

Is there a place for psychedelics in sports practice?

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Perspective

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Abstract

Growing evidence suggests that psychedelic-assisted therapies can alleviate depression, anxiety, posttraumatic stress, and substance use disorder, offering relatively safe profiles, enhanced efficacy, and lasting effects after a few applications. Athletes often experience high levels of stress and pressure, making them susceptible to these psychiatric conditions. However, the effects of psychedelic substances on athletic performance remain largely unknown. Before potential acceptance, evaluating their impact on physical and physiological measures beyond mental health outcomes is crucial. Here, we aim to explore this topic and highlight research directions to advance our understanding. Preclinical studies suggest that psilocybin/psilocin, lysergic acid diethylamide (LSD), *N,N*-dimethyltryptamine (DMT), and ayahuasca possess anti-inflammatory and anti-nociceptive properties. Studies investigating the effects of classical psychedelics or 3,4-methylenedioxymethamphetamine (MDMA) on factors such as muscle strength, motor coordination, locomotion, endurance, fluid and electrolyte balance, hormonal regulation, and metabolism are still scarce. While adhering to regulatory frameworks, further research in animal models, athletes, and non-athletes is needed to address these gaps, compare psychedelics with commonly used psychoactive drugs, and explore the potential prophylactic and regenerative benefits of specific interventions.

Highlights

- Athletes frequently experience intense stress and pressure, increasing their vulnerability to mental health challenges such as depression, anxiety, and sports-related trauma.
- While psychedelics hold the potential for alleviating these issues, their impact on physical and physiological performance in athletes remains largely unexplored.
- This perspective explores the effects of psilocybin, LSD, DMT, and MDMA on mental and physical health, identifying key knowledge gaps and proposing future research directions using rodent models relevant to athletic populations.

Summations

- Psychedelic-assisted therapies are increasingly known for their potential to mitigate symptoms of various psychiatric conditions.
- Psychedelics may offer intriguing possibilities for enhancing resilience, aiding recovery, and treating sports-related trauma.
- As scientific understanding evolves, specific psychedelic substances could emerge as complementary tools in sports medicine.

Perspectives

- Research on the effects of psychedelics on physical performance and physiological parameters is still limited in rodents and humans.
- Permitting specific psychedelics in sports competitions will require a strong scientific foundation and a revision of anti-doping regulations.
- Establishing proper guidelines, dosages, and usage contexts will be crucial to ensure their responsible application.

Introduction

Psychedelics are currently defined as psychoactive substances that alter sensory perception, thought patterns, mood, and emotional experiences, affecting numerous cognitive processes

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(Nichols, 2016). They induce profound changes in consciousness, including visual and auditory hallucinations, an altered perception of time, and a heightened sense of interconnectedness – effects often attributed to serotonin (5-HT) transmission in the brain (Osmond, 1957; Wittmann et al., 2007; Nichols, 2016; Yanakieva et al., 2019; Vollenweider & Preller, 2020).

Psychedelic compounds can be classified according to their chemical structure or mechanism of action (Mitchell & Anderson, 2024). Serotonergic psychedelics fall into two main structural categories, characterised by modifications in the tryptamine or the phenethylamine group (Mendes et al., 2022). The first category includes psilocybin (psilocin is the active metabolite) found in certain mushrooms, *N,N*-dimethyltryptamine (DMT) present in ayahuasca¹, and 5-methoxy-*N,N*-DMT (5-MeO-DMT) derived from certain toad species. The second comprises mescaline, the primary psychoactive component of peyote cacti, and synthetic compounds such as (±)-2,5-dimethoxy-4-iodoamphetamine hydrochloride (DOI). Lysergic acid diethylamide (LSD) is an ergoline-derived compound.

Classical psychedelics (psilocybin, DMT, 5-MeO-DMT, mescaline, and LSD) act as partial or full agonists at 5-HT receptors, primarily 5-HT_{2A}, 5-HT_{1A}, and 5-HT_{2C} (Werle & Bertoglio, 2024). In contrast, compounds like DOI are relatively more selective agonists at 5-HT_{2A} receptors (Werle & Bertoglio, 2024). Some substances associated with psychedelics act through distinct mechanisms. For example, 3,4-methylenedioxymethamphetamine (MDMA) produces psychoactive effects primarily by releasing monoamines (5-HT, noradrenaline, and dopamine) and inhibiting their reuptake; ketamine is a glutamate N-methyl-D-aspartate (NMDA) receptor antagonist; and ibogaine (noribogaine is the active metabolite) interacts with multiple molecular targets, including 5-HT_{2A} receptors, NMDA receptors, and monoamine transporters (Johnson et al., 2019; Mendes et al., 2022).

Activating 5-HT_{2A} receptors, primarily those expressed in the apical dendrites of human layer V cortical pyramidal neurones, is essential for the perceptual effects of psychedelic experiences (Madsen et al., 2019). The canonical 5-HT_{2A} receptor signalling pathway involves the activation of G_{αq/11}-proteins and subsequent activation of the enzyme phospholipase C, leading to hydrolysis of phosphatidylinositol-4,5-bisphosphate and the release of inositol triphosphate and diacylglycerol. 5-HT_{2A} receptors also interact with arrestins, recruiting intracellular signalling pathways dependent on these proteins (Kim et al., 2020; McClure-Begley & Roth, 2022; Wallach et al., 2023). The psychedelic potential of some phenethylamine analogues is associated with the efficacy of 5-HT_{2A}-Gq but not 5-HT_{2A}-β-arrestin-2 recruitment (Wallach et al., 2023).

Increasing evidence suggests that 5-HT_{2A} receptor agonism does not fully explain the pharmacological effects of psychedelics (Inserra et al., 2021; Mendes et al., 2022; Werle et al., 2024). Their action also involves the brain activation of other serotonergic and dopaminergic receptor subtypes (Werle & Bertoglio, 2024), tropomyosin receptor kinase B (TrkB) (Moliner et al., 2023; Shafiee et al., 2024), ionotropic glutamate receptor interactions (Heresco-Levy & Lerer, 2024), neurotransmitters release (White et al., 1996; Mason et al., 2020), increased expression of the brain-

derived neurotrophic factor (BDNF; He et al., 2005; de Almeida et al., 2019; Marton et al., 2019; Hutten et al., 2020b; Shafiee et al., 2024), and epigenetic changes (Inserra et al., 2024). How psychedelics influence the abovementioned targets/mechanisms is complex, with each substance exhibiting particular features (Ray, 2010; Cameron et al., 2023).

The ability to induce adaptive structural and functional changes in the brain is a common feature of psychedelics shown in both preclinical and clinical studies (Ly et al., 2018; Lukasiewicz et al., 2021; de Vos et al., 2021; Liao et al., 2025). These substances induce neuroplasticity in response to intrinsic or extrinsic stimuli, modifying the strength and efficacy of synaptic transmission (Calder & Hasler, 2023). The cascade of cellular and molecular events implicated includes transmembrane and cytosolic receptor activation (Preller et al., 2018; Moliner et al., 2023; Vargas et al., 2023), recruitment of secondary messengers and proteins (Olson, 2022), changes in the number or complexity of dendritic spines (Ly et al., 2018; Shao et al., 2021), generation of new neurones (Lima da Cruz et al., 2018; Morales-Garcia et al., 2020), among others. Moreover, psychedelics can induce varying effects on functional connectivity across brain networks, such as decreased connectivity within the default mode network associated with self-referential thoughts and the sense of ego (Carhart-Harris et al., 2012; Palhano-Fontes et al., 2015; Carhart-Harris, Muthukumaraswamy, et al., 2016; Preller et al., 2020; Daws et al., 2022; Siegel et al., 2024). These changes may shift rigid thought patterns into more integrated and flexible thinking, potentially leading individuals to new insights and perspectives on life experiences. The altered states of consciousness induced by psychedelics may also affect emotional processing and facilitate coping with difficult emotions or traumatic experiences, leading to improved mental health outcomes and even therapeutic benefits (Kraehenmann et al., 2015; Barrett et al., 2020; Mertens et al., 2020; Arruda Sanchez et al., 2024; Stoliker et al., 2024; Melani et al., 2025).

