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Intersecting Psychedelic Pharmacology and Gut-Brain Axis Signaling in Neurodegenerative Disorders

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ABSTRACT

Neurodegenerative diseases are marked by progressive neuronal loss, inflammation, and impaired plasticity. Although existing treatments provide limited protection for the brain or ability to slow disease progression, emerging research highlights the gut-brain axis and psychedelics as promising new areas for therapeutic development. The gut microbiome, a metabolically active ecosystem, influences brain function through immune, neural, and endocrine pathways. Gut dysbiosis has been implicated in the pathogenesis of multiple neurodegenerative disorders. Parallel to this, classical psychedelics such as psilocybin and LSD have demonstrated potent neuroplastic, anti-inflammatory, and mood-enhancing effects. Acting primarily via 5-HT_2A receptor activation and BDNF-TrkB-mTOR signaling pathways, these compounds promote neuritogenesis, synaptogenesis, and cognitive flexibility, suggesting therapeutic potential in reversing neurodegenerative pathology. Emerging data reveal that gut microbiota may modulate the pharmacodynamics of psychedelics by affecting bioavailability, immune signaling, and receptor expression. Studies show that altered microbiomes influence psychedelic responsiveness, with certain bacterial taxa. This review explores the triangular interplay between the gut, brain, and psychedelics, proposing a systems-level model in which the gut microbiota acts as both a mediator and modulator of psychedelic efficacy in neurodegeneration. It highlights the potential for microbiome-informed, personalized psychedelic therapies and discusses microbiota-targeted interventions, such as prebiotics, probiotics, and nutritional strategies, as adjunct therapies to enhance therapeutic outcomes. Though preliminary, these findings warrant deeper investigation through clinical trials and mechanistic studies. Psychedelics, when integrated with microbiome science, may redefine therapeutic approaches to brain disorders, offering a transformative opportunity for precision neuropsychiatry and neurology.

KEYWORDS: psychedelics; gut-brain axis; gut microbiome; neurodegenerative disorders; alzheimer's disease; parkinson's disease

INTRODUCTION

Neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS) are characterized by symptoms like progressive neuronal loss, cognitive and motor dysfunction. Mounting evidence implicates that the gut microbiota might have a rather large role in the development and pathophysiology of neurodegenerative disorders. Renewed scientific interest in psychedelics, such as psilocybin, lysergic acid diethylamide (LSD), and 2,5-dimethoxy-4-iodoamphetamine (DOI), has revealed their potential to modulate neuroplasticity, reduce neuroinflammation, and enhance mood and cognition in both preclinical and clinical contexts. These compounds primarily exert their effects through the 5-hydroxytryptamine 2A (5-HT_2A) receptor, a critical hub of serotonergic signaling known to be involved in learning, memory, and neuroprotection. Notably, serotonergic signaling also plays a crucial role in gut homeostasis and microbiota-brain communication, raising the possibility that psychedelic responses may be shaped by individual microbial profiles.

The gut-brain axis (GBA) is a complex, bidirectional communication network linking the central nervous system (CNS) and the gastrointestinal tract, with the gut microbiome playing a central role through its influence on immune signaling, metabolic regulation, neurotransmitter synthesis, and neuroinflammation. Gut dysbiosis (an imbalance in gut microbial composition) has been consistently associated with neurodegenerative pathologies, suggesting that microbial communities may not only reflect but also contribute to the disease pathology. Recent preclinical studies support this interplay. Animal models with altered gut microbiota demonstrate heightened behavioral and molecular responses to psychedelics. Moreover, specific microbial taxa have been found to correlate with receptor densities and behavioral responsiveness to psychedelics, indicating that the microbiome may act as a key modulator of psychedelic efficacy. The intersection of psychedelics and the gut microbiota offers a novel way to approach the management of neurodegenerative disorders. By integrating insights from microbiome science, neuropharmacology, and psychedelic research, this review aims to explore how gut-microbiota interactions may modulate the therapeutic potential of psychedelics in neurodegenerative disorders.

