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Mind over matter: the microbial mindscapes of psychedelics and the gut-brain axis

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ABSTRACT

Psychedelics have emerged as promising therapeutics for several psychiatric disorders. Hypotheses around their mechanisms have revolved around their partial agonism at the serotonin 2 A receptor, leading to enhanced neuroplasticity and brain connectivity changes that underlie positive mindset shifts. However, these accounts fail to recognise that the gut microbiota, acting via the gut-brain axis, may also have a role in mediating the positive effects of psychedelics on behaviour. In this review, we present existing evidence that the composition of the gut microbiota may be responsive to psychedelic drugs, and in turn, that the effect of psychedelics could be modulated by microbial metabolism. We discuss various alternative mechanistic models and emphasize the importance of incorporating hypotheses that address the contributions of the microbiome in future research. Awareness of the microbial contribution to psychedelic action has the potential to significantly shape clinical practice, for example, by allowing personalised psychedelic therapies based on the heterogeneity of the gut microbiota.

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1. Introduction

1.1. The microbiota-gut-brain axis

For over hundreds of thousands of years, microbes and humans have engaged in a co-evolutionary dance, forging a symbiotic relationship that has profoundly influenced their respective physiologies [105,177]. Comprising approximately 30 trillion eukaryotic cells, the human body exists in harmonious synergy with an estimated 40 trillion microbial cells [163]. Most of these microbes, consisting of bacteria, archaea, fungi, and viruses, reside in the human gastrointestinal (GI) tract and are collectively known as the *gut microbiota*. The information included in the metagenome (*i.e.,* the sum genetic information of these diverse micro-organisms) exceeds that of the human genome by approximately 100–150 times [43,8]. Many of these genes encode microbial enzymes that perform metabolic functions absent from the human genome, significantly expanding the biochemical flexibility of the host. For example, the gut microbiota is essential for the digestion of certain dietary compounds (*e.g.* fibre), is required for the production of vitamins and other biologically-active compounds, and plays a key role in the enterohepatic circulation. Additionally, these microbial genes are integral for the priming of the immune system. This priming enables the immune system to recognize self-antigens, including those from commensal microbes, and mount a response against pathogenic antigens. The intricate interplay between the microbial metagenome and host functions highlights the indispensable contributions of the gut microbiota to the overall health and functionality of the human body.

The gut microbiota is an integral component of the *gut-brain axis*, the bidirectional communication network between the GI tract and the central nervous system (CNS). This two-way interaction is mediated by immune, endocrine (*i.e.* hypothalamic-pituitary-adrenal [HPA] axis), and neural pathways, including the vagus nerve, (see [31,32] for a review of these mechanisms). This intricate crosstalk forms the basis for the 'top-down' influence, where psychological states impact gut function and microbial composition—illustrated, for instance, by the effects of stress on gastrointestinal motility, permeability, and the release of luminal neurotransmitters [121]. Simultaneously, it underscores the 'bottom-up' influence, where gut microbes exert effects on brain function and behaviour, exemplified by the impact of gut microbial composition on feeding patterns and obesity [42]. This reciprocal communication underscores the holistic integration of physiological and psychological factors within the gut-brain axis, emphasizing its pivotal role in shaping both mental and gastrointestinal well-being.

The last two decades have seen an increasing number of studies exploring the role of the microbiota-gut-brain axis on brain function and behaviour. Human studies have demonstrated significant differences in the faecal microbiota composition of healthy participants and those with depression [136,190,206,38,90], post-traumatic stress disorder (PTSD) [11,117,204,81], Parkinson's disease [10,153,16,84,87], and more, pointing to a clear relationship between abnormal brain function and variation in the gut microbiota. In addition to these association studies, causality has also been demonstrated with the ability to transfer behaviours via the microbiota. Kelly *et al.* demonstrated that inoculating antibiotic-treated rats with the faecal microbiota of depressed patients resulted in the development of behavioural symptoms of depression, including anhedonia and anxiety, alongside pathological changes observed in this disease, such as elevated plasma kynurenine and kynurenine/tryptophan ratio [94]. Similarly, a recent study by Fan *et al.* [60] demonstrated that faecal microbiota transplantation from individuals with anorexia nervosa (AN) to germ-free mice leads to the emergence of AN-like behaviour, alongside weight loss and AN-like gene expression patterns in both hypothalamic and adipose tissues in recipient mice. These studies highlight the causal relationship between microbiome composition and behaviour and makes the microbiota a powerful tool to transfer healthy behavioural and physiological traits.

1.2. Psychedelics for mental health

In the mid-2000s, concurrently with the emergence of studies demonstrating the transferability of host phenotype through the gut microbiota, a resurgence in psychedelic research unfolded, marking the onset of the *psychedelic renaissance*. A wealth of studies has since shown the remarkable therapeutic potential of these drugs for the treatment of several disorders, including treatment-resistant depression [26], anxiety [67,77], obsessive-compulsive disorder (OCD) [132] and addiction [17, 91].

Psychedelics constitute a category of psychoactive compounds well studied for their hallucinogenic properties. True to their etymology, with "psyche" and "delos" derived from the Greek words for "mind" or "soul" and "to show," respectively, psychedelic drugs exert a profound influence on consciousness. These substances induce potent subjective effects, encompassing hallucinations, distortions in self and reality perception, shifts in cognition and emotion, and, notably, the elicitation of mystical and self-transcendent experiences, often characterized by phenomena like ego dissolution [76]. The mechanisms of action of psychedelics have been described at the pharmacological and neural level, as well as at brain-circuit and psychological levels, (see [191] for a review). At the pharmacological level, activation of $5HT_{2A}$ receptors on cortical layer V pyramidal neurons, and the subsequent increase in neuronal firing [1,119], leads to synaptogenesis [113] and anti-inflammatory processes via the modulation of gene transcription [141]. $5HT_{2A}$ receptors are widely expressed throughout the brain, in both cortical and subcortical areas ([14]; [197]), and are responsible for learning and memory, perception of pain and sleep [57]. Research has shown that the subjective effects of psychedelic drugs correlate with $5HT_{2A}$ receptor occupancy [115]. At a higher level, psychedelics are thought to affect the cortico-striato-thalamo-cortical circuits, a feedback loop where inhibitory control of the thalamus by the pre-frontal cortex allows for the filtering of sensory and interoceptive inputs before this information is relayed back to higher-level cortical areas [196]. Upon activation of $5HT_{2A}$ receptors by psychedelics, negative feedback of the thalamus from the prefrontal cortex is reduced, leading to an overload of sensory information sent to the sensory cortex via the thalamus [197]. These changes in cortical-thalamic connectivity [133,152,195] are thought to underlie alterations in perception experienced by participants during the psychedelic experience [196]. Another hypothesis suggests the involvement of claustrum-cortical decoupling in the effects of psychedelics, especially effects on cognition [13,55].