Psychedelics were categorised as Schedule I substances under the Controlled Substances Act by the United States Drug Enforcement Administration in the 1970s, a decision mirrored by regulatory agencies in other countries. This classification significantly restricted academic and clinical research. However, over the past ten years, scientific and medical interest has been resurgent in exploring the pharmacological effects of these substances. As described in the following two sections, studies indicate that psychedelics have a relatively good safety profile, produce rapid benefits, and exert enduring effects after just a few doses (Riba et al., 2003; Palhano-Fontes et al., 2019; Mitchell et al., 2021; Gukasyan et al., 2022; Rhee et al., 2023; Dos Santos & Hallak, 2024; Hinkle et al., 2024). As a result, their therapeutic potential has been explored, presenting a promising approach for treating various psychiatric disorders, as detailed in Section 3 and Table 1. The subsequent sections will evaluate the potential applications of psychedelics for maintaining and improving mental wellness in athletes, their effects on physical and physiological parameters pertinent to athletic performance, and the relevant legal and regulatory frameworks.

On the safety of psychedelics

The acute toxicity of psychedelics is considered low. Reports of fatal overdoses associated with their use are rare (Haden & Woods, 2020; Darke et al., 2024; Thomas, 2024), with deaths primarily linked to relatively high doses (i.e. ≥ 20 times the typical dose) or the combination of psychedelics with other drugs or ethanol

¹It is a psychoactive brew from the Amazon, typically made from *Banisteriopsis caapi* and *Psychotria viridis*. The β-carbolines harmine, harmaline, and tetrahydroharmine present in *B. caapi* act as monoamine oxidase inhibitors, preventing the first-pass metabolism of DMT found in *P. viridis* and allowing it to become orally active. It is also worth noting that DMT is found in various other plants worldwide.

Table 1. Effects of single or repeated administration of psilocybin, LSD, ayahuasca, DMT, or MDMA on the mental health of individuals diagnosed with selected psychiatric disorders

Treatment		Participants			Study features					
Psychedelic substance	Dose, administration route, and posology	Number, age in years, sex	Ethnicity	Clinical condition	Design	Psychotherapeutic support	Effect on symptoms	Benefit duration	Report of severe adverse event(s)	Reference
Affective disorders (mainly depression)										
Psilocybin	10 and 25 mg (1 st and 2 nd session), oral, one week apart	12, 30–64, ♂♀	Mostly White or Caucasian (75%)	Moderate-to-severe MDD	Open-label	Yes	↓	At least 3 months post-treatment	No	Carhart-Harris <i>et al.</i> , 2016b
Psilocybin	1 or 3 mg/70 kg (1 st session) and 22 or 30 mg/70 kg (2 nd session), oral, 5 weeks apart	51, 56.3 ± 1.4 (mean ± SEM), ♂♀	Mostly White or Caucasian (94%)	Cancer-related anxiety and depression	R, D-B, cross-over	Yes	↓	At least 6 months post-treatment	No	Griffiths <i>et al.</i> , 2016
Psilocybin	0.3 mg/kg, oral, single administration	29, 56 ± 13 (mean ± SD), ♂♀	Mostly White or Caucasian (90%)	Cancer-related anxiety and depression	R, D-B, P-C, cross-over	Yes	↓	At least 6 months post-treatment	No	Ross <i>et al.</i> , 2016
Ayahuasca	120–200 ml (adjusted to contain 96–160 mg of DMT, and 25–42 mg of harmine), oral, single administration	17, 43 ± 12 (mean ± SD), ♂♀	n.d.	Moderate-to-severe TR-MDD	Open-label	n.d.	↓	At least 21 days post-treatment	No	Sanches <i>et al.</i> , 2016
Psilocybin	10 and 25 mg (1 st and 2 nd session), oral, 1 week apart	19, 42.8 (mean), ♂♀	n.d.	TR-MDD	Open-label	n.d.	↓	At least 5 weeks post-treatment	n.d.	Carhart-Harris <i>et al.</i> , 2017
Psilocybin	10 and 25 mg (1 st and 2 nd session), oral, one week apart	20, 44 ± 11 (mean ± SD), ♂♀	Mostly White or Caucasian (55%)	Severe MDD	Open-label	Yes	↓	At least 6 months post-treatment	No	Carhart-Harris <i>et al.</i> , 2018
Ayahuasca	1 ml/kg (adjusted to contain 0.36 mg/kg of DMT), oral, single administration	71, 42 ± 12 (mean ± SD), ♂♀	n.d.	TR-MDD	R, D-B, P-C	n.d.	n.d.	n.d.	n.d.	Galvão <i>et al.</i> , 2018
Psilocybin	10 and 25 mg (1 st and 2 nd session), oral, 1 week apart	20, 45 ± 11 (mean ± SD), ♂♀	n.d.	Moderate-to-severe TR-MDD	Open-label	Yes	↓	At least 3–5 weeks post-treatment	n.d.	Roseman <i>et al.</i> , 2018
Ayahuasca	1 ml/kg, oral, single administration	83, 42 ± 11 (mean ± SD), ♂♀	n.d.	TR-MDD	R, D-B, P-C	n.d.	n.d.	n.d.	n.d.	de Almeida <i>et al.</i> , 2019
Ayahuasca	1 ml/kg (adjusted to contain 0.36 mg/kg of DMT), oral, single administration	29, 40 ± 11 (mean ± SD), ♂♀	Mostly White or Caucasian (64%)	Moderate-to-severe TR-MDD	R, D-B, P-C	n.d.	↓	At least 7 days post-treatment	No	Palhano-Fontes <i>et al.</i> , 2019

(Continued)

Table 1. (Continued)

