Psychedelics as Novel Therapeutics in Alzheimer's Disease: Rationale and Potential Mechanisms

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Contents

Abstract Serotonin 2A receptor (5-HT_{2A}R) agonist "classic psychedelics" are drawing increasing interest as potential mental health treatments. Recent work suggests psychedelics can exert persisting anxiolytic and antidepressant effects

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lasting up to several months after a single administration. Data indicate acute subjective drug effects as important psychological factors involved in observed therapeutic benefits. Additionally, animal models have shown an important role for 5-HT_{2A}R agonists in modulating learning and memory function with relevance for Alzheimer's Disease (AD) and related dementias. A number of biological mechanisms of action are under investigation to elucidate 5-HT_{2A}R agonists' therapeutic potential, including enhanced neuroplasticity, anti-inflammatory effects, and alterations in brain functional connectivity. These diverse lines of research are reviewed here along with a discussion of AD pathophysiology and neuropsychiatric symptoms to highlight classic psychedelics as potential novel pharmacotherapies for patients with AD. Human clinical research suggests a possible role for high-dose psychedelic administration in symptomatic treatment of depressed mood and anxiety in early-stage AD. Preclinical data indicate a potential for low- or high-dose psychedelic treatment regimens to slow or reverse brain atrophy, enhance cognitive function, and slow progression of AD. In conclusion, rationale and potential approaches for preliminary research with psychedelics in patients with AD are presented, and ramifications of this line of investigation for development of novel AD treatments are discussed.

Keywords Alzheimer's disease · Dementia · Hallucinogen · Mild cognitive impairment (MCI) · Psilocybin · Psychedelic

1 Introduction

Alzheimer's Disease (AD) is a growing concern amid a rapidly increasing population aged 65 and older worldwide, and projected rising global life expectancy (He et al. 2016). Currently, more than five million adults in the USA and 36 million worldwide are living with AD, and this number is expected to triple by 2050 (Alzheimer's Association 2021). However, there has been little success in development of strategies for AD pharmacotherapy. Symptomatic treatment of AD with acetylcholinesterase inhibitors such as donepezil, rivastigmine, and galantamine has been available since the 1990s with modest benefits for some patients (Tayeb et al. 2012). The *N*-Methyl-*D*-aspartate (NMDA) antagonist memantine was approved for treating moderate to severe AD by the US Food and Drug Administration (FDA) in 2003, but to date no cure or well-established disease modifying treatment for AD is available, despite extensive research and drug development efforts involving over 240 failed candidate drugs (Dubois et al. 2014; Wimo et al. 2014). Although recent progress has been made toward developing novel antibody-based pharmacotherapies such as aducanumab (Sevigny et al. 2016) and donanemab (Mintun et al. 2021), controversy remains whether these will prove safe, accessible, and substantially effective treatments for patients with AD (Ayton 2021; Doggrell 2021; Knopman

et al. 2021). Given the enormous morbidity and mortality associated with AD, it is clear that novel approaches to AD treatment are urgently needed.

The past two decades have seen a resurgence in research involving hallucinogenic serotonin 2A receptor (5-HT_{2A}R) agonists, known as "classic psychedelics," as potential treatments across a range of medical and mental health conditions. Preliminary studies in animals and humans suggest that classic psychedelics such as psilocybin, lysergic acid diethylamide (LSD), and the dimethyltryptamine (DMT) containing decoction ayahuasca may have promising antidepressant, anxiolytic, and antiaddictive properties (Garcia-Romeu et al. 2016). So much so, that the FDA has granted psilocybin "breakthrough therapy" designation as a potential treatment for major depressive disorder, with clinical trials of therapeutic safety and efficacy currently underway (Nichols 2020). To date, psychedelics' psychological mechanisms of action appear related to acute subjective drug effects associated with positive therapeutic outcomes (Bogenschutz et al. 2015; Garcia-Romeu et al. 2014; Griffiths et al. 2016; Roseman et al. 2018; Ross et al. 2016). Additionally, preclinical and neuroimaging research indicate a number of compelling biological mechanisms of psychedelics related to stimulation of 5-HT_{2A}R and downstream signaling pathways relevant to AD. These mechanisms include promotion of structural and functional neuroplasticity (Catlow et al. 2013; Lima da Cruz et al. 2018; Ly et al. 2018), post-acute changes in key signaling pathways such as brain-derived neurotrophic factor (BDNF) (Hutten et al. 2021; Ly et al. 2018), anti-inflammatory effects (Flanagan and Nichols 2018), as well as acute and post-acute changes in brain functional connectivity (Barrett et al. 2020a, b; Carhart-Harris et al. 2012; Carhart-Harris et al. 2017; Preller et al., 2020). This review provides a detailed examination of potential mechanisms of classic psychedelics as possible treatments for patients with AD and describes the rationale for targeted investigation of psychedelics in patients with early AD (e.g., ClinicalTrials.gov NCT04123314).

2 Pathophysiology and Etiology of Alzheimer's Disease

Both normal aging and Alzheimer's Disease (AD) have been associated with decreased functional brain activity and connectivity (Dennis and Thompson 2014; Tomasi and Volkow 2012). Network hypersynchrony and abnormalities such as impaired default mode network (DMN) deactivation have been linked to cognitive dysfunction and implicated as potential targets for therapeutic intervention in AD (Palop and Mucke 2016). The neuropathological hallmarks that typically define AD are amyloid-β (Aβ) plaques, neurofibrillary tangles, and neuronal and synaptic loss (Serrano-Pozo et al. 2011a; Shoghi-Jadid et al. 2002). This neurodegeneration is associated with cognitive and functional decline typically starting with loss of episodic memory and progressing to include aphasia, apraxia, and agnosia (Butzlaff and Ponimaskin 2016; Weintraub et al. 2012). While amyloid is thought to be the "prime mover" in AD pathobiology, we are still ascertaining the mechanisms of progressive neurodegeneration, which likely include tau deposition as the next

phase, leading on to neuronal loss. Aβ accumulation has been suggested to facilitate formation of pathological tau, and together these seem to trigger additive neurotoxic effects functioning as a systemic feedback loop resulting in acute neuron death and synaptic dysfunction (Bloom 2014).