THE GUT-BRAIN AXIS

The gut and brain are in continuous and bidirectional communication through a system known as the gut-brain axis (GBA). This axis utilizes neural, endocrine, and immune pathways, to exchange information between the central nervous system (CNS) and the enteric nervous system (ENS). The vagus nerve serves as a major conduit, directly linking the ENS to the brainstem and enabling rapid neural transmission. In addition to neural routes, gut-associated lymphoid tissue (GALT), circulating immune cells, cytokines, and gut-derived hormones also participate in signaling that can influence brain function, particularly inflammation and stress responses.

A major part of this gut-brain interaction is regulated by the gut microbiota, which is a dense, diverse, and metabolically active microbial ecosystem distributed throughout the gastrointestinal tract. Once thought to play a limited role in neurology, the gut microbiota is now recognized as a key modulator of emotional and cognitive brain functions. Communication between the gut and brain also occurs through microbial metabolites. It has been discovered that certain gut microbes, such as Bifidobacteria, synthesize tryptophan, enhancing serotonin availability in the brain. J.R. Kelly et al. in 2016 provided proof that alterations in the gut microbiome can result in depression like symptoms. Different lactobacillus and bifidobacteria species have been shown to modulate depression and stress-related behaviours in animal models. They acquired 34 depressed patients and 33 healthy people. Their fecal microbiota was injected into rats that had depleted gut microbiome due to a 28-day antibiotics treatment. Rats receiving FMT (fecal microbiota transplantation) from depressed donors developed depressive-like behaviors, including anhedonia and increased anxiety-like behavior. Physiologically, these rats showed altered tryptophan metabolism, notably an elevated kynurenine-to-tryptophan ratio, paralleling the human donors. [9]

Disruptions in gut microbiota known as gut dysbiosis have also been implicated in multiple neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS), as well as psychiatric conditions like anxiety and autism spectrum disorder. Furthermore, gut dysbiosis is a known contributor to gastrointestinal disorders, including irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). [4]

While each individual's microbial composition is unique, the dominant bacterial phyla, Firmicutes and Bacteroidetes, account for over 75% of the total microbial population in healthy individuals. These microbes contribute critically to host homeostasis by supporting metabolism, immune modulation, and barrier function. Importantly, they also produce a variety of bioactive compounds, including short-chain fatty acids (SCFAs), neurotransmitters (e.g., GABA, serotonin), and other metabolites that can influence the CNS through multiple pathways. [1]

Early clinical trials using psychobiotics (probiotics with mental health benefits) have shown promising results in bipolar disorder, reducing relapse and hospitalization rates. Diet profoundly influences microbiota composition. The Western diet, high in saturated fats, processed meats, and refined sugars, promotes dysbiosis and systemic inflammation, potentially contributing to psychiatric morbidity. In contrast, plant-based and Mediterranean-style diets, rich in fiber, polyphenols, fermented foods, and omega-3 fatty acids, support microbial diversity and have been associated with lower rates of depression. Thus, nutritional interventions represent a promising adjunctive approach to mental health care. [4]

GUT-BRAIN AXIS IN NEURODEGENERATIVE DISORDERS

There is emerging evidence in the recent years on the effects of the gut microbiota on the development and pathology of neurodegenerative disorders. Alzheimer's disease is a neurodegenerative disorder