The *Relaxed Beliefs Under Psychedelics* (REBUS) model suggests that psychedelics affect the normal ability of the brain to predict incoming sensory information, and generating a prediction error to update our internal model that shapes our perception of reality [28]. This model also proposes that psychedelics increase the brain's entropy state, by enhancing the connectivity between brain areas that are not normally connected [135,27,29,30]. This loosening of prior predictions is thought to underlie the ability of psychedelics to free the mind of rigid, maladaptive thinking patterns that are characteristic of internalising disorders, like depression, PTSD, OCD, and AN.

While $5HT_{2A}$ receptors are the main target of psychedelic action, it is important to note that these drugs bind to other receptors with varying affinities: for instance, LSD binds to 5-HT subtypes 1 A, 1B, 1D, 1E, 2 A, 2B, 2 C, 5 A, 6, and 7 as well as dopaminergic receptors subtypes D1 and D2 [151], while DMT and 5-MeO-DMT, in addition to various serotonergic and dopaminergic receptor subtypes, also bind a number of ionotropic and metabotropic glutamate receptors, acetylcholine, Trace-Amine-Associated Receptors (TAAR), and the opioid-like receptor sigma-1 (Sig1R) [182,62,63]. In addition, while classic psychedelics (also known as "serotonergic psychedelics" due to their chemical and structural similarity to the serotonin molecule [139]) are characterised by partial agonism at the $5HT_{2A}$ receptor [96], non-classic psychedelics such as ketamine and MDMA, while eliciting similar subjective effects, exhibit different mechanisms of action (outside of serotonin receptors).

This review will mainly focus on classic psychedelics due to the known relationship between serotonin and the gut microbiota.

1.3. The link between psychedelics and the gut-brain axis

Many psychedelic compounds are naturally-occurring (*e.g.* psilocybin from *Psilocybe* mushrooms, ayahuasca from the *Banisteriopsis caapi* vine, mescaline from the Peyote and San Pedro cacti) and have been used in ritual and religious practices in many cultures for centuries [162]. The notion that many medicinal plants have antimicrobial properties [40], and that changes in the gut microbiota can impact brain function and behaviour via the gut-brain axis suggests that the psychological effect of psychedelic drugs is likely to be partly mediated by the gut microbiota. However, the exact impact of psychedelics on the composition of the gut microbiota remains unexplored.

In this review, we aim to present the existing evidence supportive of a role for the microbiome in mediating the psychological effects of psychedelics. Due to the lack of research directly linking the gut microbiome and psychedelics, we will draw on existing knowledge of the serotonergic system and the drugs that target it, like serotonergic antidepressants, to build hypotheses around the interaction between serotonergic psychedelics and the microbiota-gut-brain axis, and highlight the knowledge gaps that need to be addressed to facilitate and accelerate progress in this field. Then, we reflect on how knowledge on psychedelic-gut microbe interactions can shape clinical practice; specifically, how the heterogeneity of a patient's microbiota can be used to explain and predict the variability in responses to psychedelic-based therapies, towards the implementation of personalised medicine approaches. Finally, in an effort to establish new guidelines for psychedelic research, we present an example of an integrated framework that takes into account the biology of the individual patient at different systems levels, including, but not limited to, the gut microbiota.

2. Main body

2.1. Psychedelics affect microbiome composition

Rigorous scientific investigations of the impact of serotonergic psychedelics on the composition and structure of the gut microbiota are lacking. At the moment of writing this review, only one (not peer-reviewed) paper has been published around the changes induced by oral psilocybin and related tryptamines on the rat gut microbiota [202]. In this paper, 16 S ribosomal DNA sequencing of faecal samples collected from rats treated with either psilocybin or its analogue norbaeocystin demonstrated a significant increase in *Verrucomicrobia* and *Actinobacteria*, and a decrease in *Proteobacteria* relative to control rats, although overall bacterial (alpha) diversity was unaffected [202]. While still a preliminary finding, this paper supports a potential mechanism of action for psilocybin(s) that is mediated by the gut microbiome and justifies further research in this field.

Additionally, it is well established that selective serotonin reuptake inhibitors (SSRIs) can change the composition of the gut microbiota, and exhibit significant antimicrobial activity [134,93]. Similarly, anecdotal reports of the purgative and laxative effects of some psychedelics, primarily ayahuasca, place the gut microbiota as a potential target of psychedelic action. This is consistent with the notion that serotonin receptors, including the 2 A subtype, the primary target of all classic psychedelics, are expressed throughout the GI tract and that serotonin exerts local effects on gut function, for example by enhancing peristalsis [187]. Modulations in the gut environment driven by altered serotonin, including transit time and secretions, can in turn modify the community structure and function of the microbiota.

Conversely, the gut microbiota modulates serotonin synthesis via several direct and indirect mechanisms. Certain gut microbes are able to synthesise serotonin directly [146,147,167], while others are able to stimulate local serotonin synthesis and release by enterochromaffin cells [157], and alter the circulating and central concentrations of serotonin [20,203]. In fact, the bacterial enzyme tryptophanase can convert the serotonin precursor tryptophan into indole, reducing the host's availability of tryptophan for serotonin production [144]. Additionally, pro-inflammatory cytokines and other inflammatory mediators, including those derived from gut bacteria (*e.g.* lipopolysaccharides [LPS], cell wall components from Gram negative bacteria), promote the expression of the host enzyme indoleamine-2,3-dioxygenase (IDO), which converts tryptophan to kynurenine. As such, the composition of the gut microbiota, and its translocation from the gut, has important consequences on the availability of serotonin, and therefore, on mood and behaviour.