AD is thought to begin up to 20 years prior to symptoms with a lengthy preclinical, "prodromal" phase during which cleavage of Amyloid Precursor Protein (APP) by Beta-secretase 1 (BACE-1) and Gamma-secretase results in the aggregation of Aβ protein and Aβ plaques (Sperling et al. 2011). This accrual results in neurodegeneration in characteristic brain regions (including the hippocampus, posterior cingulate cortex, and precuneus) and impaired synaptic function over time (Bateman et al. 2012; Dubois et al. 2014). Post-mortem data suggest a temporal pattern of neurofibrillary tangle formation from the transentorhinal layer in early stages of AD proceeding to the entorhinal cortex before subsequent degeneration in the isocortical association areas in later stages of disease progression (Braak and Braak 1991). This focus has led to exploration in clinical trials of anti-Aβ therapies for AD treatment, which have thus far garnered little success (Karran et al. 2011; Karran and Hardy 2014). AD patients present with heterogeneous symptoms that may be conceptualized as distinct clinical syndromes with relatively greater disturbances in language, visuospatial functions, apraxia, or behavioral manifestations (Stopford et al. 2008). These variations have also been associated with particular clinical biomarkers. For instance, visual perception problems and/or spatial difficulties are often accompanied by posterior cortical atrophy including hypometabolism in these areas as observed by magnetic resonance imaging (MRI) and positron emission tomography (PET) (Graff-Radford et al. 2021; Jack Jr et al. 2019). Furthermore, while genetic variants such as apolipoprotein E4 (ApoE4) have long been known to play a role in development of AD, which is highly heritable (Tanzi 2012), contemporary research is shedding new light on genetic and environmental factors related to AD, such as amyloid precursor protein metabolism (Kunkle et al. 2019) and pesticide exposure (Killin et al. 2016). Below, we review selected aspects of AD biological mechanisms which are potentially relevant to psychedelics' mechanisms of action.

2.1 Decreased Serotonergic Neurotransmission in AD

Evidence indicates reduced serotonergic neurotransmission in AD may be associated with psychiatric symptoms (Butzlaff and Ponimaskin 2016). Animal models of AD suggest selective neurodegeneration of serotonin pathways and reduced serotonergic neurotransmission (Liu et al. 2008). Preclinical research has shown β-amyloid accumulation leads to a decline in 5-HT_{2A}R levels in the cortex of mice (Holm et al. 2010). In prodromal AD, PET imaging reveals a reduced density of serotonin transporter which is associated with early cognitive changes (Smith et al. 2017). Several studies report decreased 5-HT_{2A}R levels in widespread areas of the brain in AD (Marner et al. 2012; Mecca 2019). These changes are associated with

neuropsychiatric symptoms including agitation, depression, and psychosis in AD (Chakraborty et al. 2019). Relevant to classic psychedelics, 5-HT_{2A}R density declines in healthy aging throughout the brain and specifically in the hippocampus, and the degree of temporal lobe 5-HT_{2A}R decrease is associated with cognitive decline in AD (Marner et al. 2012; Versijpt et al. 2003). Some studies point to possible genetic influences of the serotonin system in AD, such as the 5-HT_{2A}R T102C polymorphism, where the CC genotype has been associated with risk of psychotic symptoms in AD (Tang et al. 2017). In human PET studies, neocortical regions including the orbitofrontal cortex (OFC) showed reduced 5-HT_{2A}R binding in both Mild cognitive impairment (MCI) and AD patients (Hasselbalch et al. 2008; Lai et al. 2005; Versijpt et al. 2003). In addition to serotonin, other neurotransmitter systems such as norepinephrine (Theofilas et al. 2017) and acetylcholine (Grothe et al. 2012) have been implicated in AD pathology and identified as targets for AD pharmacotherapies (Marucci et al. 2021). However, the current review focuses primarily on serotonergic neurotransmission due to its key role in psychedelics' biological mechanisms (Nichols 2016),

2.2 *Loss of Synaptic Function in AD*

Data suggest the loss of synaptic function in AD prior to neuronal loss (Selkoe 2002). For example, synaptophysin (a characteristic marker of synaptic integrity) is decreased in prodromal AD (Masliah et al. 2001; Sze et al. 1997; Yuki et al. 2014). One well-validated marker of synaptic density is synaptic vesicle glycoprotein 2 (SV2) which is expressed in virtually all synapses and is located in synaptic vesicles at presynaptic terminals (Mecca 2019). A PET tracer for imaging SV2 density in vivo is now available ([11C]UCB-J) and has demonstrated decreased SV2 density in the hippocampus of patients with AD compared to cognitively unimpaired older adults (Chen et al. 2018).

2.3 *Key Signaling Pathways in AD*

Brain-derived neurotrophic factor (BDNF), a protein critical to neuronal growth and survival, is affected by the accumulation of Aβ protein in prodromal AD (Peng et al. 2005). This accumulation interferes with the conversion of proBDNF to BDNF such that parietal cortex levels of both proBDNF and BDNF are reduced in prodromal AD and MCI, correlating with cognitive decline (Peng et al. 2005; Tanila 2017). In addition, decreased Tropomyosin receptor kinase B (TrkB) BDNF receptor expression and increased expression of TrkB.T1 (a primary inhibitor of TrkB) result in further BDNF inhibition as well as the prevention of long-term potentiation (LTP) and long-term depression (Eide et al. 1996; Michaelsen et al. 2010) – processes essential to memory formation (Minichiello 2009). The steady decrease of BDNF

and its action, which may occur as a direct result of Aβ deposition, could be a critical link between the prodromal phase of AD and the beginning of neurodegeneration and cognitive decline, eventually culminating in dementia (Arancibia et al. 2008; Ciaramella et al. 2013).