Treatment		Participants			Study features					
Psychedelic substance	Dose, administration route, and posology	Number, age in years, sex	Ethnicity	Clinical condition	Design	Psychotherapeutic support	Effect on symptoms	Benefit duration	Report of severe adverse event(s)	Reference
Psilocybin	10 and 25 mg (1 st and 2 nd session), oral, 1 week apart	19, 45 ± 11 (mean ± SD), ♂♀	n.d.	Moderate-to-severe TR-MDD	Open-label	Yes	↓	At least 5 weeks post-treatment	n.d.	Mertens et al., 2020
Psilocybin	25 mg, oral, two admin. (one every 3 weeks)	59, 43 ± 12 (mean ± SD), ♂♀	Mostly White or Caucasian (93%)	Moderate-to-severe MDD	R, D-B, controlled	Yes	↓	At least 6 weeks post-treatment	No	Carhart-Harris et al., 2021
Psilocybin	20 and 30 mg/70 kg (1 st and 2 nd session), oral, two admin. (1.6 weeks apart)	24, 40 ± 12 (mean ± SD), ♂♀	n.d.	Moderate-to-severe MDD	R	Yes	↓	At least 8 weeks post-treatment	No	Davis et al., 2021
Ayahuasca	2.2 ml/kg (adjusted to contain 0.8 mg/ml of DMT, 0.21 mg/ml of harmine, and no harmaline)	17, 43 ± 12 (mean ± SD), ♂♀	n.d.	TR-MDD	Open-label	No	↓	At least 21 days post-treatment	n.d.	Zeifman et al., 2021
DMT	0.1 or 0.3 mg/kg, i.v., two administrations (one every 48 h)	10, 24-59, ♂♀	Mostly White or Caucasian (70%)	TR-MDD	Open-label, fixed-order, dose-escalation	No	↓	At least 1 day post-treatment	Asymptomatic bradycardia and hypotension (n = 1)	D'Souza et al., 2022
Psilocybin	1, 10, or 25 mg, oral, single administration	233, 40 ± 12 (mean ± SD), ♂♀	Mostly White or Caucasian (92.3%)	TR-MDD	R, D-B, parallel-group	Yes	↔ (1 and 10 mg) ↓ (25 mg)	At least 3 weeks post-treatment	Suicidal behaviour (n = 3), codeine withdrawal syndrome (n = 1), and adjustment disorder with anxiety and depressed mood (n = 1)	Goodwin et al., 2022
Psilocybin	20 or 30 mg/70 kg, oral, two administrations (one every 2 weeks)	24, 40 ± 12 (mean ± SD), ♂♀	Mostly White or Caucasian (92%)	Moderate-to-severe MDD	R, waiting-list controlled study	Yes	↓	At least 12 months post-treatment	No	Gukasyan et al., 2022
Ayahuasca	50 ml (containing 3, 4, or 5 g of <i>Peganum harmala</i> , and 9, 15, or 16.67 g of <i>Mimosa hostilis</i>), oral, two administrations (one every 2.5 h)	20, 35 ± 10 (mean ± SD), ♂♀	n.d.	Chronic MDD (> 2 years)	Longitudinal observational study	n.d.	↓	At least 12 months post-treatment	n.d.	van Oorsouw et al., 2022

Table 1. (Continued)

Psilocybin	25 mg, oral, single administration	19, 42 ± 11 (mean ± SD), ♂♀	Mostly White or Caucasian (78.9%)	TR-MDD	Open-label	Yes	↓	At least 3 weeks post-treatment	No	Goodwin <i>et al.</i> , 2023
Psilocybin	0.3 mg/kg, oral, single administration	25, 43 ± 14 (mean ± SD), ♂♀	n.d.	TR-MDD	D-B, P-C, within-subject study	Yes	↓	At least 2 weeks post-treatment	n.d.	Skosnik <i>et al.</i> , 2023
Psilocybin	0.3 mg/kg, oral, single administration	19, 43 ± 14 (mean ± SD), ♂♀	Mostly White or Caucasian (84.2%)	TR-MDD	P-C, within-subject, fixed-order	Yes	↓	At least 2 months post-treatment	No	Sloshower <i>et al.</i> , 2023
Psilocybin	1 or 25 mg, oral, two administrations (one every 3 weeks)	59, 43 ± 10 (mean ± SD), ♂♀	Mostly White or Caucasian (93.3%)	MDD	R, D-B	Yes	↔ (1 mg) ↓ (25 mg)	At least 6 weeks post-treatment	n.d.	Zeifman <i>et al.</i> , 2023
Psilocybin	25 mg, oral, single administration	15, 38 ± 12 (mean ± SD), ♂♀	Mostly White or Caucasian (80%)	Bipolar disorder depression	Open-label	Yes	↓	At least 12 weeks post-treatment	No	Aaronson <i>et al.</i> , 2024
Psilocybin	1, 10, or 25 mg, oral, single administration	11, 45.5 (mean), ♂♀	n.d.	TR-MDD	R, D-B	Yes	n.d.	At least 12 weeks post-treatment	n.d.	Breeksema <i>et al.</i> , 2024
Psilocybin	1 or 25 mg, oral, two administrations (one every 3 weeks)	59, n.d., n.d.	n.d.	Moderate-to-severe MDD	R, D-B, two-arm, controlled trial	n.d.	↔ (1 mg) ↓ (25 mg)	At least 2 weeks post-treatment	n.d.	Peill <i>et al.</i> , 2024
Psilocybin	0.3 mg/kg, oral, single administration	15, 43 ± 14 (mean ± SD), ♂♀	Mostly White or Caucasian (84.2%)	Moderate-to-severe MDD	P-C, within-subject, fixed-order	Yes	↓	At least 16 months post-treatment	n.d.	Sloshower <i>et al.</i> , 2024
Posttraumatic stress disorder										
MDMA	125 mg, oral, two administrations (one per month)	20, 21–70, ♂♀	100% White or Caucasian	PTSD	R, D-B, P-C	Yes	↓	At least 2 months post-treatment	No	Mithoefer <i>et al.</i> , 2011
MDMA	125–187.5 mg, oral, two administrations (one per month)	19, n.d., n.d.	100% White or Caucasian	PTSD	Prospective long-term follow-up	Yes	↓	17–74 months post-treatment	n.d.	Mithoefer <i>et al.</i> , 2013
MDMA	37.5 or 187.5 mg, oral, three administrations (interval n.d.)	12, 41 ± 11 (mean ± SD), ♂♀	n.d.	PTSD	R, D-B, active-P-C	Yes	↔ (37.5 mg) ↓ (187.5 mg)	At least 12 months post-treatment	No	Oehen <i>et al.</i> , 2013
MDMA	30, 75, or 125 mg, oral, two administrations (one every 3–5 weeks)	26, 37 ± 10 (mean ± SD), ♂♀	Mostly White or Caucasian (85%)	PTSD	R, D-B	Yes	↔ (30 mg) ↓ (75 and 125 mg)	At least 12 weeks post-treatment	No	Mithoefer <i>et al.</i> , 2018

(Continued)

Table 1. (Continued)

Treatment		Participants			Study features					
Psychedelic substance	Dose, administration route, and posology	Number, age in years, sex	Ethnicity	Clinical condition	Design	Psychotherapeutic support	Effect on symptoms	Benefit duration	Report of severe adverse event(s)	Reference
MDMA	40, 100, or 125 mg, oral, two administrations (one per month)	28, 42 ± 13 (mean ± SD), ♂♀	n.d.	PTSD	R, D-B	Yes	↔ (40 mg) ↓ (100 or 125 mg)	At least 2 months post-treatment	No	Ot'alora et al., 2018
MDMA	75 to 125 mg, oral, 2 or 3 administrations (one every 3–5 weeks)	105, 40 ± 11 (mean ± SD), ♂♀	Mostly White or Caucasian (87.6%)	PTSD	R, D-B, P-C	Yes	↓	At least 1–2 months after two experimental sessions	No	Mithoefer et al., 2019
MDMA	75–187.5 mg, oral, two administrations (one every 3–5 weeks)	60, 41 ± 12 (mean ± SD), ♂♀	Mostly White or Caucasian (84.4%)	PTSD	R and two-blinded	Yes	↓	At least 1–2 months post-treatment	n.d.	Gorman et al., 2020
MDMA	75–125 mg, oral, 2 or 3 administrations (one every 2–3 weeks)	107, 40 ± 11 (mean ± SD), ♂♀	Mostly White or Caucasian (89.7%)	PTSD	Blinded study segment, open-label cross-over, long-term follow-up	Yes	↓	At least 12 months post-treatment	n.d.	Jerome et al., 2020
MDMA	125 mg, oral, two administrations (one every 2–4 weeks)	18, 55 ± 8 (mean ± SD), ♂♀	Mostly White or Caucasian (60%)	Psychiatric medical history diagnosis of anxiety, major depression, PTSD, or/and insomnia	R, D-B, P-C	Yes	↓	At least 12 months post-treatment	n.d.	Wolfson et al., 2020
MDMA	75–187.5 mg, oral, three administrations (one per month)	3, 40.3 (mean), 1 ♂ and 2 ♀	One Afro-Brazilian and two Caucasian	PTSD	Open-label	Yes	↓	At least 2 months post-treatment	n.d.	Jardim et al., 2021
MDMA	80–180 mg, oral, three administrations (one every 4 weeks)	90, 41 ± 12 (mean ± SD), ♂♀	Mostly White or Caucasian (76.7%)	Severe PTSD	R, D-B, P-C	Yes	↓	At least 18 weeks post-treatment	n.d.	Mitchell et al., 2021
MDMA	75–187.5 mg, oral, 2 or 3 administrations (one every 3–5 weeks)	63, 41 ± 11 (mean ± SD), ♂♀	Mostly White or Caucasian (85.7%)	PTSD	R, D-B, P-C	Yes	↓	At least 2 months post-treatment	n.d.	Ponte et al., 2021