While the direct effect of serotonin on gut microbes remains unclear, Fung *et al.* reported an increase in some species of spore-forming gut bacteria from *Turicibacteraceae*, *Clostridiales*, *Lachnospiraceae* and *Ruminococcaceae* after oral administration of serotonin to wildtype rats [64], along with the ability of some of these species (*e.g. Turicibacter sanguinis*) to take up serotonin thanks to a sodium symporter-related protein with sequence and structural homology to mammalian serotonin reuptake transporter SERT [64]. This reciprocal interaction between serotonin and the gut microbiota suggests that serotonergic psychedelics may directly and indirectly affect the composition of the gut microbiota.

In addition, there is preliminary evidence that some of the chemical compounds found in psychedelics have anti-microbial, anti-viral and even mild antibiotic effects. For example, a phytochemical analysis of the main constituents of the ayahuasca vine resulted in the identification of compounds, like *B. caapi* and *P. harmala*, that inhibited the growth of four pathogenic and antibiotic-resistant Gram-positive and four Gram-negative bacteria [70]. Similarly, components of the Peyote cactus (*Lophophora Williamii*) were shown to be effective against 18 different penicillin-resistant strains of Staphylococcus aureus [124]. Additionally, alkaloids often found in psychedelic plants, like mescaline and ayahuasca, are able to intercalate into the bacterial cell wall and/or DNA [40] and exhibit antibacterial, anti-fungal [106] and anti-viral properties [36].

These results indicate that, like serotonergic antidepressant drugs [111,126,166,44,56], psychedelic compounds are likely to affect the composition of the gut microbiota. Given the crosstalk between the gut microbiome and the brain, it is possible that these microbial alterations contribute to the impact of serotonergic psychedelics on brain function.

2.2. The microbiome modulates responses to psychedelics

Several human and animal studies have demonstrated the modulatory effects of the gut microbiome on drug responses [104,178,205,207]. Thus, in addition to being a potential target, the gut microbiome is also likely to play a significant role in shaping the individual response to psychedelic drugs. Firstly, this may be due to the known impact of gut microbial composition on drug metabolism and bioavailability. The mechanisms through which the gut microbiota can alter drug metabolism were reviewed in [51]. In brief, different species of gut bacteria can metabolise a broad range of xenobiotics, converting them it into their active, inactive and even toxic forms. Gut microbes can also intercalate into host metabolism, in a process known as host-microbial co-metabolism. An example is enterohepatic recycling: in the liver, host enzymes inactivate a drug (*e.g.* by conjugation), but after biliary excretion from the gall bladder into the gut, microbes can reactivate the drug (*e.g.* by deconjugation) before reabsorption into the systemic circulation through the hepatic portal vein [198,37]. Metabolism of a compound by the microbiota can also lead to toxic by-products, contributing to adverse drug responses. Some drugs can bind the bacterial cell directly, while others can compete with bacteria (or their metabolites) for the same host substrates. Other indirect interactions include the ability of gut microbial metabolites to modulate host gene expression via epigenetics mechanisms, and to modulate immune pathways in the host, with downstream effects on drug efficacy and

responses. In patients with major depressive disorder, for example, the efficacy of SSRIs was associated with high relative abundance of *Blautia*, *Bifidobacterium* and *Coprococcus* species [66].

An increase in the hallucinogenic effect of the psychedelic 2,5-dimethoxy-4-iodoamphetamine (DOI) was observed in a mouse model of maternal immune activation (MIA) that presented with cognitive impairments, altered gut microbial composition and upregulated 5-HT_{2A} receptors in the frontal cortex [160]. The hallucinogenic effect was assessed via the head-twitch response, rapid side-to-side rotational head movement considered as a proxy of hallucinogenic effects mediated by the activation of 5-HT_{2A} receptors. Specifically, a significant association was found between certain bacterial taxa and the density of 5-HT_{2A} receptors (*Ruminococcaceae* and *Candidatus* (*saccharibacteria*) were positively correlated; *Lactobacillaceae* were negatively correlated). The notion that gut microbes can interact with and modulate serotonergic receptors is notable as it suggests that the effect of psychedelics on these receptors can be modulated by the individual's unique gut microbial composition.

2.3. Mechanisms of gut-brain axis modulation by psychedelic-microbe interplay

The evidence reviewed thus far suggests that psychedelics may alter gut microbial composition, and that the gut microbiome may shape responses to psychedelics (Fig. 1). However, how does this interplay affect transmission via the gut-brain axis? How does it affect behaviour?

One possible mechanism lies in the modulation of serotonergic neurotransmission: both serotonergic psychedelics and certain gut microbes are able to modulate central serotonin levels. Other mechanisms may include their effect on immune and neuroendocrine (*i.e.* the HPA axis) systems, on brain connectivity networks and neuroplasticity processes. These biological systems/processes (summarised in Table 1) are shared targets of both psychedelic drugs and the gut microbiome and point to potential interconnected mechanisms of action. The details of these processes will be explained below.

2.3.1. The immune system

A common target of psychedelics and gut microbiota is the immune system. The anti-inflammatory and immune-modulating properties of psychedelics are well-established [179,181,183,186], and are in line with the known anti-inflammatory effect of serotonin [180,50,59].

Psilocybin inhibits the production of TNF-α and IL-1β in human U937 macrophage cells treated with the pro-inflammatory stimulus LPS [143]. Psilocin (the active component of psilocybin) and DMT were shown to decrease the expression of the bacterial toll-like receptor 4 (TLR4), p65 and CD80, and increase the mRNA abundance of the TREM2 receptor in mouse primary microglia [102]. Animal studies reported that LSD (100 μM) inhibited B lymphocyte and NK cell proliferation and pro-inflammatory cytokine release (IL-2, IL-4, and IL-6) in an *in vitro* mouse study [86], while DOI suppressed TNF-α levels in a 5-HT_{2A} receptor-dependent manner [137,139], as well as TNF-α-induced pro-inflammatory markers in the small intestine [137]. In humans, ayahuasca decreases CD4+ and CD3+ T lymphocytes and increase in NK cells [54]; it also decreases the circulatory levels of the inflammatory marker C-reactive protein (CRP) [65]. The effect of ketamine on the immune system is less clear, as an increase [150] and decrease [35] in the pro-inflammatory cytokine IL-6 has been reported. Overall, these results suggest that immunomodulatory properties are common to all class of psychedelic compounds.

