live animals, we demonstrated that DOI increases the rate of spine formation over the course of 24 h without impacting the

rate of spine elimination (Cameron et al. 2021). Kwan and co-workers recently extended our findings by demonstrating that a single dose of psilocybin increases cortical spine density in mice for at least a month (Shao et al. 2021). These changes in neuronal structure are accompanied by changes in protein expression. Using human cerebral organoids, Rehen and co-workers performed proteomic studies to demonstrate that 5-MeO-DMT modulates levels of proteins associated with microtubule dynamics and cytoskeleton rearrangement (Dakic et al. 2017).

The long-lasting effects of psychedelics on neuronal structure could be explained by their ability to activate AMPA receptors, TrkB receptors, and mTOR signaling. In fact, short stimulations (15 min – 1 h) are sufficient for psychedelics to turn on growth signaling in cortical neurons lasting for an extended period of time (Ly et al. 2020a). Psychedelic-induced growth is completely blocked by inhibitors of AMPA receptors, TrkB, or mTOR and these proteins are known to be involved in an autoregulatory feedback loop. Activation of AMPA receptors leads to BDNF secretion (Jourdi et al. 2009; Takei et al. 2004), which stimulates TrkB ultimately resulting in the activation of mTOR and the production of proteins necessary for neuronal growth including additional BDNF. BDNF can then induce glutamate release in cortical neurons via a nonexocytotic pathway (Takei et al. 1998), which could lead to sustained AMPA receptor activation. It seems that psychedelics serve as a catalyst to initiate this growth process. Activation of neurotrophic factor signaling pathways by psychedelics could potentially mitigate neuronal loss observed in neurodegenerative disorders, or even regrow lost neurites, spines, and synapses. However, overactivation of mTOR has been associated with Alzheimer's disease (Hoeffer and Klann 2010; Oddo 2012), so it will be important to demonstrate that psychedelics do not exacerbate phenotypes in rodent models of Alzheimer's disease.

While several therapeutic approaches have emerged targeting synaptogenesis for the treatment of neurodegenerative disorders (Jackson et al. 2019), psychedelics might offer several advantages given that they also promote spinogenesis and dendritogenesis in addition to promoting synapse formation in the cortex. For example, the marine natural product bryostatin 1 has entered clinical trials for Alzheimer's disease (Farlow et al. 2019; Nelson et al. 2017) due to its robust synaptogenic effects; however, bryostatin 1 actually decreases dendritic spine density in cortical cultures (Ly et al. 2020b), which is in sharp contrast to the effects of psychedelics.

In addition to promoting structural and functional neuroplasticity via activation of 5-HT_{2A} receptors, many psychedelics also target a number of other serotonin receptors implicated in plasticity and neurodegenerative diseases including 5-HT_6 and 5-HT_7receptors (Quiedeville et al. 2014; Upton et al. 2008; Meneses 2014; Speranza et al. 2017; Crispino et al. 2020). The unique polypharmacology of specific psychedelics might offer advantages (Oña and Bouso 2021) when trying to develop medicines for complex disorders like neurodegenerative diseases.

Role of the 5-HT_{2A} receptors in mitochondrial function

Mitochondrial dysfunction, which can lead to oxidative stress, is a hallmark of many neurodegenerative diseases including AD, PD, and Huntington's disease (HD) (Wang et al.

2019). Furthermore, impaired mitochondrial biogenesis is evident in patients with AD and PD (Sheng et al. 2012; Thomas et al. 2012). Using a combination of selective antagonists and KO animals, Vaidya and co-workers demonstrated that activation of 5-HT_{2A} receptors promotes mitochondrial biogenesis and improves mitochondrial function, potentially improving the ability of neurons to buffer stress (Fanibunda et al. 2019). In cortical cultures, stimulation of 5-HT_{2A} receptors with DOI protected neurons against both kainate- and H_2O_2-induced cell death (Fanibunda et al. 2019). Moreover, mitochondrial biogenesis was promoted by both the hallucinogenic 5-HT_{2A} agonist DOI and the non-hallucinogenic agonist lisuride (Fanibunda et al. 2019). This effect does not seem to be limited to neurons, as other cell types expressing 5-HT_{2A} receptors will undergo mitochondrial biogenesis and/or increase mitochondria oxidative capacity following stimulation with 5-HT_{2A} agonists (Rasbach et al. 2010; Harmon et al. 2016; Damiano et al. 2021).

