Psychedelic Rejuvenation Hypothesis A Framework for Cellular and Psychological Restoration

Tony Montgomery, PhD

INTRODUCTION

Recent estimates place the economic burden of mental illness in the United States at approximately $282 billion annually [1]. Chronic disease adds substantially to this strain: in 2014, 60% of U.S. adults were living with at least one chronic condition, and 42% had multiple conditions [2]. At the same time, U.S. life expectancy has plateaued since 2010 and continues to lag behind that of peer nations [3]. These trends are compounded by the structure of the U.S. healthcare system, which remains predominantly reactive, focusing on treating disease after onset rather than maintaining health and preventing illness [4]. In recent years, there has been a growing push to reorient research and healthcare delivery toward preventive medicine, yet the shift faces significant systemic, economic, and logistical barriers [5]. The aim of preventive healthcare is clear: to maintain and promote health, reduce risk factors, enable early diagnosis, and prevent complications before they arise.

There has been a resurgence of interest in the use of psychedelics to treat mental health illnesses, with astonishing results and very low addiction and risk profiles [6–8]. Psychedelics have emerged as some of the most promising tools in modern psychiatry, with psilocybin for depression and 3,4-Methylenedioxymethamphetamine (MDMA) for post-traumatic stress disorder (PTSD) under active regulatory consideration with uncertain timelines [9]. Despite growing attention to psychedelics in clinical psychiatry, their potential as tools to preserve or enhance health in already well-functioning individuals remains largely unexplored. The possibility that psychedelics might preserve or even *enhance* health in already well-functioning individuals has been largely unexplored in clinical trials, despite mounting mechanistic evidence suggesting such potential.

The rationale for this preventative approach lies in the intersection of several established facts: (1) many mental and physical disorders share upstream biological processes, including chronic inflammation, mitochondrial dysfunction, and reduced neuroplasticity [10–13]; (2) classical psychedelics engage pathways that directly modulate these processes [14–19]; and (3) lifestyle interventions, such as exercise, meditation, and diet, alongside periodic guided psychedelic use, may help maintain these systems and collectively serve as pillars of preventative medicine.

Beyond the neurobiological benefits of psychedelic use to improve longevity, there is the mystical experience that comes along with it. Mystical experiences may not only induce lasting changes in perspective and psychological flexibility, but also correlate with improvements in physical health and reduced biomarkers of stress, both of which are relevant to aging and resilience [20]. The greater the level of the mystical experience has been demonstrated to have a linear correlation with rates of improvement of the mental disorder [20]. They offer shifts in how one views the world, with awe-inspiring experiences, a sense of oneness, and a higher affinity for loving the other [20,21]. These experiences, when felt outside of a psychedelic experience, have been shown to improve mental and physical health [22,23]. The Relaxed Beliefs Under Psychedelics (REBUS) model proposed by Carhart-Harris and Friston (2019) offers a theoretical foundation, positing that psychedelics relax high-level priors in the brain's predictive coding hierarchy, allowing for greater cognitive flexibility and emotional

opennes s. We extend this by hypothesizing that, under certain dosing regimens, psychedelics can *regress the brain toward a more youthful state*, not just a disrupted one, characterized by high neural entropy, rich sensory processing, and reduced self-referential rigidity, thus reversing aspects of psychological and neurological aging.

If correct, our *Psychedelic Rejuvenation Hypothesis* positions psychedelics alongside exercise and cognitive training as candidate interventions for mental health preservation, physical resilience, longevity, and wellbeing. We propose a model of guided psychedelic interventions, intentional, periodically administered psychedelic experiences conducted within supportive frameworks that prioritize preparation, integration, and psychological safety. While distinct from formal psychedelic-assisted therapy (PAT) for clinical disorders, these interventions rely on the same core principles: the importance of set and setting, trained facilitation, and post-experience integration. This approach aims to preserve mental health and enhance psychological resilience in already well-functioning individuals.

This paper introduces the *Psychedelic Rejuvenation Hypothesis*, the idea that classical psychedelics promote long-term health not only by treating psychiatric symptoms, but by rejuvenating cellular and psychological systems linked to aging. By enhancing neuroplasticity, reducing chronic inflammation, supporting mitochondrial efficiency, and reopening critical periods of learning and adaptation, psychedelics may help return the brain and body to a more youthful, resilient state, disrupting negative learned patterns and cognitive biases. Much like exercise induces biological rejuvenation via hormetic stress, psychedelics may unlock an adaptive plastic window in both mind and body, promoting long-term resilience (Figure 1). While emerging preclinical and early human data point to potential preventive effects of psychedelics on neuroplasticity, inflammation, and mitochondrial health, evidence in *healthy populations* remains limited. This paper advances a **testable hypothesis**, not a definitive claim, that psychedelics may act as candidate geroprotective agents.

Mechanistic Basis for Preventative Effects

Neuroplasticity and Cognitive Processing

Brain aging is a gradual yet detectable process that begins as early as the third decade of life. Around the age of 30, individuals begin to experience measurable declines in brain-derived neurotrophic factor (BDNF) levels, neurogenesis, synaptic density, and functional connectivity. These changes are accompanied by cognitive slowing, mitochondrial dysfunction, and increased neuroinflammation [25–29]. Although overt symptoms of cognitive aging often emerge later in life, research suggests that subtle declines in neuroplasticity, synaptic density, and cognitive flexibility may begin as early as mid-adulthood, often progressing silently before noticeable clinical signs appear. [30]. Lifestyle interventions such as regular physical activity, quality sleep, and nutrient-dense diets have demonstrated measurable efficacy in slowing, and in some cases partially reversing, age-related neurological decline [31,32]. We propose that guided psychedelic interventions could serve as a synergistic complement to existing lifestyle strategies, such as diet and exercise, which often suffer from high dropout rates. By enhancing neuroplasticity and modulating aging-related pathways, psychedelics may improve not only the physiological impact of these interventions but also adherence by facilitating lasting changes in motivation, behavior, and habit formation. By increasing emotional salience, openness, and behavioral flexibility, psychedelics may reinforce sustained engagement in health-promoting behaviors across the lifespan.

Psilocybin, Lysergic acid diethylamide (LSD), N,N-Dimethyltryptamine (DMT), and mescaline all act primarily via serotonin (5-HT_2A) receptor agonism on layer V pyramidal neurons in the prefrontal cortex. This receptor activation triggers glutamate release and downstream cascades involving BDNF (brain-derived neurotrophic factor) and mTOR (mechanistic target of rapamycin) signaling, both essential for dendritic spine growth and synaptogenesis [18,33]. These neuroplastic pathways are particularly relevant in the context of age-related cognitive decline, where conditions like Alzheimer's disease and dementia begin developing silently, often decades before symptoms emerge. Amyloid accumulation, tau misfolding, and microglial activation can begin decades before symptoms are present [34]. Early declines in BDNF expression are accompanied by increases in oxidative stress and rising neuroinflammation, which occur as early as age 35 [34]. Recent preclinical data offer compelling early evidence for psychedelics in promoting longevity. In one study, 19-month-old mice (a model for late-life human aging) that received an initial low dose of 5mg of psilocybin followed by monthly doses of 15 mg over a 10-month period showed a 30% higher survival rate compared to untreated controls [16]. They found improvements in key biological markers of aging, with reductions in oxidative stress, enhanced DNA repair mechanisms, and maintained telomere length [16]. Building on this, clinical trials have begun exploring the use of low-dose LSD in early-stage Alzheimer's disease, testing whether it may improve cognitive function or slow neurodegeneration. These early signals suggest that psychedelics may not only promote plasticity but could also support long-term brain resilience and repair [16].

Chronic stress is a major contributor to cognitive decline, acting through mechanisms such as neuroinflammation, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, and mitochondrial dysfunction, all of which are strongly associated with mental health disorders and reduced lifespan [35,36]. Psychedelics have shown promise in counteracting these effects by reducing chronic stress, along with increases in BDNF and neurogenesis in the hippocampus, the brain area responsible for learning and memory [17,18]. A central theory in depression research emphasizes that many pharmacological treatments exert their effects by enhancing neuroplasticity [37]. Ly et al. (2018) demonstrated that various psychedelics (LSD, DMT, and 2,5-Dimethoxy-4-iodoamphetamine (DOI)) induced robust growth of dendritic spines and branches in cortical neurons, increasing the complexity of neuronal arborization and synaptic density. DMT was recently shown to activate neural stem cells and enhance neurogenesis in the mouse hippocampus [38]. This pro-neurogenic effect was mediated through the sigma-1 receptor, an auxiliary receptor located on the endoplasmic reticulum; notably, blocking sigma-1 eliminated the pro-neurogenic response, highlighting its critical role. Although direct observation of neurogenesis in living humans remains technically unfeasible, indirect evidence is accumulating. Ingesting ayahuasca (DMT and Harmine) has been shown to lead to acute increases in plasma BDNF [39]. Similarly, ingestion of psilocybin and microdosing of LSD have shown a transient increase in BDNF and elevated gene expression of BDNF [40]. This plasticity appears to rely on the same pathways as fast-acting antidepressants by activating mTOR and related protein kinases, which have been implicated in the growth of new synaptic proteins and neurites [39,41]. Consistently, experiments show that blocking TrkB or mTOR can attenuate the neuritogenic effect of psychedelics, linking back to the necessity of BDNF signaling for these neural changes [42].

