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Abstract

Serotonergic psychedelics induce transient changes in perception, cognition, emotion, and the functional organization of brain networks. Their central effects are primarily associated with 5-HT2A receptor agonism, glutamatergic modulation, and the activation of mechanisms related to neuronal plasticity. In parallel, these substances exert measurable effects on the autonomic nervous system, including transient elevations in blood pressure, heart rate, body temperature, and neuroendocrine activity. Although the acute state is predominantly sympathomimetic, it is hypothesized that the subsequent window of plasticity may facilitate the functional recalibration of circuits responsible for integrating brain activity, emotional processing, and visceral physiology. This hypothesis does not imply a literal neurological reset, but rather a temporary reduction in the rigidity of neural, interoceptive, and autonomic patterns, potentially followed by greater sympathovagal flexibility and more efficient physiological recovery after stress. Within this model, the gut microbiota may represent a modulator of the metabolic, neuroimmune, and autonomic conditions under which the psychedelic experience occurs. Psychobiotics selected according to precision medicine criteria could hypothetically contribute to preparing and stabilizing this biological terrain without necessarily intensifying the acute psychedelic effect. This article critically examines this hypothesis, distinguishes established evidence from mechanistic inference, and discusses the limitations that must guide future investigation.

Keywords: *psychedelics, psilocybin, neuroplasticity, autonomic nervous system, vagus nerve, gut microbiota, psychobiotics, precision medicine*

Introduction

The resurgence of scientific research on psychedelics has challenged the traditional understanding of how pharmacological interventions may act on neuropsychiatric conditions. Unlike medications administered continuously to maintain relatively stable plasma concentrations, certain psychedelic interventions are being investigated for their capacity to induce a time-limited acute experience followed by psychological and functional changes that may persist after the substance has been eliminated.

Classic psychedelics include psilocybin, lysergic acid diethylamide, LSD, dimethyltryptamine, DMT, and mescaline. Despite their structural, pharmacokinetic, and phenomenological differences, these substances share partial or full agonism at serotonin 5-HT2A receptors as a central component of their pharmacological activity.

Most scientific literature has focused on effects within the central nervous system, CNS. However, the psychedelic experience simultaneously involves changes in heart rate, blood pressure, body temperature,

respiration, gastrointestinal activity, hormonal secretion, and the perception of internal bodily signals. Psychedelic effects therefore cannot be adequately understood without considering the autonomic nervous system, ANS.

More recently, the gut microbiota has been incorporated into this conceptual framework. The composition and metabolic activity of the intestinal ecosystem can influence immune signaling, tryptophan metabolism, short-chain fatty acid production, intestinal barrier integrity, and communication among the enteric nervous system, vagus nerve, and brain. The possible interaction between the microbiota and psychedelic response has contributed to the emerging concept of the psilocybiome, in which microbial, pharmacological, environmental, and individual factors constitute a bidirectional system.

The relevant scientific question is therefore not only whether psychedelics alter brain function, but also under which metabolic, neuroimmune, and autonomic conditions the brain enters a state of increased plasticity.

What Would Neurological reorganization Mean?

The expression neurological reset is appealing but scientifically imprecise. The brain is not switched off, its action potentials are not reset to zero, and its neural connections do not return to an original configuration. Psychedelic exposure does not necessarily regenerate lost neurons or automatically restore impaired functions.

The more plausible phenomenon is a transient destabilization of excessively rigid functional patterns, accompanied by an increased capacity for synaptic reorganization and the development of new connectivity patterns. During the psychedelic state, certain brain networks show reduced internal coherence, while regions that typically interact less extensively may display increased functional connectivity. Neuroimaging studies have described increased diversity of brain states, a temporary reduction in the modularity of certain networks, and a greater influence of environmental context on the organization of brain activity.

Neurological reorganization therefore does not consist of correcting isolated electrical impulses. It involves changes in neuronal excitability, synchronization among neuronal populations, the functional weight of synaptic connections, and the manner in which different brain regions process internal and external information. The brain does not return to factory settings. At most, it may temporarily enter a more editable state.