Effects of psychedelics on the immune system

In addition to promoting neuronal growth and simulating mitochondrial biogenesis, psychedelics produce potent anti-inflammatory effects by binding to 5-HT_{2A} receptors on immune cells in the periphery (Szabo 2015; Flanagan et al. 2018). The first evidence suggesting that psychedelics might have anti-inflammatory effects was reported by Miller and co-workers. They found that DOI inhibits inducible nitric oxide synthase (iNOS) activity in cultured C6 glioma cells via activation of 5-HT_{2A} receptors (Miller and Gonzalez 1998; Miller et al. 1997). However, this finding remained largely unexplored until 2008, when Nichols and co-workers demonstrated that in cultured rat aortic smooth muscle cells, DOI potently inhibits proinflammatory gene expression in response to TNF-α (IC_{50}s in the pM range) (Yu et al. 2008). Subsequent studies from the Nichols laboratory further supported the anti-inflammatory effects of psychedelics. Not only does DOI block generalized TNF-α-induced inflammation in vivo, it also prevents symptoms of allergic asthma and TH2 cell polarization in mice (Nau et al. 2015; Flanagan et al. 2019a) as well as reduces the expression of inflammatory markers in mice fed a high-fat diet (Flanagan et al. 2019b). These important findings inspired future structure-activity relationship studies that identified a putative anti-inflammatory pharmacophore and extended anti-inflammatory properties beyond amphetamines to other chemical classes of serotonergic psychedelics (Flanagan et al. 2021). Taken together, these studies support the role of 5-HT_{2A} receptors in both innate and adaptive immune responses. Alongside these studies, other research groups have demonstrated that the naturally occurring psychedelics DMT and 5-MeO-DMT produce immunomodulatory effects through inhibition and downregulation of the NF-κB signaling pathway in human iPSC-derived cerebral organoids (Dakic et al. 2017), and inhibition of LPS-induced inflammation in cultured human monocyte-derived dendritic cells (Szabo et al. 2014).

The anti-inflammatory effects of psychedelics have primarily been studied in vitro and have focused on the peripheral immune system. While evidence suggests that reducing peripheral inflammation could have beneficial effects for treating neurodegenerative disorders (Wood 2018), the role of neuroinflammation in disease pathophysiology is increasingly being recognized. Aberrant pro-inflammatory signaling in the CNS due to the presence of persistent insult can disrupt a myriad of processes leading to excessive synaptic pruning,

synaptic dysfunction, reduced blood-brain barrier integrity, and neuronal death (Heneka et al. 2014; Lyman et al. 2014). Though chronic neuroinflammation is present in most neurodegenerative diseases (Lyman et al. 2014; Haim et al. 2015; Pekny et al. 2016; Von Bernhardi et al. 2010), this review will focus on neuroinflammation induced by β-amyloid accumulation associated with Alzheimer's Disease (AD).

Oligomeric Aβ species have been shown to activate several glial pattern recognition receptors including Toll-like receptors (TLRs), triggering receptors expressed on myeloid cells 2 (TREM2), α6β1 integrin, CD14, CD47, and scavenger receptors such as CD36. The binding of Aβ species to these receptors ultimately leads to increased phagocytic activity and the release of pro-inflammatory cytokines such as TNF-α and IL-1β, chemokines, and reactive oxygen and nitrogen species (Von Bernhardi et al. 2010; Heppner et al. 2015; Venegas and Heneka 2017; Liu et al. 2012; Murgas et al. 2012; Alawieyah Syed Mortadza et al. 2018; Husemann et al. 2001; Ulland and Colonna 2018). Upon activation, both microglia and astrocytes exhibit phenotypic and functional changes, such as the release of inflammatory signaling molecules and digestive enzymes, retraction of their surveilling processes, and increased phagocytic activity to neutralize and clear the triggering insult (Sofroniew and Vinters 2010; Alvarex et al. 2008; Rouach et al. 2008; Eroglu and Barres 2010; Jessen et al. 2015; Liddelow and Barres 2017). These reactive states come at the expense of protective and supportive functions normally performed by these cell types (Hong et al. 2016; Alvarex et al. 2013; Liddelow et al. 2017; Lian et al. 2015; Lian et al. 2016) and eventually lead to detrimental effects in the CNS such as excessive synaptic pruning (Salter and Stevens 2017; Stephan et al. 2012) and triggering of apoptotic pathways (Allaman et al. 2010; Yan et al. 2013; Kisler et al. 2017; Winkler et al. 2015; Van Kralingen et al. 2014; Wang et al. 2012). Evidence suggests that over time, excessive stimulation of glial cells can lead to a shift from a hyperresponsive state to a dystrophic states characterized by decreased immunosurveillance, loss of homeostatic functions, and dysregulated phagocytic activity, allowing for further accumulation of neurotoxic Aβ species (Heppner et al. 2015; Venegas and Heneka 2017; Tischer et al. 2016; Streit et al. 2009; Minett et al. 2016; Varnum and Ikezu 2012). Given the expression of 5-HT_2 receptors on glial cells, it is possible that 5-HT_2 ligands like psychedelics could impact neuroinflammation.