Recent research led by Dr. Nolan Williams has investigated the therapeutic

potential of ibogaine, particularly in a magnesium-ibogaine f ormulation, for veterans with traumatic brain injury (TBI). They reported improvements in cognitive performance following treatment, including enhancements in executive function and cognitive inhibition [43]. Functional MRI (fMRI) and EEG showed altered cortical oscillatory activity and increased neural complexity, suggesting a neurorestorative effect on disrupted brain networks commonly impaired in TBI [44]. Ibogaine led to measurable gains in cognitive domains post-treatment, implying neuroplastic recovery potential [45]. These effects are thought to result from ibogaine's unique modulation of glutamatergic and serotonergic systems, its anti-inflammatory properties [46], and the facilitation of neurotrophic signaling, though further mechanistic validation in humans is ongoing.

Recent work demonstrated that certain psychedelics reopen critical periods of social and sensory learning in mice [47]. They found that this reopening was temporally gated, lasting days to weeks, depending on how long the psychedelic lasted in the system. The longer the duration of the drug, the longer this window remained open. This effect was dependent on oxytocin signaling and 5-HT_2A receptor activity [47]. Under the REBUS model by Carhart-Harris and Friston (2019), they posit that psychedelics relax hierarchical prediction error suppression, which may create a temporary brain state conducive to plasticity. Still, expression depends on context, circuit, and neuromodulators. What emerges is a compelling hypothesis: psychedelics may reengage dormant neuroplastic pathways that are otherwise inaccessible in adulthood. This could facilitate meaningful psychological rewiring, from reshaping maladaptive habits to transforming entrenched self-beliefs and emotional responses. However, this potential is not automatic. The integration process becomes a decisive factor in determining whether the insights and neural flexibility achieved during the psychedelic experience result in meaningful change. Without deliberate post-journey integration, these reopened windows of neuroplasticity may close without effect, or worse, reinforce maladaptive patterns. Unfortunately, integration remains underexplored in many clinical trials despite its recognized importance in practitioner circles. Emerging literature emphasizes that structured integration support, such as psychotherapy, journaling, somatic practices, and behavioral interventions, can significantly enhance therapeutic outcomes and long-term benefits [48,49]. Studies show that integration helps translate transient states into enduring traits, reinforcing shifts in cognition, emotion, and behavior long after the acute effects wear off [50,51]. This critical phase warrants deeper investigation and should be viewed as an essential element of the psychedelic healing process, not an optional add-on.

Taken together, the evidence for increased neuroplasticity, neurogenesis, and now, the reopening of critical periods, supports the provocative idea that psychedelics may help render the brain younger, more flexible, and healthier. Future research should prioritize targeted interventions that harness these effects to promote lasting, functional change across the lifespan.

Anti-Inflammatory and Immunomodulatory Effects

Chronic low-grade inflammation, often referred to as "inflammaging," plays a central role in the progressive decline of both mental and physical health, contributing to neurodegeneration, metabolic dysfunction, and psychiatric disorders [52]. Classical psychedelics have demonstrated potent, context-dependent immunomodulatory effects in preclinical models and early human studies [17].

In a recent systematic review of 40 preclinical studies, Low et al. (2025) examined the impact of classical psychedelics on

inflammatory markers. Among the 36 studies that measured cytokine levels, 29 reported significant reductions in at least one pro-inflammatory cytokine following psychedelic administration. Commonly observed decreases included IL-6, TNF-α, and IL-1β, particularly in rodent models of chronic stress, immune activation, or neuroinflammation. Importantly, the immune effects of psychedelics appear to be context-dependent. In disease or stress states characterized by elevated inflammation, psychedelics tended to suppress immune overactivity, leading to a reduction in pro-inflammatory cytokines. However, under normal baseline conditions, some compounds were found to produce a transient increase in certain cytokines or immune cell activity, suggesting an acute adaptive response rather than harmful overactivation [17]. This nuanced immunological profile implies that psychedelics may function as immune system balancers, helping to restore homeostasis where it's needed while avoiding chronic suppression or overstimulation. In this sense, psychedelics may operate in an adaptogenic manner, modulating immune function based on the body's existing physiological state, a potentially valuable mechanism in aging-related inflammatory diseases, mental health disorders, and systemic stress conditions.

At the cellular level, immune cells such as macrophages and T cells express serotonin receptors, including 5-HT_2A, the primary target of classical psychedelics. In addition to macrophages and T cells, microglia, central nervous system immune cells, also express 5-HT_2A receptors and exhibit reduced activation following psychedelic exposure [17]. Activation of these receptors on immune cells can directly alter their behavior. For example, one *in vitro* study demonstrated that exposing human peripheral blood mononuclear cells to psilocybin led to a reduction in inflammatory gene expression, an effect abolished by blocking 5-HT_2A receptors, confirming a receptor-mediated mechanism [14]. In *in vivo* models, psychedelics also modulate the neuroimmune axis, particularly in the context of stress. In a groundbreaking study, Chung et al. (2023) identified a pathway where stress triggers inflammatory monocytes to accumulate in the brain's meninges, releasing IL-1β, a pro-inflammatory cytokine that enters the brain and drives fear-related behavior. Remarkably, both psilocybin and MDMA were found to disrupt this pathological neuroimmune signaling, preventing excessive monocyte recruitment and reducing IL-1β levels. This effect was entirely dependent on 5-HT_2A receptor activity, as receptor blockade eliminated the benefit (Chung et al., 2025). These anti-inflammatory effects may also be mediated by inhibition of Toll-Like Receptor 4 (TLR4) and NF-κB signaling, central pathways in innate immune activation and chronic inflammation [17]. It is important to note that these effects vary between in vitro, in vivo, and human studies, reflecting the complexity in translating findings across systems. These findings position psychedelics as potent regulators of immune-brain communication, with the potential to protect against stress-induced inflammation and fear-based disorders.

Such anti-inflammatory properties may significantly contribute to the emerging view of psychedelics as agents of preventative medicine. Chronic low-grade inflammation underlies numerous conditions, including Alzheimer's disease, where neuroinflammation accelerates neurodegeneration, and depression, which is frequently associated with elevated markers like C-reactive protein (CRP). In one clinical study, a single high dose of psilocybin lowered circulating CRP levels weeks later, even in healthy participants [53], suggesting persistent anti-inflammatory effects. Similarly, ayahuasca has been shown to transiently increase cortisol, which suppresses pro-inflammatory markers (IL-1β, TNF-α, and IL-6) and shift cytokine

profiles in a direction linked to improvements in mood and depressive symptoms [39]. However, these effects may be context- and individual-dependent. In healthy subjects, ayahuasca can also produce a brief increase in immune activity, suggesting that its immunomodulatory effects may operate via adaptive, bidirectional regulation rather than simple suppression of inflammation [54]. This underscores the importance of baseline physiology, dosage, and therapeutic context in shaping the immune outcomes of psychedelic use. Taken together, these data suggest that classical psychedelics function as adaptive immunomodulators, tending toward an anti-inflammatory bias, especially in states of prior immune dysregulation [17]. By reducing systemic and neuroinflammation, psychedelics may not only slow biological aging but also enhance brain health, mood stability, and cognitive resilience. Immunomodulatory outcomes appear to be dose-dependent, and standardization of psychedelic dosing remains a challenge for clinical translation [17]. While initial findings are promising, the lack of large-scale, placebo-controlled human trials limits definitive conclusions about the systemic immunomodulatory effects of psychedelics. In this light, their therapeutic value may extend well beyond symptom relief, potentially supporting health at a fundamental, systemic level.

While several studies report reductions in pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β following psychedelic administration, the evidence is not uniformly consistent. For example, transient increases in cytokines have been observed in some healthy-subject contexts and in certain in vitro models, suggesting acute immune activation rather than suppression. Moreover, outcomes vary substantially by compound (psilocybin vs. ayahuasca vs. LSD), by dose, and by the baseline physiological state of the organism (stressed vs. healthy) [17]. This heterogeneity underscores the need to avoid framing psychedelics as straightforward "immune balancers." Instead, they appear to exert *context- and state-dependent immunomodulation* that may trend anti-inflammatory in dysregulated systems but can provoke short-term immune activation under baseline conditions.