5-HT2A Receptors and the Reorganization of Brain Networks

5-HT2A receptors are widely distributed throughout the cerebral cortex, with relevant expression in pyramidal neurons involved in integrating sensory, cognitive, and emotional information. Activation of these receptors modifies cortical excitability and promotes changes in glutamatergic signaling.

Antagonism of 5-HT2A receptors with ketanserin substantially reduces the subjective effects of substances such as LSD and psilocybin, supporting the central role of this receptor. Nevertheless, final effects do not depend exclusively on 5-HT2A signaling. Depending on the compound, 5-HT1A and 5-HT2C receptors, dopaminergic and glutamatergic systems, and intracellular signaling mechanisms may also participate.

Activation of these systems alters networks associated with perception, sense of self, autobiographical memory, threat evaluation, salience, and emotional integration. Acute effects may include greater sensitivity to environmental stimuli, increased flexibility of cognitive models, emotional intensification, and changes in bodily perception. This flexibility is not inherently therapeutic. A brain that is more plastic and sensitive to context may also consolidate adverse experiences. Potential benefit depends on the interaction among pharmacology, environment, psychological condition, support, and subsequent integration processes.

Psychedelics as Inducers of a Window of Plasticity

Preclinical evidence indicates that psychedelics may increase the formation and remodeling of dendritic spines. In mice, a single exposure to psilocybin produced an approximately 10 percent increase in dendritic spine density and size in the frontal cortex, associated with increased formation of new spines. Some of these changes remained detectable after the acute phase.

Different psychedelics may also promote retention of the tropomyosin receptor kinase B, TrkB, at the neuronal surface and

facilitate its interaction with brain-derived neurotrophic factor, BDNF. This signaling pathway participates in neuronal survival, modification of synaptic strength, and formation of new connections.

Most structural demonstrations originate from cell cultures or animal models. Furthermore, a meta-analysis involving 29 studies found no consistent evidence of increased peripheral BDNF concentrations in humans after interventions involving psychoplastogens. The absence of changes in blood does not necessarily invalidate effects in the brain, but peripheral BDNF is not currently a reliable clinical biomarker of psychedelic-induced plasticity. The most defensible interpretation is that psychedelics may create a transient window of increased plasticity. This window expands the possibility of change but does not determine its direction or guarantee functional restoration.

The Autonomic Nervous System and the Psychedelic Experience

The ANS regulates involuntary functions required for physiological adaptation. The sympathetic component mobilizes resources in response to effort, novelty, or threat. The parasympathetic component contributes to energy conservation, digestion, recovery, and visceral regulation.

This division should not be understood as a rigid balance in which activation of one branch necessarily produces complete inhibition of the other. Sympathetic and parasympathetic systems can display alternating dominance, coactivation, or coinhibition. A healthy autonomic system is not permanently parasympathetic. It can activate appropriately in response to demand and return efficiently to recovery after the demand has ended.

During the acute phase, classic psychedelics generally increase sympathetic activity. Effects may include elevated blood pressure, increased heart rate, pupillary dilation, sweating, changes in body temperature, nausea, and neuroendocrine activation. In a randomized controlled study, LSD predominantly increased sympathetic activity measured by heart rate variability, HRV. Ketanserin reduced psychedelic effects and shifted autonomic parameters toward greater parasympathetic influence. Direct comparisons between LSD and psilocybin showed cardiostimulatory properties for both compounds, with psilocybin producing a relatively greater increase in blood pressure and LSD exerting a more pronounced effect on heart rate.

These findings were obtained primarily in carefully selected and monitored participants. They cannot be generalized to people with cardiovascular disease, psychiatric instability, or concomitant medications with interaction potential.