Conversely, the immune system is in constant dialogue with the microbiome. Microbe-immune interactions in early life prime the immune system to recognise and respond to threats while "ignoring" self-antigens, and the crosstalk between the gut microbiota and the immune system is an essential component of the gut-brain axis [200,92]. Chronic inflammation is also an important underlying factor in both gut dysbiosis [52] and psychopathology [129], including depression and trauma. Thus, psychedelics may impact on brain function and psychological state by modulating microbe-immune interactions.

2.3.2. The HPA axis

The HPA axis, the main component of the neuroendocrine system, controls an individual's physiological response to stress, and its function is known to be abnormally heightened in psychiatric disorders, including depression and anxiety [22,6,80].

It has become clear, since early microbiome studies, that the HPA axis is one of the main communication pathways between the gut and the brain. In fact, cortisol receptors are expressed along the GI tract, and gut epithelial cells, enteroendocrine cells as well as local cells of the immune system are responsive to cortisol, with downstream effects on gut microbial composition [123,185,25]. Specifically, an overactive HPA axis (and chronically elevated cortisol levels) have been reported to alter the composition of the gut microbiota and lead to inflammation via a leaky gut barrier [118]. Additionally, the absence of a gut microbiome has been shown to lead to an overreactive HPA axis and stress response in germ-free mice [176], suggesting the importance of the gut microbiome for a normal physiological response to stress.

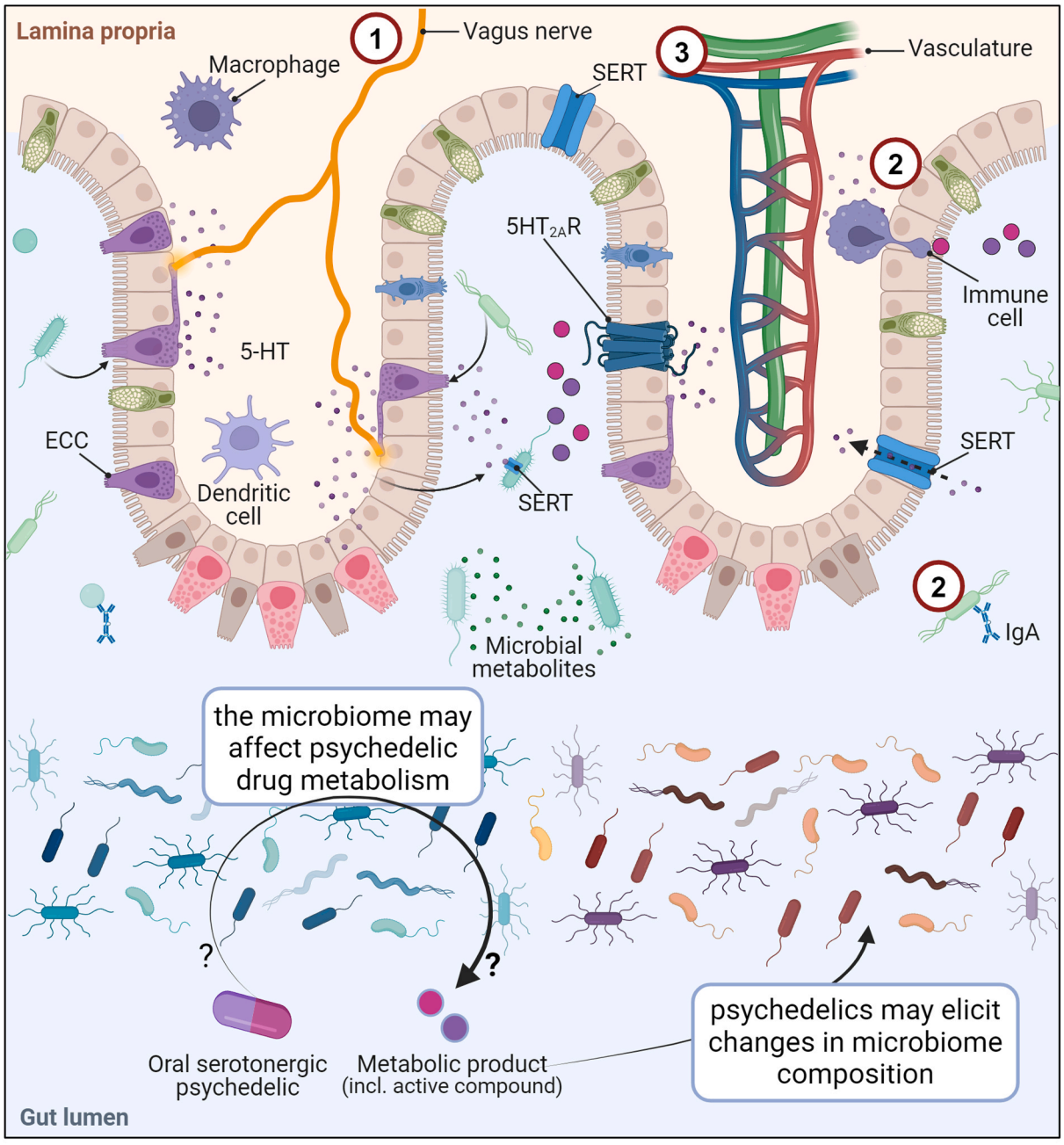
Similarly, several studies have reported a significant effect of psychedelics on the HPA axis. Human studies have indicated that intake of psychedelic drugs like LSD [161,172], psilocybin [79], ayahuasca [53] and DMT [174] increase adrenocorticotropic hormone (ACTH) and cortisol secretion. A dose-dependent increase in ACTH and corticosterone was also reported in rats treated with DOI and the related 1-(2, 5-dimethoxy-4-bromophenyl)-2-aminopropane (DOB) [128,23,4,82]. While evidence is still scarce, these results suggest that the HPA axis may be another pathway through which psychedelic-induced changes to the microbiota may affect emotional state and behaviour.

