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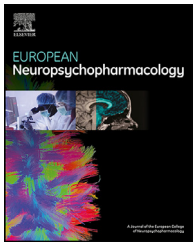

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REVIEW

The potential of psychedelics for the treatment of Alzheimer's disease and related dementias

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Abstract
Alzheimer's Disease (AD) is a currently incurable but increasingly prevalent fatal and progressive neurodegenerative disease, demanding consideration of therapeutically relevant natural products and their synthetic analogues. This paper reviews evidence for effectiveness of natural and synthetic psychedelics in the treatment of AD causes and symptoms. The plastogenic effects of serotonergic psychedelics illustrate that they have efficacy for addressing multiple facets of AD pathology. We review findings illustrating neuroplasticity mechanisms of classic (serotonergic) and non-classic psychedelics that indicate their potential as treatments for AD and related dementias. Classic psychedelics modulate glutamatergic neurotransmission and stimulate synaptic and network remodeling that facilitates synaptic, structural and behavioral plasticity. Up-regulation of neurotrophic factors enable psychedelics to promote neuronal survival and glutamate-driven neuroplasticity. Muscimol modulation of $GABA_AR$ reduces $A\beta$-induced neurotoxicity and psychedelic Sig-1R agonists provide protective roles in $A\beta$ toxicity. Classic psychedelics also activate mTOR intracellular effector pathways in brain regions that show atrophy in AD. The potential of psychedelics to treat AD involves their ability to induce structural and functional neural plasticity in brain circuits and slow or reverse brain atrophy. Psychedelics stimulate neurotrophic pathways, increase neurogenesis and produce long-lasting neural changes through rewiring pathological neurocircuitry. Psychedelic effects on 5-HT receptor target genes and induction of synaptic, structural, and functional changes in neurons

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and networks enable them to promote and enhance brain functional connectivity and address diverse mechanisms underlying degenerative neurological disorders. These findings provide a rationale for immediate investigation of psychedelics as treatments for AD patients.

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia and a leading cause of death globally (7th), reaching a staggering population prevalence above 30% in people over 85 (Gauthier et al., 2021). Currently, there are no medical cures for AD, creating an urgent need for new treatments. Central features of AD and other neurodegenerative disorders are manifested in dysfunctions from cellular to neural network levels that contribute to global cognitive decline (Saeger and Olson, 2022). Animal research shows that the serotonergic system has direct relevance for AD through its effects in modulating learning and memory functions and by addressing the selective neurodegeneration in serotonin receptor pathways and reduced activity at serotonergic synapses (Garcia-Romeu et al., 2022). Psychedelics such as psilocybin, N,N-dimethyltryptamine (DMT) and lysergic acid diethylamide (LSD) exhibit neuromodulatory effects mainly via the serotonin (5-hydroxytryptamine, 5-HT) 2A receptors (Nichols 2016).

We review evidence that neurotrophic and neuroplastogenic mechanisms elicited by "classic" (serotonergic, mainly 5HT2A agonists) natural psychedelic compounds and their synthetic analogues indicate they are potential therapeutic agents for addressing both causes and symptoms of AD and other dementias. A search in PubMed on August 20, 2022 using the MeSH term Alzheimer's AND the following terms found few articles and none involving clinical studies in humans: Psychedelic-5; Hallucinogen-5; Ibogaine-1; Muscarine-8; Muscimol-4; Harmine-8; Psilocybin-0; LSD-0. The most significant of these findings are incorporated into our narrative review that also includes other relevant literature on psychedelics' effects as plastogens and neuroplasticity agents with potential applications to AD. (Aleksandrova and Phillips, 2021; Garcia-Romeu et al., 2022; Inserra et al., 2021; Lukasiewicz et al., 2021; Ly et al., 2018; Martin and Nichols, 2016; Saeger and Olson, 2022; Vargas et al., 2021; Vollenweider and Smallridge, 2022).

The potential therapeutic applications of psychedelics in AD is an emerging topic, and recent, outstanding papers provide a forum for relevant scientific discussions in this field (Jones and O'Kelly, 2020; Garcia-Romeu et al., 2022). Here we offer a different approach to the topic by including several additional receptor systems in the discourse other than serotonergic ones (e.g. cholinergic, GABAergic, sigma receptors, etc., and their modulators, e.g. muscimol, ibogaine, etc.) at the intersection of dementia and psychedelic research. Furthermore, we also offer an in-depth overview on the molecular neurobiology of interacting downstream pathways and effects of psychedelics on cell types other than neurons, such as glial and immune cells.

2. The neuropathology of AD

AD is a neurodegenerative disorder with a clinical presentation of severe impairment in memory, speech, object recognition and visuospatial processing-related executive functions (Knopman et al., 2021). AD and other dementias have a neurodegenerative component that impairs the brain's ability to compensate for progressive injury. However, preservation of a variety of functions in AD, and individual differences in disease progression, suggest a potential for neuroplastic responses, especially in early-onset cases (Hill et al., 2011).

AD primarily involves synaptic dysfunction resulting from cellular, molecular, micro- and macroscale cortical deficiencies that render cortical information processing defective and maladjusted. AD's multifaceted pathophysiology encompasses observable subcellular and morphological alterations such as: the presence of β-amyloid containing extracellular deposits, called Aβ plaques (Chen et al., 2017); the accumulation of tau-containing neurofibrillary tangles in neurons; and the loss of glial and neuronal homeostasis and neuronal network integrity (Golde et al., 2018; Knopman et al., 2021). Knowledge of the biochemical processes of tau and Aβ/APP and how their interactions relate to AD etiology and pathophysiology is incomplete (van der Kant et al., 2020). Hypotheses regarding their intra and intercellular interactions include glial cells, the synaptic cleft and associated structures, and the endosomal/proteasomal/lysosomal system (Leyns et al., 2019).