The 5-HT_{2A} receptor is expressed in nearly all immune cell types including cells derived from the macrophage lineage such as microglia (Glebov et al. 2015; Herr et al. 2017; Minje et al. 2020; Wu et al. 2019; Baganz and Blakely 2013) as well as astrocytes (Willins et al. 1997; Wu et al. 1999). Moreover, most serotonergic psychedelics have high affinities for the 5-HT_{2B} and 5-HT_{2C} receptors, which are also expressed on most immune cells including microglia and astrocytes (Herr et al. 2017; Minjie et al. 2020; Wu et al. 2019; Baganz and Blakely 2013; Glebov et al. 2015). In general, serotonin activates innate immune responses and increases pro-inflammatory signaling; however, the effects of serotonin on inflammation are complex and depend on receptor profiles of the specific cells stimulated (Herr et al. 2017; Minjie et al. 2020; Wu et al. 2019; Baganz and Blakely 2013). Selective engagement of 5-HT_{2A} receptors on immune cells of macrophage lineage tends to be anti-inflammatory. The 5-HT_{2A} receptor agonist DOI was shown to potently dampen peripheral TNF-α-induced inflammatory signaling in vivo, an effect that was abolished in 5-HT_{2A} receptor KO mice

(Nau et al. 2013; Nau et al. 2015; Flanagan et al. 2019; Flanagan et al. 2021). However, whether similar effects are observed in the CNS is just starting to be investigated.

In 2011, Kettenmann and co-workers demonstrated that DOI promotes microglial migration and decreases the phagocytic activity of cultured neonatal microglia (Krabbe et al. 2012). Walter and co-workers later showed that activation of 5-HT_2 receptors on microglia promotes the release of exosomes in vitro (Glebov et al. 2015). Finally, the non-selective 5-HT1 and 5-HT_2 receptor agonist meta-chlorophenylpiperazine (mCPP) dampened the production of TNF-α and IL-1β in glial cultures stimulated with LPS (Hwang et al. 2008)_. Pro-inflammatory cytokines released by activated microglia including TNF-α and IL-1β upregulate enzymes involved in the production of pathogenic Aβ through activation of NF-κB (Chen et al. 2012). In addition to activated pro-inflammatory microglia, dystrophic or senescent microglia are also observed in close proximity to Aβ plaques (Tischer et al. 2016; Streit et al. 2018; Streit et al. 2020). These dystrophic microglia, which are thought to arise from chronic exposure to Aβ species, contribute to disease progression by releasing pro-inflammatory factors why failing to phagocytose and degrade Aβ species (Ritzel et al. 2019; Angelova et al. 2019; Hickman et al. 2008). In unpublished work, Kozłowska, Figiel, and co-workers demonstrated that the classic psychedelics psilocin and DMT reduce expression of pro-inflammatory markers and increase expression of TREM2 on microglia in vitro (Kozlowska et al. 2021), which is associated with protective microglial responses to Aβ (Ulland and Colonna 2018; Wang et al. 2015; Wang et al. 2016).