To capture this complexity, **Table 1** summarizes representative findings across models, highlighting both decreases and increases in cytokine expression, stratified by compound, dose, and experimental context. Such mixed outcomes highlight both the promise and the limitations of current evidence, and they point to the need for standardized dosing, longitudinal follow-up, and head-to-head comparisons across compounds.

Mitochondrial Function and Cellular Longevity

Mitochondrial dysfunction is a recognized hallmark of aging and a key contributor to both psychiatric and neurodegenerative disorders [25]. Emerging research suggests that classical serotonergic psychedelics, particularly 5-HT_2A receptor agonists such as psilocybin, LSD, and DMT, may exert multi-faceted benefits on mitochondrial function, oxidative resilience, and cellular health [15,16], positioning them as promising tools in the pursuit of an extended health span.

A comprehensive review by Fissler et al. (2023) outlines the ability of psychedelics to promote mitochondrial biogenesis, enhance ATP production, and improve intracellular mitochondrial transport, particularly in conditions of metabolic stress or neuroinflammation. Preclinical studies show that 5-HT_2A agonists like DOI and psilocybin derivatives increase mitochondrial DNA (mtDNA) copy number, a marker of new mitochondrial formation [15]. In vitro, DOI enhanced ATP output by 45% in rabbit kidney cells, while neuroimaging in humans revealed that psilocybin boosts brain glucose metabolism within 90

minutes of administration, indicating acute upregulation of cerebral energy supply [55]. These mitochondrial enhancements appear to be mediated by the SIRT1–PGC-1α signaling pathway, a master regulator of mitochondrial function, energy homeostasis, and longevity [56]. Activation of this axis by psychedelics has been demonstrated in rodent cortical neurons and mirrors the mechanisms engaged by well-established anti-aging interventions such as exercise and caloric restriction [15,56].

Furthermore, psychedelics have been shown to alter mitochondrial morphology by promoting elongation, branching, and increased volume in cortical neurons, hallmarks of healthier, fusion-prone mitochondria that resist stress and delay senescence [15]. Beyond energy production, classical psychedelics appear to reduce mitochondrial reactive oxygen species (ROS) and enhance antioxidant enzyme expression (e.g., SOD2, GPx), thereby improving cellular redox balance and resilience to oxidative stress [15,57]. Additionally, early evidence suggests psychedelics may stimulate autophagic pathways, including mitophagy, the selective recycling of damaged mitochondria, a critical process for maintaining cellular health and preventing metabolic decline [15].

Psychedelics may also play a role in regulating markers of biological aging. Germann (2020) proposed the "psilocybin–telomere hypothesis," suggesting that the sustained psychological benefits of psychedelics, especially stress reduction and increased emotional resilience, may contribute to telomere preservation. Chronic stress, depression, and oxidative damage accelerate telomere shortening, while positive affective states are associated with telomere maintenance and longer replicative lifespan [58]. Recent experimental data support this hypothesis. In a 2025 preclinical study by Kato et al., aged mice receiving monthly low doses of psilocybin for 10 months exhibited a 30% increase in survival compared to controls, along with reduced oxidative stress, improved fur and hair regrowth, and preserved telomere length. In parallel, human fibroblasts exposed to psilocin, the active metabolite of psilocybin, showed a >50% increase in replicative lifespan and enhanced DNA repair enzyme activity (XRCC1, PARP), suggesting a genomic-stabilizing effect that may extend to human aging [16]. Furthermore, psychedelic-induced changes in gene expression and epigenetic remodeling, particularly upregulation of neuroplasticity-related genes like BDNF and NEGR1, mirror those observed in meditation and other mind-body interventions known to slow epigenetic clocks [40,59]. This reinforces the hypothesis that psychedelics may not only alter states of consciousness but also shift cellular aging trajectories through epigenomic mechanisms. Taken together, this growing body of evidence frames psychedelics as potential geroprotective agents that act on fundamental biological processes, including mitochondrial dynamics, oxidative stress, DNA repair, and telomere maintenance. Future human trials should incorporate validated aging biomarkers such as mtDNA copy number, ROS levels, telomere length, and DNA methylation-based epigenetic clocks to directly test whether psychedelics can slow or reverse cellular aging [60,61]. If confirmed, classical psychedelics could be categorized as a novel class of senotherapeutics, interventions aimed at rejuvenating cellular function and extending healthspan.

Based on the physiological mechanisms outlined above, it is plausible that the mental health benefits of psychedelics could stem in part from their effects on the body itself. Enhancing mitochondrial function, reducing inflammation, promoting neuroplasticity, and extending cellular lifespan are all processes known to improve mental health. In this sense, psychedelics may help heal the body in order to heal the mind. However, evidence from brain imaging and psychological research suggests a deeper synergy, where

biological and psychological transformations interact, amplifying one another for more profound and lasting outcomes.

Wellbeing and Psychological Transformations

Psychedelics have shown compelling efficacy in the treatment of various mental health disorders, including PTSD, depression, anxiety, obsessive-compulsive disorder, and addiction. Remarkably, clinical trials report sustained improvements after just one or two sessions, with benefits lasting from several months to even years in some cases [7,8,20,62,63]. These outcomes are accompanied by a low risk of addiction or serious adverse effects, although larger and longer-term studies are still needed to confirm safety and durability. While the precise mechanisms underlying these effects remain under investigation, several prevailing theories point to the role of neuroplasticity, inflammation modulation, and emotional processing as key drivers. Notably, the downstream biological effects seen with psychedelics, such as enhanced BDNF expression, synaptic remodeling, and stress regulation, mirror mechanisms previously linked to improved mental health outcomes even outside of psychedelic use [31,35,37,64,65]. Together, this convergence of neurobiological and psychological effects highlights why psychedelics represent a promising therapeutic class worthy of continued investigation.

The REBUS (Relaxed Beliefs Under Psychedelics) theory, proposed by Carhart-Harris and Friston (2019), posits that psychedelics promote cognitive flexibility and preserve mental function by increasing neural entropy, essentially disrupting overly rigid predictive processing in the brain. This hypothesis is supported by neuroimaging data showing increased global functional connectivity within several brain regions, including the default mode network (DMN), salience network, central executive network, thalamus, visual cortex, am ygdala, hippocampus, parahippocampal gyrus, brainstem, raphe nuclei, cerebellum, auditory cortex, and claustrum, which are typically segregated networks [66–69]. Such reorganization facilitates a loosening of entrenched cognitive patterns, such as depressive rumination, habitual thought loops, or age-related reductions in learning adaptability [67,70]. When paired with intentional integration, the deliberate, structured process of making meaning and applying insights from the psychedelic experience, these altered states may foster lasting, adaptive cognitive and behavioral shifts. Interestingly, the neurophysiological state induced by psychedelics, characterized by heightened plasticity and cross-network communication, has been likened to the brain activity of infants, based on similarities in EEG studies [71]. This supports the broader hypothesis that psychedelics can return the brain to a more youthful, open state of learning and perception. Subjective reports echo this idea: many psychedelic users describe their experiences as seeing the world "with new eyes," often accompanied by awe, curiosity, and a childlike sense of wonder [72]. These experiential shifts may underlie the well-documented psychological benefits seen in both clinical and non-clinical populations [21,73]. Moreover, psychedelics have been associated with durable personality changes. Notably, users demonstrate sustained increases in openness, up to one standard deviation above baseline [74], as well as reductions in neuroticism and increases in agreeableness and social connectedness [75]. These personality shifts align with broader improvements in well-being and may play a central role in the long-term therapeutic effects of psychedelic interventions. While psychedelic experiences can catalyze profound psychological shifts, it is the intentional integration of these insights, through lifestyle change, reflective practices, and environmental restructuring, that determines whether the effects endure. Integration is not

an optional afterthought; it is the behavioral bridge through which temporary neuroplasticity becomes sustained transformation.

The Entropic Brain Hypothesis, proposed by Carhart-Harris (2018), suggests that psychedelics increase neural entropy, a measure of signal diversity and unpredictability in brain activity. This heightened entropy disrupts rigid patterns of connectivity, especially within the DMN, allowing for greater cognitive flexibility and the potential for therapeutic change. Increased entropy has been correlated with enhanced psychological outcomes, including reductions in depression, anxiety, and addictive behaviors [77,78]. This concept can be meaningfully compared to principles in exercise physiology, where physiological adaptation is driven by overload and novelty. The overload principle states that for a muscle or system to grow stronger, it must be challenged with a stimulus beyond its current capacity. Likewise, novel stimuli induce biological change by disrupting homeostasis and forcing adaptive recalibration [79]. Psychedelics appear to operate under a similar model: they act as a neurocognitive overload and a novel stimulus that temporarily destabilizes habitual brain states, requiring the system to reorganize. This disruption promotes neuroplasticity, allowing for the unlearning of maladaptive patterns and the formation of healthier psychological frameworks [18,80]. This hypothesis is further supported by animal models of voluntary vs. forced stress exposure. For instance, when rats are allowed to voluntarily engage in exercise, they exhibit positive neurobiological adaptations such as increased BDNF and reduced HPA axis activation. In contrast, forced exercise leads to stress-like responses and diminished neuroplastic gains [81]. Translating this to human experience, trauma can be conceptualized as an imposed stressor that strips agency, reinforcing rigid neural and psychological maladaptive patterns. Psychedelics, on the other hand, represent a chosen stressor, an act of agency, that opens the brain to flexibility, emotional processing, and reorganization.

