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COMMENT

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The combination of exercise and psychedelics for the treatment of major depressive disorder

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Abstract

Upwards of 50% of people do not respond to the primary treatment modalities for major depressive disorder (MDD), which has led to increased attention and use of alternative methods, including exercise and psychedelics. While interventions using either exercise or psychedelics have demonstrated largely positive results in isolation, their synergistic potential has yet to be explored. As such, this commentary provides an overview of exercise/psychedelics as a treatment for depression and their potential synergy and/or complementarity. From a biological perspective, psychedelics acutely enhance brain-derived neurotrophic factor (BDNF) signalling, while exercise provides sustained BDNF elevation; psychedelics enhance neuroplasticity largely in the cortex (with only modest effects in the hippocampus), while exercise boosts hippocampal neurogenesis; psychedelics increase glutamate release via stimulation of 5-HT_{2A} receptors on pyramidal neurons, while exercise enhances glutamatergic transmission via the endocannabinoid system and reduction of systemic inflammation; both boost serotonin release; and psychedelics temporarily disrupt functional connectivity between the hippocampus and default mode network (DMN), while exercise normalizes this connectivity, which may sustain post-psychedelic gains. Through the lens of psychological and behaviour change, psychedelics appear to facilitate the adoption or maintenance of physical activity habits, increase psychological flexibility, and since exercise is associated with emotional resilience to acute stress, this may allow users to experience deeper immersion and exploration during their psychedelic experience, improving antidepressant outcomes. In summary, exercise and psychedelics have numerous potential complementary mechanisms, therefore, future research is warranted to explore the efficacy, tolerability, safety, and neurobiology of this combination.

Keywords Physical activity, Exercise, Psychedelic, Psilocybin, Major depressive disorder, Depression

1 Background

Major depressive disorder (MDD) affects approximately 290 million people globally and is associated with significant morbidity and mortality [1, 2]. Traditionally, the primary treatment modalities for depression include antidepressants and therapy. While effective

in some instances, up to 50% of people do not respond to these treatments [2]. As such, there has been increased attention on the use of alternative methods, including exercise and psychedelics, for the treatment of depression. While exercise and psychedelic interventions have demonstrated largely positive results in isolation, their synergistic potential has yet to be explored. We believe this combination has potential and set out the evidence and gaps in this opinion piece.

2 Exercise as a treatment for depression

Physical activity is any movement that uses energy, while exercise is a planned, structured form of physical activity aimed at improving fitness [3]. Being physically active, even at levels below the public health recommendations, has a significant protective effect against depression [4]. For those with depression, exercise has proven to be an effective treatment, with similar efficacy to first-line measures such as medications or therapy, and a Number Needed to Treat of 2 [5–7]. As such, it has been adopted as a first-line treatment in guidelines for depression globally [8–10]. Beyond treatment of depressive symptoms, exercise has also demonstrated improved neuroplasticity, the potential to decrease suicide attempts and improve overall health [11–16].

3 Psychedelics as a treatment for depression

Psychedelics are a class of psychoactive drugs that induce changes in perception, mood, and cognitive processes. One of the most widely studied psychedelics, psilocybin, is a psychoactive tryptamine alkaloid found in the *Psilocybe* genus species of mushrooms. The use of psilocybin for the treatment of mental disorders dates back to the 1950s; however, the sociopolitical environment of the 1970s resulted in the classification of psilocybin and other psychedelics as schedule I substances, halting research [17]. There has been a recent resurgence of interest in the use of psychedelics to treat several mental disorders, including depression [17]. Typically, a supportive psychotherapy regime is combined with classic psychedelics (most commonly psilocybin), in a process known as psychedelic-assisted psychotherapy. Meta-analyses have demonstrated medium effect size as measured by clinician rating scales in the treatment of major depressive disorder, with trials finding similar efficacy to antidepressant medications, however effects which persist after the drug is no longer present [18–20]. Beyond antidepressant effects, psychedelics have demonstrated increased neuroplasticity and potential for the reduction of suicidal ideation in those with depression [21].

4 The potential synergy between exercise and psychedelics

While psychedelics and exercise are both emerging treatments in isolation, their combined effects have yet to be fully explored. These treatment modalities are both well-tolerated and generally positively received by participants highlighting their combination at a practical level. Beyond this, they have numerous overlapping biological, psychological and behavioural mechanisms which may lead to synergistic effects and antidepressant outcomes.