Table 1. (Continued)

MDMA	80–240 mg, oral, three administrations (one every 4 weeks)	89, 41 ± 12 (mean ± SD), ♂♀	Mostly White or Caucasian (78.16%)	PTSD	R, D-B, P-C pivotal trial	Yes	↓	n.d.	n.d.	Brewerton <i>et al.</i> , 2022
MDMA	80–190 mg, oral, three administrations (interval n.d.)	127, 37.9 (mean), ♂♀	Mostly White or Caucasian (81.9%)	PTSD	Two Phase 2 open-label trials and a Phase 3 R, blinded P-C trial	n.d.	↓	n.d.	No	Ching <i>et al.</i> , 2022
MDMA	120–180 mg, oral, three administrations (one every 3–4 weeks)	82, 41 ± 12 (mean ± SD), ♂♀	Mostly White or Caucasian (80.25%)	PTSD plus SUD	R, three-blind, P-C	Yes	↓	At least 6 months post-treatment	n.d.	Nicholas <i>et al.</i> , 2022
MDMA	120–180 mg, oral, three administrations (one per month)	104, 38 ± 11 (mean ± SD), ♂♀	Mostly White or Caucasian (69.8%)	Moderate-to-severe PTSD	R, D-B, P-C	Yes	↓	At least 18 weeks post-treatment	No	Mitchell <i>et al.</i> , 2023
MDMA	30, 75, or 125 mg, oral, two administrations	9, 41 ± 11 (mean ± SD), ♂♀	Mostly White or Caucasian (89%)	PTSD	R, D-B	Yes	↓	At least 2 months post-treatment	n.d.	Singleton <i>et al.</i> , 2023
MDMA	120–180 mg, oral, three administrations (one every 4 weeks)	90, 41 ± 12 (mean ± SD), ♂♀	Mostly White or Caucasian (80.3%)	PTSD	R, D-B, P-C, multi-site	Yes	↓	At least 2 months post-treatment	n.d.	van der Kolk <i>et al.</i> , 2024
Anxiety disorders										
Psilocybin	0.2 mg/kg, oral, single administration	8, 36–58, ♂♀	n.d.	Advanced-stage cancer and anxiety	R, D-B, P-C	Yes	↓	At least 3–6 months post-treatment	No	Grob <i>et al.</i> , 2011
LSD	20 or 200 µg, oral, two administrations (one every 2–3 weeks)	11, 52 ± 9 (mean ± SD), ♂♀	n.d.	Anxiety associated with life-threatening diseases	R, D-B, active P-C	Yes	↓	At least 12 months post-treatment	No	Gasser <i>et al.</i> , 2014
LSD	20 or 200 µg, oral, two administrations (one every 4–6 weeks)	10, 51.1 (mean), ♂♀	n.d.	Anxiety associated with life-threatening	R, D-B, active P-C study followed by cross-over study	Yes	↓	At least 12 months post-treatment	No	Gasser <i>et al.</i> , 2015
Psilocybin	1 or 3 mg/70 kg (1 st session) and 22 or 30 mg/70 kg (2 nd session), oral, 5 weeks apart	51, 56 ± 1 (mean ± SEM), ♂♀	Mostly White or Caucasian (94%)	Cancer-related anxiety and depression	R, D-B, cross-over	Yes	↓	At least 6 months post-treatment	No	Griffiths <i>et al.</i> , 2016

(Continued)

Table 1. (Continued)

Treatment		Participants			Study features					
Psychedelic substance	Dose, administration route, and posology	Number, age in years, sex	Ethnicity	Clinical condition	Design	Psychotherapeutic support	Effect on symptoms	Benefit duration	Report of severe adverse event(s)	Reference
Psilocybin	0.3 mg/kg, oral, single administration	29, 56 ± 13 (mean ± SD), ♂♀	Mostly White or Caucasian (90%)	Cancer-related anxiety and depression	R, D-B, P-C, cross-over	Yes	↓	At least 6 months post-treatment	No	Ross <i>et al.</i> , 2016
MDMA	15, 100, or 125 mg, oral, two admin. (one per month)	12, 31 ± 9 (mean ± SD), ♂♀	Mostly White or Caucasian (50%)	Autism with social anxiety	R, D-B, P-C	Yes	↔ (15 mg) ↓ (100 or 125 mg)	At least 6 months post-treatment	No	Danforth <i>et al.</i> , 2018
Ayahuasca	2 ml/kg, oral, single administration	17, 25 (mean) years, ♂♀	n.d.	SAD	R, D-B, P-C, parallel-group	No	↓	n.d.	n.d.	dos Santos <i>et al.</i> , 2021
LSD	200 µg, oral, two admin. (one every 6 weeks)	42, 45 ± 12 (mean ± SD), ♂♀	n.d.	Anxiety with and without a life-threatening illness	R, D-B, P-C, cross-over	Yes	↓	At least 16 weeks post-treatment	Acute transient anxiety (2%)	Holze <i>et al.</i> , 2023
Eating disorders										
Psilocybin	25 mg, oral, single administration	10, 28 ± 4 (mean ± SD), ♀	Mostly White or Caucasian (90%)	Anorexia nervosa	Open-label	Yes	↓	At least 3 months post-treatment	No	Peck <i>et al.</i> , 2023
Psilocybin	25 mg, oral, single administration	12, 34 ± 9 (mean ± SD), ♂♀	Mostly White or Caucasian (75%)	Moderate-to-severe non-delusional body dysmorphic disorder unresponsive to serotonin reuptake inhibitor(s)	Open-label	Yes	↓	At least 12 weeks post-treatment	No	Schneier <i>et al.</i> , 2023
Substance use disorders										
Psilocybin	20 or 30 mg/70 kg, oral, two administrations (one every 2 weeks)	15, 51 ± 10 (mean ± SD), ♂♀	Mostly White or Caucasian (93%)	Nicotine-dependent smokers	Open-label	Yes	↓	n.d.	No	Johnson <i>et al.</i> , 2014
Psilocybin	0.3 or 0.4 mg/kg, oral, two administrations (one every 8 weeks)	10, 40 ± 10 (mean ± SD), ♂♀	Native American/ Alaska Native (n = 2), African American (n = 1), Hispanic (n = 4), and White non-Hispanic (n = 3)	Ethanol dependence	Open-label	Yes	↓	At least 36 weeks post-treatment	No	Bogenschutz <i>et al.</i> , 2015

Table 1. (Continued)