2.3.3. Brain connectivity networks

Interestingly, the same cortical networks that are affected by psychedelics (mainly via serotonergic receptors in cortical layer V) are also responsive to both inflammatory/stress-related and microbial signals. One of these networks is the default mode network (DMN), comprising of precuneus, posterior cingulate cortex (PCC), medial prefrontal cortex (mPFC) and inferior parietal cortex. It is involved in mind-wandering and self-referential processes, including autobiographical memories [21], but is inactive during active cognitive tasks [155]. Research has implicated abnormalities in DMN functional connectivity in psychiatric disorders, like depression [107,15,165,75,85], anxiety [3], OCD [171, 69,99], PTSD [2,45], attention deficit hyperactive disorder (ADHD, [168,58]), schizophrenia [103,199,78,100], and AN [110,125,34,41]. In fact, hyperconnectivity in the DMN is associated to tendencies of excessive rumination and negative self-referential thoughts.

Importantly, resting-state brain imaging studies consistently report the DMN as a target of psychedelic drugs [68]. For example, acute treatment with both psilocybin and LSD leads to a decrease in functional connectivity within different nodes of the DMN, like the mPFC, the PCC the medial posterior DMN, while increasing connectivity between the DMN and other resting-state networks [122,127,169,170,19,193,27,30, 47,7,74]. DMT (ayahuasca) was shown to decrease the thickness of the PCC [149,188,194]. The overall "decoupling" effect of these drugs on the DMN is thought to be responsible for the decrease in rumination following treatment with psychedelics.

There is evidence that the DMN is responsive to signals from the immune system and the gut microbiota. In patients with Crohn's disease, an inflammatory bowel disease characterised by chronic inflammation and gut dysbiosis, the functional connectivity of the DMN is abnormally high [101]. Several papers report an association between plasma pro-inflammatory markers, *e.g.* IL-6, suggestive of systemic inflammation, and a reduction in DMN connectivity [120,12,97]. A study by Xi *et al.* showed that correlations normally exist between specific bacterial taxa and DMN functional connectivity, which become disrupted in bipolar depression [201]. Similarly, a negative relationship exists between



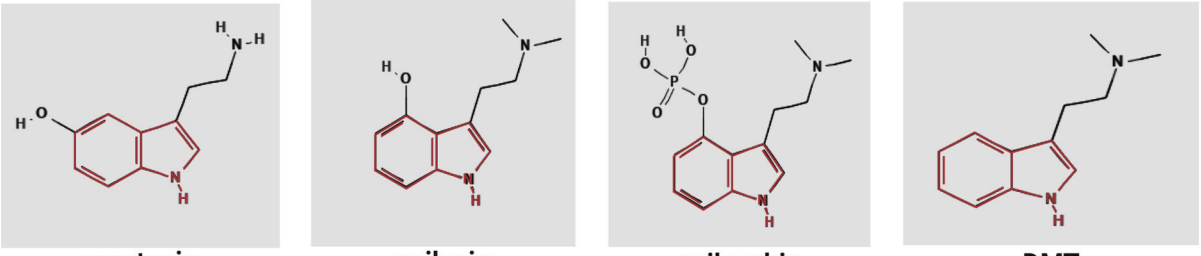


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Fig. 1. Potential local and distal mechanisms underlying the effects of psychedelic-microbe crosstalk on the brain. Serotonergic psychedelics exhibit a remarkable structural similarity to serotonin. This figure depicts the known interaction between serotonin and members of the gut microbiome. Specifically, certain microbial species can stimulate serotonin secretion by enterochromaffin cells (ECC) and, in turn, can take up serotonin via serotonin transporters (SERT). In addition, the gut expresses serotonin receptors, including the 2 A subtype, which are also responsive to psychedelic compounds. When oral psychedelics are ingested, they are broken down into (active) metabolites by human (in the liver) and microbial enzymes (in the gut), suggesting that the composition of the gut microbiome may modulate responses to psychedelics by affecting drug metabolism. In addition, serotonergic psychedelics are likely to elicit changes in the composition of the gut microbiome. Such changes in gut microbiome composition can lead to brain effects via neuroendocrine, blood-borne, and immune routes. For example, microbes (or microbial metabolites) can (1) activate afferent vagal fibres connecting the GI tract to the brain, (2) stimulate immune cells (locally in the gut and in distal organs) to affect inflammatory responses, and (3) be absorbed into the vasculature and transported to various organs (including the brain, if able to cross the blood-brain barrier). In the brain, microbial metabolites can further bind to neuronal and glial receptors, modulate neuronal activity and excitability and cause transcriptional changes via epigenetic mechanisms. Created with BioRender.com.

faecal *Bacteroides* and the functional connectivity between the left dorsolateral prefrontal cortex (dlPFC) and the DMN in major depression [173]. Interventions targeted to the gut microbiota can be effective in modulating brain connectivity, as demonstrated by a study where a 4-week multi-strain probiotic administration resulted in beneficial changes in DMN functional connectivity [9]. Therefore, there is evidence that psychedelic-induced shifts in gut microbial composition may lead to beneficial changes in brain connectivity.

2.3.4. Neuroplasticity

Neuroplasticity is a physiological process that describes the ability of the brain to respond and adapt to external stimuli by changing its structure and connections. This usually occurs via the formation of new neurons (neurogenesis), synapses (synaptogenesis) and dendrites (dendritogenesis). The vagus nerve, through its innervation of the GI tract, is a potential route by which changes in the local gut environment (*e.g.* gut microbial composition, or the presence of active compounds, like psychedelics) can stimulate neuroplasticity in crucial brain circuits involved in arousal, reward and cognition [39]. In fact, central BDNF levels are responsive to electrical stimulation of the vagus nerve [5], and in turn, can be dampened by severing afferent vagal fibres [175]. Psychiatric and neurodevelopmental disorders like depression [154] and autism spectrum disorder [148] are characterised by abnormalities in neurogenesis.