4.1 Biological mechanisms

Exercise and psychedelics share many overlapping mechanisms, which may be relevant to their potential synergistic effect. First, the neurotrophic hypothesis of depression

posits that depression stems from a deficit in brain-derived neurotrophic factor (BDNF) and impaired neuronal plasticity, leading to neuronal damage, atrophy, and inflammation [22]. Exercise has been demonstrated to increase levels of BDNF, particularly within the hippocampus and prefrontal cortex [23]. The tropomyosin receptor kinase (TrkB) receptor is the primary receptor for BDNF. Psychedelics directly bind to TrkB and enhance BDNF signaling, independent of serotonin 2 A receptor (5-HT_{2A}) activation [24]. The binding occurs at the transmembrane domain of the receptor, facilitating downstream mammalian target of rapamycin (mTOR) activates, which drives rapid spinogenesis and synaptogenesis [24]. While psychedelics induce these changes within hours (lasting days to weeks), exercise provides sustained BDNF elevation through repeated sessions over time [23, 24]. As such, exercise may be capable of supplying more BDNF to mediate the enhanced receptor sensitivity from psychedelics, maximizing downstream effects. This raises the question of whether exercise may act as a moderator or mediator of the neuroplastic effects induced by psychedelics, whereby exercise may shape, amplify or sustain psychedelic-induced neuroplasticity. Second, psychedelics stimulate 5-HT_{2A} receptors on pyramidal neurons, releasing glutamate and increasing α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor activity, which strengthens long-term potentiation (a persistent strengthening of synapses between neurons due to activation, which is a key process for learning and memory). Similarly, exercise is capable of enhancing glutamatergic transmission and long-term potentiation through the endocannabinoid system and reduction of systemic inflammation [25, 26]. Third, exercise boosts serotonin release and 5-HT_{2A} receptor sensitivity, whereas psychedelics primarily act via these 5-HT_{2A} receptors, which have potential for rapid and sustained mood elevation. Fourth, from a structural perspective, psychedelics primarily affect cortical regions with high 5-HT_{2A} density [27]. Several studies have investigated the ability of psychedelics to enhance neuroplasticity, and those that focused on the hippocampus found modest effects compared to the cortex [27]. Here, exercise, which has been shown to boost hippocampal neurogenesis, increase the size of the hippocampus, and improve memory, could lead to broader brain-wide neuroplasticity when paired with psychedelics [28]. Fourth, increased functional connectivity between the hippocampus and default mode network (DMN) is associated with depressive symptoms, and decreased connectivity is associated with a reduction in depression [29, 30]. Interestingly, while psychedelics seem to temporarily desynchronize and decrease this connectivity, exercise often enhances this connectivity [31, 32]. While at surface-level, this may seem to counteract one another, the temporary disruption induced by psychedelics may be beneficial to disrupt rigid, maladaptive patterns while exercise may be capable of normalizing this connectivity thereafter, sustaining post-psychedelic gains. Fifth, both exercise and psychedelics enhance dopaminergic signalling, which can contribute to reward, motivation and mood. Specifically, acute exercise increases dopamine release in the striatum and nucleus accumbens (NAc), while chronic physical activity upregulates dopamine D2 receptors [33, 34]. Although psychedelics have minimal direct dopamine affinity, they are able to indirectly boost dopamine via 5-HT_{2A} receptor activation which modulates ventral tegmental area (VTA) firing to increase dopamine levels in the prefrontal cortex (PFC) and NAc [35]. Lastly, as the endogenous opioid system is implicated in emotional pain and social bonding, it is a biological target of interest for exercise and psychedelics in MDD [36]. While exercise activates mu-opioid receptors via beta-endorphin release,

psychedelics can either indirectly (psilocybin modulating opioid release via 5-HT_{2A} activation) or directly (ibogaine functioning as an agonist of kappa-opioid receptors) engage the opioid system, resulting in potential synergistic effects [37, 38].

4.2 Psychological and behavioral mechanisms

Promoting exercise behaviors is a major obstacle in health promotion. Interestingly, some studies suggest that the use of psychedelics may be related to the adoption or maintenance of physical activity habits. Foundational work in this area has demonstrated long-term changes in behaviour and motivation following high-dose psilocybin, including a willingness to engage in daily meditation and support groups, and an increased openness to new experiences [39, 40]. In the treatment of MDD, psilocybin has demonstrated not only the aforementioned antidepressant effects, but direct increases in openness, which may lead to patients engaging in beneficial exercise and new healthy habits [41]. In two studies where participants reported that psychedelics helped them reduce their use of alcohol or of other psychoactive substances (e.g. opiods, cannabis), a substantial number of participants also reported increases in physical activity [42, 43]. Ayahuasca users are also typically more physically active than non-users [44, 45], and in at least one study looking at "major life changes" associated with ayahuasca use, one quarter of participants cited more physical exercise as one of those changes [46]. Additionally, in one of the trials looking into psilocybin therapy for depression, qualitative data indicated that up to half of the sample reported "improvements to diet, exercise, and cutting down on drinking alcohol" [47]. Another source of evidence, albeit indirect, to support an association between psychedelic use and health-enhancing behaviors is studies showing lower rates of chronic diseases like heart disease, obesity, and diabetes in individuals with lifetime psychedelic use, compared to non-users [48, 49]. Perhaps as a result of the findings reported here, behavioral aspects of psychedelics and their relevance to public health are now the object of more direct inquiry [50, 51].