In the developing CNS, microglia prune immature synapses upon recognition of the complement proteins C1q and C3, a function that is crucial for the proper formation of neural circuits. However, activation of these complement pathways have implications for neurodegenerative diseases as well (Salter and Stevens 2017; Stephan et al. 2012; Schafer et al. 2012; Paolicelli et al. 2011). Elevated levels of C1q and C3 have been observed in AD mouse models (Hong et al. 2016; Stephan et al. 2012), and Aβ species can lead to C1 activation (Tacnet-Delorme et al. 2001). The loss of dendritic spines and synapses is believed to contribute to cognitive decline in AD and is observed near Aβ plaques (Hong et al. 2016; Stephan et al. 2012; Spires-Jones et al. 2007). Since 5-HT_{2A} receptor activation has been shown to reduce microglial phagocytic activity in vitro (Krabbe et al. 2012), it is possible that psychedelics could reduce excessive synaptic pruning characteristic of neurodegenerative disorders and thereby slow cognitive decline. Taken together, these studies support the therapeutic potential of 5-HT_{2A} ligands for modulating aberrant microglial function and neuroinflammation characteristic of AD, though additional research is warranted.

Compared to microglial 5-HT_{2A} receptors, less is known about the function of astroglial 5-HT_{2A} receptors. Elevated astrocyte 5-HT_{2A} receptor expression has been noted in patients with neurodegenerative diseases (Wu et al. 1999), suggesting it could play a role in disease pathology. Activation of astrocytic 5-HT_2 receptors has been shown to increase intracellular Ca^{2+} levels via Gq-mediated signaling (Hagberg et al. 1998) which may lead to the release of gliotransmitters to modulate synaptic function (Agulhon et al. 2008) and trophic factors such as S100β (Tramontina et al. 2008).

In general, reduction of pro-inflammatory signaling appears to be beneficial in AD. The anti-inflammatory antibiotic minocycline reduced levels of TNF-α, reduced levels of IL-1β, and improved spatial memory in a mouse model of AD (Garcez et al. 2017), The caspase-1 inhibitor VX-765 slows the accumulation of Aβ and reduces neuroinflammation, resulting in improvements of AD-associated cognitive function in the J20 AD mouse model (Flores et al. 2018). These studies suggest that decreasing TNF-α- and IL-1β-associated neuroinflammation can alleviate AD pathology and symptoms. Considering that psychedelics suppress TNF-α-induced inflammation in the periphery (Nau et al. 2015; Flanagan et al. 2019a; Flanagan et al. 2019b; Flanagan et al. 2021), it is plausible that psychedelics might attenuate AD-associated neuroinflammation by improving microglial function.

Psychedelics and the cognitive, behavioral, and psychological symptoms of dementia

The impact of 5-HT_{2A} receptor activation on learning and memory is complex (Zhang and Stackman 2015), with psychedelics producing both positive and negative effects on memory in humans (Healy 2021). In preclinical models, there is some evidence that psychedelics can facilitate learning and memory under specific conditions. For example, bulbectomised rats exhibit deficits in active avoidance learning that can be reversed by LSD (Buchborn et al. 2014). Additionally, stimulation of 5-HT_{2A} receptors can enhance object recognition and fear memory depending on exactly when the compound is administered (Zhang et al. 2013). Finally, activation of 5-HT_{2A} receptors in the medial septum-diagonal band of Broca complex with TCB-2 has been shown to improve working memory in rats exhibiting hemiparkinsonism (Li et al. 2015).

While evidence suggesting that psychedelics might improve memory in patients with dementia is relatively weak, it is more reasonable to hypothesize that these compounds will impact the behavioral and psychological symptoms of dementia (BPSD), which include, but are not limited to, depression, anxiety, and hallucinations (Cerejeira et al. 2012)—symptoms that decrease quality of life for both the patient and their caregivers. Nearly 90% of AD patients exhibit BPSD, and these are believed to result at least in part from disruptions to the serotonergic system (Chakraborty et al. 2012). Given the numerous clinical trials indicating that psychedelics produce rapid and sustained antidepressant effects (Davis et al. 2021; Carhart-Harris et al. 2021; Carhart-Harris et al. 2016), reduce anxiety in patients with terminal cancer (Grob et al. 2011) and are effective at treating post-traumatic stress disorder (Mitchell et al. 2021; Bouso et al. 2008; Mithoefer et al. 2011), it seems logical that they might help to ameliorate BPSD.