Aβ-containing plaques are derived from amyloid precursor protein (APP), a transmembrane protein expressed in neuronal synapses (Haass and Selkoe, 2007). Following cleavage of APP by β and γ-secretases, Aβ peptides are produced and secreted into the extracellular space as monomers (Thinakaran and Koo, 2008). Due to their biochemical structure, these monomers have the tendency to aggregate. The aggregated, oligomeric form of Aβ is cytotoxic, interacting with several receptor types including N-methyl-D-aspartate (NMDA), metabotropic glutamate receptor 5, α7 nicotinic acetylcholine receptor, as well as insulin receptors (Spires-Jones and Hyman, 2014). Properly regulated APP cleavage has important physiological roles, such as modulation of synaptic transmission, endosomal and lysosomal functions, etc. (Rice et al., 2019; Small and Petsko, 2020). Improperly regulated APP processing may also have deleterious effects on synaptic function in addition to *de facto* neurotoxicity caused by accumulated Aβ plaques. The gut microbiota can also release soluble forms of amyloid proteins and those may influence neurodegeneration through the promotion of amyloid formation and by enhancing inflammatory responses to extracellular amyloid deposits (Friedland and Chapman, 2017).

The microtubule-associated protein tau is a normal intracellular component in the axonal cytoplasm, and is also present in the pre- and post-synaptic compartments in close association with the nuclear membrane (Eftekharzadeh et al., 2018). Its main function is microtubule stabilization (Eftekharzadeh et al., 2018), but it can be prone to aggregation due to abnormal post-translational modifications (De Calignon et al., 2012). After pathological aggregation, the hyperphosphorylated form of tau is accumulated in cell bodies and dendrites and can subsequently be released into the extracellular space by synaptic activity, where it is internalized by postsynaptic neurons and glial cells (Wu et al., 2016) and may exert direct cytotoxic and neuroinflammatory effects.

Neuroinflammation and dysregulated immune responses in the brain are core facets of AD pathology and related dementias (Leng and Edison, 2021). Overactive microglia and abnormal microglia-astroglia crosstalk may drive an inflammatory environment in the CNS that consequently allows the ingress of peripheral immune cells into the brain, provoking a vicious cycle of amplified neuroinflammation. Activated immunocompetent cells produce inflammatory cytokines and chemokines in the brain and attract and activate blood circulating lymphocytes and myeloid cells that favor a long-term, chronic neuroinflammatory phenotype observed in many neuropsychiatric disorders (Khandaker et al., 2015; Szabo et al., 2022). Chronic neuroinflammation exacerbates both tau and Aβ pathologies and may be a crucial link and central mechanism in the pathogenesis of AD (Kinney et al., 2018).

Elevated and prolonged neuroinflammation causes cellular stress with mitochondrial and endoplasmic reticulum involvement which lead to unfolded protein response (UPR), which if sustained causes apoptotic cell death. Targeting several elements of the cellular stress like endoplasmic reticulum stress, UPR, mitochondrial and oxidative stresses may have benefits in treatment of AD (Moren et al., 2022; Sidhom et al., 2022; Trushina et al., 2022).

3. Neuromechanisms of potential AD therapies

Pro-cognitive and neuroplasticity modulating capacities of serotonin receptors are implicated in AD (Svob Strac et al., 2016; Vann Jones and O'Kelly, 2020) through several mechanisms: One involves 5-HT2A receptor modulation of gene expression of neuroplasticity-enhancing neurotrophins in the hippocampus and neocortex (Vaidya et al., 1997). Another mechanism is from enriched 5-HT2A associated with fine-tuning of cortical signaling regulating cognition, memory, and synaptic plasticity in cortical areas affected in AD (Zhang and Stackman, 2015). The classical view of neurotransmitter receptors localized on the postsynaptic membrane within the synaptic cleft and involved in the transfer of action potentials between neurons cannot be fully applied to serotonin receptors, which are mostly localized intraneurally at extrasynaptic locations and mediate long-lasting metabotropic effects (Bockaert et al., 2006). Serotonin output from the raphe nuclei is paramount in restoring networks and their function after CNS injury (Fabbiani et al., 2018; Leibinger et al., 2021). Serotonin is a ubiquitous and important modulator of a vast array of processes taking part in neural development, regeneration and plasticity (Salvan et al., 2023).

The opioid-like orphan receptor sigma-1 receptor (Sig-1R) is a potential therapeutic target in multiple neurodegenerative disorders including AD (Penke et al., 2018; Ryskamp et al., 2019b). Sig-1R is a small transmembrane protein mostly expressed and enriched in the endoplasmic reticulum (ER) - mitochondria-associated membrane system (Hayashi and Su, 2007). It has a very important biochemical chaperone role in assisting and controlling cellular stress responses, metabolic adaptation, and protein folding, and has been proposed to play a role in the etiology and pathophysiology of neurodegenerative disorders.

Sig-1R plays a mitigating role in cellular stress signaling, downregulating endoplasmic reticulum stress and UPR. Activation of Sig-1R provides neuroprotection in cell cultures and animal studies (Bogar et al., 2022); the Sig-1R agonists DMT and 5-MeO-DMT exert anti-inflammatory responses (Szabo et al., 2014). Furthermore, clinical trials demonstrated Sig-1R agonists (pridopidine, ANAVEX3–71, fluvoxamine, dextrometorphan) have neuroprotective effects by fine-tuning stress resilience, and modulating metabolic and survival pathways in cortical neurons. Pathways targeted by these experimental drugs are similar to those modulated by psychedelics that display agonistic activity at Sig-1R sites (Bogar et al., 2022).

Several Sig-1R agonists display anti-amnesic properties and protective roles in Aβ toxicity (Maurice and Goguadze, 2017), boosting neurogenesis in the hippocampus (Moriguchi et al., 2013) and improving synaptic stability and remodeling (Ryskamp et al., 2019a). Sig-1R agonists are neuroprotective *in vivo* models of AD (Tsai et al., 2009). Studies suggest that Sig-1R-related signaling interacts with genes involved in AD (presenilin 1 and presenilin 2), with mutations in these genes disrupting regulation of intracellular Ca^{2+} release from the ER. Sig-1R agonists might interfere with this dysregulation in hippocampal neurons by modulating ER leakage, increasing stress resilience and improving neuroplasticity (Ryskamp et al., 2019b).

AD, and dementias in general, are associated with abnormalities in cholinergic and noradrenergic neurotransmission (Voss et al., 2017), with AD neuropathology associated with loss of GABAergic inhibitory functions (Huang and Mucke, 2012). Cholinergic modulators and cholinesterase inhibitors are reported effective in alleviating symptoms of dementias including AD and are currently being tested as potential treatment options in these disorders (Colovic et al., 2013).