caused by the accumulation of amyloid plaques which are cleavage products of amyloid precursor protein (APP). They primarily consist of amyloid-β (Aβ) peptides. The microglial cells in the brain are responsible for getting rid of pathogens, cellular debris and Aβ peptides, but with age, they are not able to efficiently do so. Recent research has shown that the gut microbiota affects the microglial cells through the vagus nerve. These afferent fibers transmit information about gut-derived inflammation and cytokine levels to the brain, modulating neuroimmune responses. Studies in germ-free mice have shown that the absence of microbial input alters microglial morphology and density. Further research has demonstrated that disruptions in microglial activity can in turn affect gut microbial composition, particularly within the phylum Proteobacteria. [20] Cattaneo et al. provided compelling evidence that patients with cognitive decline and brain amyloid deposition exhibited higher levels of the pro-inflammatory genus Escherichia/Shigella and lower levels of the anti-inflammatory Eubacterium rectale compared to both amyloid-negative cognitively impaired individuals and healthy controls. These microbial shifts corresponded with increased blood levels of pro-inflammatory cytokines IL-6, IL-1β, CXCL2, NLRP3 and reduced levels of the anti-inflammatory cytokine IL-10. Prior research has shown that NLRP3 inflammasome is upregulated in AD brains and contributes to Aβ aggregation and neuroinflammation. The study confirms that gut-derived Escherichia/Shigella may activate NLRP3 pathways, linking gut inflammation to amyloid pathology. Conversely, Eubacterium rectale, a butyrate-producing, anti-inflammatory gut bacterium, was depleted in subjects with brain amyloid deposition. Since butyrate exerts protective effects against inflammation and has been shown to modulate immune responses positively, its reduction may leave the brain more vulnerable to inflammatory damage. The abundance of Escherichia/Shigella was positively correlated with these pro-inflammatory markers, while Eubacterium rectale abundance correlated negatively. This indicated inflammatory shift associated with microbiota imbalance. [3]

Impairment of the gut or blood brain barrier due to aging or increase in intestinal permeability and systemic inflammation due to gut dysbiosis can facilitate the entry of microbial products and pathogens such as Herpes simplex virus type 1, Chlamydia pneumoniae, spirochetes, and gut-derived neurotoxins into circulation and it can infiltrate the CNS. One such microbial metabolite, β-N-methylamino-L-alanine (BMAA), produced by cyanobacteria, has been shown to induce neurodegeneration, astrogliosis, and tau pathology in experimental models. Lipopolysaccharide (LPS), a proinflammatory microbial endotoxin, has been implicated in promoting Aβ fibril formation and activating NF-κB–mediated inflammatory pathways in the brain. Additionally, microbiota-derived amyloids may act synergistically with cerebral Aβ to enhance innate immune activation, exacerbating amyloid pathology. [17]

Systemic exposure to LPS could also be seen in Parkinson's disorder (PD) due to increasing gut permeability caused by decline in SCFA-producing microbes. Recent evidence shows reduced levels of Prevotellaceae, beneficial gut commensals involved in producing mucins and short-chain fatty acids (SCFAs), and increased levels of Enterobacteriaceae, which are associated with more severe postural and gait instability contributes to gut microbiota dysbiosis in PD pathogenesis and progression. PD is a multisystem neurodegenerative disorder marked by progressive alpha-synuclein accumulation in

neurons, leading to the formation of Lewy bodies. LPS can cross the gut wall and enter the bloodstream, where it activates immune signaling pathways (e.g., TLR4-NF-κB) and elevates pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. These mediators disrupt the blood-brain barrier (BBB) and promote alpha-synuclein misfolding and dopaminergic neuronal loss. Additional microbiome alterations in PD include reduced levels of butyrate-producing bacteria (e.g., Faecalibacterium, Roseburia, Coprococcus, Blautia) and increased pro-inflammatory taxa (e.g., Ralstonia, Proteobacteria, Enterococcaceae). PD patients also show elevated expression of LPS biosynthesis genes in fecal samples. Furthermore, small intestinal bacterial overgrowth (SIBO) and infections such as Helicobacter pylori have been linked to worsening motor symptoms and may contribute to disease progression. [17] Two studies in particular by Keshavarzian et al. (2015) and Hasegawa et al. (2015)—support the hypothesis that pro-inflammatory gut profiles can initiate or exacerbate pathological misfolding of proteins such as α-synuclein, which is implicated in PD. [11][6] Keshavarzian's study focused on both fecal and mucosa-associated microbiota, using high-throughput 16S rRNA gene sequencing. They found that control subjects exhibited higher levels of butyrate-producing, anti-inflammatory taxa in their feces compared to PD patients. Additionally, Faecalibacterium was more abundant, and Proteobacteria less prevalent, in the colonic mucosa of controls, highlighting a gut microbial imbalance in PD. Hasegawa et al. used qPCR to quantify 19 bacterial taxa in PD patients and controls, reporting a higher abundance of Lactobacilli and lower levels of Clostridium coccoides and Bacteroides fragilis in PD. Together, these findings support a consistent pattern of reduced microbial diversity and anti-inflammatory capacity in PD, similar to observations in AD-related dysbiosis. Emerging therapeutic strategies focus on restoring microbial balance through probiotics. Strains like Lactobacillus casei Shirota and Bifidobacterium spp. have been shown to improve GI symptoms and reduce inflammation in PD patients. Notably, certain Bacillus species can convert L-tyrosine to L-DOPA, a dopamine precursor, suggesting a possible microbial contribution to dopaminergic modulation.