The clinical effects of psychedelics on mood and anxiety have been bolstered by several preclinical studies. Psilocybin has been shown to promote fear extinction in mice (Catlow et al. 2013), and produce long-lasting antidepressant like effects in rats subjected to the forced swim test (Hibicke et al. 2020). Similarly, both a single high dose of DMT or chronic, intermittent low doses facilitates fear extinction and produces antidepressant-like effects in the forced swim test in rats (Cameron et al. 2018; Cameron et al. 2019). Psilocybin has also been shown to decrease stress-induced anhedonia as measured using the sucrose

preference and female urine stiffing tests (Hesselgrave et al. 2021), and psilocybin reduced the proportion of escape failures in a learned helplessness paradigm (Shao et al. 2021).[13]

Many of the antidepressant and anxiolytic effects of psychedelics observed in preclinical species are known to involve the PFC (Vargas et al. 2021).[3] Thus, it is perhaps unsurprising that psychedelics have profound effects on both the structure and function of layer V pyramidal neurons in the PFC. Both LSD and DOI have been shown to elevate glutamate release in the PFC via stimulation of 5-HT_{2A} receptors (Muschamp et al. 2004; Scruggs et al. 2000), and single-unit recordings have revealed that LSD leads to excitation of the prefrontal cortex (Inserra et al. 2021). In fact, the PFC has been the most studied locus of psychedelic action, and our group recently reported that psychedelics promote both structural and functional plasticity in layer V pyramidal neurons of the PFC (Ly et al. 2018), possibly explaining the sustained antidepressant-like effects of these drugs in rodent behavioral tests relevant to mood and anxiety. Due to degeneration of the frontal cortex, FTD primarily manifests as deficits in executive function including apathy and impaired emotional regulation. Reversal of neuronal atrophy in the frontal cortex therefore has the potential to slow progression of the disease and alleviate the psychiatric symptoms that accompany it.

Though evidence suggests that psychedelics might be effective in treating BPSD related to depression and anxiety, they might exacerbate dementia-related psychosis. In fact, psychedelic-assisted psychotherapy is contraindicated for patients suffering from schizophrenia or related psychotic illnesses (Vargas et al. 2021). Moreover, 5-HT_{2A} antagonists are commonly prescribed for the treatment of dementia-related psychosis and the selective 5-HT_{2A} antagonist pimavanserin was recently approved by the FDA for Parkinson’s disease psychosis (Cummings et al. 2020).

Unique Properties of Ayahuasca

The abilities of psychedelics to target multiple receptors at once likely plays a significant role in their therapeutic properties (Oña et al. 2021). Moreover, many psychedelics are commonly ingested as components of botanical mixtures, and the unique polypharmacology profiles of these mixtures could potentially have synergistic effects (Oña et al. 2020). Perhaps the best-known example of a psychedelic-related botanical mixture with unique properties compared to its individual components is the Amazonian tisane ayahuasca (Cameron and Olson 2018). While preparations of ayahuasca can vary, they typically contain tryptamine psychedelics such as DMT and/or 5-MeO-DMT as well as harmala alkaloids such as harmine, harmaline, and tetrahydroharmine, among others. The pharmacological profile of each compound needs to be considered, as well as how these profiles might interact.

The tryptamines contained in ayahuasca preparations potently promote neuroplasticity through activation of 5-HT_2 receptors (Ly et al. 2018), but they can also produce anti-inflammatory, neuroprotective, and neurogenic effects through activation of other receptors (Szabo et al. 2014; Da Silva et al. 2021). For instance, DMT is a sigma-1 agonist (Fontanilla et al. 2009), and sigma-1 is known to play a role in endoplasmic reticulum (ER) stress (Hayashi 2019). Activation of sigma-1 receptors can also have anti-inflammatory effects.

Following stimulation of monocyte-derived dendritic cells with lipopolysaccharide or poly I:C, both DMT and 5-MeO-DMT inhibited the production of pro-inflammatory cytokines, and the effect was partially blocked by knockdown of sigma-1 receptors (Szabo et al. 2014). Additionally, inhalation of 5-MeO-DMT decreased IL-6 levels in human saliva (Uthaug et al. 2020).

Under hypoxic conditions, DMT promotes the survival of human cortical neurons derived from induced pluripotent stem cells, and this neuroprotective effect was completely blocked following sigma-1 receptor knockdown (Szabo et al. 2016). In vivo, activation of sigma-1 receptors by DMT mitigates ischemia-induced neurodegeneration, reduces infarct size, and promotes functional recovery (Szabo et al. 2021; Nardai et al. 2020). Other non-psychedelic sigma-1 agonists have demonstrated therapeutic promise as well, with SA4503 protecting motor neurons in a mouse model of amyotrophic lateral sclerosis (ALS)(Ono et al. 2014) and PRE-084 demonstrating neurorestorative properties in a mouse model of PD (Francardo et al. 2014).