3.1. Plastogens: general mechanisms of psychedelics in addressing dementia

Psychoplastogens are compounds that can produce structural and functional neural plasticity in brain circuits, making them promising treatments of neuropsychiatric diseases through regenerating pathological neural circuitry, restoring network-level functioning and enhancing diverse processes of neuroplasticity (Vargas et al., 2021). CNS plasticity is produced through various processes (axonal sprouting, long-term potentiation and expression of plasticity re-

lated genomic responses) and found across brain levels from gene expression and signal transduction to synaptic and neuronal levels and whole-brain networks (De Gregorio et al., 2021). Neuroplasticity (neural plasticity, synaptic plasticity, cortical plasticity and cortical re-mapping) involve abilities of the nervous system to change in response to both internal and external stimuli via changes in its structure and connections (De Gregorio et al., 2021; Inserra et al., 2021). Neurogenesis is a component of neuroplasticity that involves processes that induce progenitor activity, stimulate precursor cell division and promote cellular processes underlying the growth of the dendrites and axons for synaptic formation. Neuroplasticity builds neural networks and reorganizes neuronal activity, functions, and interconnections among networks by removing and adding new cellular components (neurite branches, synaptic endings) and even cells (nerve cells and associated glial cells) and their connections and structures. Neuroplasticity is both a cellular substrate for learning and memory formation and a complex dynamic of functional changes associated with development of synapses (synaptic plasticity), axon and dendrite regeneration. Cellular mechanisms of neuroplasticity include modification of synaptic transmission, synaptogenesis, synaptic restructuring, neurogenesis, dendritic remodeling, and axonal sprouting (Teter and Ashford, 2002). Neuroplasticity also manifests through higher-order phenomenological processes involving changes in neurobehavioral patterns and psychological and sociological activities (Teter and Ashford, 2002) and guiding adaptive behavior in adjusting to a dynamic environment (Aleksandrova and Phillips, 2021).

3.2. Psychedelics as plastogens

Recent peer-reviewed articles (Aleksandrova and Phillips, 2021; Garcia-Romeu et al., 2022; Inserra et al., 2021; Lukasiewicz et al., 2021; Ly et al., 2018; Martin and Nichols, 2016; Saeger and Olson, 2022; Vargas et al., 2021; Vollenweider and Smallridge, 2022) address the potential of psychedelics for treatment of AD by slowing down or reversing brain atrophy and enhancing cognitive function, suggesting that they could provide novel pharmacotherapies for a range of heretofore incurable dementias. Lukasiewicz et al. (Lukasiewicz et al., 2021) call psychedelics psychoplastogens in reference to their broad therapeutic effectiveness through acting as catalysts for increased brain neuroplasticity and reconfiguring neuronal networks. Psychedelics produce neuroplastic effects through stimulation of neurotrophic pathways, increasing neurogenesis and cognitive flexibility and producing long-lasting neural changes (De Gregorio et al., 2021; Vargas et al., 2021).

Psychedelics' rapid plastogenic effects on diverse processes of cognition, learning and memory (Garcia-Romeu et al., 2022; Saeger and Olson, 2022) and their robust and sustained therapeutic effects involve stimulation of structural and functional dynamics of neuroplasticity, modification of synaptic plasticity, induction of anti-inflammatory effects, and rewiring pathological neurocircuitry (Aleksandrova and Phillips, 2021; Bogenschutz et al., 2015). This makes them ideal agents to address neurological, behavioral and psychological features of cortical or subcortical atrophy exhibited in neurodegenerative conditions. Convergent downstream mechanisms of action occur via effector mechanisms of serotonin receptor target genes, inducing and regulating synaptic, structural, and functional changes in PFC pyramidal neurons (Aleksandrova and Phillips, 2021).

Studies (Inserra et al., 2021; Ly et al., 2018) on roles of neural plasticity in therapeutic effects of psychedelic serotonergic 5HT2A agonists illustrates they promote structural and functional plasticity of synapses and enhance brain functional connectivity. Serotonergic psychedelics promote neuroplasticity through (post-acute) changes in signaling pathways and anti-inflammatory effects (Garcia-Romeu et al., 2022), illustrating their relevance for AD treatments as neuroplasticity-enhancing agents capable of addressing diverse mechanisms underlying degenerative neurological disorders (De Vos et al., 2021).

Through up-regulation of neurotrophic factors they promote neuronal survival and produce persistent enhancement in glutamate-driven neuroplasticity in frontocorticolimbic pyramidal neurons by stimulating interactions between glutamate and serotonin systems (Aleksandrova and Phillips, 2021), affecting regional synaptic homeostasis and counteracting synaptic deficits and neuronal atrophy. Acute psychedelic effects characterized by profound perceptual, cognitive, and emotional changes may be mediated by short-term action potential transfers through synaptic 5-HT2A receptors or from fast-acting mechanisms that induce long-lasting structural modifications (Aleksandrova and Phillips, 2021); but the bulk of long-term neuroplastic changes are probably related to intracellular metabotropic serotonin receptors (Bockaert et al., 2006). These findings suggest that psychedelics' pharmacological modulation of neurotransmitter systems may potentially reverse neurocognitive deficits pertaining to dementias via fine-tuning neuroplasticity.

3.3. Classic psychedelics (Indolealkylamines and phenylalkylamines) as modulators of neuroplasticity and neuroprotection

Human psychopharmacological studies demonstrated the binding profile of classic psychedelics in the brain is predominantly characterized by 5-HT2A occupancy and functional activity (Madsen et al., 2019; Vollenweider et al., 1998). Naturally occurring psychedelics are not strictly 5-HT2A selective, with other receptors and receptor-systems also mediating their neurophysiological effects (Banks et al., 2021; Pokorny et al., 2016). Indolealkylamine tryptamine- and lysergic acid derivatives commonly have both 5-HT2A and 1A receptor binding affinity and partial agonistic activity at Sig-1R, dopamine, adrenergic and acetylcholine receptors (Rickli et al., 2016). The receptor affinity profile of phenylalkylamines, such as 2,5-dimethoxy-4-iodoamphetamine (DOI) and mescaline, are more polarized towards 5-HT2A and, to a lesser extent, to 5-HT2C receptors (Halberstadt and Geyer, 2011; Ray, 2010). These receptors are primary pharmacological mechanisms for classic psychedelics' neurological, psychological and behavioral effects although their therapeutic potential might also involve other receptor types; recent studies indicate metabotropic glutamate receptors are also involved (Carbonaro et al.,

2015). Many psychedelics also target 5-HT6 and 5-HT7 serotonin receptors that enhance plasticity and address neurodegeneration (Saeger and Olson, 2022). Various serotonergic tryptamines modulate Sig-1R receptors in both the central nervous system and in peripheral tissues and cell types, including immune cells (Frecska et al., 2013; Szabo, 2015).