Psilocybin	20 or 30 mg/70 kg, oral, two administrations (one every 2 weeks)	15, 51 (mean), ♂♀	Mostly White or Caucasian (93%)	Nicotine-dependent smokers	Open-label	Yes	↓	At least 16 months post-treatment	No	Johnson <i>et al.</i> , 2017
Psilocybin	25 mg/70 kg (1 st session) and 25 to 40 mg/70 kg (2 nd session), oral, 4 weeks apart	96, 46 ± 12 (mean ± SD), ♂♀	Mostly White or Caucasian (79%)	Ethanol dependence	R, D-B, controlled trial	Yes	↓	At least 36 weeks post-treatment	No	Bogenschutz <i>et al.</i> , 2022
Psilocybin	25 mg/70 kg, oral, single administration	11, 49 ± 11 (mean ± SD), ♂♀	Mostly White or Caucasian (72%)	AUD	R, D-B, P-C	Yes	n.d.	n.d.	n.d.	Pagni <i>et al.</i> , 2024

Legend: ↔ = relatively no changes; ↓ = reduction; ♂ = men; ♀ = women; AUD = alcohol use disorder; D-B = double-blind; i.v. = intravenous route; MDD = major depressive disorder; MDMA = 3,4-methylenedioxymethamphetamine; n.d. = not described; DMT = N,N-dimethyltryptamine; P-C = placebo-controlled; PTSD = posttraumatic stress disorder; R = randomised; SAD = social anxiety disorder; SEM = standard error of mean; SUD = substance use disorder; TR-MDD = treatment-resistant major depressive disorder.

(Schlag *et al.*, 2022; Lake & Lucas, 2024; Kopra *et al.*, 2025). Clinical studies conducted in supervised settings have also demonstrated low addictive potential (Johnson *et al.*, 2008; Johansen & Krebs, 2015; Johnson *et al.*, 2018; Schlag *et al.*, 2022; Hinkle *et al.*, 2024). Compared to ethanol, opioids, cocaine, crack, amphetamines, and some psychostimulants, they have a low risk of addiction and intoxication (Johnson *et al.*, 2018). Noteworthy, clinical evidence suggests that psychedelics can alleviate psychological and physiological symptoms associated with dependence on other psychoactive substances (Vamvakopoulou & Nutt, 2024; Yao *et al.*, 2024).

Challenging emotional experiences (e.g. anxiety and panic attacks), sensory and spatial distortions, headache, nausea and vomiting, and elevations in heart rate and blood pressure are changes induced by psychedelics as *transient* effects observed after administering usual doses but infrequently manifest in protocols using microdoses (Nichols, 2016; Polito & Stevenson, 2019; Schlag *et al.*, 2022; Wsól, 2023; Murphy *et al.*, 2024; Neumann *et al.*, 2024; Yerubandi *et al.*, 2024) or when used in controlled settings with appropriate inclusion criteria (Rhee *et al.*, 2023; Hinkle *et al.*, 2024; Klaiber *et al.*, 2024; Romeo *et al.*, 2024; Simon *et al.*, 2024; Sabé *et al.*, 2025). These relatively limited adverse reactions are associated with stimulating various 5-HT receptors (Johnson *et al.*, 2008; Family *et al.*, 2022; Holze *et al.*, 2022). For example, the potential cardiovascular risk associated with serotonergic psychedelics is attributed to their interaction with 5-HT_{1B}, 5-HT_{2B}, and 5-HT₄ receptors (Wsól, 2023). However, no associations have been established between the lifetime use of classical psychedelics and the development of cardiometabolic diseases (Simonsson *et al.*, 2021).

The relationship between psychedelic use and the risk of seizures is not fully understood, as clinical studies typically exclude individuals with a history of seizures or convulsions. While psychedelics may theoretically increase the risk in predisposed individuals due to cortical 5-HT_{2A} receptor hyperstimulation, most studies suggest that these substances have a low epileptogenic potential when used in controlled settings. The risk may be elevated when psychedelics are combined with factors common in athletic environments, such as sleep deprivation, stimulant use, or high-stress conditions, particularly in susceptible individuals. However, further investigation is needed to understand better the underlying mechanisms and associated risk factors (Freidel *et al.*, 2024; Lewis *et al.*, 2024; Soto-Angona *et al.*, 2024). Based on this, caution is advised for athletes with a history of seizures and those using medications (e.g. bupropion) or supplements (e.g. high-dose caffeine) that may lower the seizure threshold.

The use of psychedelics, particularly MDMA, has been associated with an increased risk of hyponatremia in humans, primarily due to increased antidiuretic hormone (also known as vasopressin) release from the posterior pituitary and excessive fluid intake, leading to water retention and sodium dilution (Atila *et al.*, 2024). This mechanism is attributed to MDMA's elevation of hypothalamic 5-HT and dopamine levels, stimulating vasopressin release and promoting water retention via vasopressin-2 receptors in the kidneys. Excessive water intake, driven by hyperthermia, dry mouth, and stimulant effects in physically demanding or hot environments, may exacerbate sodium dilution. Although this effect is self-limiting and observed mainly acutely, this condition may be particularly concerning for endurance athletes. Temporary hyponatremia outside of competition may contribute to longer-term consequences, potentially predisposing them to a higher risk

of injuries or reduced performance in subsequent training or competitions.

Evidence from both rodent and human studies has demonstrated an association between MDMA use and an increased risk of hyperthermia and rhabdomyolysis. MDMA-treated rodents exhibited significant increases in body temperature, sustained muscle contraction, and muscle damage resembling rhabdomyolysis. These effects were related to increases in neurotransmitters, primarily 5-HT and dopamine, and activation of the sympathetic nervous system (Sprague *et al.*, 2004; Duarte *et al.*, 2005; Rusyniak *et al.*, 2005; Sprague *et al.*, 2005; de Bragança *et al.*, 2017). In humans, clinical and observational studies have reported similar effects, especially in intoxication or recreational settings involving prolonged physical activity, crowded environments, and inadequate thermoregulation (Screaton *et al.*, 1992; Lehmann *et al.*, 1995; Halachanova *et al.*, 2001; Sue *et al.*, 2002; Vanden Eede *et al.*, 2012; Doyle *et al.*, 2020). This could be relevant for endurance athletes if their MDMA use and physical exercise are not adequately spaced apart, as MDMA-induced hyperthermia and rhabdomyolysis can be exacerbated by the physiological demands of prolonged exertion, increasing the risk of severe complications and impairing athletic performance. Although the cited articles did not assess athletes under the acute effects of psychedelic substances, their findings indirectly underscore the importance of understanding the risks associated with MDMA use in physically demanding contexts, as well as the need for proper monitoring of signs and symptoms.

Evidence indicates that 5-HT is a key neuromodulator of locomotor activity (Bacqué-Cazenave *et al.*, 2020; Flaive *et al.*, 2020). As reviewed by Werle and Bertoglio (2024), published studies have demonstrated the biphasic effects of psychedelic substances on locomotion. In the open-field test, rats and mice exhibit either hyperlocomotion or hypolocomotion, depending on the dose. These effects are mediated by mechanisms involving the activation of 5-HT_{1A}, 5-HT_{2C}, and 5-HT_{2A} receptors (in the case of MDMA, they also involve the release of 5-HT and dopamine). Each substance has its particularities, although hypolocomotor effects (suggestive of sedation) generally predominate at moderate to high doses (Werle & Bertoglio, 2024). While it is unlikely and strongly discouraged for individuals to participate in sports while under the acute influence of psychedelics, it is worth noting that rodent studies suggest psilocybin, LSD, DMT, ayahuasca, and MDMA can influence locomotor activity.