The Mammalian Target of Rapamycin (mTOR) signaling pathway also has a role in LTP and memory formation (Cammalleri et al. 2003; Hoeffer and Klann 2010). Hyperactivation of mTOR complex I leads to downstream inhibition of cell autophagy, which could result in further Aβ deposition and tau hyperphosphorylation (Caccamo et al. 2013). Conversely, the activated mTOR signaling pathway has also been shown to induce structural plasticity and neuritogenesis by regulating the behavior of axonal growth cones, dendrite arborization, and dendritic spine morphology via control of local protein synthesis (Jaworski and Sheng 2006). Targeting mTOR signaling in key cognitive brain regions could help delay or even prevent cognitive decline during the neurodegeneration phase of AD (Tramutola et al. 2017).

2.4 *Inflammation in AD*

Accumulating evidence has implicated neuroinflammation in the progression of AD (Kinney et al. 2018; Zotova et al. 2010). In post-mortem studies, brain tissue of patients with AD exhibits signs of persisting inflammatory activity, such as activated microglia and astrocyte clusters (Serrano-Pozo et al. 2011b). These in turn release proinflammatory cytokines and interleukins (e.g., interleukin [IL]-1β, IL-6, and tumor necrosis factor-α [TNF-α]), which cause tissue damage with prolonged exposure, and interact with accumulating Aβ and NFT to contribute to neuronal loss (Garwood et al. 2011; Wang et al. 2015). Early patient data suggested use of medications such as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) may be associated with reduced severity of AD symptoms (Rich et al. 1995) and reduced risk of developing AD (Stewart et al. 1997). To date, clinical trials of NSAIDs as a treatment for AD have not shown positive results (Miguel-Álvarez et al. 2015). However, targeted strategies for modulating neuroinflammation remain a viable pathway for developing novel AD therapeutics that continue to be explored (Ozben and Ozben 2019).

2.5 *Changes in Brain Metabolism and Functional Connectivity in AD*

In addition to cellular and molecular mechanisms, human neuroimaging and post-mortem studies provide insight into the neurobiology of AD. PET is a critical tool for understanding and diagnosing AD, allowing Aβ and tau deposition to be evaluated

in vivo (Brier et al. 2016), and using ligands such as fluorodeoxyglucose (FDG) to assess functional brain metabolism (Rice and Bisdas 2017). These methods have demonstrated differential patterns of atrophy, hypometabolism, and Aβ and tau aggregation across the course of disease progression, informing the neurodegenerative processes underlying AD (Joie et al. 2012; Ossenkoppele et al. 2016). Current imaging data suggest early-stage AD is marked by Aβ deposition, atrophy, and metabolic dysfunction in posterior cortical regions, which are active during memory retrieval in healthy individuals (Buckner et al. 2005). As cognitive function declines, concurrent increases in tau deposition are observed in the temporal lobe (Brier et al. 2016) and other key domain-specific regions (e.g., occipital cortex for individuals with visual impairment) (Ossenkoppele et al. 2016).

Functional MRI data also show notable decrease in connectivity in normal aging across several brain networks, while AD mainly shows alterations in the default mode network (DMN), dorsal attention network (DAN), and the precuneus (Hafkemeijer et al. 2012; Klaassens et al. 2017; Tomasi and Volkow 2012). The DMN is primarily composed of the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), precuneus, and angular gyrus, which are involved in episodic memory retrieval (Sestieri et al. 2011), a function known to deteriorate in older adults with AD (Mevel et al. 2011; Weintraub et al. 2012). In some cases of AD, DMN desynchronization has been posited to contribute to cognitive decline, consistent with evidence that differences in DMN activation in the precuneus and PCC predicted lower Mini-Mental State Exam (MMSE) scores, typically indicative of more severe dementia (Schwindt et al. 2013). Amyloid accumulation may also affect DMN function, for instance leading to hypoconnectivity within the DMN in early AD (Buckner et al. 2005; Palmqvist et al. 2017). The salience network (SN) has also shown reduced gray matter volume and altered functional connectivity in AD that were associated with neuropsychiatric symptoms (Balthazar et al. 2014), as well as cognitive impairment (He et al. 2014). It has been hypothesized that increased SN connectivity in AD is associated with greater "emotionality" which might contribute to the expression of affective and other neuropsychiatric symptoms (Zhou and Seeley 2014). Lasting alterations in brain network connectivity have been observed after a single dose of psilocybin (Barrett et al. 2020a) and are correlated with psilocybin's antidepressant effects (Carhart-Harris et al. 2017), indicating a potential biological mechanism by which psychedelics could affect AD progression and related symptoms. Notably, the medial temporal lobes have been found to show increases in activation during MCI and early-stage AD, which may be associated with local tau formation and subsequent neurodegeneration and hypoactivation in these regions that then spreads as AD progresses (Pasquini et al. 2019; Putcha et al. 2011).

2.6 Neuropsychiatric Comorbidities in AD

Patients with AD have a high prevalence of comorbid neuropsychiatric symptoms, with more than 40% exhibiting clinically significant symptoms of depression (Lyketsos et al. 2002; Zhao et al. 2016). Beyond other challenges posed by AD, depression adversely impacts both patient and caregiver quality of life (Karttunen et al. 2011; Shin et al. 2005). Moreover, depression is known to mediate the progression of AD, with more pronounced symptoms being associated with greater risk of cognitive decline (Dotson et al. 2010; Herbert and Lucassen 2016; Ruthirakuhan et al. 2019). Typical antidepressant medications have not shown clear evidence of efficacy in patients with dementia, indicating a need for novel treatments (Banerjee et al. 2013; Nelson and Devanand 2011; Rosenberg et al. 2010). Neuropsychiatric symptoms are frequently the first symptoms of prodromal dementia (Leoutsakos et al. 2015) and associated with early manifestations of AD biomarkers (Banning et al. 2021), which has led to the concept of Mild Behavioral Impairment defining five domains of such symptoms which are predictive of incident MCI and dementia (Ismail et al. 2017).