5-HT2A receptors directly signal via G-protein-coupled receptors (GPCRs) of the G_q subtype. Stimulation of 5-HT2A receptors triggers the intracellular synthesis of inositol triphosphate (IP3) by phospholipase C (PLC) activation, which leads to mobilization of cytoplasmic Ca^{2+}, a common downstream signaling effector of GPC-receptors. Release of Ca^{2+} from intracellular storage compartments modulates a plethora of acute and long-term cellular physiological effects including changes in excitability, neurogenesis and differentiation (neurons and neural stem cells), fine-tuning of neurotransmission (via glial cells), as well as modulation of functional pathways related to cell survival, apoptosis, metabolic regulation and stress resilience (see Fig. 1). Signaling through $G_{i/o}$ family elements, another GPCR downstream pathway controlled by 5-HT2A receptor activation, is associated with production of intracellular cyclic adenosine monophosphate (cAMP), a critically important second messenger in many biological processes. Modulation of both G_q and $G_{i/o}$ pathways via 5-HT2A can mobilize and promote neuroplasticity and are implicated in therapeutic effects of serotonergic psychedelics (Fig. 1) (Banks et al., 2021).

Classic psychedelics boost dendritic spine and neurite formation via the modulation of the mammalian target of rapamycin (mTOR) and tropomyosin receptor kinase B (TrkB) by 5-HT2A both *in vitro* and *in vivo* (Ly et al., 2018). This is critically important, since these pathways are heavily involved in the production of brain-derived neurotrophic factor (BDNF) and positive neuroplasticity changes in the prefrontal cortex (PFC) (Banks et al., 2021; Meunier et al., 2017). Psilocybin, ayahuasca alkaloids, and 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) also effectively induce neurogenesis in the mammalian hippocampus (Lima da Cruz et al., 2018; Reckweg et al., 2022; Saeger and Olson, 2022) (Fig. 1). Psychedelic effects in promoting synaptic plasticity depend on intracellular roles of both TrkB/BDNF and mTOR signaling pathways (De Gregorio et al., 2021; Inserra et al., 2021; Lukasiewicz et al., 2021). Psychedelics share the ability with BDNF and TrkB agonists to activate mTOR, intracellular effector pathways highly expressed in brain regions related to sensory and cognitive processing that atrophy in AD and related dementias (Saeger and Olson, 2022). Changes induced by psilocybin positively affected memory, attention span and perception in humans (Barrett et al., 2020; Preller et al., 2020), which suggests their therapeutic potential in AD and related dementias (Fig. 1).

Serotonergic psychedelics may also drive systems-level, neurotrophin-based functional changes in the brain parenchyma via 5-HT2A that could contribute to significant therapeutic effects in dementias through modulation of persistent, long-term changes that underlie cognitive improvements. Classic psychedelics increase brain connectivity and neuroplasticity in healthy adults (Preller et al., 2018, 2019) and the resultant connectivity alterations in higher-order regions (Barrett et al., 2020; Preller et al., 2020; Roseman et al., 2014; Sampedro et al., 2017) illustrate the importance of investigating their potential long-term cognitive-behavioral effects.

Martin and Nichols (2016) provide evidence that specific 5-HT2A-expressing excitatory neurons are activated by psychedelics, and this recruits astrocytes and inhibitory somatostatin and parvalbumin GABAergic interneurons. They conclude that DOI (and presumably other serotonergic psychedelics) transcriptionally activate heterogeneous populations of inhibitory and excitatory cells that subsequently activate heterogeneous populations of cells in the medial PFC (mPFC) and somatosensory cortex. While the immediate early gene induction varies across brain region and cell type, psychedelics activate specific 5-HT2A-expressing neurons in the mPFC, somatosensory cortex, and claustrum, including 5-HT2A-excitatory neurons, which subsequently recruit somatostatin and parvalbumin interneurons (Martin and Nichols, 2016).

Classic psychedelics also produce downstream modulatory effects on gamma-aminobutyric acid (GABA), dopaminergic and glutamatergic systems (Vollenweider and Smallridge, 2022). Effects on glutamatergic receptors are via N-methyl-D-aspartate (NMDA) with additional effects on the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor systems (De Gregorio et al., 2021). Glutamate neurotransmission also effects NMDARs, which have a role in induction of long-term synaptic plasticity (Aleksandrova and Phillips, 2021). LSD modulates glutamatergic neurotransmission, and since glutamate is an excitatory neurotransmitter involved in neuroplasticity, cognition, learning, memory and other homeostatic processes, these results suggest a neuroplasticity-modulating potential for LSD (De Vos et al., 2021; Ly et al., 2018). Molecular, electrophysiological, neuroimaging and clinical studies show that 5HT2A psychedelics all modulate glutamatergic neurotransmission and stimulate synaptic and network remodeling that facilitates synaptic, structural and behavioral plasticity (Aleksandrova and Phillips, 2021).

4. Non-serotonergic psychedelics

While serotonin 5HT2A receptors are implicated in the major effects of classic psychedelics, especially visionary experiences typified in the concept of hallucinogens, perturbations in a variety of neurotransmitter systems also may result in visionary experiences. Hobson (Hobson, 2001) shows the reduction of serotonergic and noradrenergic control allows for ascendance of acetylcholine and dopamine systems that produce visual syndromes, typified in hallucinations. Similarly, the following sections present evidence non-serotonergic psychedelics have potential implications for treatment of AD and related dementias through receptor-affinity involving other receptor families (dopaminergic, adrenergic, or cholinergic) (Nichols, 2016).