In addition to anti-inflammatory properties, sigma-1 activation might also promote neurogenesis, and there is some evidence to suggest that neurogenesis is impaired in AD and PD (Scopa et al. 2020; Van Bulck et al. 2019).= In mice, DMT induces neurogenesis in the subgranular zone of the dentate gyrus. This effect was blocked by a sigma-1 antagonist but not a 5-HT_2 antagonist (Morales-Garcia et al. 2020). Similarly, a single dose of 5-MeO-DMT can increase the number of granule cells in the dentate gyrus, and these newborn neurons have dendritic arbors that are significantly more complex (Lima da Cruz et al. 2018).

Tryptamines are not the only compounds in ayahuasca that can promote neurogenesis. Harmine and several other related alkaloids promoted neurogenesis in neurospheres prepared from progenitor cells harvested from the subventricular zone and dentate gyrus of adult mice (Morales-Garcia et al. 2017). While harmala alkaloids are potent monoamine oxidase inhibitors (MAOIs) that enhance the oral bioavailability of tryptamine psychedelics, their abilities to stimulate the proliferation of neural progenitor cells likely results from the inhibition of dual specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A) (Dakic et al. 2016). This kinase plays a key role in cell proliferation and neurodevelopment (Tejedor and Hämmerle 2011). People with Down syndrome have an extra copy of DYRK1A as it is located on the Down syndrome critical region of chromosome 21 (Duchon and Herault 2016). These patients develop early onset AD (Head et al. 2012), and the overexpression of DYRK1A is believed to be involved (Stotani et al. 2016; Smith et al. 2012). Normalization of DYRK1A gene dosage in a mouse model of Down syndrome rescues multiple AD related phenotypes including degeneration of cholinergic neurons, increased Aβ load in the cortex, and hyperphosphorylated tau in the hippocampus (García -Cerro et al. 2017). This important study indicates that it is the gene dosage of DYRK1A, not the trisomy per se, that gives rise to many AD phenotypes observed in a mouse model of Down syndrome. Harmine itself has been found to decrease tau phosphorylation at several sites implicated in AD (Frost et al. 2011).

Given the effects of 5-HT_{2A} stimulation, sigma-1 activation, and DYRK1A inhibition, the specific polypharmacology of ayahuasca might endow it with unique properties for treating neurodegenerative diseases compared to individual psychedelic compounds. For example, increased BDNF levels are commonly observed in both humans (De Almeida et al. 2019) and animals (Colaço et al. 2020) administered ayahuasca. While psychedelics increase *BDNF* expression in the cortex, they tend to decrease its expression in the hippocampus (Vaidya et al. 1997). In contrast, harmine increases BDNF protein levels in the hippocampus (Fortunato et al. 2009; Fortunato et al. 1996). Thus the combination of DMT and harmine found in ayahuasca could provide neuroprotection across more brain regions than either compound could alone. To the best of our knowledge, the effects of ayahuasca on brain structure have not been measured in either patients with a neurodegenerative disorder or relevant mouse models. However, in healthy people, long-term use of ayahuasca led to increased cortical thickness in the anterior cingulate cortex (ACC), but thinning of the posterior cingulate cortex (PCC) (Bouso et al. 2015).

Non-hallucinogenic psychoplastogens

Psychedelics belong to a more general class of compounds known as psychoplastogens (Olson 2018)—compound capable of rapidly promoting induced plasticity (iPlasticity) (Castrén and Antila 2017) in the cortex. These small molecules can readily cross the blood-brain barrier (BBB) to produce rapid and sustained increases in neuronal growth and have enormous potential for producing sustained therapeutic effects because they rectify underlying pathological changes in circuitry instead of simply masking disease symptoms. The recently FDA-approved fast-acting antidepressant ketamine is perhaps the best known psychoplastogen. It modulates cortical function by increasing dendritic spine and synapse density in the PFC (Li et al. 2010; Browne and Lucki 2013; Moda-Sava et al. 2019), and it has shown promise for treating addiction (Krupitsky et al. 2002) and PTSD in addition to depression (Berman et al. 2000; Ionescu et al. 2016; Zarate et al. 2012). Ketamine's sustained antidepressant effects have recently been shown to depend on spine growth in the PFC (Moda-Sava et al. 2019). Due to its ability to promote neuroplasticity, some researchers have suggested that ketamine should be explored for treating neurodegenerative diseases as well (Smalheiser 2019; Fan et al. 2017; Vecchia et al. 2021).