Gut dysbiosis is a critical contributor to the pathophysiology of multiple sclerosis (MS). RRMS patients exhibit a decreased abundance of commensal bacteria that support anti-inflammatory immune responses, such as Parabacteroides distasonis, Prevotella copri, Faecalibacterium, and certain Clostridium species while showing increased levels of potentially pro-inflammatory taxa including Dorea, Blautia, and Akkermansia muciniphila. These microbial shifts are associated with reduced short-chain fatty acid (SCFA) production, particularly butyrate, which is essential for maintaining regulatory T cell (Treg) populations and suppressing autoreactive T cell responses. The gut microbiota may also influence MS pathogenesis via microbial metabolites and toxins. Clostridium perfringens type B has been identified in some MS patients and produces epsilon toxin, which compromises the blood–brain barrier (BBB) and induces oligodendrocyte and neuronal damage. [17]

Gut dysbiosis and impaired intestinal barrier integrity has been implicated in the early stages of ALS. ALS mice and patients exhibit reduced levels of butyrate-producing bacteria including Butyrivibrio, Lachnospira, Oscillibacter, and Anaerostipes, alongside an increased abundance of Dorea, which may generate harmful metabolites such as ethanol. Administration of sodium butyrate in ALS mice has shown promise in delaying disease progression by restoring gut barrier integrity. Furthermore, elevated

plasma concentrations of bacterial endotoxins such as lipopolysaccharide (LPS) and the cyanobacterial neurotoxin β-N-methylamino-L-alanine (BMAA) have been reported in ALS patients. These molecules can traverse compromised gut and brain barriers, promoting neuroinflammation and motor neuron degeneration. [17]

PSYCHEDELICS AND NEUROPLASTICITY

Psychedelic compounds exhibit a unique capacity to promote structural and functional neuroplasticity, modulate immune responses, and restore cognitive flexibility. Psychedelics such as psilocybin and DMT are now being explored for their therapeutic potential in mood disorders and neurodegenerative conditions, offering a novel multimodal approach to CNS repair. Ly et. al in 2018 investigated whether psychedelics could promote neuronal growth and plasticity in cultured cortical neurons. Using Sholl analysis (Ristanovic et al., 2006) [16], they observed that various psychedelics across different structural classes increased dendritic arbor complexity to a degree comparable with ketamine, a known rapid-acting antidepressant. Psychedelics from the tryptamine (DMT, psilocin), amphetamine (DOI, MDMA), and ergoline (LSD) classes all promoted neuritogenesis. A structurally unrelated psychoplastogen, 7,8-dihydroxyflavone (DHF), also induced similar effects, further supporting the neuroplasticity-promoting potential of these compounds. Researchers also found that BDNF signaling may underlie the plasticity and behavior-enhancing effects of psychedelics like DMT. [14]