The symptoms of AD also extend beyond cognitive complaints to include highly prevalent, comorbid neuropsychiatric symptoms such as agitation, apathy, sleep disturbances, and anxiety (Lyketsos et al. 2002; Steinberg et al. 2008). These symptoms contribute to disability, worse life quality, impaired activities of daily living, caregiver burden, institutionalization, and accelerated mortality (Lanctôt et al. 2017; Lyketsos et al. 2011; Peters et al. 2015; Soto et al. 2015). While practice guidelines consistently refer to managing such symptoms as central to treating AD (Lyketsos et al. 2006), there are no established effective treatments, highlighting this as an important area for further research into novel therapies. In particular, depressed mood, anxiety, apathy, and reduced quality of life represent compelling targets for brief interventions involving moderate to high-dose psychedelic administration based on existing clinical research described in more detail below. Conversely, other neuropsychiatric symptoms related to AD such as delusions and hallucinations are generally considered contraindications for high-dose psychedelic treatments (Johnson et al. 2008), and it remains unclear how symptoms such as motor disturbances may be influenced by psychedelics.

3 Neurobiology of Psychedelics

A growing body of research supports the administration of 5-HT_{2A}R agonist classic psychedelics such as psilocybin and LSD as a potential treatment for various conditions, including anxiety, mood, and substance use disorders (Garcia-Romeu et al. 2016; Reiff et al. 2020). These compounds represent a novel frontier in the field of psychiatry as possibly transdiagnostic pharmacotherapies with low toxicity and addiction risk, and the potential for long-lasting benefits (Johnson et al. 2018). The

underlying neurobiological mechanisms responsible for these effects are now being explored in basic translational and clinical research, indicating additional potential for these substances as possible novel treatment options for patients with AD.

3.1 Data on the Role of 5-HT$_{2A}$R in Learning and Memory

Evidence indicates that serotonin has a key modulatory role in learning alongside other neurotransmitters such as dopamine (Aznar and Hervig 2016; Frick et al. 2015; Harvey et al. 2004). In particular, 5-HT$_{2A}$R agonists like psilocybin have long been studied as potential modulators of learning and memory with early experiments identifying pretreatment with 25ug/kg LSD as a facilitator of reversal learning in rats compared to placebo (King et al. 1972). More recently, administration of a selective 5-HT$_{2A}$R antagonist was shown to dose-dependently impair spatial reversal learning and increase perseverative errors in rats, further implicating 5-HT$_{2A}$R signaling in cognitive flexibility processes (Boulougouris et al. 2008). Similarly, reversal learning deficits in chronically stressed rats can be alleviated with chronic SSRI treatment, and this improvement is blocked by injection of a 5-HT$_{2A}$R antagonist (Furr et al. 2012).

Additionally, LSD injections in the hippocampus have been shown to accelerate classical conditioning of the eyeblink response in rabbits, with chronic LSD injections desensitizing 5-HT$_{2A}$R but not 5-HT$_{2C}$R-mediated behavioral responses (Romano et al. 2010). Related work found that chronic treatment of rabbits with an inverse 5-HT$_{2A}$R agonist increased 5-HT$_{2A}$R density in the frontal cortex and produced similar acceleration in classical conditioning (Harvey et al. 2004). The extinction of fear memories in rats can be accelerated by administration of 5-HT$_{2A}$R agonist (4-Bromo-3,6-dimethoxybenzocyclobuten-1-yl)methylamine hydrobromide (TCB-2) and delayed by administration of a 5-HT$_{2A}$R antagonist (Zhang et al. 2013). Low doses of psilocybin likewise facilitate the extinction of fear memories and may increase hippocampal neurogenesis in rats (Catlow et al. 2013). Furthermore, the spatial tuning of neurons in the prefrontal cortex of rhesus monkeys performing a visual working memory task can be accentuated or attenuated by the delivery of a 5-HT$_{2A}$R agonist or antagonist, respectively (Williams et al. 2002). The 5-HT$_{2A}$R agonist TCB-2 can also improve the working memory of rats with medial forebrain bundle lesions intended to mimic the cognitive effects of Parkinson's Disease (Li et al. 2015). Hippocampal TCB-2 injection during memory consolidation enhances the object memory of mice, and this effect is blocked by pretreatment with a 5-HT$_{2A}$R antagonist, further supporting a key role for 5-HT$_{2A}$R in modulating memory (Zhang et al. 2016).

In addition to animal studies, research in humans has suggested a role for 5-HT$_{2A}$R in regulating mood and memory functions. Genetic research has found that variations of 5-HT$_{2A}$R can influence memory task performance in humans, with carriers of the heterozygous 5-HT$_{2A}$ H452Y polymorphism making more errors during memory tasks (de Quervain et al. 2003), and displaying less right anterior

hippocampal activation in response to novel stimuli compared to their homozygous counterparts (Schott et al. 2011). These data suggest a robust influence of 5-HT_{2A}R activation in diverse learning and memory processes that are relevant to AD (Zhang and Stackman Jr 2015), raising the possibility that low- or high-dose psychedelic administration may have cognition-enhancing effects in patients with AD. Approaches testing low-dose psychedelics might use a chronic dosing regimen every few days over the course of several weeks to assess pre- and post-treatment performance on validated measures of episodic memory, working memory, visuo-spatial processing, and executive function (e.g., Mini-Mental State Exam, Hopkins Verbal Learning Test, Trail Making Test, Raven's Progressive Matrices, Category Fluency). A similar design could be employed to examine effects of one or more high-dose psychedelic sessions with psychological support, preferably with patients in earlier stages of AD, where there would be less ethical concerns about informed consent regarding study procedures (Kim 2011). Should any signal of cognitive-enhancing effects emerge in initial research, this would pave the way for further study of biological mechanisms using neuroimaging and other biomarker assessment.