Increasing evidence suggests that the subjective effects of drugs like ketamine and serotonergic psychedelics might not be necessary for their sustained beneficial effects on neuroplasticity and behavior (Olson 2020; Cameron and Olson 2021; Peters and Olson 2021), though this remains a subject of intense debate (Yaden and Griffiths 2020). In general, the 5-HT_{2A} receptor is a highly druggable target with numerous compounds currently on the market that possess mechanisms of action involving the 5-HT_{2A} receptor. Importantly this GPCR exhibits a high degree of functional selectivity (González-Maeso et al. 2007; González-Maeso et al. 2003; González-Maeso et al. 2008; Berg et al. 1998; Schmid et al. 2008; Schmid et al. 2010; Fribourg et al. 2011), which has enabled us to produce non-hallucinogenic, plasticity-promoting ligands from a variety of chemical classes (Cameron et al. 2021; Dunlap et al. 2021; Dong et al. 2021). These compounds have demonstrated exceptional safety profiles, PK/ADME properties, and in vivo efficacies in multiple models of neuropsychiatric disorders. In fact, a single administration of the non-hallucinogenic

psychoplastogen tabernanthalog (TBG) is able to repair neural circuitry damaged by chronic stress, highlighting its disease-modifying potential (Lu et al. 2021).

Currently, it is unclear if agonists or antagonists of 5-HT_{2A} receptors are better suited for treating various aspects of AD and related disorders. For instance, the 5-HT_2 receptor antagonist clozapine has been shown to reduce neuroinflammation by inhibiting the overactivation of microglia (Hu et al. 2012; Jeon et al. 2018; Ceylan et al. 2021). Moreover, long-term clozapine administration improves memory and reduces amyloid plaques in a mouse model of Alzheimer's disease (Choi et al. 2017). Similar effects have been noted following administration of the 5-HT_{2A} antagonists volinanserin (MDL-100,907) and pimavanserin (Yuede et al. 2021). The protective effects of these compounds were absent in 5-HT_{2A} receptor KO mice. Because non-hallucinogenic psychoplastogens like TBG act as both agonists and antagonists of 5-HT_{2A} receptors depending on the specific assay (Cameron et al. 2021; Dong et al. 2021), they might possess unique properties for treating neurodegenerative diseases as compared to either psychedelics or antipsychotics. Given the hallucinogenic effects of psychedelics, non-hallucinogenic psychoplastogens might be better options for treating neuronal atrophy observed in patients with dementia-related psychosis.

Key unanswered questions

While the ability of psychedelics and related psychoplastogens to promote neuronal growth suggest that they might serve as disease-modifying therapeutics for reversing neuronal atrophy characteristic of neurodegenerative disorders, it is also possible that they could have prophylactic effects. Others have suggested that psychedelics have the potential to serve as prophylactics for neuropsychiatric diseases (Vargas et al. 2021), and preclinical studies indicate that ketamine might increase resilience to the development of neuropsychiatric disease phenotypes (McGowan et al. 2017; Brachman et al. 2016; Parise et al. 2021). Moreover, a single dose of TBG can have a long-lasting protective effect on heroin relapse (Cameron et al. 2021). Studies investigating the ability of psychedelics to prevent the onset of neurodegeneration-related phenotypes are lacking, but they would be of great interest.