Brain-derived neurotrophic factor (BDNF) is known to drive both neurite and dendritic spine growth. Since previous studies suggest that psychedelics may increase neurotrophic factors, the researchers tested whether BDNF and psychedelics like DOI have additive effects on neuronal growth. They found that both BDNF and DOI individually enhanced neuritogenesis to similar levels, but combining them had no additional effect, implying they act through the same pathway. Crucially, when neurons were co-treated with ANA-12, a TrkB receptor antagonist, the ability of both BDNF and psychedelics to promote neuritogenesis and spinogenesis was completely blocked. Because TrkB activation is known to trigger the mTOR signaling pathway which is essential for synapse formation and structural plasticity, the researchers used rapamycin (an mTOR inhibitor) and found it entirely prevented psychedelic-induced neurite growth. These findings confirm that psychedelics promote structural plasticity via BDNF-TrkB-mTOR signaling. [14] Moliner and team in 2023 found that a single dose of LSD significantly increases the survival of dentate granule cells in the hippocampus of wild-type mice, doubling their number after four weeks. This effect is absent in TrkB mutant mice, indicating that LSD's impact on neuronal survival is mediated via the TrkB receptor, which is a key component of BDNF signaling. These findings align with previous research showing that both chronic antidepressants and ketamine promote hippocampal neurogenesis and plasticity through similar TrkB-dependent mechanisms. Previous research has shown that antidepressants and ketamine can reactivate plasticity in the adult visual cortex. Similarly, LSD promotes visual plasticity by shifting ocular dominance toward the open eye in mice after monocular deprivation. In a chronic stress model, LSD produced lasting antidepressant-like effects in wild-type mice but not in mice with mutated TrkB. These effects

were not blocked by 5-HT2A antagonists, showing that LSD's antidepressant action requires TrkB but not 5-HT2A activation. [15]

The central nervous system maintains neuronal integrity and adaptability through a network of growth factors that bind to receptor tyrosine kinases, initiating intracellular cascades essential for neuronal morphology, excitability, and survival. Psychedelic compounds, notably those targeting 5-HT2A receptors, have emerged as alternative modulators of neuronal plasticity. These receptors are densely expressed in cortical pyramidal neurons, which are particularly susceptible to degeneration in disorders such as AD and frontotemporal dementia (FTD). Psychedelics exhibit anti-inflammatory properties by engaging 5-HT2A receptors on peripheral immune cells. Activation of 5-HT2A receptors exerts complex effects on learning and memory. Psychedelics such as psilocybin and DMT have shown rapid and sustained antidepressant and anxiolytic effects in clinical and preclinical settings, including facilitation of fear extinction and reversal of stress-induced anhedonia. Renewed clinical trials now demonstrate that psychedelics, especially psilocybin, can produce significant and sustained antidepressant effects following just one or two doses. Researchers confirmed that plasticity-enhancing effects of psychedelics depend on the 5-HT2A receptor, the key receptor responsible for their hallucinogenic activity. They concluded that 5-HT2A receptor activity is crucial across both classical and non-classical psychoplastogens. [14] Modulation of the 5-HT_2A receptor is closely linked to cognitive enhancement and neuroplasticity in Alzheimer's disease (AD). Activation of this receptor increases neurotrophin expression in the hippocampus and neocortex and enhances synaptic plasticity and memory regulation in cortical regions vulnerable to AD-related damage.

The neuroplastic, anti-inflammatory, and pro-cognitive effects of serotonergic psychedelics position them as promising therapeutic candidates for the treatment of Alzheimer's disease and other neurodegenerative disorders. By engaging key molecular targets, these compounds activate signaling pathways that promote synaptic remodeling, neurogenesis, and network-level reorganization. Psychedelics induce profound changes in consciousness, altering perception, mood, and cognition, which has renewed interest in their therapeutic potential for mental health disorders such as depression, anxiety, and PTSD. [8] Importantly, emerging evidence supports both hallucinogenic and non-hallucinogenic psychoplastogens in enhancing brain function and resilience without chronic dosing. While further research is needed to confirm efficacy and safety in clinical neurodegenerative populations, psychedelics represent a compelling new direction in the treatment for neurodegenerative disorders.