Psychedelics and mental health

Psychedelics can provide significant benefits across multiple domains of mental health and well-being in healthy individuals (Lebedev *et al.*, 2016; Schmid & Liechti, 2018; Hutten *et al.*, 2020a; Perkins *et al.*, 2022). Of particular relevance to athletes are several potential effects, including reduced pain (Ramaekers *et al.*, 2021; Askey *et al.*, 2024; Strand *et al.*, 2025) and improvements in sleep (Allen *et al.*, 2024). Additionally, psychedelics may enhance stress management by reducing anxiety levels and promoting greater emotional resilience (Griffiths *et al.*, 2011; Arruda Sanchez *et al.*, 2024).

The growing interest and acceptance of psychedelic substances have driven clinical trials, advancing our understanding of their potential benefits (Nichols, 2016; Reiff *et al.*, 2020; Nutt & Carhart-Harris, 2021; McClure-Begley & Roth, 2022). Their contribution to alleviating symptoms of depression, anxiety, posttraumatic stress disorder (PTSD), eating disorders, and substance use disorders has

been documented (Reiff *et al.*, 2020; Barber & Aaronson, 2022; Brewerton *et al.*, 2022; Cavarra *et al.*, 2022; Cuerva *et al.*, 2024; Dos Santos & Hallak, 2024; Doss *et al.*, 2024; Zaretsky *et al.*, 2024). Table 1 presents the details and primary findings of human studies examining the effects of psilocybin, LSD, DMT, ayahuasca, and MDMA on the mental health of individuals diagnosed with the aforementioned psychiatric conditions. Noteworthy, the association of psychedelics with psychotherapeutic support (i.e. psychedelic-assisted psychotherapy) has been shown to improve the integration of psychedelic experiences (Luoma *et al.*, 2020).

Some of the studies reviewed (Table 1) also report that these substances are associated with significant and long-lasting symptom reduction, with therapeutic effects persisting for weeks or months following only a few administrations, even in patients resistant to typical pharmacological treatment. Psychedelics have also presented a favourable safety profile, as indicated by the relatively low incidence of severe adverse reactions when administered under controlled clinical conditions. Such features may be particularly relevant for health care in athletes, who often endure high levels of physical and mental stress and are vulnerable to various psychiatric disorders (Edwards, 2024). Hypothetically, psychedelic therapy could serve as a valuable tool for enhancing well-being in this population with minimal risk of impairing performance.

However, it is essential to address the methodological limitations of the studies published to date, as well as the gaps that still need to be clarified to enable a responsible application of psychedelic therapies in clinical practice. Some reviewed studies included small sample sizes and lacked double-blind methodologies or inactive placebos, which limits the generalisability of the observed results and increases the chance of confirmation bias. Furthermore, the majority of participants were White or Caucasian, which may limit the extrapolation of findings to other ethnic groups with distinct cultural or genetic characteristics, thus impacting the representativeness of these results when psychedelics are applied on a larger scale. Another issue is the variability in study protocols (e.g. dosage, number of administrations, and intervals between treatments). Greater methodological rigour and standardisation are needed to understand better the actual clinical impact of psychedelic therapy on both the general population and athletes. Future research should also incorporate more objective evaluation methods, ideally including physiological or neurobiological measurements that can be correlated with the health status (or psychiatric disorder under investigation).

Mental health issues in athletes

Studies indicate that the prevalence of psychiatric disorders in high-performance athletes (both amateur and professional) may be similar or even higher than in the general population, which likely arises from intense physical and emotional stressors often experienced (Gouttebarga *et al.*, 2019; Reardon *et al.*, 2019; Glick *et al.*, 2020; Mari-Sanchis *et al.*, 2022; McDonald *et al.*, 2023; Smith *et al.*, 2023; Thuan *et al.*, 2023; Beable, 2024). Among them are the high demand for physical and sports performance, overtraining, interpersonal conflicts in competitions, the imbalance between personal life and training, injuries, and early retirement (Chang *et al.*, 2020). Furthermore, due to self-pressure to demonstrate mental resilience, athletes may not report their health concerns, accept professional assistance, or adhere to treatment. Additionally, athletes may often avoid pharmacological treatment due to concerns about doping, potential adverse reactions, and the

effects of medication on athletic performance (Reardon, 2016; Bomfim, 2020). As a result, a cycle of untreated suffering can develop, compromising both mental health and physical aspects. Early identification of these factors and appropriate clinical intervention are essential to ensure performance and longevity in sports practice, as well as the psychological well-being of athletes (Glick *et al.*, 2012; Chang *et al.*, 2020). Consequently, there is growing interest in sports research to assess the mental health of athletes such as long-distance runners, cyclists, swimmers, triathletes, and others (Berger *et al.*, 2024).

Drugs currently available for the management of psychiatric disorders in athletes present significant limitations (Morris, 2015; Reardon & Creado, 2016; Tso & Pelliccia, 2022). Antidepressants and anxiolytics currently approved for clinical use are administered daily and can cause side effects that negatively affect athletic performance, such as drowsiness, changes in appetite, and weight gain (Reardon, 2016; Reardon & Creado, 2016; Edwards, 2024). In addition, individual variability in response to these medications can hinder treatment effectiveness. For example, while approximately 15% of participants in clinical trials experience a significant antidepressant effect beyond that of a placebo (Stone *et al.*, 2022), around 30% of individuals diagnosed with major depressive disorder are resistant to conventional treatment, further increasing the social and economic burden of this condition (McIntyre *et al.*, 2023). In this scenario, psychedelic therapy could emerge as either a complementary or an alternative for the treatment of psychiatric disorders in athletes.

Psychedelics to maintain and improve mental health in athletes

Several clinical studies have demonstrated the efficacy of psychedelic-assisted psychotherapy (Table 1; Nichols, 2016; Reiff *et al.*, 2020; Nutt & Carhart-Harris, 2021; Cavarra *et al.*, 2022; Knudsen, 2023). Following approval by the Therapeutic Goods Administration in 2023, Australia became the first country to authorise and regulate the medicinal use of psilocybin and MDMA for the treatment of depression and PTSD, respectively (Nutt *et al.*, 2024). Similarly, Oregon and Colorado became the first American states to legalise psilocybin, issuing official licences to specialised mental healthcare service centres for use (Korthuis *et al.*, 2024).

To date, the potential of psychedelics to enhance mental health or treat psychiatric disorders in athletes remains unknown. However, considering the evidence from the general population (Table 1), several aspects of psychedelic therapy may be beneficial for these individuals (Carhart-Harris & Goodwin, 2017; Barber & Aaronson, 2022; Holze *et al.*, 2024). In healthy athletes, the administration of psychedelics may offer benefits in promoting mental health and well-being, aiding in the management of psychological and emotional challenges. By enhancing resilience and emotional flexibility, psychedelic therapy could mitigate the effects of everyday stressors in high-performance sports, including intensive training routines, self-imposed demands for physical performance, and sustained competitiveness. Moreover, in athletes diagnosed with psychiatric disorders, psychedelic-assisted psychotherapy could offer some advantages over conventional treatments. Unlike daily medications, only a few sessions spaced over days to weeks are typically sufficient to promote long-term mental health benefits that are maintained over several months (Yao *et al.*, 2024). Furthermore, the half-life of these substances lasts only a few hours, not producing withdrawal symptoms. Although psychedelic

therapy may result in adverse reactions, they are transient and manifest mainly in the following hours after administration. Thus, potential concerns associated with impaired sports performance can be reduced, even if athletes are in training or competition periods (Reardon & Creado, 2016; Edwards, 2024). Yousefi *et al.* (2025) have meta-analysed psilocybin's acute effects on executive functions and attention. Psilocybin increased reaction times dose-dependently without significantly affecting accuracy, suggesting an impairment in executive function that may be relevant to specific sports. However, its impact on performance is potentially less concerning, as athletes are not expected to compete while under the influence of psychedelics.