The absence of a normal gut microbiota was shown to lead to deficits in neurogenesis and in its underlying processes, like long-term potentiation (LTP), in the hippocampus of germ-free mice [145,46] and antibiotic-treated mice [109,130]. Interestingly, gut microbiome-induced deficits in neurogenesis have been reconducted to microglia activation, indicating a role for the brain's immune system in the formation of new neurons [159]. Importantly, treatment with probiotics was effective in restoring neurogenesis, promoting hippocampal LTP and dendritogenesis and in increasing brain-derived neurotrophic factor (BDNF) levels [130,158,184]. Similarly, cortical plasticity changes that are normally observed as a result of environmental enrichment were abolished in antibiotic-treated mice, but could be normalised via a microbiota transfer from healthy donor mice [112].

The relationship between psychedelics and neurogenesis is more complex: psilocybin increases hippocampal neurogenesis at low doses (0.1 mg/kg), but decreases it at higher doses (1.0 mg/kg) [33]; however, repeated administration of a high dose (1.5 mg/kg weekly for 4 weeks) was reported to increase the formation of new neurons in the dorsal ganglia [33]. DMT and 5-MeO-DMT stimulated neurogenesis both *in vitro* and *in vivo* [108,131], while LSD and DOI had no significant effect in rats [89]. Nevertheless, a large number of studies indicate that psychedelics, including psilocybin, LSD, DMT and DOI, increase the expression of intermediate early genes (IEGs) and other genes involved in neuroplasticity [138,140,142,189,49,72,73,88], promote LTP and stimulate the formation and growth of new synapses and dendrites [113,114,156,164,24,48,49]. In conclusion, there is potential that psychedelic-induced alterations to the microbiota may perturb their influence on neuroplasticity, possibly via the vagus nerve.

In summary, several biological processes are responsive to both psychedelic drugs and to shifts in gut microbial composition. This suggests that these processes may act as shared mechanisms of action, explaining how the interplay between microbial and psychedelic 'forces' modulate transmission via the gut-brain axis to affect brain function and behaviour. For example, it is possible that psychedelics impact on psychological state by modulating the cross-talk between gut microbes and (1) the serotonergic system, (2) inflammation, (3) the HPA axis, (4) brain connectivity networks and/or (5) neuroplasticity. Alternatively, it is possible that the composition of a person's gut microbiome modulates responses to psychedelics by altering (1) serotonergic neurotransmission, (2) immune state, (3) HPA axis reactivity, (4) brain connectivity networks and/or (5) neuroplasticity processes.

2.4. Comments on causality and directionality

While the effects of psychedelics on brain function have been described with significant resolution at the molecular, cellular and network level [191], whether and how much of these effects are also due to peripheral action (outside of the brain, *e.g.* on the microbiota) remains unclear. This review reports existing evidence that part of the effects of psychedelics on psychological state may be due to their impact on the gut microbiome and its related systems (*e.g.* the immune system). However, questions remain on the directionality of these relationships, and on the role that the microbiota plays in them.

A first possibility is that psychedelics improve psychological symptoms by modulating the composition and metabolic function of the gut microbiota (Fig. 2**A**). A favourable shift in microbial composition can improve brain and mental health via the gut-brain axis. In this case, the microbiome is a direct target of psychedelics and a mediator of psychedelic action on psychopathology.

A second possibility is that psychedelics act directly on psychopathology, but the magnitude of their effect is dependent on gut microbial composition (Fig. 2**B**). An example of this situation would be gut bacteria affecting drug metabolism (or any of the processes described in Table 1), contributing to the heterogeneity in responses to psychedelics. In this case, the microbiome is a modulator of psychedelic action.

A third possibility is that psychedelics act directly on psychological state, and that changes in mental state cause downstream changes in microbial composition (Fig. 2**C**). This implies that the microbiome is an indirect player in this relationship and that changes in the microbiota is a response to the psychedelic intervention.

Our take is that all of these options may be true: beautifully worded in [95], at the interface between the human host and the environment, the gut microbiome can be thought of as the "convergence hub" between multiple biofeedback systems regulating multiple aspects of human physiology. Accordingly, it becomes imperative for future research to adopt a systems biology approach, interpreting data within the framework of complex interactions that intertwine these interconnected systems. This necessitates an exploration across all levels, from micro to macro, and consideration of different time scales to unveil the nuanced dynamics at play.

Table 1
Shared targets between psychedelics and microbiome. The table below summarises some biological processes that are responsive to both psychedelic drugs and to shifts in gut microbial composition, which could explain the effect of psychedelic-microbe crosstalk on the brain.