THE INTERPLAY BETWEEN THE GUT, PSYCHEDELICS AND THE BRAIN

As we have seen throughout the paper, the gut microbiome plays a crucial role in overall health, influencing not only physical well-being but also brain function and behavior, including mood, cognition, and stress regulation. As interest in psychedelic therapies like psilocybin and LSD grows, understanding the gut microbiome's role in these treatments is increasingly important. Since the gut

microbiota can impact brain function and behavior through the gut-brain axis, it is plausible that their influence on these gut microbes might mediate part of the psychological effects of psychedelics. Many psychedelics, such as psilocybin, ayahuasca, and mescaline, are naturally occurring compounds, and medicinal plants often have antimicrobial properties and can influence the microorganisms in our gut. [2] However, the precise effects that psychedelics have on changing the composition of the gut microbiota are still largely unknown and have not been thoroughly investigated.

Recent research suggests the microbiota-gut-brain (MGB) axis may modulate responses to psychedelic therapy, acting as a feedback system that influences treatment outcomes. Since psychedelics are foreign compounds (xenobiotics) that gut microbes can metabolize, the microbiome may influence their bioavailability and therapeutic impact. Psychedelics such as psilocybin, LSD, and DMT promote neuroplasticity by increasing neurogenesis, synaptogenesis, and activation of genes involved in neuronal growth. These effects may be influenced by gut microbiota, which can modulate neuroplasticity pathways. The microbiota itself can influence neuroplasticity through mechanisms like production of neuroactive compounds, modulation of immune responses, and affecting signaling pathways. Changes in microbiota composition could therefore alter how psychedelics impact neuroplasticity and brain function. Microbiota may impact psychedelic effects through various routes, such as metabolizing the drugs, influencing their bioavailability, or affecting the host's neuroimmune system, which in turn modulates neuroplasticity and behavioral responses. The gut microbiome could help identify individuals likely to benefit, modify drug metabolism during therapy, and support lasting behavioral improvements post-treatment. The bacterium Bifidobacterium modulates the metabolism of DMT, an active component of ayahuasca. Other bacteria have enzymes that convert psilocybin into psilocin or degrade LSD. These findings suggest that individual differences in gut microbiota composition can have an effect on psychedelic efficacy and variability in responses. [8] It is a complex bidirectional relationship where the psychedelics can influence microbiota composition and neuroplasticity, and the microbiota, in turn, can modulate the effects of psychedelics on brain and behavior. This reciprocal interaction suggests that understanding microbiota-psychedelic dynamics could enhance personalized treatment strategies.

Scientific research on how serotonergic psychedelics impact gut microbiota is still very limited. Currently, only one study has examined the effects of oral psilocybin and related compounds on the rat gut microbiome. This study found that treatment with psilocybin or its analogue norbaeocystin increased levels of certain beneficial bacteria such as Verrucomicrobia and Actinobacteria, while decreasing potentially harmful Proteobacteria, without changing overall bacterial diversity. Although preliminary, this suggests that the gut microbiome could be a mediator of psilocybin’s effects, warranting further investigation. Psychedelics, especially ayahuasca, are reported to cause purgative effects, implicating the gut microbiome as a potential target. Serotonin receptors, including the key 5-HT2A receptor targeted by classic psychedelics, are abundant throughout the gastrointestinal tract and regulate gut motility, which in turn influences microbiota structure and function. Conversely, the

microbiota can regulate serotonin levels by producing serotonin directly or stimulating its synthesis and release from gut cells and they can influence mood and behavior. Some spore-forming gut bacteria respond to serotonin by increasing in abundance, and certain species can actively uptake serotonin via proteins similar to human serotonin transporters, indicating a two-way interaction between serotonin and gut microbes. This reciprocal relationship suggests serotonergic psychedelics could indirectly and directly modulate microbiome composition.