Several psychedelic substances produce prosocial effects in rodent and human studies (Dumont *et al.*, 2009; Hysek *et al.*, 2014; Kamilar-Britt & Bedi, 2015; Griffiths *et al.*, 2018; De Gregorio *et al.*, 2021; Bhatt & Weissman, 2024). While systematic research on psychedelics in sports is limited, their potential prospective effects may include improved social dynamics during training or competition, team cohesion, reduced anxiety, enhanced resilience among athletes, and sports-related mild traumatic brain injury (e.g. concussion) (VanderZwaag *et al.*, 2024). However, the use of psychedelics in sports raises potential issues. Serotonergic psychedelics and related compounds produce varying effects in tests of negative social interactions, often assessing aggression, in rodents through their actions on 5-HT_{2A} and 5-HT_{1A} receptors (Odland *et al.*, 2022). Future studies must establish optimal dosages, contexts, and protocols that maximise potential benefits while minimising risks.

Scientific evidence on the interactions between psychedelic substances and antidepressants, antipsychotics, anxiolytics, and mood stabilisers remains limited. However, it has been reported that psychedelics and certain psychiatric medications may share overlapping pharmacological targets, molecular pathways interactions, and hepatic metabolism via similar enzymes (Sarparast *et al.*, 2022; Rhee *et al.*, 2023; Halman *et al.*, 2024). Consequently, drug interactions between psychedelic substances and medications already used by athletes should be considered, as they may potentiate or attenuate the actions of both substances. Therefore, adequate clinical monitoring will be essential to mitigate the risks of adverse reactions, toxicity, or inadequate management of psychiatric symptoms.

Effects of psychedelics on physical and physiological parameters

Administration of the psychedelic substance DOI has been shown to reduce circulating levels of total cholesterol and low-density lipoprotein (LDL) in a high-fat diet-fed apolipoprotein E knockout mice model without affecting food intake or body weight. DOI administration was also associated with a reduction in the increased serum levels of the pro-inflammatory cytokine CXCL10 induced by high-fat diet-fed and reduced expression of pro-inflammatory marker genes in the aortic arch (Flanagan *et al.*, 2019a). On the other hand, preclinical studies have shown potentially conflicting results of the psilocybin administration on metabolic parameters and body weight regulation. Although the administration of a high dose of psilocybin was associated with a modest but significant reduction in body weight, decreased consumption of the high-calorie diet, and decreased central adiposity in a rodent model of obesity (Huang *et al.*, 2022), neither a single nor repeated administration of psilocybin had significant metabolic effects. It did not lower body weight or food intake in

diet-induced obese mice or genetic mouse models of obesity (Fadahunsu *et al.*, 2022). Moreover, increased creatine kinase, aspartate aminotransferase, and chloride have been reported in male and female mice treated with psilocybin (Shakir *et al.*, 2024). Preclinical studies have shown that MDMA treatment may increase serum levels of total and LDL cholesterol, corticosterone, aspartate transaminase, alanine transaminase, or glucose in rodents (Graham *et al.*, 2010; Shahraki & Irani, 2014; Golchoobian *et al.*, 2017), although hypoglycaemia has also been reported (Soto-Montenegro *et al.*, 2007; Golchoobian *et al.*, 2017).

In addition to regulating body weight, lipid metabolism is also essential for cellular mechanisms related to inflammation and nociception/pain, and the anti-inflammatory and immunomodulatory properties of psychedelics have also been reported (Flanagan & Nichols, 2022). Lipid mediators, including arachidonic acid (AA), can be metabolised by cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP450) enzymes and converted to pro-inflammatory metabolites such as prostaglandins, thromboxane, leukotrienes, and hydroxyeicosatetraenoic acids. In rodents, the psychedelic bufotenine has been shown to induce an anti-nociceptive effect and promote the downregulation of inflammatory mediators from COX, LOX, CYP450, linoleic acid, docosahexaenoic acid, and other pro-inflammatory pathways (Wang *et al.*, 2021a; Shen *et al.*, 2022). Askey *et al.* (2024) have reviewed the psilocybin potential as an anti-nociceptive agent, focusing on preclinical animal models and exploring serotonergic mechanisms and neuroplastic actions that improve functional connectivity in brain regions involved in chronic pain. They also discuss its broader effects on pain and associated emotional and inflammatory components. The review by Strand *et al.* (2025) has examined psilocybin, LSD, and ketamine as potential treatments for chronic pain. It focuses on their pharmacology, effects on neuropathic pain, clinical implications, safety profiles, and patient responses.

Preclinical and clinical data also indicate that psychedelics increase the release of anti-inflammatory interleukins (e.g. IL-10) and reduce the expression and activity of other pro-inflammatory markers, including IL-6, IL-1 β , tumour necrosis factor- α (TNF- α), and nuclear factor kappa B (NF- κ B). Thus, administration of these substances may attenuate the activation of genes and downstream signalling pathways that contribute to inflammation (dos Santos, 2014; Boxler *et al.*, 2018; Flanagan & Nichols, 2022; Mason *et al.*, 2023; Low *et al.*, 2025). DOI can inhibit TNF- α -induced inflammation by mitigating the expression of genes encoding intracellular adhesion molecule-1, vascular cell adhesion molecule-1, and IL-6 through serotonin 5-HT_{2A} receptor activation in both *in vitro* and *in vivo* (Yu *et al.*, 2008; Nau *et al.*, 2013). Furthermore, DOI administration blocked the activation and translocation of NF- κ B and decreased nitric oxide synthase activity (Yu *et al.*, 2008).

In vitro studies have demonstrated that psilocybin-containing mushroom extracts inhibited lipopolysaccharide (LPS)-induced increases in TNF- α and IL-1 β , besides decreasing COX-2 concentrations in treated human U937 macrophage cells (Nkadimeng *et al.*, 2021; Laabi *et al.*, 2024). In healthy volunteers, a single dose of psilocybin reduced plasma levels of TNF- α immediately after administration, and IL-6 and C-reactive protein were reduced in the psilocybin group seven days later. The persisting reductions in pro-inflammatory markers correlated with clinical improvement of mood and sociability (Mason *et al.*, 2023).

Possible opposite effects have been reported regarding MDMA. Acute administration of MDMA appears to promote an anti-inflammatory effect. It impairs the secretion of IL-1 β and TNF- α

induced by LPS administration in rodents (Connor *et al.*, 2000), besides suppressing innate IFN- γ production by increasing IL-10 levels (Boyle & Connor, 2007). On the other hand, in human plasma samples collected at different time points after a single oral administration of MDMA, an increase in cortisol and lipidic mediators of inflammation was observed, suggesting stimulation of inflammatory pathways (Boxler *et al.*, 2018).