While the pharmacological action of psychedelics plays a pivotal role in facilitating psychological transformation, the long-term benefits are deeply influenced by the context in which these experiences unfold. The concepts of *set* (an individual's mindset, expectations, and psychological preparation), *setting* (the physical and social environment), and *integration* (the process of making meaning from the experience and incorporating it into daily life) are essential to ensuring positive, enduring change. Research consistently shows that supportive environments and intentional preparation increase the likelihood of transformative insights, emotional breakthroughs, and lasting improvements in well-being [82–84]. Conversely, unsupportive or unstructured contexts may yield confusing or even distressing outcomes, emphasizing the need for skilled guides and structured follow-up [85]. Integration, in particular, serves as the bridge between transient states of insight and durable psychological growth, allowing individuals to reframe core beliefs, shift behavior patterns, and sustain changes in personality and mood [50,86]. Reframing integration as a *core mechanism* rather than an afterthought may be critical in leveraging psychedelics not just as treatments, but as tools for preventive medicine and systemic health optimization. As such, the therapeutic potential of psychedelics is not pharmacological alone; it is relational, contextual, and deeply experiential.

Taken together, the transformative psychological effects of psychedelics, when guided by proper set, setting, and integration, suggest not merely symptom relief but a deeper restoration of emotional and cognitive vitality. By disrupting rigid mental frameworks, facilitating emotional release, and enhancing openness, these experiences mirror qualities of youthful psychological flexibility and curiosity. The fact that psychedelics can

induce enduring shifts in personality trai ts, emotional resilience, and connectedness reinforces their potential as tools not only for healing but for psychological renewal. When combined with their demonstrated impact on neuroplasticity, inflammation, mitochondrial health, and even cellular aging markers, the convergence of data supports a bold but increasingly plausible hypothesis: psychedelics may function as agents of systemic rejuvenation. In this way, they offer more than a treatment; they may open a gateway to mental and biological youthfulness.

Caution and Context – Limitations and Risks

While this manuscript proposes a compelling framework for the rejuvenating potential of psychedelics, it is essential to balance optimism with caution. Psychedelics are powerful tools that interact with sensitive neural systems, and their outcomes are not universally beneficial. Adverse psychological reactions, including anxiety, psychosis, or emotional destabilization, can occur, particularly in individuals with underlying psychiatric vulnerabilities or without adequate preparation and support [84,87].

Moreover, the notion of psychedelics as "preventive medicine" does not imply guaranteed rejuvenation. The therapeutic and physiological benefits discussed in this paper appear to depend heavily on factors such as dose, compound, frequency, individual neurobiology, and, crucially, the psychosocial context, including set, setting, and integration. Without these safeguards, the plasticity-enhancing effects may lead to maladaptive rather than restorative changes.

Additionally, overuse or high-frequency use may pose physiological risks not yet fully characterized. There is a pressing need for long-term, diverse-population studies to better understand both the durability of benefits and the potential for unintended harm.

Evidence linking psychedelics to preventive medicine is **indirect**. Nearly all longevity and anti-inflammatory findings derive from animal models or acute human studies. Translating to long-term healthspan requires caution. Furthermore, risks in non-clinical populations, such as psychosis vulnerability, HPPD, or cardiovascular responses, are poorly studied. Frequency ceilings and integration methods must be established before preventive application is considered viable. As the field evolves, clinicians, researchers, and participants must tread with both scientific curiosity and ethical responsibility, ensuring that psychedelic medicine develops as a safe, equitable, and evidence-based practice.

Conclusion

Psychedelics are rapidly shifting from stigmatized substances to promising tools for mental health and systemic rejuvenation. This paper has proposed the Psychedelic Rejuvenation Hypothesis, for consideration that classical psychedelics may operate not only as treatments but also as preventive agents that preserve cognitive, emotional, and cellular vitality (Table 2).

Key contributions of psychedelics to preventive medicine include:

- **Neuroplasticity:** Reopening critical periods, enhancing cognitive flexibility, and supporting long-term resilience.
- **Immune modulation:** Reducing chronic inflammation and restoring immune balance in stress or disease states.
- **Mitochondrial health:** Stimulating mitochondrial biogenesis, energy metabolism, and oxidative stress resistance.
- **Cellular aging:** Preserving telomere length, enhancing DNA repair, and potentially slowing epigenetic aging.
- **Psychological transformation:** Disrupting rigid patterns of thought, increasing

openness, and fostering lasting personality shifts.
- **Integration as a catalyst:** Transforming transient states into durable lifestyle and behavioral change.

Future directions:

- Longitudinal studies tracking biomarkers of cellular aging (telomere length, mitochondrial DNA, epigenetic clocks).
- Research in non-clinical and aging populations to test preventive rather than reactive applications.
- Integration protocols that combine psychedelics with exercise, nutrition, sleep, and mindfulness to extend benefits.
- Comparative trials with established interventions (e.g., exercise, meditation) to define psychedelics' unique role.

If validated, psychedelics may emerge as a new class of senotherapeutics, agents that not only heal but also preserve and extend healthspan. To reach that potential, research must prioritize safety, ethics, and structured integration, ensuring these powerful compounds are developed as tools of *preventive medicine* rather than crisis intervention.

AUTHOR INFORMATION

Tony Montgomery Ph.D.
(tony.montgomery@okstate.edu)

Montgomery, T (2025, September). Psilocybin-Assisted Therapy for Obsessive-Compulsive Disorder: A Review. *The Journal of Psychedelic Psychiatry*, *7*(2).

REFERENCES:

1. Abramson, B., Boerma, J., & Tsyvinski, A. (2024). *Macroeconomics of Mental Health* (w32354; p. w32354). National Bureau of Economic Research. https://doi.org/10.3386/w32354
2. Buttorff, C., Ruder, T., & Bauman, M. (2017). *Multiple Chronic Conditions in the United States*. https://www.rand.org/pubs/tools/TL221.html
3. Dattani, S., Rodés-Guirao, L., Ritchie, H., Ortiz-Ospina, E., & Roser, M. (2023). Life Expectancy. *Our World in Data*. https://ourworldindata.org/life-expectancy
4. Levine, S. (2019). Health Care Industry Insights: Why the Use of Preventive Services Is Still Low. *Preventing Chronic Disease*, *16*. https://doi.org/10.5888/pcd16.180625
5. AbdulRaheem, Y. (2023). Unveiling the Significance and Challenges of Integrating Prevention Levels in Healthcare Practice. *Journal of Primary Care & Community Health*, *14*, 21501319231186500. https://doi.org/10.1177/21501319231186500
6. Barber, G. S., & Aaronson, S. T. (2022). The Emerging Field of Psychedelic Psychotherapy. *Current Psychiatry Reports*, *24*(10), 583–590. https://doi.org/10.1007/s11920-022-01363-y
7. Luoma, J. B., Chwyl, C., Bathje, G. J., Davis, A. K., & Lancelotta, R. (2020). A Meta-Analysis of Placebo-Controlled Trials of Psychedelic-Assisted Ther: 14 *Journal of Psychoactive Drugs*, *52*(4), 289–299. https://doi.org/10.1080/02791072.2020.1769878
8. Romeo, B., Kervadec, E., Fauvel, B., Strika-Bruneau, L., Amirouche, A., Verroust, V., Piolino, P., & Benyamina, A. (2024). Safety and risk assessment of psychedelic psychotherapy: A meta-analysis and systematic review. *Psychiatry Research*, *335*, 115880. https://doi.org/10.1016/j.psychres.2024.115880