While no study has directly investigated potential underlying mechanisms for the observations presented before, several psychological factors stand out as likely candidates. Relaxed prior beliefs and increased psychological flexibility are likely to favor changes in previously entrenched behaviors, such as dietary patterns and sedentary lifestyles. For example, psychological flexibility is a central feature of Acceptance and Commitment Therapy, which is not only popular in psychedelic-assisted therapies [52] but has been used successfully in many lifestyle change interventions [53]. Self-determination theory is another useful framework to explain how psychedelic experiences may influence health behavior change, including physical activity. This theory emphasises the role of internal ("intrinsic") forms of motivation through increases in perceived autonomy, competence and relatedness (or connectedness), factors which psychedelics may potentially affect (see [54]). Interestingly, these same factors have been associated with improved mental health and well-being [55]. In addition, as highlighted above, the fact that both psychedelics and exercise improve mental health indicates that using them in combination may be complementary or even have synergistic effects. For instance, low energy and anhedonia are major barriers to exercise in depression, which could be attenuated by the rapid mood-enhancing effects of psychedelics [3]. Also, both psychedelics and exercise often include interpersonal dimensions (e.g., group exercise, integration groups) which could be mutually reinforcing and actively explored in future

interventions. On the other hand, psychedelics with mindfulness exercise interventions or nature-based light exercise have demonstrated amplification of motivation, and decreases in rumination and negative affect [56, 57].

5 Effect of exercise on pharmacokinetics and pharmacodynamics

When discussing any pharmacotherapy in the context of exercise, it is important to consider how physical activity influences both pharmacokinetics and pharmacodynamics, including absorption, distribution, metabolism, and excretion, and psychedelics are no exception [58]. Exercise induces a predictable pattern of physiological adaptations, including reductions in splanchnic, renal, and hepatic blood flow, enhanced perfusion of skeletal muscle and cutaneous tissues, increased pulmonary ventilation and alveolar gas exchange, and augmented cardiac output [58, 59]. These changes can substantially alter drug disposition. While oral absorption appears to be only modestly affected, absorption from intramuscular, subcutaneous, and transdermal sites is consistently accelerated, with potential clinical consequences for agents with narrow therapeutic indices [58]. Redistribution of blood flow during exercise also increases drug binding and sequestration within active skeletal muscle, while reducing distribution to adipose and inactive tissues, thereby altering the effective volume of distribution [58]. Metabolically, exercise reduces clearance of high-extraction drugs due to diminished hepatic perfusion, while exerting little effect on capacity-limited pathways [58]. Similarly, reductions in renal plasma flow and urine output during physical exertion elevate plasma levels of renally excreted agents [59]. With respect to psychedelics, which are typically administered orally, intranasally, or parenterally, these changes could influence both time to onset and peak plasma concentrations. Beyond pharmacokinetics, exercise-induced adaptations in mitochondrial function, oxidative stress regulation, and neuroplasticity may also interact with the pharmacodynamics of psychedelics. For example, in rodent models, exercise mitigated MDMA-induced mitochondrial dysfunction, reducing oxidative stress and improving cognitive outcomes [60], while also modulating hyperthermia by influencing hypothalamic locomotor pathways [61]. Collectively, these findings highlight that exercise is not merely a contextual factor in psychedelic research but may actively modulate drug disposition and effect, with implications for both safety (e.g., thermoregulation, cardiovascular load) and therapeutic efficacy.

6 Conclusion

In summary, independently, exercise and psychedelic-assisted therapies have demonstrated efficacy comparable to standard first-line treatment options for depression; however, their combination has yet to be formally explored. Exercise and psychedelics have numerous potential complementary mechanisms, which may lead to synergistic antidepressant effects. Beyond this, the combination of exercise and psychedelics may benefit other difficult to treat and highly comorbid chronic ailments that intersect with MDD (e.g., fibromyalgia). Therefore, future research is warranted to explore the efficacy, tolerability, safety, and neurobiology of this combination.

Author contributions
Fabiano conceptualized the idea and wrote the original draft. Fabiano, Stubbs, Lawrence, Rosenblat, Teixeira, Wong, Zhou, and Carhart-Harris critically reviewed, contributed to the final version of this work, and approved it.

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Data availability
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Not applicable.

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