3.2 Psychoplastogenic Effects of Psychedelics and Related Signaling Pathways

Data from cellular and molecular models additionally suggest classic psychedelics may have potential in treating early-stage AD. A recent study found classic psychedelics to selectively induce structural and functional neuroplasticity in vitro and in vivo in the rat prefrontal cortex at an extent comparable to BDNF, with resulting effects posited as "psychoplastogenic" (Ly et al. 2018). Psychoplastogenic compounds are defined to produce a measurable change in neuroplasticity within 24–72 h of a single administration. Measurable changes in plasticity include changes in neurite growth, dendritic branching, dendritic spine density, synapse number, and intrinsic excitability, among others (Olson 2018). Recently published data consistent with psychoplastogenic effects found a single dose of psilocybin led to significant, rapid increases in the formation, size, and density of dendritic spines in mouse medial frontal cortex occurring within 24 h of dosing, with structural changes persisting up to a month later (Shao et al. 2021). Psilocybin was also found to increase excitatory postsynaptic current frequency and to reduce behavioral signs of learned helplessness in a prolonged stress paradigm in mice (Shao et al. 2021). Psychedelics are thought to induce such psychoplastogenic effects via 5-HT_{2A}R receptor stimulation, which upregulates Ania gene expression and affects glutamatergic function (Nichols and Sanders-Bush 2002). Specifically, this activity amplifies α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor signaling, resulting in downstream activation of the mTOR pathway – one of the proposed mechanisms for the neural plasticity – promoting effects of

psychoplastogens (Cavalleri et al. 2018). Recent data indicate that 5-HT_{2A}R stimulation may impact BDNF (Hutten et al. 2021; Tsybko et al. 2020), and result in upregulated activity-regulated cytoskeleton-associated (Arc) protein expression thought to be involved in cytoskeletal rearrangements for synaptic plasticity (Nichols et al. 2003; Nichols and Sanders-Bush 2002).

Additional preclinical research provides further evidence on relevant mechanisms for classic psychedelics to positively impact biological pathways relevant to AD. In rats, a single LSD administration has been shown to increase expression of immediate early genes (IEGs) implicated in synaptic plasticity in various brain regions including the PFC, midbrain, and hippocampus (Nichols et al. 2003; Nichols and Sanders-Bush 2002). Similarly, psilocybin and other 5-HT_{2A}R agonists can induce IEG expression in the mouse cortex (González-Maeso et al. 2007). Psilocybin has also shown dose-dependent and differential alterations in transcriptional regulation in the PFC and hippocampus across multiple plasticity-related genes in rats (Jefsen et al. 2021). Additionally, preliminary data indicate a single administration of the psychedelic 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) can increase dendritic structural density and plasticity in the PFC, enhance fear extinction, and enhance LTP in mice (Revenga et al. 2021). These effects were mediated by 5-HT_{2A}R as evidenced by lack of such effects in 5-HT_{2A}R knockout mice. Furthermore, DOI induced lasting changes up to a week post-drug administration in frontal cortex gene expression in mice further suggesting transcriptional and epigenetic mechanisms may mediate lasting effects of serotonergic psychedelics (Revenga et al. 2021). Chronic administration of DOI and other 5-HT_{2A}R agonists produced increased proBDNF levels and downregulation of TrkB receptors in mice (Tsybko et al. 2020). Furthermore, the psychedelic 5-MeO-DMT has also been shown to induce neuroplastic changes after a single dose including increased cell growth and maturation in the dentate gyrus of mice (Lima da Cruz et al. 2018).

Finally, a series of recent studies conducted in pigs have also shown lasting changes in PFC gene expression up to a week after a single dose of psilocybin (Donovan et al. 2021). Increased hippocampal synaptic vesicle protein 2A (SV2A) density and decreased hippocampal and PFC 5-HT_{2A}R density have been found 24 h post-psilocybin administration, and significant, ongoing increases in SV2A density have been detected at 1 week post-psilocybin administration (Raval et al. 2021). SV2A protein levels are thought to reflect presynaptic density, suggesting psilocybin may increase synaptogenesis up to a week after a single psilocybin exposure in pigs (Raval et al. 2021). Furthermore, novel evidence suggests 5-HT_{2A}R inverse agonist administration quickly and significantly reduced brain Aβ levels and improved cognitive function in a mouse model of AD, though this effect was not observed in 5-HT_{2A}R knockout mice (Yuede et al. 2021). Taken together, this preclinical evidence suggests classic psychedelics may act via a host of 5-HT_{2A}R mediated biological mechanisms to promote rapid changes in genetic expression leading to longer lasting functional and structural brain changes, which may in turn be associated with therapeutic effects observed in human trials (Fig. 1). Although it remains to be seen whether the mechanisms described here lead to clinical improvement in humans, preclinical data on 5-HT_{2A}R agonist effects on learning and memory,