To realize the true therapeutic potential of psychedelics and other psychoplastogens, we must determine the optimal treatment regimen for several reasons. First, many 5-HT_{2A} receptor agonists induce tachyphylaxis, and chronic treatment with psychedelics can result in desensitization of 5-HT_{2A} receptors and suppression of BDNF/TrkB signaling (Tsybko et al. 2020). It is important to note that a single high dose of DMT leads to increased spinogenesis in the cortex of rats (Cameron et al. 2018); however, the chronic, intermittent dosing of DMT actually causes spine retraction in the cortex of female rats (Cameron et al. 2019). Moreover, chronic dosing with LSD produces deleterious phenotypes (Martin et al. 2014). Second, chronic treatment with psychedelics could lead to cardiac valvulopathy via agonism of 5-HT_{2B} receptors in the heart (Rothman et al. 2000). Taken together, these studies highlight the importance of optimizing dosing frequency to achieve lasting beneficial effects with minimal side effects

In rodents, longitudinal imaging of dendritic spine density following drug treatment (Shao et al. 2021; Phoumthipphavong et al. 2016) could potentially be used to determine how long psychoplastogenic effects last for, and thus, determine optimal dosing frequency. However,

these results may not extend to humans. To determine optimal dosing in humans, we must develop robust biomarkers of psychoplastogenic effects. Fortunately, progress is being made in this area. Two new PET tracers—[^{11}C]UCB-J (Nabulsi et al. 2016) and [^{18}F]UCB-J (Li et al. 2019)—are capable of labeling the synaptic protein SV2A in vivo. Using [^{11}C]UCB-J, researchers have demonstrated that SV2A density is decreased in patients with AD (Chen et al. 2018; Mecca et al. 2020). Moreover, Knudsen and co-workers have used a UCB-J tracer to show that psilocybin increases SV2A density in pig cortex (Raval et al. 2021), offering the tantalizing possibility that SV2A density might serve as a translatable biomarker relevant to psychoplastogenic effects.

CONCLUSION

To the best of our knowledge psychedelics have never been tested in animal models of neurodegenerative disorders. However, they upregulate neurotrophic factors that encourage neuronal survival, promote neuronal growth, and have profound effects on the immune system. Thus, there are ample reasons to believe that these compounds might have disease-modifying properties relevant to treating neurodegenerative disorders. Moreover, the effects of psychedelics on depression and anxiety could potentially be harnessed to address many of the neuropsychiatric symptoms associated with dementia. Given the complexity of neurodegenerative diseases, the polypharmacological profiles of psychedelics and/or psychedelic mixtures like ayahuasca might prove advantageous. Despite their promise, many outstanding questions remain to be answered including which neurodegenerative diseases can be treated with psychedelics or related psychoplastogens, which compounds are most efficacious, and which dosing regimens maximize efficacy while minimizing side effects. Overall, the current literature supports cautious optimism about the use of psychedelic-inspired approaches for treating neurodegenerative diseases.

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ABBREVIATIONS

5-HT	Serotonin
5-MeO-DMT	5-methoxy-dimethyltryptamine
Aβ	β-amyloid
ACC	Anterior cingulate cortex
AD	Alzheimer’s disease
ADME	Absorption distribution metabolism excretion
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BDNF	Brain-derived neurotrophic factor

BPSD	Behavioral and psychological symptoms of dementia
CNS	Central nervous system
DMT	*N,N*-Dimethyltryptamine
DOI	2,5-dimethoxy-4-iodoamphetamine
DYRK1A	Dual specificity tyrosine-phosphorylation-regulated kinase 1A
sEPSC	Spontaneous excitatory postsynaptic current
ER	Endoplasmic reticulum
FTD	Frontotemporal dementia
GDNF	Glial-derived neurotrophic factor
GFP	Green fluorescent protein
GPCR	G-protein coupled receptor
HTR	Head-twitch response
H_2O_2	Hydrogen peroxide
IEG	Immediate early gene
IL	Interleukin
iNOS	Inducible nitric oxide synthase
iPSC	Induced pluripotent stem cell
KO	Knock-out
LPS	Lipopolysaccharide
LSD	Lysergic acid diethylamide
MAOI	Monoamine oxidase inhibitor
mGlu2R	Metabotropic glutamate 2 receptor
mTOR	Mammalian target of rapamycin
NF-κB	Nuclear factor κB
PCC	Posterior cingulate cortex
PD	Parkinson’s disease
PET	Positron emission tomography
PFC	Prefrontal cortex
PK	Pharmacokinetic

PTSD	Post-traumatic stress disorder
SUD	Substance use disorder
SV2A	Synaptic vesicle glycoprotein 2A
TBG	Tabernanthalog
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor α
TREM2	Triggering receptors expressed on myeloid cells 2
TrkB	Tyrosine receptor kinase B

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