4.1. *Amanita muscaria* and muscimol

The psychedelic mushroom *Amanita muscaria* (and other *Amanita* species) contain the compounds muscimol and ibotenic acid, as well as small amounts of muscarine and

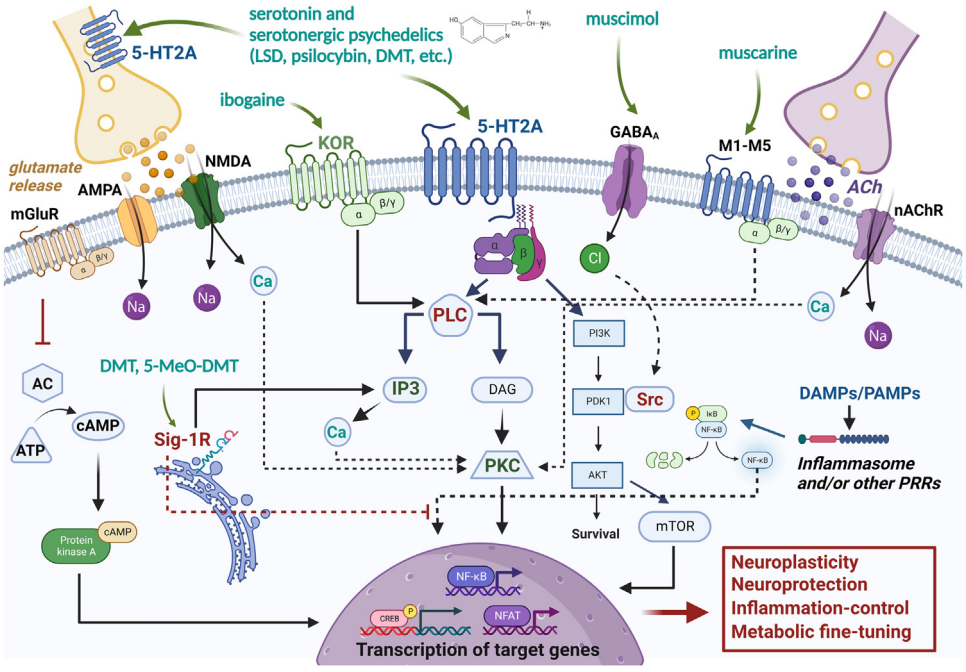

Fig. 1 Interaction of receptors and pathways involved in the therapeutic action of classic and non-classic psychedelic substances. Fig. 1 represents interacting pathways and typical receptors for psychedelics discussed in this paper. The center of the figure represents a neural or glial cell expressing these receptors. One pathway (upper left) involves glutamatergic presynaptic neurons that express 5-HT2A receptors that modulate glutamate release, leading to the ligation and activation of AMPA, NMDA, and metabotropic glutamate receptors (mGluR). Another pathway (upper right) involves presynaptic cholinergic neurons that release acetylcholine (ACh) activating muscarinic (M1-M5 type) and nicotinic cholinergic receptors (nAChR). Classic serotonergic pathways (LSD, DMT, psilocybin; upper center) mainly activate 5-HT2A receptors, which are 7-transmembrane G-protein-coupled receptors (GPCRs). Atypical psychedelics activate either other types of GPCRs (e.g., ibogaine modulates the kappa-opioid receptor – KOR), $GABA_A$ (muscimol), or muscarinic receptors (muscarine). DMT and 5-MeO-DMT-modulated pathways (middle left) exhibit affinity at sigma-1 receptor (Sig-1R) sites at the mitochondria-associated endoplasmic reticulum membranes. Upon activation by their specific ligands, these receptors converge into three major pathways: 1) Phospholipase C (PLC) - Protein kinase C (PKC) effector pathway that regulates intracellular Ca^{2+} levels and control transcription factors modulating cellular survival/death, neuroprotection and metabolic fine-tuning (in the center; involving diacylglycerol – DAG); 2) Catalyze the formation of cyclic AMP (cAMP) from ATP (Adenosine triphosphate) by AC (Adenylate cyclase), and thereby activating Protein kinase A that controls several survival- and neuroplasticity-related genes (lower left); 3) Phosphoinositide 3-kinase (PI3K) – AKT – mammalian target of rapamycin (mTOR) effector axis that regulates protein synthesis, stress-adaptation, neurorestorative and neuroplasticity-related genes and mechanisms. This effector pathway also likely involves genes controlled by the nuclear factor CREB (cAMP response element-binding protein; lower right). Both classic and non-classic psychedelics can modulate inflammation control via the modulation of the transcription factor Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and its target genes via unknown mechanisms. In immunocompetent glial cells, such as microglia and astrocytes, this mechanism involves pattern recognition receptors (PRRs) and inflammasomes that are expressed either on the cell surface or localized on intracellular membranes or in the cytoplasm. PRRs recognize various sets of pathogenic or self-derived structures (pathogen-associated molecular patterns – PAMPS, or endogenous damage-associated molecular patterns – DAMPs), and transduce signals through the NF-κB pathways. The interaction of a specific PAMP/DAMP with PRRs results in downstream signaling through various adaptor proteins. This receptor-adaptor interaction leads to the activation of specific kinases, and leads to the subsequent phosphorylation of NF-κB. This transcription factor then translocates into the nucleus regulating the transcription of inflammatory cytokine and chemokine genes, such as IL-1β, IL-6, IL-8, IL-18, and TNFα. Classic psychedelics, typically via 5-HT2A and/or Sig-1R signaling, can modulate intracellular Ca^{2+} levels through inositol trisphosphate (IP3). 5-HT2A and Sig-1R can also interfere with both PKC and PRR-mediated NF-κB signaling. Thus, the NF-κB and PKC downstream pathways may have a cardinal role in both the collaboration and essential signaling processes of PRRs, 5-HT2A, and Sig-1R in modulating inflammation-control in general, and local neuroinflammation in the brain. Arrows represent activation, red T-arrows represent inhibition/inhibitory effect. Created with BioRender.com.

muscazone (Michelot and Melendez-Howell, 2003). The psychedelic properties of *Amanita* are notable in spite of their differences from psilocybin's typical effects. Instead of the typical serotonergic agonist effects of 5-HT2A psychedelics, the primary psychoactive agent of *A. muscaria* (muscimol) resembles the neurotransmitter GABA and interacts with GABA receptors. The other psychoactive compound, ibotenic acid acts on glutamate receptors. Recent analyses of trip reports by (Feeney, 2020) suggest that it is appropriate to characterize *A. muscaria* as a

psychedelic in spite of mostly distinct effects from serotonergic psychedelics. More typical psychedelic effects include a sense of unfamiliarity to reality, a surreal dream-like quality to the experiences and reports of ego loss, and dislocation of the mind's eye from body perspective and one's head. Some of the unique constellation of effects of *Amanita* include a frame reduction, involving a slowing of processing of visual frames, prolonged visual frames, size distortion of image, and visionary dreams experienced as an entry into a hallucinatory dream-like reality separate from the physical world.