9. Behera, H. K., Joga, R., Yerram, S., Karnati, P., Mergu, T., Gandhi, K., M, S., Nathiya, D., Singh, R. P., Srivastava, S., & Kumar, S. (2024). Exploring the regulatory framework of psychedelics in the US & Europe. *Asian Journal of Psychiatry*, *102*, 104242. https://doi.org/10.1016/j.ajp.2024.104242
10. Kalisch, R., Russo, S. J., & Müller, M. B. (2024). Neurobiology and systems biology of stress resilience. *Physiological Reviews*, *104*(3), 1205–1263. https://doi.org/10.1152/physrev.00042.2023
11. Maletic, V., Robinson, M., Oakes, T., Iyengar, S., Ball, S. G., & Russell, J. (2007). Neurobiology of depression: An integrated view of key findings. *International Journal of Clinical Practice*, *61*(12), 2030–2040. https://doi.org/10.1111/j.1742-1241.2007.01602.x
12. Morozova, A., Zorkina, Y., Abramova, O., Pavlova, O., Pavlov, K., Soloveva, K., Volkova, M., Alekseeva, P., Andryshchenko, A., Kostyuk, G., Gurina, O., & Chekhonin, V. (2022). Neurobiological Highlights of Cognitive Impairment in Psychiatric Disorders. *International Journal of Molecular Sciences*, *23*(3), 1217. https://doi.org/10.3390/ijms23031217
13. Pedersen, B. K. (2019). Physical activity and muscle–brain crosstalk. *Nature Reviews Endocrinology*, *15*(7), 383–392. https://doi.org/10.1038/s41574-019-0174-x
14. Chung, E. N., Lee, J., Polonio, C. M., Choi, J., Akl, C. F., Kilian, M., Weiß, W. M., Gunner, G., Ye, M., Heo, T. H., Drake, S. S., Yang, L., d'Eca, C. R. G. L., Lee, J.-H., Deng, L., Farrenkopf, D., Schüle, A. M., Lee, H.-G., Afolabi, O., … Wheeler, M. A. (2025). Psychedelic control of neuroimmune interactions governing fear. *Nature*, *641*(8065), 1276–1286. https://doi.org/10.1038/s41586-025-08880-9
15. Fissler, P., Vandersmissen, A., Filippi, M., Mavioglu, R. N., Scholkmann, F., Karabatsiakis, A., & Krähenmann, R. (2023). Effects of serotonergic psychedelics on mitochondria: Transdiagnostic implications for mitochondria-related pathologies. *Journal of Psychopharmacology*, *37*(7), 679–686. https://doi.org/10.1177/02698811231164707
16. Kato, K., Kleinhenz, J. M., Shin, Y.-J., Coarfa, C., Zarrabi, A. J., & Hecker, L. (2025). Psilocybin treatment extends cellular lifespan and improves survival of aged mice. *Npj Aging*, *11*(1), 55. https://doi.org/10.1038/s41514-025-00244-x
17. Low, Z. X. B., Ng, W. S., Lim, E. S. Y., Goh, B. H., & Kumari, Y. (2025). The immunomodulatory effects of classical psychedelics: A systematic review of preclinical studies. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *136*, 111139. https://doi.org/10.1016/j.pnpbp.2024.111139
18. Ly, C., Greb, A. C., Cameron, L. P., Wong, J. M., Barragan, E. V., Wilson, P. C., Burbach, K. F., Zarandi, S. S., Sood, A., Paddy, M. R., Duim, W. C., Dennis, M. Y., McAllister, A. K., Ori-McKenney, K. M., Gray, J. A., & Olson, D. E. (2018). Psychedelics Promote Structural and Functional Neural Plasticity. *Cell Reports*, *23*(11), 3170–3182. https://doi.org/10.1016/j.celrep.2018.05.022
19. Shao, L.-X., Liao, C., Gregg, I., Davoudian, P. A., Savalia, N. K., Delagarza, K., & Kwan, A. C. (2021). Psilocybin induces rapid and persistent growth of dendritic spines in frontal cortex

in vivo. *Neuron*, *109*(16), 2535-2544.e4. https://doi.org/10.1016/j.neuron.2021.06.008

20. Ko, K., Knight, G., Rucker, J. J., & Cleare, A. J. (2022). Psychedelics, Mystical Experience, and Therapeutic Efficacy: A Systematic Review. *Frontiers in Psychiatry*, *13*, 917199. https://doi.org/10.3389/fpsyt.2022.917199
21. Mosurinjohn, S., Roseman, L., & Girn, M. (2023). Psychedelic-induced mystical experiences: An interdisciplinary discussion and critique. *Frontiers in Psychiatry*, *14*, 1077311. https://doi.org/10.3389/fpsyt.2023.1077311
22. Monroy, M., & Keltner, D. (2022). Awe as a Pathway to Mental and Physical Health. *Perspectives on Psychological Science*, *18*(2), 309. https://doi.org/10.1177/17456916221094856
23. Van Lente, E., & Hogan, M. J. (2020). Understanding the Nature of Oneness Experience in Meditators Using Collective Intelligence Methods. *Frontiers in Psychology*, *11*, 2092. https://doi.org/10.3389/fpsyg.2020.02092
24. Carhart-Harris, R. L., & Friston, K. J. (2019). REBUS and the Anarchic Brain: Toward a Unified Model of the Brain Action of Psychedelics. *Pharmacological Reviews*, *71*(3), 316–344. https://doi.org/10.1124/pr.118.017160
25. Mattson, M. P., & Arumugam, T. V. (2018). Hallmarks of Brain Aging: Adaptive and Pathological Modification by Metabolic States. *Cell Metabolism*, *27*(6), 1176–1199. https://doi.org/10.1016/j.cmet.2018.05.011
26. Petanjek, Z., Judaš, M., Šimic, G., Rasin, M. R., Uylings, H. B. M., Rakic, P., & Kostovic, I. (2011). Extraordinary neoteny of synaptic spines in the human prefrontal cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(32), 13281–13286. https://doi.org/10.1073/pnas.1105108108
27. Salthouse, T. A. (2009). When does age-related cognitive decline begin? *Neurobiology of Aging*, *30*(4), 507–514. https://doi.org/10.1016/j.neurobiolaging.2008.09.023
28. Sorrells, S. F., Paredes, M. F., Cebrian-Silla, A., Sandoval, K., Qi, D., Kelley, K. W., James, D., Mayer, S., Chang, J., Auguste, K. I., Chang, E. F., Gutierrez, A. J., Kriegstein, A. R., Mathern, G. W., Oldham, M. C., Huang, E. J., Garcia-Verdugo, J. M., Yang, Z., & Alvarez-Buylla, A. (2018). Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults. *Nature*, *555*(7696), 377–381. https://doi.org/10.1038/nature25975
29. Ziegenhorn, A. A., Schulte-Herbrüggen, O., Danker-Hopfe, H., Malbranc, M., Hartung, H.-D., Anders, D., Lang, U. E., Steinhagen-Thiessen, E., Schaub, R. T., & Hellweg, R. (2007). Serum neurotrophins—A study on the time course and influencing factors in a large old age sample. *Neurobiology of Aging*, *28*(9), 1436–1445. https://doi.org/10.1016/j.neurobiolaging.2006.06.011
30. Fjell, A. M., & Walhovd, K. B. (2010). Structural brain changes in aging: Courses, causes and cognitive consequences. *Reviews in the Neurosciences*, *21*(3), 187–221. https://doi.org/10.1515/revneuro.2010.21.3.187
31. Erickson, K. I., Miller, D. L., & Roecklein, K. A. (2012). The Aging Hippocampus: Interactions between Exercise, Depression, and BDNF. *The Neuroscientist*, *18*(1), 82–97.

https://doi.org/10.1177/10738584103970 54

32. Firth, J., Solmi, M., Wootton, R. E., Vancampfort, D., Schuch, F. B., Hoare, E., Gilbody, S., Torous, J., Teasdale, S. B., Jackson, S. E., Smith, L., Eaton, M., Jacka, F. N., Veronese, N., Marx, W., Ashdown-Franks, G., Siskind, D., Sarris, J., Rosenbaum, S., … Stubbs, B. (2020). A meta-review of "lifestyle psychiatry": The role of exercise, smoking, diet and sleep in the prevention and treatment of mental disorders. *World Psychiatry: Official Journal of the World Psychiatric Association (WPA)*, *19*(3), 360–380. https://doi.org/10.1002/wps.20773
33. Halberstadt, A. L. (2015). Recent advances in the neuropsychopharmacology of serotonergic hallucinogens. *Behavioural Brain Research*, *277*, 99–120. https://doi.org/10.1016/j.bbr.2014.07.01 6
34. Jack, C. R., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., Holtzman, D. M., Jagust, W., Jessen, F., Karlawish, J., Liu, E., Molinuevo, J. L., Montine, T., Phelps, C., Rankin, K. P., Rowe, C. C., Scheltens, P., Siemers, E., Snyder, H. M., … Contributors. (2018). NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *14*(4), 535–562. https://doi.org/10.1016/j.jalz.2018.02.01 8
35. Daniels, T. E., Olsen, E. M., & Tyrka, A. R. (2020). Stress and Psychiatric Disorders: The Role of Mitochondria. *Annual Review of Clinical Psychology*, *16*(Volume 16, 2020), 165–186. https://doi.org/10.1146/annurev-clinpsy-082719-104030
36. Karin, O., Raz, M., Tendler, A., Bar, A., Korem Kohanim, Y., Milo, T., & Alon, U. (2020). A new model for the HPA axis explains dysregulation of stress hormones on the timescale of weeks. *Molecular Systems Biology*, *16*(7), e9510. https://doi.org/10.15252/msb.20209510
37. Duman, R. S., & Li, N. (2012). A neurotrophic hypothesis of depression: Role of synaptogenesis in the actions of NMDA receptor antagonists. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *367*(1601), 2475–2484. https://doi.org/10.1098/rstb.2011.0357
38. Morales-Garcia, J. A., Calleja-Conde, J., Lopez-Moreno, J. A., Alonso-Gil, S., Sanz-SanCristobal, M., Riba, J., & Perez-Castillo, A. (2020). N,N-dimethyltryptamine compound found in the hallucinogenic tea ayahuasca, regulates adult neurogenesis in vitro and in vivo. *Translational Psychiatry*, *10*(1), 331. https://doi.org/10.1038/s41398-020-01011-0
39. de Almeida, R. N., Galvão, A. C. de M., da Silva, F. S., Silva, E. A. D. S., Palhano-Fontes, F., Maia-de-Oliveira, J. P., de Araújo, L.-S. B., Lobão-Soares, B., & Galvão-Coelho, N. L. (2019). Modulation of Serum Brain-Derived Neurotrophic Factor by a Single Dose of Ayahuasca: Observation From a Randomized Controlled Trial. *Frontiers in Psychology*, *10*, 1234. https://doi.org/10.3389/fpsyg.2019.0123 4
40. Calder, A. E., & Hasler, G. (2023). Towards an understanding of psychedelic-induced neuroplasticity. *Neuropsychopharmacology*, *48*(1), 104–112. https://doi.org/10.1038/s41386-022-01389-z
41. Ruffell, S. G. D., Crosland-Wood, M., Palmer, R., Netzband, N., Tsang, W., Weiss, B., Gandy, S., Cowley-Court, T., Halman, A., McHerron, D., Jong, A., Kennedy, T., White, E., Perkins, D., Terhune, D. B., & Sarris, J. (2023).