From Acute Sympathetic Activation to Autonomic Recalibration

The predominance of acute sympathetic activation may initially appear incompatible with the hypothesis of vagal rebalancing. Immediate pharmacological effects and delayed physiological adaptation, however, are not necessarily equivalent. Physical exercise acutely increases heart rate, blood pressure, and sympathetic activity, yet it can improve parasympathetic recovery over time. This comparison does not demonstrate that psychedelics produce the same adaptation, but it illustrates that transient sympathetic activation and subsequent autonomic improvement are not physiologically contradictory.

The proposed hypothesis is that the psychedelic state generates intense physiological activation while simultaneously modifying the central interpretation of bodily signals. If this activation occurs in a context perceived as safe, the brain may experience increased heart rate, respiratory changes, and emotional intensification without these responses resulting in actual harm or threat.

During the window of plasticity, this experience could weaken rigid associations between physiological activation and danger. The body would not cease producing alert signals, but the brain might learn to interpret them in a manner more proportional to the actual context. The hypothetical outcome would not be a permanent increase in vagal tone. It would be greater autonomic flexibility, characterized by an appropriate sympathetic response to demand and more efficient parasympathetic recovery after that demand has ended.

The Central Autonomic Network

Autonomic regulation depends on a distributed cerebral network that includes the medial prefrontal cortex, insular cortex, cingulate cortex, amygdala, hypothalamus, periaqueductal gray, nucleus of the solitary tract, nucleus ambiguus, and medullary regions involved in

cardiovascular and respiratory control.

Neuroimaging meta-analyses identify the dorsal anterior insula and midcingulate cortex as central components of this network. These regions simultaneously participate in emotional processing, salience detection, and autonomic regulation. The insula receives and integrates information concerning heartbeats, respiration, temperature, and visceral state. The cingulate cortex contributes to transforming these signals into motivational, emotional, and autonomic responses.

Because psychedelics alter the connectivity of regions belonging to the central autonomic network, it is biologically plausible that they may also modify the way the brain interprets bodily signals and coordinates sympathetic and parasympathetic responses.

Interoception and Autonomic Relearning

Interoception is the process through which the nervous system detects and interprets the body's internal state. Heartbeats, respiration, gastrointestinal distension, temperature, pain, and muscle tension form a continuous stream of information directed toward the brain.

These signals do not possess a fixed emotional meaning. An increased heart rate may be interpreted as fear, excitement, physical effort, or positive anticipation. Its meaning depends on context, previous experiences, and the predictive models employed by the brain. Altered interoceptive processing has been identified in conditions characterized by anxiety, hypervigilance, dissociation, and emotional dysregulation. The insula and cingulate cortex constitute a bridge between bodily perception and autonomic response.

During the psychedelic experience, bodily signals may become more intense and conscious. In an inadequate environment, this amplification may facilitate anxiety and defensive responses. Under conditions perceived as safe, the same signals may be reinterpreted without an automatic association with threat. A possible vagal recalibration could therefore be partially mediated by interoceptive relearning: physiological activation, conscious perception, reinterpretation of meaning, absence of actual threat, emotional resolution, and autonomic recovery. This sequence remains hypothetical, but it offers a biologically coherent model for explaining how acute sympathetic activation might be followed by improved physiological regulation.

Heart Rate Variability and Vagal Balance

HRV is frequently used as an indirect indicator of cardiac autonomic modulation. Under appropriate conditions, particularly when analyzed together with respiration, certain HRV parameters may reflect vagal influence on the heart.

However, HRV does not directly measure the entire activity of the vagus nerve. It is influenced by age, posture, respiratory frequency, physical activity, time of day, medications, and analytical methodology. There is also no single ratio between frequency bands that perfectly represents sympathovagal balance.

In a controlled DMT study, electrocardiogram-derived measures indicated that sympathetic and parasympathetic coactivation during the experience was associated with the intensity of spiritual or insightful subjective experiences. Certain autonomic patterns were also associated with improved well-being two weeks later. The study included only 17 participants and did not demonstrate causality or persistent vagal stimulation. The relevant variable may therefore be the capacity for coordination between the two branches of the ANS rather than isolated parasympathetic predominance.