Muscarine and muscimol hold promise for therapy of neurodegenerative disorders associated with cognitive decline and severe amnestic impairment. Muscarine is a high affinity selective agonist of muscarinic acetylcholine receptors (mAChRs), a group of GPCRs located on several neuron types, including the postganglionic fibers of the parasympathetic nervous system (Eglen, 2006). Some of the subtypes of mAChRs are enriched in the human cerebral cortex, especially the M1, M2, and M4 receptors which are predominant in the CNS and involved in regulation of neuronal excitability and neuroplasticity. Their localization and substantial functional selectivity make them ideal targets in the treatment of AD and schizophrenia. Although the naturally occurring form of muscarine is not able to cross the blood-brain barrier (BBB), its chemically modified BBB-crossing analogs may offer promising treatment models in neurodegenerative disorders (Kruse et al., 2014).

Muscimol is a psychotropic isoxazole produced from ibotenic acid via decarboxylation and thus the latter is considered as a prodrug for muscimol in mammalian systems (Bowden et al., 1965). Ibotenic acid is rapidly metabolized by the liver to the more stable and bioactive muscimol in mammals, which makes muscimol a more attractive pharmacological target for therapeutic applications (Stebelska, 2013). Upon enteral or parenteral administration, muscimol rapidly crosses the BBB, displaying selective and potent agonistic activity at $GABA_A$ receptor ($GABA_AR$) sites, and consequently has depressant, sedative-hypnotic and hallucinogenic characteristics (Johnston, 2014).

Unlike other GABAergic drugs, such as benzodiazepines and barbiturates that allosterically modulate the receptor, muscimol binds directly to binding the site of $GABA_AR$ (Frolund et al., 2002). $GABA_ARs$ are widely expressed in the human brain, displaying significant enrichment in cortical areas and in the hippocampus. *In vivo* rodent studies of AD treatment with muscimol showed potent enhancing effects on memory and learning (Pilipenko et al., 2015), even at very low doses (Pilipenko et al., 2018). This effect involves muscimol-mediated significant downregulation of hippocampal and cortical proteins involved in neuroinflammation and astrocyte reactive gliosis, such as GFAP, as well as modulated enzymes critical for GABA synthesis (Pilipenko et al., 2018). These results are very important, since large-scale neural network activity is abnormally increased in the brain of patients with AD, and animal models show decreased GABAergic inhibitory neuron activity may contribute to the observed Aβ-induced cognitive deficits (Xu et al., 2020). Chronic modulation of $GABA_AR$ with muscimol greatly reduces Aβ-induced neurotoxicity in cultured rat cortical neurons, an effect entirely inhibited/prevented by bicuculine, a specific $GABA_AR$ antagonist (Lee et al., 2005). Low-dose muscimol adiminstered directly into subthalamic nuclei also reversed Parkinsonism in a small human study (Levy et al., 2001), and ameliorated cognitive deficits and improved spatial memory in an APP/PS1 mouse model of AD (Fu et al., 2019), suggesting the therapeutic potential of muscimol in both Aβ and tau neuropathologies and homeostasis.

4.2. Ibogaine

Ibogaine, a psychotropic indole alkaloid found in *Tabernanthe iboga* and related species, exhibits high affinity for multiple receptor types, including μ- and κ-opioid receptors, NMDA and sigma receptors, as well as serotonin transporters (Floresta et al., 2019). Ibogaine has potent, selective agonistic action at κ-opioid and Sig-2Rs (Mach et al., 1995) and modulatory effects on dopamine release via sigma- and NMDA receptors in striatal neurons (Sershen et al., 1996), but the cellular and systemic physiological effects remain under-researched.

The neuroplasticity-enhancing and modulating effects of ibogaine are associated with increasing BDNF levels and glial cell-derived neurotrophic factor (GDNF), another potent mammalian neurotrophin. Ibogaine increases production of GDNF in the rat midbrain, including the ventral tegmental area (VTA) and expression of elements of the GDNF pathway, receptor, adaptors, and downstream kinases in the VTA (He et al., 2005). An *in vitro* study demonstrated short-term ibogaine exposure increases levels of *GDNF* mRNA, leading to GDNF protein expression and activation of its signaling pathway via a long-lasting, autocrine feedback loop (He and Ron, 2006). Low doses of ibogaine significantly increased BDNF transcript levels in the nucleus accumbens, substantia nigra and PFC of the rat brain, while large doses (40 mg/kg) caused observable increase in BDNF mRNA levels in the VTA (Marton et al., 2019). GDNF mRNA was selectively upregulated in the substantia nigra and VTA regions, and large doses significantly increased GDNF secretion in the VTA. Both low and high doses of ibogaine increased *in vivo* protein levels of precursor BDNF (proBDNF) in the nucleus accumbens (Marton et al., 2019).

Toxicity-related safety concerns have hindered clinical research into effects of ibogaine in humans. However, tabernanthalog, a novel, non-psychoactive, nontoxic analog of ibogaine, promotes robust structural neuroplasticity and anti-depressant-like effects in rodents (Cameron et al., 2021), indicating a promising treatment option for neurodegenerative and neuropsychiatric disorders.

4.3. Harmine

The β-carboline alkaloid harmine is a reversible inhibitor of the monoamine oxidase enzyme (MAO-A) that makes DMT sources in ayahuasca bioavailable after oral ingestion. Harmine may have cognition-enhancing and neuroprotective effects, resulting in improved memory and learning in several animal models and producing neuroprotective effects through increased BDNF levels and reduced neurotoxicity, inflammation, and oxidative

stress (Dos Santos and Hallak, 2017). Therapeutic mechanisms proposed include harmine's dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) inhibitor (Becker and Sippl, 2011) and neurogenic, progenitor stimulating activity (Morales-Garcia et al., 2017). DYRK1A regulates cell proliferation and brain development and harmine enhances proliferation of human neural progenitor cells, suggesting DYRK1A inhibition was responsible for the effect (Dakic et al., 2016). Several classes of DYRK1A inhibitors are promising candidates for developing drugs against degenerative diseases (Abbassi et al., 2015).