Ayahuasca: A review of historical, pharmacological, and therapeutic aspects. *PCN Reports: Psychiatry and Clinical Neurosciences*, *2*(4), e146. https://doi.org/10.1002/pcn5.146

42. Moliner, R., Girych, M., Brunello, C. A., Kovaleva, V., Biojone, C., Enkavi, G., Antenucci, L., Kot, E. F., Goncharuk, S. A., Kaurinkoski, K., Kuutti, M., Fred, S. M., Elsilä, L. V., Sakson, S., Cannarozzo, C., Diniz, C. R. A. F., Seiffert, N., Rubiolo, A., Haapaniemi, H., … Castrén, E. (2023). Psychedelics promote plasticity by directly binding to BDNF receptor TrkB. *Nature Neuroscience*, *26*(6), 1032–1041. https://doi.org/10.1038/s41593-023-01316-5
43. Lissemore, J. I., Chaiken, A., Cherian, K. N., Buchanan, D., Espil, F., Keynan, J. N., Sridhar, M., Rolle, C. E., Saggar, M., Keller, C. J., & Williams, N. R. (2025). Magnesium–ibogaine therapy effects on cortical oscillations and neural complexity in veterans with traumatic brain injury. *Nature Mental Health*, *3*(8), 918–931. https://doi.org/10.1038/s44220-025-00463-x
44. Cherian, K. N., Faerman, A., Anker, L. A., Brown, R. E., Keynan, O., TJ, Ford, Keller, J., & Williams, N. R. (2023). 22 The Effect of Ibogaine on Cognitive Functioning. *Journal of the International Neuropsychological Society*, *29*(s1), 898–899. https://doi.org/10.1017/S1355617723011049
45. Cherian, K. N., Keynan, J. N., Anker, L., Faerman, A., Brown, R. E., Shamma, A., Keynan, O., Coetzee, J. P., Batail, J.-M., Phillips, A., Bassano, N. J., Sahlem, G. L., Inzunza, J., Millar, T., Dickinson, J., Rolle, C. E., Keller, J., Adamson, M., Kratter, I. H., & Williams, N. R. (2024). Magnesium–ibogaine therapy in veterans with traumatic brain injuries. *Nature Medicine*, *30*(2), 373–381. https://doi.org/10.1038/s41591-023-02705-w
46. Michele, B. M. M., & Sophie, A. A. (2023). A review of the mechanisms involved in the neuroprotection and neurotoxicity of Iboga alkaloids. *Pharmacological Research - Natural Products*, *1*, 100006. https://doi.org/10.1016/j.prenap.2023.100006
47. Nardou, R., Sawyer, E., Song, Y. J., Wilkinson, M., Padovan-Hernandez, Y., De Deus, J. L., Wright, N., Lama, C., Faltin, S., Goff, L. A., Stein-O'Brien, G. L., & Dölen, G. (2023). Psychedelics reopen the social reward learning critical period. *Nature*, *618*(7966), 790–798. https://doi.org/10.1038/s41586-023-06204-3
48. Pilecki, B., Luoma, J. B., Bathje, G. J., Rhea, J., & Narloch, V. F. (2021). Ethical and legal issues in psychedelic harm reduction and integration therapy. *Harm Reduction Journal*, *18*(1), 40. https://doi.org/10.1186/s12954-021-00489-1
49. Tadmor, N., Halperin, D., & Simon, G. (2025). Integration of personal psychedelic experiences into clinical practice: A phenomenological study in mental health professionals. *Journal of Psychedelic Studies*, *9*(2), 136–148. https://doi.org/10.1556/2054.2024.00372
50. Gorman, I., Nielson, E. M., Molinar, A., Cassidy, K., & Sabbagh, J. (2021). Psychedelic Harm Reduction and Integration: A Transtheoretical Model for Clinical Practice. *Frontiers in Psychology*, *12*, 645246. https://doi.org/10.3389/fpsyg.2021.645246
51. Thomas, K., Malcolm, B., & Lastra, D. (2017). Psilocybin-Assisted Therapy: A Review of a Novel Treatment for Psychiatric Disorders. *Journal of Psychoactive Drugs*, *49*(5), 446–455.

https://doi.org/10.1080/02791072.2017.1320734

52. Baechle, J. J., Chen, N., Makhijani, P., Winer, S., Furman, D., & Winer, D. A. (2023). Chronic inflammation and the hallmarks of aging. *Molecular Metabolism*, *74*, 101755. https://doi.org/10.1016/j.molmet.2023.101755
53. Mason, N. L., Szabo, A., Kuypers, K. P. C., Mallaroni, P. A., de la Torre Fornell, R., Reckweg, J. T., Tse, D. H. Y., Hutten, N. R. P. W., Feilding, A., & Ramaekers, J. G. (2023). Psilocybin induces acute and persisting alterations in immune status in healthy volunteers: An experimental, placebo-controlled study. *Brain, Behavior, and Immunity*, *114*, 299–310. https://doi.org/10.1016/j.bbi.2023.09.004
54. Dos Santos, R. G., Rocha, J. M., Rossi, G. N., Osório, F. L., Ona, G., Bouso, J. C., Silveira, G. D. O., Yonamine, M., Marchioni, C., Crevelin, E. J., Queiroz, M. E., Crippa, J. A., & Hallak, J. E. C. (2022). Effects of ayahuasca on the endocannabinoid system of healthy volunteers and in volunteers with social anxiety disorder: Results from two pilot, proof-of-concept, randomized, placebo-controlled trials. *Human Psychopharmacology: Clinical and Experimental*, *37*(4), e2834. https://doi.org/10.1002/hup.2834
55. Vollenweider, F. X., Leenders, K. L., Scharfetter, C., Maguire, P., Stadelmann, O., & Angst, J. (1997). Positron emission tomography and fluorodeoxyglucose studies of metabolic hyperfrontality and psychopathology in the psilocybin model of psychosis. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *16*(5), 357–372. https://doi.org/10.1016/S0893-133X(96)00246-1
56. Fanibunda, S. E., Deb, S., Maniyadath, B., Tiwari, P., Ghai, U., Gupta, S., Figueiredo, D., Weisstaub, N., Gingrich, J. A., Vaidya, A. D. B., Kolthur-Seetharam, U., & Vaidya, V. A. (2019). Serotonin regulates mitochondrial biogenesis and function in rodent cortical neurons via the 5-HT2A receptor and SIRT1-PGC-1α axis. *Proceedings of the National Academy of Sciences of the United States of America*, *116*(22), 11028–11037. https://doi.org/10.1073/pnas.1821332116
57. da Silva Joaquim, L., da Rosa, L. R., Strickert, Y., Machado, R. S., Lanzzarin, E., Bernardes, G., de Souza Ramos, S., de Novais, L. R., Steiner, B., Farias, B., Mathias, K., Martins, H. M., Lins, E. M. F., Chaves, J. S., Camilo, D., da Silva, L. E., de Oliveira, M. P., da Silva, M. R., Barcelos, P. M. P., … de Bitencourt, R. M. (2025). Ayahuasca reverses ischemic stroke-induced neuroinflammation and oxidative stress. *Behavioural Brain Research*, *485*, 115521. https://doi.org/10.1016/j.bbr.2025.115521
58. Germann, C. B. (2020). The Psilocybin-Telomere Hypothesis: An empirically falsifiable prediction concerning the beneficial neuropsychopharmacological effects of psilocybin on genetic aging. *Medical Hypotheses*, *134*, 109406. https://doi.org/10.1016/j.mehy.2019.109406
59. Revenga, M. de la F., Zhu, B., Guevara, C. A., Naler, L. B., Saunders, J. M., Zhou, Z., Toneatti, R., Sierra, S., Wolstenholme, J. T., Beardsley, P. M., Huntley, G. W., Lu, C., & González-Maeso, J. (2021). Prolonged epigenomic and synaptic plasticity alterations following single exposure to a psychedelic in mice. *Cell Reports*, *37*(3).