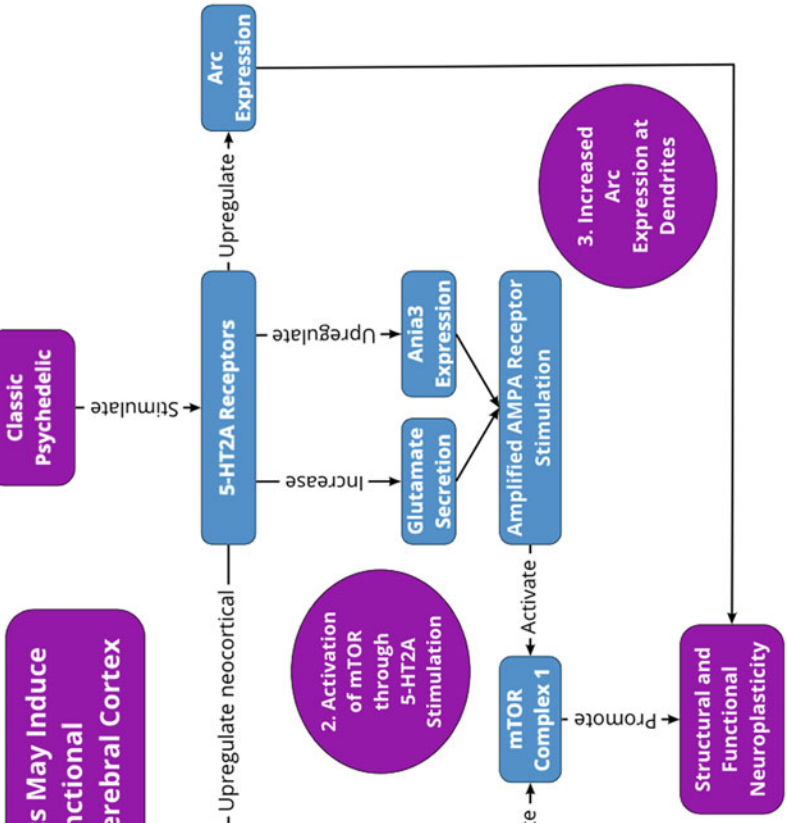

Fig. 1 A diagram of three converging pathways that may be responsible for induced neural plasticity, potentially resulting in lasting beneficial effects following psychedelic administration: 5-HT_{2A}R upregulation of neocortical BDNF, amplification of AMPA receptor activity resulting in downstream activation of mTOR, and upregulated Arc protein expression

combined with the observed neurological, antidepressant, and anxiolytic effects of psychedelics discussed below, present a compelling rationale for targeted investigation of 5-HT_{2A}R agonist effects in patients with AD. Psychoplastogenic effects could present a potential mechanism to slow or reverse atrophy in key brain regions affected by AD and could be studied after chronic low-dose or one or more high-dose psychedelic administration sessions in AD patients using pre- and post-neuroimaging and neuropsychological testing, parallel to research in healthy volunteers described in more detail below (Madsen et al. 2020). Similarly, preclinical findings on 5-HT_{2A}R mediated reductions in Aβ levels (Yuede et al. 2021) could be studied in clinical trials administering classic psychedelics to early-stage AD patients and assessing longitudinal impact on Aβ, cognitive function, and disease progression, providing another possible, complementary therapeutic mechanism for advancing AD treatment.

3.3 Psychedelics as Anti-inflammatory Agents

Preclinical studies have shown robust anti-inflammatory effects of classic psychedelics (Flanagan and Nichols 2018). The 5-HT_{2A}R agonist psychedelics (R)-2,4-dimethoxy-4-iodoamphetamine [(R)-DOI] and LSD (among others) have been found to suppress TNF-α induced inflammation in rat aortic smooth muscle cells, with (R)-DOI exhibiting substantial potency in this regard (Yu et al. 2008). These effects were consistent in vivo in mice, showing anti-inflammatory effects of (R)-DOI in aorta, small intestine, and blood at low-dose levels, which were blocked by co-administration of a selective 5-HT_{2A}R antagonist, indicating a central role for 5-HT_{2A}R in anti-inflammatory effects (Nau Jr et al. 2013). In addition to 5-HT_{2A}R mediated anti-inflammatory effects, cellular models suggest some classic psychedelics such as DMT and 5-MeO-DMT may exert additional anti-inflammatory effects via the Sigma-1 receptor, including inhibition of IL-1β, IL-6, and TNF-α (Szabo et al. 2014), proinflammatory cytokines known to be involved in AD pathology (Wang et al. 2015). Furthermore, a recent study demonstrated the DMT containing admixture ayahuasca, but not placebo, significantly reduced levels of the inflammatory biomarker C-reactive protein from pre- to 48 h-post administration, and these reductions were correlated with mood improvements in patients with treatment-resistant depression (Galvão-Coelho et al. 2020). Anti-inflammatory effects of psychedelics have not yet been conclusively studied in human clinical populations but may be observed after repeated low doses of psychedelics or single high doses. Such effects could be studied in AD patients via prospective measurement of cytokines and related inflammatory biomarkers that may also serve as a therapeutic target for treatment during early-stage AD or possibly in later stages using chronic low-dose regimens.

3.4 Psychedelics' Effects in Humans

Recent imaging data provide insight into the activity of the brain during and after acute psychedelic effects. Resting state network connectivity during psilocybin peak effects shows increased between-network functional connectivity and simultaneous decreased within-network connectivity in the DMN, visual networks, and auditory networks (Mason et al. 2020). This altered network connectivity may be due in part to psilocybin's ability to reduce overall activity in both sides of the claustrum, a key structure in the executive control of behavior, while simultaneously modifying the connectivity of the claustrum with different networks such as the frontoparietal task network (Barrett et al. 2020b). These acute effects are time-dependent and may be predicted by baseline global brain connectivity (Preller et al. 2020).

Psilocybin also may mediate glutamate concentration in areas like the hippocampus and medial prefrontal cortex via 5-HT_{2A}R, ultimately leading to the activation of AMPA receptors and the increased expression of BDNF (Hutten et al. 2021; Mason et al. 2020). During acute psilocybin effects, working memory may appear unchanged or impaired, perhaps due to attentional deficits stemming from an impaired ability to ignore irrelevant stimuli (Barrett et al. 2018; Carter et al. 2005). However, although the acute subjective effects of psilocybin last a matter of hours, fMRI research has found longer term effects in the brain such as decreased amygdala response during affective processing tasks a week after administration and increased global functional brain connectivity a full month after administration (Barrett et al. 2020a). Such long-term effects suggest that psilocybin may induce a period of heightened neuroplasticity lasting weeks after initial psilocybin administration.