Harmine is neurotoxic in high doses, with elevated levels in the blood associated with essential tremor (Louis et al., 2002). In humans, toxic symptoms appear above the 3 mg/kg dose (Marwat and Rehman, 2011). Nonetheless, cognition-enhancing and neuroprotective effects of harmine should be further investigated in animal and human studies of AD. Appropriate dosing is crucial since memory impairment was reported in rats at 5, 10, and 15 mg/kg doses (Libanio et al., 2021).

5. Discussion

The possible long-term therapeutic effects of serotonergic psychedelics in dementias likely involve three different mechanisms:

1) *The modulation of serotonergic/psychedelic-specific alterations in the global brain transcriptome.* A single dose of psilocybin or 5-MeO-DMT causes significant changes in neuroplasticity-related gene transcripts in the hippocampus and PFC *in vivo* (Jefsen et al., 2021), and functionally related changes in the proteome of human stem cell-derived cerebral organoids (Dakic et al., 2017). DOI increases gene expression of the neurotrophin BDNF and upregulates highly neuroplasticity-specific gene pathways in the rodent neocortex and hippocampus (Desouza et al., 2021; Tsybko et al., 2020) implicated in dementias with a neurodegenerative component (Allen et al., 2011; Schindowski et al., 2008). Human clinical studies also reported elevated plasma levels of BDNF following administration of serotonergic psychedelics (De Almeida et al., 2019; Hutten et al., 2021) that may contribute to long-term pro-neuroplastic effects at both the transcriptomic and proteomic levels (De Vos et al., 2021; Martin and Nichols, 2018).
2) *Modulation of the epigenetic landscape in the brain.* The epigenetic control of neuroplasticity-related genes has global effects on brain functions, neural networks, structural and functional recovery following acute injury and in chronic conditions like AD (Wang et al., 2018). Histone modifications and direct methylation of DNA associated with neurorestorative and neuroprotective mechanisms provide promising targets in AD. Serotonin can directly act on the genome by modifying histone proteins through serotonylation. Similar epigenetic mechanisms are implicated in neural plasticity and their dysregulation is connected to age-related memory decline and AD (Maity et al., 2021). Preclinical and genome-wide association studies suggest memory, learning, and aging-related single or cluster-like gene expression changes in the brain may occur independently of alterations in epigenetic patterns (Lopez-Atalaya and Barco, 2014). Furthermore, most of the epigenetic changes that affect memory, learning, neuroinflammation and age-related alterations in AD occur in regulatory and enhancer regions, which makes it extremely complicated to localize and/or identify gene expression changes at the single-gene level. DMT and related psychedelic tryptamines are hypothesized to exert therapeutic activity via epigenetic changes mediated by Sig-1R (Inserra, 2018). This is in agreement with previous *in vitro* results demonstrating the neuroprotective effects of DMT in human stem cell-derived cortical neurons and glia-like cells (Szabo et al., 2016), and in rodents following experimental stroke (Nardai et al., 2020). Furthermore, LSD administration significantly modulated DNA methylation in the mouse PFC and caused concomitant changes in expression of gene pathways and proteins related to neurotrophic- and neuroplasticity signaling and function (Inserra et al., 2022). These results warrant further investigations into the complex epigenetic effects of psychedelics in neuropsychiatric disorders.
The relevance of epigenetic changes from psychedelics are illustrated by the study of Ruffell et al. (Ruffell et al., 2021) which performed an epigenetic analysis on pre- and post- saliva samples collected at an ayahuasca retreat. They report that DNA methylation showed a statistically significant increase for the Sig-1R assay. The changes in methylation scores for Sig-1R were significantly correlated with scores on a Childhood Trauma Questionnaire assessing emotional, physical, and sexual abuse and emotional and physical neglect indicating that ayahuasca increased methylation for those with higher degree of childhood trauma. They interpret their results as suggesting that ayahuasca has effects on Sig-1R epigenetic regulation but caution that it remains uncertain whether there are biological impacts of this change in DNA methylation or any alterations to gene expression. Nonetheless their findings suggest that there are potential epigenetic processes that may regulate Sig-1R expression relevant in the psychosocial context of healing trauma. In addition, de la Fuente Revenga et al. (2021) also found evidence of psychedelic-induced epigenetic changes in a study of a single administration to mice of the phenethylamine DOI, which produced a variety of effects via the 5-HT2A receptor that persisted for days following a single administration. Their study found changes in chromatin organization at enhancer regions of genes involved in synaptic assembly (de la Fuente Revenga et al., 2021). The alterations in the neuronal epigenome induced by DOI overlap with specific genetic loci associated with a variety of mental disorders, such as schizophrenia, depression, and attention deficit hyperactivity disorder. They interpret their findings as supporting other evidence of long-lasting psychedelic action based in epigenomic-driven changes in synaptic plasticity. The group characterize these DOI induced changes in-depth molecular structures and resultant modifications in behavioral adaptations of mice

as suggesting the molecular mechanisms of persistent post-dose effects on synaptic plasticity likely reflect brain plasticity mechanisms involving structural and functional modification of dendritic spines. Their study provides important and direct evidence of DOI's post-acute effects via 5-HT2AR-dependent mechanisms on dendritic spine structure that underlie long-lasting alterations in frontal cortex gene expression and chromatin organization (de la Fuente Revenga et al., 2021). These exogenous psychedelic effects on the epigenetic landscape, particularly at the enhancer regions of genes in the cortex, seem to be of particular interest with regards to future therapeutic applications.