https://doi.org/10.1016/j.celrep.2021.109836

60. Horvath, S. (2013). DNA methylation age of human tissues and cell types. *Genome Biology*, *14*(10), R115. https://doi.org/10.1186/gb-2013-14-10-r115
61. Lu, A. T., Quach, A., Wilson, J. G., Reiner, A. P., Aviv, A., Raj, K., Hou, L., Baccarelli, A. A., Li, Y., Stewart, J. D., Whitsel, E. A., Assimes, T. L., Ferrucci, L., & Horvath, S. (2019). DNA methylation GrimAge strongly predicts lifespan and healthspan. *Aging*, *11*(2), 303–327. https://doi.org/10.18632/aging.101684
62. Kim, S., Yang, S., Jung, J., Choi, J., Kang, M., & Joo, J. (2025). Psychedelic Drugs in Mental Disorders: Current Clinical Scope and Deep Learning-Based Advanced Perspectives. *Advanced Science*, *12*(15), 2413786. https://doi.org/10.1002/advs.202413786
63. McIntyre, R. S., Kwan, A. T. H., Mansur, R. B., Oliveira-Maia, A. J., Teopiz, K. M., Maletic, V., Suppes, T., Stahl, S. M., & Rosenblat, J. D. (2025). Psychedelics for the Treatment of Psychiatric Disorders: Interpreting and Translating Available Evidence and Guidance for Future Research. *American Journal of Psychiatry*, *182*(1), 21–32. https://doi.org/10.1176/appi.ajp.20230902
64. Cotman, C. W., Berchtold, N. C., & Christie, L.-A. (2007). Exercise builds brain health: Key roles of growth factor cascades and inflammation. *Trends in Neurosciences*, *30*(9), 464–472. https://doi.org/10.1016/j.tins.2007.06.011
65. Mahar, I., Bambico, F. R., Mechawar, N., & Nobrega, J. N. (2014). Stress, serotonin, and hippocampal neurogenesis in relation to depression and antidepressant effects. *Neuroscience & Biobehavioral Reviews*, *38*, 173–192. https://doi.org/10.1016/j.neubiorev.2013.11.009
66. Bedford, P., Hauke, D. J., Wang, Z., Roth, V., Nagy-Huber, M., Holze, F., Ley, L., Vizeli, P., Liechti, M. E., Borgwardt, S., Müller, F., & Diaconescu, A. O. (2023). The effect of lysergic acid diethylamide (LSD) on whole-brain functional and effective connectivity. *Neuropsychopharmacology*, *48*(8), 1175–1183. https://doi.org/10.1038/s41386-023-01574-8
67. Carhart-Harris, R. L., Erritzoe, D., Williams, T., Stone, J. M., Reed, L. J., Colasanti, A., Tyacke, R. J., Leech, R., Malizia, A. L., Murphy, K., Hobden, P., Evans, J., Feilding, A., Wise, R. G., & Nutt, D. J. (2012). Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. *Proceedings of the National Academy of Sciences*, *109*(6), 2138–2143. https://doi.org/10.1073/pnas.1119598109
68. E, T., L, R., M, K., C, O., Sd, M., K, M., H, L., R, L., J, M., N, C., E, B., T, W., M, B., A, F., Dj, N., & R, C.-H. (2016). Increased Global Functional Connectivity Correlates with LSD-Induced Ego Dissolution. *Current Biology : CB*, *26*(8). https://doi.org/10.1016/j.cub.2016.02.010
69. Timmermann, C., Roseman, L., Haridas, S., Rosas, F. E., Luan, L., Kettner, H., Martell, J., Erritzoe, D., Tagliazucchi, E., Pallavicini, C., Girn, M., Alamia, A., Leech, R., Nutt, D. J., & Carhart-Harris, R. L. (2023). Human brain effects of DMT assessed via EEG-fMRI. *Proceedings of the National Academy of Sciences*, *120*(13). https://doi.org/10.1073/pnas.2218949120
70. Av, L., M, L., G, R., A, F., Dj, N., & Rl, C.-H. (2015). Finding the self by losing the self: Neural correlates of ego-

dissolution under psilocybin. *Human Brain Mapping*, *36*(8). https://doi.org/10.1002/hbm.22833

71. Nayak, C. S., & Anilkumar, A. C. (2024). Neonatal EEG. In *StatPearls [Internet]*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK536953/
72. Hovmand, O. R., Poulsen, E. D., & Arnfred, S. (2024). Assessment of the acute subjective psychedelic experience: A review of patient-reported outcome measures in clinical research on classical psychedelics. *Journal of Psychopharmacology*, *38*(1), 19–32. https://doi.org/10.1177/02698811231200019
73. Velit-Salazar, M. R., Shiroma, P. R., & Cherian, E. (2024). A Systematic Review of the Neurocognitive Effects of Psychedelics in Healthy Populations: Implications for Depressive Disorders and Post-Traumatic Stress Disorder. *Brain Sciences*, *14*(3), 248. https://doi.org/10.3390/brainsci14030248
74. Sjöström, D. K., Claesdotter-Knutsson, E., & Kajonius, P. J. (2024). Personality traits explain the relationship between psychedelic use and less depression in a comparative study. *Scientific Reports*, *14*(1), 10195. https://doi.org/10.1038/s41598-024-60890-1
75. Weiss, B., Nygart, V., Pommerencke, L. M., Carhart-Harris, R. L., & Erritzoe, D. (2021). Examining Psychedelic-Induced Changes in Social Functioning and Connectedness in a Naturalistic Online Sample Using the Five-Factor Model of Personality. *Frontiers in Psychology*, *12*, 749788. https://doi.org/10.3389/fpsyg.2021.749788
76. Carhart-Harris, R. L. (2018). The entropic brain—Revisited. *Neuropharmacology*, *142*, 167–178. https://doi.org/10.1016/j.neuropharm.2018.03.010
77. Roy, A. V., Thai, M., Klimes-Dougan, B., Westlund Schreiner, M., Mueller, B. A., Albott, C. S., Lim, K. O., Fiecas, M., Tye, S. J., & Cullen, K. R. (2021). Brain entropy and neurotrophic molecular markers accompanying clinical improvement after ketamine: Preliminary evidence in adolescents with treatment-resistant depression. *Journal of Psychopharmacology (Oxford, England)*, *35*(2), 168–177. https://doi.org/10.1177/0269881120928203
78. Tagliazucchi, E., Carhart-Harris, R., Leech, R., Nutt, D., & Chialvo, D. R. (2014). Enhanced repertoire of brain dynamical states during the psychedelic experience. *Human Brain Mapping*, *35*(11), 5442–5456. https://doi.org/10.1002/hbm.22562
79. Kraemer, W. J., & Ratamess, N. A. (2004). Fundamentals of Resistance Training: Progression and Exercise Prescription: *Medicine & Science in Sports & Exercise*, *36*(4), 674–688. https://doi.org/10.1249/01.MSS.0000121945.36635.61
80. Doss, M. K., Madden, M. B., Gaddis, A., Nebel, M. B., Griffiths, R. R., Mathur, B. N., & Barrett, F. S. (2022). Models of psychedelic drug action: Modulation of cortical-subcortical circuits. *Brain: A Journal of Neurology*, *145*(2), 441–456. https://doi.org/10.1093/brain/awab406
81. Greenwood, B. N., Foley, T. E., Day, H. E. W., Campisi, J., Hammack, S. H., Campeau, S., Maier, S. F., & Fleshner, M. (2003). Freewheel running prevents learned helplessness/behavioral depression: Role of dorsal raphe serotonergic neurons. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *23*(7), 2889–2898.