Volunteers with treatment-resistant depression were found to have decreased amygdala cerebral blood flow and increased DMN integrity 1 day after psilocybin administration, which has been proposed as a potential "reset" mechanism of psychedelics in which networks like the DMN may experience "modular disintegration" acutely and then "re-integration" afterwards associated with therapeutic outcomes (Carhart-Harris et al. 2017). Post-acute changes in functional connectivity have also been found in healthy volunteers 1 day after administration of the classic psychedelic admixture ayahuasca, including increased connectivity within the salience network, decreased connectivity within the DMN, and greater connectivity between the salience network and DMN, with the latter showing association with acute affective changes (Pasquini et al. 2020). Although these findings are not completely consistent with prior post-acute functional connectivity data on psilocybin in depressed patients (Carhart-Harris et al. 2017), they do represent a relevant area for further study using psychedelics and functional neuroimaging in patients with AD, who have shown differential patterns of connectivity alterations related to neuropsychiatric symptoms (Balthazar et al. 2014).

Memory Effects Human studies of psychedelics' effects on memory have largely focused on performance during drug effects, with most finding acute, dose-dependent impairment under the influence of moderate or high doses of psychedelics such as psilocybin (Barrett et al. 2018), LSD (Jarvik et al. 1955; Pokorny et al.

2020), and ayahuasca (Bouso et al. 2013) on various memory and cognitive tasks (Healy 2021). These impairments have been demonstrated across a number of domains such as working memory (Bouso et al. 2013; Wittmann et al. 2007) and word recall (Barrett et al. 2018). However, acute changes in autobiographical memory during psychedelic effects have also been reported, suggesting LSD (Langs 1967) and psilocybin (Carhart-Harris et al. 2012) can facilitate recall and vividness of salient life memories, a potentially relevant mechanism for treatment of AD, which is known to entail episodic memory impairment (Tromp et al. 2015). If psychedelic administration has any long-term effects on human memory, data on persisting brain and mood effects (e.g., Barrett et al. 2020a) suggest that they may not resemble acute effects. However, post-acute effects of psychedelics on cognition and memory in clinical populations have yet to be rigorously studied.

Reducing Depression, Anxiety, and Existential Distress A major focus of recent research has been examining classic psychedelics' effects on mood and anxiety symptoms. Revisiting promising work from the earlier era of research on psychedelics (Grof et al. 1973; Richards et al. 1977), recent double-blind, controlled studies found a single moderate dose of the classic psychedelic psilocybin to produce clinically significant antidepressant effects and reduced anxiety in patients with life-threatening cancer diagnoses (Griffiths et al. 2016; Grob et al. 2011; Ross et al. 2016). In the largest of these contemporary trials, 51 cancer patients were administered a moderate to high dose of psilocybin under supportive conditions, with a majority showing therapeutic reductions in depression and anxiety and improved quality of life that persisted for 6 months (Griffiths et al. 2016). Additional pilot studies have found persisting anxiolytic effects of high-dose LSD treatment in patients with life-threatening illness (Gasser et al. 2014), as well as rapid, sustained antidepressant effects of psilocybin in patients with treatment-resistant major depression lasting 3 months (Carhart-Harris et al. 2016), and rapid antidepressant effects of ayahuasca lasting at least 7 days (Palhano-Fontes et al. 2019). Recent controlled trials have provided further support for antidepressant effects of psilocybin (Carhart-Harris et al. 2021; Davis et al. 2021).

One study of psilocybin in 27 individuals with major depression used a wait-list controlled design, randomizing participants to either an immediate treatment condition in which they received a moderate (20 mg/70 kg) and high (30 mg/70 kg) dose of psilocybin approximately 2 weeks apart with psychological support throughout, or to a control condition in which participants began an identical treatment after an 8-week delay period during which their mood was monitored. Twenty-four individuals completed the study, showing significantly greater decreases in GRID-Hamilton Depression Rating Scale (GRID-HAMD) scores in the immediate treatment group at 1 and 4 weeks after the second psilocybin session compared to the wait-list control group at corresponding timepoints (Davis et al. 2021). After receiving the psilocybin intervention, the wait-list control group also showed statistically significant decreases from baseline in GRID-HAMD and other depression and anxiety measures lasting 4 weeks after the second psilocybin session, with more than half the

sample overall (54%) meeting criteria for remission of depression at 4 weeks post-treatment.

Another study used a double-blind, randomized comparative efficacy design to assess effects of two high doses (25 mg) of psilocybin approximately 3 weeks apart compared with 6 weeks of daily oral escitalopram, an approved selective serotonin reuptake inhibitor (SSRI) antidepressant medication in a sample of 59 participants with moderate to severe major depression (Carhart-Harris et al. 2021). Results found significant reductions in depressive symptoms in both groups, with participants who received psilocybin showing greater improvements overall. Although these improvements did not meet statistical significance for superiority of psilocybin in the primary outcome (i.e., Quick Inventory of Depressive Symptomatology-Self-Report), depression remission was found in 57% of participants in the psilocybin condition at the 6 week timepoint compared with 28% in the escitalopram condition, and secondary outcome measures also favored psilocybin, indicating two high doses of psilocybin are at least as effective – if not more so – in treating depression than 6 weeks of daily escitalopram.

Increased Wellbeing and Life Satisfaction A growing body of work has shown sustained well-being benefits after classic psychedelic administration across diverse samples, from healthy volunteers (Griffiths et al. 2008, 2018) and older long-term AIDS survivors (Anderson et al. 2020) to people with a range of health conditions including cancer-related distress (Agin-Liebes et al. 2020; Swift et al. 2017), alcohol dependence (Bogenschutz et al. 2018), nicotine dependence (Noorani et al. 2018), and major depression (Watts et al. 2017). In many cases, such persisting effects are correlated with enduring personality changes such as increased openness, as well as increased life satisfaction and overall well-being (Erritzoe et al. 2018; Griffiths et al. 2008; MacLean et al. 2011; Madsen et al. 2020; Schmid and Liechti 2018; Smigielski et al. 2019a). Although the mechanisms for post-acute alterations in personality, behavior, and well-being are still under investigation, they have been linked to acute psychoactive drug effects that include a sense of insight and meaning (Erritzoe et al. 2018; Griffiths et al. 2008; Smigielski et al. 2019a), spiritual or mystical-type effects characterized by a sense of oneness (Garcia-Romeu et al. 2014; MacLean et al. 2011; Schmid and Liechti 2018), and changes in 5-HT_{2A}R binding (Madsen et al. 2020) and brain network functional connectivity (Barrett et al. 2020a; Sampedro et al. 2017; Smigielski et al. 2019b). That classic psychedelics have shown these persisting benefits across such a wide range of individuals provides good impetus to study them in patients with AD who are known to suffer from substantial decrements to quality of life overall (Karttunen et al. 2011; Shin et al. 2005).