The Microbiota Gut Brain Axis as a Peripheral Modulator

The gut microbiota participates in several processes capable of influencing the CNS and ANS. These include tryptophan metabolism, short-chain fatty acid production, bile acid transformation, intestinal barrier regulation, and cytokine modulation.

Gut-brain communication can occur through neural, endocrine, metabolic, and immune pathways. The vagus nerve constitutes one of these routes, particularly through afferent fibers that transmit visceral information to the nucleus of the solitary tract. Nevertheless, not every microbiota-related effect is transmitted through the vagus nerve, and not every cerebral effect of a probiotic necessarily depends on this pathway.

The psilocybiome concept proposes that microbiota, host, and psychedelic agent may interact bidirectionally. Baseline microbiota-gut-brain axis activity could influence the response to a

psychedelic, while the psychedelic experience, behavioral changes, dietary patterns, and pharmacological exposure could subsequently alter the intestinal ecosystem. Recent reviews also propose that microbial metabolism may contribute to individual differences in responses to psychotropic agents and potentially to psychedelics. This influence has not yet been conclusively demonstrated in clinical trials evaluating combined interventions.

Precision Psychobiotics as Modulators of the Biological Terrain

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. The term psychobiotic is applied to microorganisms or microbiome-directed interventions capable of influencing functions associated with the gut-brain axis.

Probiotic effects depend on strain, composition, administered amount, viability, delivery matrix, duration of exposure, host characteristics, and evaluated outcome. It is not scientifically appropriate to treat probiotics as a pharmacologically uniform category. There is also insufficient clinical evidence to claim that probiotics directly increase psychedelic intensity, enhance 5-HT2A receptor occupancy, or extend the window of plasticity.

The more prudent hypothesis is that psychobiotics selected through precision medicine could modulate the baseline biological conditions under which the experience occurs. Potential targets include neuroimmune signaling, microbial tryptophan metabolism, production of bioactive metabolites, intestinal barrier integrity, gut-brain communication, physiological responses to stress, autonomic stability, and gastrointestinal symptoms potentially relevant to tolerability.

Within this model, the psychobiotic would not be used to make the psychedelic experience stronger. Its hypothetical purpose would be to make the biological terrain more predictable, individualized, and compatible with adaptive reorganization.

Precision Medicine Applied to the Microbiota Psychedelic Axis

The response to psychedelics is characterized by substantial interindividual variability. Dose, metabolism, genetics, expectations, personality, emotional state, environment, previous experiences, and psychological support can all modify the effects. The microbiota may represent an additional layer of this heterogeneity.

A precision medicine framework could integrate microbiome composition and function, microbial metabolites, inflammatory markers, tryptophan metabolism, autonomic parameters, sleep quality, hypothalamic-pituitary-adrenal axis responses, clinical and pharmacological profiles, and psychological and interoceptive characteristics.

The purpose would not be to select one generic probiotic for every individual. It would be to identify phenotypes in which a specific microbiome-directed intervention has biological plausibility. Some individuals may predominantly exhibit inflammatory alterations, whereas others may present metabolic, gastrointestinal, or autonomic abnormalities. The same intervention is unlikely to be equally appropriate for everyone. Precision medicine requires recognition of this heterogeneity before synergy can be claimed.

An Integrated Three Phase Model

Preparatory phase. The hypothetical objective would be to characterize and, when scientifically justified, modulate the baseline metabolic, intestinal, neuroimmune, and autonomic state. The microbiome-directed intervention would act on the physiological terrain rather than on the intensity of the psychedelic experience.

Acute phase. The psychedelic would induce 5-HT2A activation, brain network reorganization, interoceptive intensification, and predominantly sympathetic autonomic activation. The microbiota might theoretically contribute to metabolic and physiological variability, but this role has not been adequately quantified in humans.