https://doi.org/10.1523/JNEUROSCI.23-07-02889.2003
82. Carhart-Harris, R. L., Roseman, L., Haijen, E., Erritzoe, D., Watts, R., Branchi, I., & Kaelen, M. (2018). Psychedelics and the essential importance of context. *Journal of Psychopharmacology*, *32*(7), 725–731. https://doi.org/10.1177/0269881118754710
83. Hartogsohn, I. (2016). Set and setting, psychedelics and the placebo response: An extra-pharmacological perspective on psychopharmacology. *Journal of Psychopharmacology*, *30*(12), 1259–1267. https://doi.org/10.1177/0269881116677852
84. Johnson, M., Richards, W., & Griffiths, R. (2008). Human hallucinogen research: Guidelines for safety. *Journal of Psychopharmacology*, *22*(6), 603–620. https://doi.org/10.1177/0269881108093587
85. Sloshower, J., Guss, J., Krause, R., Wallace, R. M., Williams, M. T., Reed, S., & Skinta, M. D. (2020). Psilocybin-assisted therapy of major depressive disorder using Acceptance and Commitment Therapy as a therapeutic frame. *Journal of Contextual Behavioral Science*, *15*, 12–19. https://doi.org/10.1016/j.jcbs.2019.11.002
86. Watts, R., & Luoma, J. B. (2020). The use of the psychological flexibility model to support psychedelic assisted therapy. *Journal of Contextual Behavioral Science*, *15*, 92–102. https://doi.org/10.1016/j.jcbs.2019.12.004
87. Studerus, E., Kometer, M., Hasler, F., & Vollenweider, F. X. (2011). Acute, subacute and long-term subjective effects of psilocybin in healthy humans: A pooled analysis of experimental studies. *Journal of Psychopharmacology (Oxford, England)*, *25*(11), 1434–1452. https://doi.org/10.1177/0269881110382466

Tables:

Compound	Model / Context	Cytokine(s) Affected	Direction (↑/↓)	Time Course	Reference(s)
Psilocybin	Rodent stress models	IL-6, TNF-α, IL-1β	↓	24–72 hrs	Low et al., 2025
Psilocybin	Healthy human volunteers	CRP, IL-6	↓ (CRP) but transient ↑ IL-6	Acute to 2 wks	Mason et al., 2023
Ayahuasca	Clinical depression patients	IL-1β, TNF-α, IL-6	↓	24–48 hrs	de Almeida et al., 2019
Ayahuasca	Healthy human volunteers	IL-1β, TNF-α, IL-6	Transient ↑ then ↓	Acute (hours)	Dos Santos et al., 2022
LSD	In vitro PBMC (human cells)	IL-6, IL-10	Mixed (↑ IL-10, ↓ IL-6)	Hours	Low et al., 2025
MDMA	Rodent neuroimmune stress model	IL-1β, TNF-α	↓	24 hrs	Chung et al., 2023/2025
Mixed (5-HT2A agonists)	Microglia, macrophages (in vitro)	Pro-inflammatory gene expression	↓ (5-HT2A mediated)	Hours–days	Chung et al., 2025

Table 1. Mixed immunomodulatory effects of classical psychedelics across compounds, models, and contexts. Evidence demonstrates both pro- and anti-inflammatory responses depending on compound, dose, physiological state, and timing. Rather than acting as uniform "immune balancers," psychedelics appear to exert context-dependent effects that may trend anti-inflammatory in dysregulated systems but can provoke transient immune activation in healthy conditions.

Mechanism/Pathway	Primary Biomarkers	Matrix/Assay	Windows	Expected Δ (Clinical/Stressed)	Expected Δ (Healthy Baseline)	Confounders/Controls	Falsifiers	References
Neuroplasticity (global signal diversity)	EEG Lempel–Ziv complexity; rs-fMRI global connectivity	EEG; fMRI	Acute (2–12h), Subacute (24–72h)	↑ complexity/connectivity	↑ acute; returns toward baseline	Motion, caffeine/sleep, meds; pre-reg preprocessing	No Δ vs control; ↓ complexity	Carhart-Harris & Friston, 2019; Timmermann et al., 2023
Neurotrophins / Synaptogenesis	Plasma/serum BDNF; NTRK2 transcripts	ELISA/qPCR	Acute (6–24h), Subacute (48–72h)	↑ BDNF (transient)	Small/none; transient ↑ possible	Platelet release; diurnal timing; recent exercise	Sustained ↓ BDNF vs control	Fissler et al., 2023; Low et al., 2025
Inflammation (systemic)	CRP, IL-6, TNF-α	Serum; multiplex	Acute (6–24h), Early (1–2w), Medium (1–3m)	↓ CRP/IL-6/TNF-α by 1–2w	Transient ↑ IL-6 acute, none by 1–2w	Infection, BMI, menstrual phase	↑ CRP/IL-6/TNF-α at 1–2w	Mason et al., 2023; Chung et al., 2023; de Almeida et al., 2019
Neuroimmune axis (stress→meninges)	IL-1β; CD14++CD16+ monocytes; ex vivo LPS	Flow cytometry; cytokine release	Acute (6–24h), Early (1–2w)	↓ IL-1β; normalized subsets	Minimal change	Illness, vaccines, handling	↑ pro-inflammatory monocytes at 1–2w	Dos Santos et al., 2022; Chung et al., 2025
Mitochondrial function/biogenesis	PBMC mtDNA copy #; ATP; citrate synthase	qPCR; enzymatic	Early (2–4w), Medium (1–3m)	↑ mtDNAcn; ↑ ATP	Small ↑/none	Infection; leukocyte shifts	↓ mtDNAcn vs control	Kato et al., 2025; Low et al., 2025
Oxidative stress/redox	F2-isoprostanes; GSH:GSSG	LC-MS/MS; enzymatic	Early (1–2w), Medium (1–3m)	↓ F2-iso; ↑ GSH:GSSG	Minimal change	Diet; exercise bouts	↑ oxidative stress at 1–3m	Low et al., 2025; Fissler et al., 2023
DNA/telomere stability & repair	Leukocyte TL; PARP/XRCC1 activity	qPCR; activity	Long (6–12m)	Preservation; ↑ repair	Preservation/no change	Leukocyte mix; batch	Accelerated shortening vs control	Fissler et al., 2023; Kato et al., 2025
Epigenetic aging	DNAm GrimAge, PhenoAge, DunedinPACE	DNAm arrays	Medium (3m), Long (6–12m)	↓ GrimAge/PhenoAge; ↓ DunedinPACE	Small slowing	Smoking; cell deconvolution	No Δ vs control; acceleration	Low et al., 2025; Horvath, 2013
HPA axis regulation	CAR; diurnal cortisol slope	Salivary cortisol	Early (1–2w), Medium (1–3m)	Normalized CAR/slope	No material change	Wake time; shift work	More flattened slope	Mason et al., 2023; Carhart-Harris & Friston, 2019
Personality/behavior	NEO Openness; WHO-5; PA/sleep (wearables)	Surveys; actigraphy	Medium (1–3m), Long (6–12m)	↑ openness/well-being; ↑ adherence	Small ↑ openness; adherence	Demand bias; seasonality	No behavioral Δ	MacLean et al., 2011; Mason et al., 2023
Critical period proxies	Auditory MMN; perceptual learning rate	EEG ERP; psychophysics	Acute (24–72h), Early (1–2w)	↑ MMN; ↑ learning	Smaller ↑	Practice effects	No Δ vs control	Keesey et al., 2024; Carhart-Harris, 2018
Safety signals	BP/HR; C-SSRS; YMRS; BPRS; HPPD screen	Vitals; clinical scales	Acute → Long	Within safe bounds	Within safe bounds	Anxiety; co-ingestants	AEs exceed thresholds	Strassman et al., 1994; Johnson et al., 2008

Table 2. Mechanisms proposed for preventive psychedelic effects mapped onto measurable biomarkers, assays, temporal windows, expected outcomes, and falsifiers. References illustrate representative evidence (animal, clinical, or translational). The table highlights both opportunities and limitations, aiming to render the framework actionable and falsifiable in future trials

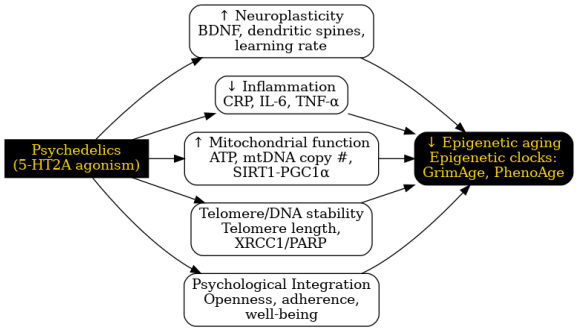

Figure 1. Conceptual framework linking psychedelic mechanisms to measurable biomarkers and potential preventive outcomes. Psychedelics acting via 5-HT2A agonism may enhance neuroplasticity, reduce inflammation, support mitochondrial function, and stabilize DNA/telomeres, while psychological integration reinforces behavior change. Collectively, these pathways are hypothesized to slow biological aging trajectories (e.g., GrimAge, PhenoAge epigenetic clocks). The model highlights candidate biomarkers and mechanistic targets for testing preventive applications in future trials.