Several psychedelic plant compounds have demonstrated antimicrobial, antiviral, and mild antibiotic effects. For instance, components of ayahuasca and peyote have inhibited growth of various pathogenic and antibiotic-resistant bacteria. Alkaloids found in psychedelic plants can intercalate bacterial cell walls or DNA, displaying antibacterial, antifungal, and antiviral properties. These antimicrobial actions, akin to those of some antidepressants, further support that psychedelics may alter gut microbial communities, potentially influencing brain function through the microbiome-gut-brain axis. [2] In patients with major depressive disorder, higher levels of certain bacterial genera (Blautia, Bifidobacterium, Coprococcus) have been linked to better treatment outcomes. Animal studies highlight the microbiome's role in psychedelic responsiveness. In a mouse model with altered gut microbiota and immune activation, the psychedelic DOI produced enhanced hallucinogenic effects measured by the head-twitch response, which is mediated by 5-HT2A receptor activation. Specific bacterial taxa correlated with 5-HT2A receptor density in the brain, suggesting that the gut microbiome can influence psychedelic effects by modulating these key receptors. [10]

There is increasing interest in leveraging the gut microbiome for personalized medicine. Microbial signatures have been linked to key metabolic traits such as plasma glucose, lipid profiles, and responses to exercise, all influenced by diet, lifestyle, and genetics. Interventions targeting the microbiome, such as prebiotics, probiotics, fecal microbiota transplantation (FMT), phage therapy, and postbiotics, can individually modulate gut community structures and host gene expression. For example, a randomized controlled trial of the prebiotic inulin in obese individuals showed minimal mood or cognitive changes overall but revealed distinct microbial and inflammatory profiles in responders versus non-responders, highlighting the complexity and potential of personalized microbiome approaches. [10]

Clinical studies typically exclude individuals with risk factors like family history of psychosis or cardiac issues. Although rare, reports from recreational users include psychosis, mania, unpredictable behavior, serotonin syndrome, and Hallucinogen Persisting Perception Disorder (HPPD). A large survey of magic mushroom users found only 0.2% sought emergency medical help, mostly linked to poor set and setting or mixing substances. [12] Emerging clinical trial data are clarifying psilocybin's side effect profile. In a small placebo-controlled study, no serious adverse effects or withdrawals occurred after a single dose. The largest trial to date reported common side effects on dosing day, including headache, nausea, dizziness, fatigue, and anxiety. [5] In treatment-resistant depression patients continuing SSRIs, psilocybin was well tolerated, with most adverse events being mild. Given serotonin's role in gut motility, the diet–diet-microbiota-gut-brain axis may subtly influence gastrointestinal and autonomic side effects during psychedelic therapy.

CONCLUSION

Psychedelic pharmacology has reached new heights with the potential to develop personalized psychedelic treatments informed by an individual's gut microbiota profile for the management of neurodegenerative disorders. Understanding individual microbial composition could enable clinicians to optimize dosage, administration route, or co-interventions, thereby enhancing therapeutic efficacy and safety. The gut microbiome may play a role in modulating psychedelic effects via the gut-brain axis, which involves complex neural, hormonal, immune, and metabolic interactions. Gut microbes can influence neurotransmitter production and stress responses. Stress and environmental factors can also disrupt gut health. Microbiota works as both a mediator and modulator of psychedelic effects on brain function, behavior, and mental health. It advocates for adopting comprehensive models of psychedelic action. Such an approach could lead to the design of personalized, multi-layered treatment strategies that account for complex inter-system interactions and individual biological signatures, ultimately advancing precision medicine in mental health. However, our understanding of these interactions remains limited There are still a lot of areas that require future investigations like how gut microbes influence drug breakdown and activation, how individual microbial patterns correlate with variability in therapeutic outcomes and evaluating the safety and efficacy of strategies like probiotics to optimize psychedelic effects.

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