Target	Relation to psychedelics	Relation to gut microbiome
Serotonergic system		• $5HT_{2A}$ receptors are expressed in the gastrointestinal tract [61] • serotonin exerts local effects on gut function, for example by enhancing peristalsis [187]
	• Structural similarity between serotonin and classical psychedelics, e.g. indole ring [139]	• selective serotonin reuptake inhibitors (SSRIs) can change the composition of the gut microbiota, and exhibit significant antimicrobial activity [134,93] • Gut microbes are able to stimulate local serotonin synthesis and release by enterochromaffin cells [157] and can modulate the circulating and central concentrations of serotonin [20] • increase in some species of spore-forming gut bacteria from *Turicibacteraceae*, *Clostridiales*, *Lachnospiraceae* and *Ruminococcaceae* after oral administration of serotonin to wildtype rats [64]
	• Classic psychedelics are $5HT_{2A}$ receptor agonist, with some activity at the $5HT_{1A}$ and $5HT_{2C}$ receptors [96]	• 5HT2A receptors are expressed on cells of the immune system [83]
		• some bacterial species (e.g. *Turicibacter sanguinis*) to transport serotonin thanks to a sodium symporter-related protein with sequence and structural homology to mammalian serotonin transporter SERT [64] • serotonergic antidepressant drugs alter the composition of the gut microbiota [111,126,44] • *Ruminococcaceae*, *Candidatus* and *Lactobacillaceae* were significantly correlated with the density of 5HT2A receptors and the hallucinogenic effects of DOI
Immune system	• anti-inflammatory and immune-modulating properties [179,181,182,186]	• Microbe-immune interactions in early life are essential for normal development of the immune system [200,92] • Chronic inflammation is an important underlying factor in gut dysbiosis [52]
Neuroendocrine system (HPA axis)	• Increased ACTH and cortisol in response to LSD [161,172], psilocybin [79], ayahuasca [53] and DMT [174] in humans	• cortisol receptors are expressed in the gut [123,185,25]
	• Dose-dependent increase in ACTH and corticosterone was also reported in rats treated with DOI and DOB [128,23,4,82]	• An overactive HPA axis (and chronically elevated cortisol levels) alter the composition of the gut microbiota and lead to inflammation via a leaky gut barrier [118] • Germ-free mice exhibit an overreactive HPA axis and an exaggerated stress response [176]
Intrinsic (brain) connectivity networks	• psychedelic drugs like psilocybin, LSD decrease functional connectivity within different nodes of the default mode network (DMN)	• In diseases characterised by chronic inflammation and gut dysbiosis, like Crohn's disease, the functional connectivity of the DMN is abnormally high (N. [101]) • correlations normally exist between specific bacterial taxa and DMN functional connectivity, which become disrupted in bipolar depression [201] • a negative relationship exists between faecal Bacteroides and the functional connectivity between the left dorsolateral prefrontal cortex (dlPFC) and the DMN in major depression [173] • a 4-week multi-strain probiotic administration resulted in benefitcial changes in DMN functional connectivity [9]
Neurogenesis	• psilocybin increases hippocampal neurogenesis at a single low dose (0.1 mg/kg), but it decreases it at a higher dose (1.0 mg/kg); repeated administration of a high dose (1.5 mg/kg weekly for 4 weeks) increases neurogenesis [33]	• Germ-free mice exhibit deficits in neurogenesis and LTP [145,46]
	• DMT and 5-MeO-DMT stimulated neurogenesis both *in vitro* and *in vivo* [108,131]	• Mice treated with antibiotics show impaired neurogenesis [109,130]
	• LSD and DOI had no significant effect on neurogenesis in rats [89]	• Different probiotic mixes were effective in restoring neurogenesis, promoting hippocampal LTP and dendritogenesis and in increasing BDNF levels [130,158,184]
	• psilocybin, LSD, DMT and DOI, increase the expression of intermediate early genes (IEGs) and other genes involved in neuroplasticity [138,140,142,189,49,72,73,88]	• Enrichment-related cortical plasticity was abolished in antibiotic-treated mice, but could be normalised via a microbiota transfer from healthy donor mice [112]
	• Many psychedelic drugs promote LTP and stimulate the formation and growth of new synapses and dendrites [113,114,156,164,24,48,49]	

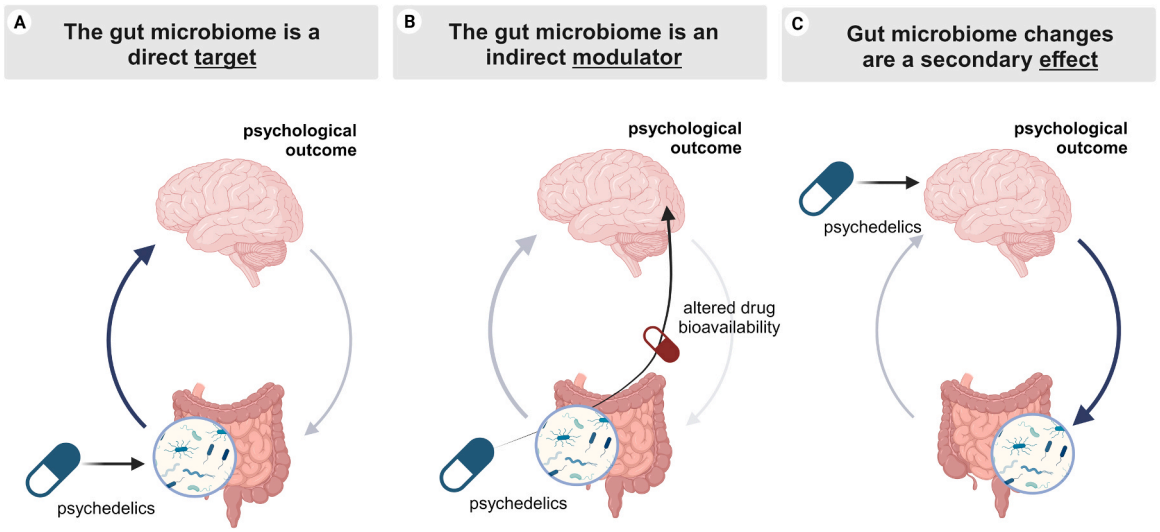

Fig. 2. Models of psychedelic-microbe interactions. This figure shows potential models of psychedelic-microbe interactions via the gut-brain axis. In (**A**), the gut microbiota is the direct target of psychedelics action. By changing the composition of the gut microbiota, psychedelics can modulate the availability of microbial substrates or enzymes (*e.g.* tryptophan metabolites) that, interacting with the host via the gut-brain axis, can modulate psychopathology. In (**B**), the gut microbiota is an indirect modulator of the effect of psychedelics on psychological outcome. This can happen, for example, if gut microbes are involved in metabolising the drug into active/inactive forms or other byproducts. In (**C**), changes in the gut microbiota are a consequence of the direct effects of psychedelics on the brain and behaviour (*e.g.* lower stress levels). The bidirectional nature of gut-brain crosstalk is depicted by arrows going in both directions. However, upwards arrows are prevalent in models (A) and (B), to indicate a bottom-up effect (*i.e.* changes in the gut microbiota affect psychological outcome), while the downwards arrow is highlighted in model (C) to indicate a top-down effect (i.e. psychological improvements affect gut microbial composition). Created with BioRender.com.

3. Conclusion

3.1. Implications for clinical practice: towards personalised medicine

One of the aims of this review is to consolidate existing knowledge concerning serotonergic psychedelics and their impact on the gut microbiota-gut-brain axis to derive practical insights that could guide clinical practice. The main application of this knowledge revolves around precision medicine.