Integration phase. After the experience, factors related to sleep, diet, stress, physical activity, microbiota, and psychosocial support could influence consolidation. During this phase, a psychobiotic intervention might hypothetically contribute to metabolic and autonomic stability without being considered independently responsible for the outcome.

The integrated model can be summarized as follows: individual phenotype, precision characterization, modulation of the biological terrain, psychedelic window of plasticity,

neuroautonomic reorganization, consolidation, and follow-up.

Central Hypothesis

The integrated hypothesis is that serotonergic psychedelics induce a transient window of plasticity during which brain networks involved in perception, emotion, interoception, and autonomic regulation become less rigid and more sensitive to context.

If the experience occurs under conditions capable of promoting safety, adaptive interpretation of bodily signals, and resolution of emotional responses, greater autonomic flexibility may emerge after the acute phase. The microbiota-gut-brain axis may influence this process by modulating the individual's neuroimmune, metabolic, and visceral state. Psychobiotics selected according to precision criteria could prepare or stabilize this biological terrain, but they should not be presented as proven enhancers of psychedelic pharmacodynamics.

The expected outcome would not be a literal neurological reset or a permanent increase in vagal tone. It would be a potentially improved capacity to adapt to internal and external stimuli, distinguish physiological activation from actual threat, interrupt prolonged hypervigilance, recover more efficiently after stress, and integrate bodily and emotional signals more effectively.

Limitations and Risks of Interpretation

The principal limitation is the absence of robust clinical trials evaluating psychedelics in combination with precision psychobiotics. Most available literature consists of mechanistic reviews, hypotheses, observational evidence, and preclinical studies.

Changes in microbiota composition do not automatically demonstrate functional benefit. An increase or decrease in a bacterial group cannot be classified in isolation as beneficial or harmful without considering the ecological and metabolic context. Modification of the microbiota by a psychedelic, microbiota-related influence on pharmacological exposure, modulation of subjective response, and persistent clinical improvement are distinct phenomena. They may be related, but they are not equivalent.

Diet, sleep, behavior, physical activity, and medication use following the experience can modify both microbiota and autonomic function. The expression vagal rebalancing should therefore be used as a hypothesis of functional reorganization rather than an established clinical outcome. Demonstration would require convergence among HRV, baroreflex sensitivity, cardiovascular recovery, respiration, electrodermal activity, neuroendocrine markers, inflammatory measurements, and neuroimaging of the central autonomic network.

Safety Considerations

Psychedelics are not risk-free interventions. They may produce intense anxiety, perceptual disorganization, elevated blood pressure, increased heart rate, nausea, and psychologically challenging experiences.

Individuals with certain cardiovascular conditions, a history of mania or psychotic disorders, clinical instability, or use of medications with interaction potential require specific assessment. Tolerability observed in controlled studies should not be extrapolated to unsupervised use.

Likewise, probiotics and psychobiotics should not automatically be considered safe for every individual. Risks and benefits depend on characteristics of the intervention and host, particularly in severe immunosuppression, compromised biological barriers, or the presence of invasive devices. The combination of two biologically active interventions must be investigated as a combination. Its safety and effects cannot simply be inferred from the separate safety profile of each component.

Conclusion

Serotonergic psychedelics may induce a transient reorganization of brain connectivity and create a window of increased plasticity. During the acute phase, their autonomic effects are predominantly sympathetic. This initial activation does not exclude the possibility of a later adaptation characterized by greater autonomic flexibility and more efficient parasympathetic recovery.

The vagal recalibration hypothesis is based on the interaction among neuronal plasticity, the central autonomic network, interoception, stress responses, and the context of the experience. It is biologically plausible but has not yet been established as a persistent effect.

The gut microbiota adds a systemic dimension to this model. Rather than considering psychobiotics as direct enhancers of

psychedelic effects, it is more prudent to investigate them as precision modulators of the metabolic, neuroimmune, and autonomic conditions under which the window of plasticity develops.

The future of this field may not lie in making the psychedelic experience more intense, but in making it more biologically understandable, individualized, predictable, and compatible with durable adaptive change.

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