4 Rationale and Approaches for Researching Psychedelics in Patients with AD

The data presented above provide good evidence that for some patients with AD, classic psychedelics may provide potential therapeutic benefits worth exploring further. To this end, we are currently conducting a pilot study to examine the potential of psilocybin to treat neuropsychiatric symptoms (NPS) in patients with early-stage AD and MCI. The trial is the first to our knowledge using moderate (15 mg/70 kg) and high-dose (25 mg/70 kg) psilocybin in patients with early-stage AD or MCI and depressed mood (ClinicalTrials.gov NCT04123314). Because of potential risks in more advanced cases of AD which may include symptoms such as delusions or hallucinations that could be exacerbated by high-dose psychedelic administration (Scarmeas et al. 2005), this research is geared toward earlier phases of the disease, consistent with recommendations that "the field should explore whether the long prodromal phase of AD creates novel possibilities to maintain cellular functionality and brain homeostasis to postpone the phase of irreparable damage and decay" (Sala Frigerio and De Strooper 2016, p. 71).

Clinical research to date has found benefits related largely to higher dose administration of classic psychedelics (Anderson et al. 2020; Bogenschutz et al. 2015; Carhart-Harris et al. 2021; Davis et al. 2021; Griffiths et al. 2016; Johnson et al. 2014). These data also suggest mood, quality of life, and general well-being improvements associated with high-dose psychedelic administration as potential therapeutic targets for patients with AD. Other approaches may consider use of lower repeated dosing of classic psychedelics in this population (Family et al. 2020). Currently available data on psychedelic microdosing (using chronic sub-perceptual doses that are not profoundly psychoactive) have failed to demonstrate consistent benefits in controlled trials (Bershad et al. 2019; Family et al. 2020; Hutten et al. 2020). However, this area remains open for further investigation to expand our understanding of the possible benefits, risks, and mechanisms of psychedelic treatments in AD. Additionally, the potential of classic psychedelics to treat other neurodegenerative disorders represents another compelling direction for future research.

5 Conclusion

Classic psychedelics with psychoplastogenic properties have the potential to be a powerful tool in the treatment of early-stage AD or MCI. Their ability to encourage neuronal growth similar to BDNF, a key protein that MCI patients produce at reduced levels, could possibly slow or even reverse the effects of a disease characterized by neurodegeneration. Agents that selectively induce neural plasticity in the cerebral cortex via direct action on 5-HT_{2A}R, which are highly expressed in layer 5 pyramidal neurons of the cortex, represent an as yet uninvestigated

pharmacological class in patients with AD. In sum, three converging biological pathways may be responsible for induced neural plasticity resulting in long-lasting and profound effects following psychedelic administration: 5-HT_{2A}R upregulation of neocortical BDNF, amplification of AMPA receptor activity resulting in downstream activation of mTOR, and upregulated Arc protein expression (Fig. 1). These plasticity-promoting pathways could represent a novel disease modifying treatment approach to treat AD that selectively induces neural plasticity in key cognitive brain regions like the prefrontal cortex, that as a result of the disease are deficient in endogenous plasticity-promoting compounds like BDNF. In addition, classic psychedelics' antidepressant and anxiolytic effects could provide important inroads for promoting psychological benefits in patients struggling with AD and neuropsychiatric comorbidities such as depression and apathy.

Questions remain as to the primary therapeutic mechanisms underlying psychedelic-assisted treatments. Some propose that characteristic mystical-type or ego-dissolving subjective effects of high-dose psychedelics are necessary for psychological benefits, (Yaden and Griffiths 2021) and others posit purely biological mechanisms as necessary and sufficient to achieve lasting positive effects (Olson 2021). It is our contention that there may be truth to both. Neuroplasticity inducing and anti-inflammatory properties of classic psychedelics suggest the potential for purely biological therapeutic activity across several mechanisms, even at doses that would not produce strong psychoactive effects (Flanagan and Nichols 2018; Ly et al. 2018; Shao et al. 2021). Thus, low-dose psychedelic treatments could have specific applications that may not necessitate subjective effects, such as reducing brain atrophy in neurodegenerative conditions, or recent work showing persisting reductions in migraine after a single dose of psilocybin that were not associated with psychoactive effects (Schindler et al. 2021). However, for particular conditions like depression, anxiety, addictions, and existential distress, current evidence suggests the subjective effects of classic psychedelics play a pivotal role, likely driven by their ability to alter core cognitive, emotional, and self-referential processes that can facilitate therapeutic insight, catharsis, and behavior change (Garcia-Romeu et al. 2014; Griffiths et al. 2016; MacLean et al. 2011; Roseman et al. 2018). As such, we recommend continued research of both low- and high-dose psychedelic therapy approaches and to tailor treatments according to clinical target and population.

The present discussion aims to inform the nascent field of clinical psychedelic research in patients with AD (George and Hanson 2019; Vann Jones and O'Kelly 2020). The data presented here, along with ongoing pilot research, set the stage to examine psychedelic treatments as potential avenues to affect disease progression and to enhance well-being and quality of life for patients with AD. We believe this work is both timely and promising, and represents a viable path forward for development of novel therapeutics in AD.

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