Several factors are known to predict the response to psychedelic therapy. Polymorphism in the CYP2D6 gene, a cytochrome P450 enzymes responsible for the metabolism of psilocybin and DMT, is predictive of the duration and intensity of the psychedelic experience. Poor metabolisers should be given lower doses than ultra-rapid metabolisers to experience the same therapeutic efficacy [98]. Similarly, genetic polymorphism in the HTR2A gene can lead to heterogeneity in the density, efficacy and signalling pathways of the 5-HT_{2A} receptor, and as a result, to variability in the responses to psychedelics [71]. Therefore, it is possible that interpersonal heterogeneity in microbial profiles could explain and even predict the variability in responses to psychedelic-based therapies. As a further step, knowledge of these patterns may even allow for microbiota-targeted strategies aimed at maximising an individual's response to psychedelic therapy. Specifically, future research should focus on working towards the following aims:

(1) **Can we target the microbiome to modulate the effectiveness of psychedelic therapy?**

Given the prominent role played in drug metabolism by the gut microbiota, it is likely that interventions that affect the composition of the microbiota will have downstream effects on its metabolic potential and output and, therefore, on the bioavailability and efficacy of psychedelics. For example, members of the microbiota that express the enzyme tyrosine decarboxylase (e.g., *Enterococcus* and *Lactobacillus*) can break down the Parkinson's drug L-DOPA into dopamine, reducing the central availability of L-DOPA [116,192]. As more information emerges around the microbial species responsible for psychedelic drug metabolism, a more targeted approach can be implemented. For example, it is possible that targeting tryptophanase-expressing members of the gut microbiota, to reduce the conversion of tryptophan into indole and increase the availability of tryptophan for serotonin synthesis by the host, will prove beneficial for maximising the effects of psychedelics. This hypothesis needs to be confirmed experimentally.

(2) **Can we predict response to psychedelic treatment from baseline microbial signatures?**

The heterogeneous and individual nature of the gut microbiota lends itself to provide an individual microbial "fingerprint" that can be related to response to therapeutic interventions. In practice, this means that knowing an individual's baseline microbiome profile could allow for the prediction of symptomatic improvements or, conversely, of unwanted side effects. This is particularly helpful in the context of psychedelic-assisted psychotherapy, where an acute dose of psychedelic (usually psilocybin or MDMA) is given as part of a psychotherapeutic process. These are usually individual sessions where the patient is professionally supervised by at least one psychiatrist. The psychedelic session is followed by "integration" psychotherapy sessions, aimed at integrating the experiences of the acute effects into long-term changes with the help of a trained professional. The individual, costly, and time-consuming nature of psychedelic-assisted psychotherapy limits the number of patients that have access to it. Therefore, being able to predict which patients are more likely to benefit from this approach would have a significant socio-economic impact in clinical practice. Similar personalised approaches have already been used to predict adverse reactions to immunotherapy from baseline microbial signatures [18]. However, studies are needed to explore how specific microbial signatures in an individual patient match to patterns in response to psychedelic drugs.

(3) **Can we filter and stratify the patient population based on their microbial profile to tailor different psychedelic strategies to the individual patient?**

In a similar way, the individual variability in the microbiome allows to stratify and group patients based on microbial profiles, with the goal of identifying personalised treatment options. The wide diversity in the existing psychedelic therapies and of existing pharmacological treatments, points to the possibility of selecting the optimal therapeutic option based on the microbial signature of the individual patient. In the field of psychedelics, this would facilitate the selection of the optimal dose and intervals (*e.g.* microdosing vs single acute administration), route of administration (*e.g.* oral vs intravenous), the psychedelic drug itself, as well as potential augmentation strategies targeting the microbiota (*e.g.* probiotics, dietary guidelines, *etc*.).

3.2. Limitations and future directions: a new framework for psychedelics in gut-brain axis research

Due to limited research on the interaction of psychedelics with the gut microbiome, the present paper is not a systematic review. As such, this is not intended as exhaustive and definitive evidence of a relation between psychedelics and the gut microbiome. Instead, we have collected and presented indirect evidence of the bidirectional interaction between serotonin and other serotonergic drugs (structurally related to serotonergic psychedelics) and gut microbes. We acknowledge the speculative nature of the present review, yet we believe that the information presented in the current manuscript will be of use for scientists looking to incorporate the gut microbiome in their investigations of the effects of psychedelic drugs. For example, we argue that future studies should focus on advancing our knowledge of psychedelic-microbe relationships in a direction that facilitates the implementation of personalised medicine, for example, by shining light on:

(1) the role of gut microbes in the metabolism of psychedelics;
(2) the effect of psychedelics on gut microbial composition;
(3) how common microbial profiles in the human population map to the heterogeneity in psychedelics outcomes; and
(4) the potential and safety of microbial-targeted interventions for optimising and maximising response to psychedelics.

In doing so, it is important to consider potential confounding factors mainly linked to lifestyle, such as diet and exercise.

3.3. Conclusions

This review paper offers an overview of the known relation between serotonergic psychedelics and the gut-microbiota-gut-brain axis. The hypothesis of a role of the microbiota as a mediator and a modulator of psychedelic effects on the brain was presented, highlighting the bidirectional, and multi-level nature of these complex relationships. The paper advocates for scientists to consider the contribution of the gut microbiota when formulating hypothetical models of psychedelics' action on brain function, behaviour and mental health. This can only be achieved if a systems-biology, multimodal approach is applied to future investigations. This cross-modalities view of psychedelic action is essential to construct new models of disease (*e.g.* depression) that recapitulate abnormalities in different biological systems. In turn, this wealth of information can be used to identify personalised psychedelic strategies that are targeted to the patient's individual multi-modal signatures.

CRediT authorship contribution statement

Simon G. D. Ruffell: Writing – review & editing. **WaiFung Tsang:** Writing – review & editing. **Giorgia Caspani:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Wilfred A. Jefferies:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Conceptualization. **Jonathan R. Swann:** Writing – review & editing. **Nige Netzband:** Writing – review & editing. **Cyrus Rohani-Shukla:** Writing – review & editing.

Declaration of Competing Interest

WAJ is a founder and shareholder of the University of British Columbia Start-up Mynd Life Sciences. All other authors declare no known competing interests.

Data Availability

No data was used for the research described in the article.

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