3) *Modulation of neuroinflammation.* Inflammation and dysregulated inflammatory glial functions are core mechanisms in the pathogenesis of AD and related dementias while modulation of the CNS serotonergic system is associated with significant immunomodulatory potential and inflammation-control (Herr et al., 2017; Szabo et al., 2018). Preclinical studies demonstrated classic psychedelics display potent anti-inflammatory effects via 5-HT2A and Sig-1R receptors (Flanagan et al., 2021; Flanagan and Nichols, 2018, 2019; Nau et al., 2013; Szabo, 2015; Szabo et al., 2014; Thompson and Szabo, 2020). Mouse studies show psychedelics enhance AD-associated cognitive function by reducing neuroinflammation, suggesting reduction in human AD pathology and symptoms could be achieved by decreasing neuroinflammation associated with inflammatory cytokine (e.g., TNF-α and IL-1β) related effector mechanisms (Saeger and Olson, 2022). This may result from psychedelics' stimulation of 5-HT2A receptors that modulate immunomodulatory and anti-inflammatory responses (De Gregorio et al., 2021; Flanagan and Nichols, 2018) and promote cortical neuron growth and neuronal survival mechanisms that counter age-induced chronic inflammation (Aleksandrova and Phillips, 2021). These selective anti-inflammatory effects may derive from psychedelic-mediated biased signaling cascades and 5-HT2A receptor stabilization that recruit anti-inflammatory signal transducers which inhibit TNF-α receptor and NF-kB transcription factor-mediated proinflammatory signaling (De Gregorio et al., 2021). The ability of 5-HT2A psychedelics to suppress peripheral inflammation caused by TNF-α (Flanagan et al., 2021) indicates that AD pathology and symptoms induced by chronic inflammation might be attenuated by enhanced functioning of microglial cells as these phagocytic cells selectively remove dead neural cells from brain parenchyma (Saeger and Olson, 2022).

Inflammatory cytokines, produced by activated immune cells and immune-competent glia (microglia and astrocytes), significantly interfere with complex, higher level neural functions as reported in multiple neuropsychiatric disorders with neurodegenerative, neuroinflammatory, and neurocognitive components (Akkouh et al., 2021; Khandaker et al., 2015; Miller and Raison, 2016; Szabo et al., 2022). Neuroinflammation also aggravates all facets of the neuropathology of AD, making it a target in recent pharmacotherapies (Kinney et al., 2018). A combined therapeutic approach of modulating both neuroinflammation and neuroplasticity with serotonergic psychedelics is now emerging in the clinical field, including a recent phase 1 trial involving older volunteers using LSD (Banks et al., 2021; Family et al., 2020).

5.1. A path forward to psychedelic trials for AD

AD patients represent a particularly vulnerable population especially those individuals at the more advanced stage of neurodegeneration (Johnston et al., 2022). Direct immune and inflammatory modulation must also be closely monitored to avoid potential side effects, such as immunosuppression, impaired beta-amyloid phagocytosis, or decreased cancer immunosurveillance in elderly patients. These cautions have to be taken seriously and warrant further preclinical and clinical research.

These sober assessments suggest that while some caution is still necessary, appropriate management of psychedelic dose and setting can provide new treatment opportunities for AD. Given the known low toxicity risks of serotonergic psychedelics, we do not have to bridle our optimism for studying the potential contributions of psychedelics to treatment of AD and other neurogenerative diseases. Vann Jones and O'Kelly (2022) conclude that the "potential for psychedelic compounds to influence and enhance functional neuronal connectivity, stimulate neurogenesis, restore brain plasticity, reduce inflammation and enhance cognition provides a new therapeutic target and compelling argument for further investigation of the potential for psychedelics as a disease modifying compound in conditions where currently none exists."

The known effects on inflammation, neuroplasticity and neurophysiologic mechanisms indicate psychedelics have the potential to enhance well-being in older adults. Given the general lack of toxicity and high therapeutic index of these substances and the lack of complications in the many studies of younger populations, studies with small doses of psychedelics in older adults may proceed without undue concern. As noted earlier (George and Hanson, 2019) "the path to using psychedelics as therapeutic adjuncts in dementia care is daunting, but worth consideration;" implementation of such psychedelic therapies necessitates training of caregivers in skills that assure proper environments and usage and facilitate positive outcomes.

Despite recent, ongoing research efforts, the immediate use of psychedelics for treating AD are substantially stymied by their Schedule 1 classification by the FDA at the writing of this paper (i.e., LSD, psilocybin, ibogaine). While harmaline's classification as Schedule III opens possibilities for future use, it is unlikely we will see a billion-dollar drug trial for an unpatentable natural substance. Muscimol, an approved drug, opens distinct possibilities for off-label use and exploration of possible remedial effects for AD, but the same prohibitive costs and the lack of a patentable substance thwarts any likely drug development trials. The current scheduling and lack of financial incentives for studying natural substances makes the conventional pathway to drug approval for natural psychedelic treatments of AD unlikely.

Nonetheless there may be immediate paths forward to evaluate this treatment for AD. A novel and growing set of

methodologies for assessing the effects of untested drugs is available in a combination of citizen science initiatives (Land-Zandstra et al., 2021) and N of 1 trials (Nickles and Mitchell, 2015). Citizen science provides a range of methods through which data is collected by ordinary citizens, including people taking conventional pharmaceuticals or self-administering approved or unapproved drugs and wishing to evaluate their individual responses (versus a blinded placebo condition) in what are essentially a series of cross-over trials.

6. Conclusions

Preclinical evidence indicates that both classic and non-classic psychedelics modulate a range of biological mechanisms that result in rapid changes in gene expression and sustained functional and structural alterations in the brain involving global neuroplasticity-enhancing and anti-inflammatory effects. Some of the observed mechanisms are serotonin-, sigma-, NMDA, and GABA receptor-mediated, and involve improved functional synaptic plasticity and neurorestorative processes in brain areas that are especially affected in neurodegenerative disorders. The widespread therapeutic potential of psychedelics reported from human studies, combined with evidence of their plastogenic and neurogenic effects from *in vitro* and animal *in vivo* studies, suggest potent beneficial effects on behavior, cognition, learning and memory, and provide a compelling rationale for targeting psychedelics for the treatment of AD and related dementias.

Data statement

The data has not been previously presented orally or by poster at scientific meetings.

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Author contributions

MJW organized the idea for the paper, performed the literature searches and summarized information, and wrote the initial draft; AS edited this information and elaborated the key ideas, wrote several sections on neurochemical and immune mechanisms, and made the figure; EF wrote several sub-sections of the paper, and curated the references. All authors significantly contributed to the final draft.

Conflict of interest

The authors have declared that no competing interests exist.

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