Immunomodulatory effects of psychedelic substances and other chemical compounds derived from ayahuasca have also been reported (dos Santos, 2014; Galvão-Coelho *et al.*, 2020). Harmine has been proposed to exert anti-inflammatory and antioxidant effects through several mechanisms, such as AMPK/Nrf2 pathway activation, reduced caspase-3 expression by repressing the Bax/Bcl2 ratio, inhibition of the c-Jun N-terminal kinase (JNK), downregulation of LC3B II/I, p38 MAPK, TLR4, and NF- κ B levels. Furthermore, it appears to increase the expression of p62, Bcl-2, Beclin1, ULK1, and p-mTOR (Hamsa & Kuttan, 2010; Liu *et al.*, 2017a; Niu *et al.*, 2019; Ma *et al.*, 2024; Tabaa *et al.*, 2024). Harmine also attenuated bone destruction induced by an inflammatory response. It shifted the polarisation of macrophages from M1 to M2 phenotypes both *in vitro* and *in vivo* in a murine model (Wang *et al.*, 2021b). A three-day ayahuasca treatment prevented anxiety and oxidative stress induced by an inflammatory insult in rats. Additionally, it increased cortical levels of the anti-inflammatory cytokine IL-4 and BDNF (de Camargo *et al.*, 2024).

Although the precise molecular mechanisms related to the effects of psychedelics on immunity and inflammatory responses remain to be elucidated, the involvement of 5-HT_{2A} receptor activation has been proposed. 5-HT_{2A} receptor is widely distributed in tissues and cells, regulating innate and adaptive immune responses, such as the spleen, thymus, circulating lymphocytes, T cells, eosinophils, and mononuclear cells (Herr *et al.*, 2017; Thompson & Szabo, 2020). While the 5-HT_{2A} receptor activation by 5-HT primarily contributes to inflammation, psychedelics appear to recruit anti-inflammatory intracellular signalling pathways through activation of the same receptor, possibly by stabilising it in a slightly different structural and functional conformation, that is, biased agonism (Raote *et al.*, 2007; Shan *et al.*, 2012; Flanagan *et al.*, 2024). The anti-inflammatory effects of psychedelics resulting from the activation of the 5-HT_{2A} receptor have also been associated with improved respiratory and neurological function, demonstrating benefits in animal models of asthma (Stankevicius *et al.*, 2012; Nau *et al.*, 2015; Flanagan *et al.*, 2019b; Flanagan *et al.*, 2020) and attenuating the functional consequences of neuroinflammation (Zhong *et al.*, 2015; Liu *et al.*, 2017b; Sun *et al.*, 2019; Nardai *et al.*, 2020; Xin *et al.*, 2021; Goulart da Silva *et al.*, 2022; Zanicov *et al.*, 2023; Zheng *et al.*, 2023; Floris *et al.*, 2024).

A significant knowledge gap in psychedelic research, particularly regarding their potential use in athletes, is the lack of studies evaluating their effects on physical health and metabolic parameters. Based on the evidence outlined above and its potential translational implications, treating athletes with psychedelic substances may offer benefits. The improved mental well-being and emotional control associated with psychedelic therapy could contribute to performance by making them more focused and resilient. At the same time, these substances' anti-inflammatory and analgesic effects could mitigate physical stress, reduce muscle fatigue, and facilitate recovery after prolonged or intense exercise. By reducing inflammation, psychedelics could also improve mental health and reduce symptoms in individuals with psychiatric disorders such as depression or anxiety, as convergent evidence points to an increase



Figure 1. An overview of the current landscape of psychedelics and athletic performance.

in inflammatory markers in these clinical conditions and the significant role of inflammation in their pathophysiology (Bauer & Teixeira, 2019; Beurel *et al.*, 2020; Zeng *et al.*, 2024). Since research on the use of psychedelic substances in sports contexts is incipient (Fig. 1), far more studies are needed before potentially establishing guidelines on their safe and effective use.

Psychedelics in sports competitions: legal and regulatory considerations

Psychedelic substances have been classified as prohibited or controlled substances in most countries, posing challenges for establishing potential guidelines that ensure treatment efficacy and

safety under appropriate regulatory oversight. In sports competitions, the World Anti-Doping Agency (WADA; <https://www.wada-ama.org/en/prohibited-list>) does not list psychedelics as 'prohibited substances', except for MDMA, which is classified as a stimulant amphetamine.

For a substance or method to be included in WADA's Prohibited Substances List under the World Anti-Doping Code, it must meet at least two of the following three criteria: (1) it enhances or has the potential to enhance sports performance, (2) it poses an actual or potential risk to athlete health, and (3) it violates the spirit of sport as defined in the Code (<https://www.wada-ama.org/en/resources/world-anti-doping-code-and-international-standards/world-anti-doping-code>). To date, no clinical

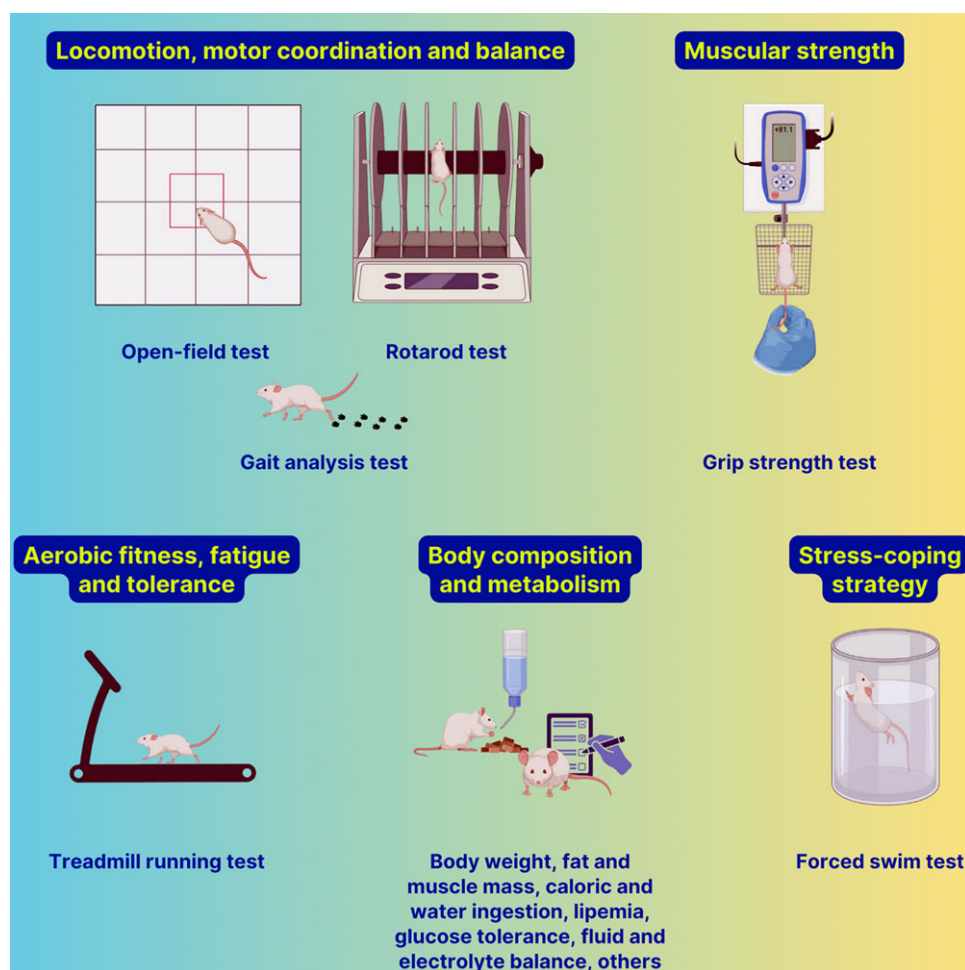


Figure 2. Helpful behavioural and physiological responses in rodents for inferring the physical effects of psychedelic drugs in humans.

evidence has suggested that psychedelics act as ergogenic aids. WADA regularly updates its prohibited and restricted substances list based on evolving scientific evidence. For example, while cannabis/ Δ^9 -tetrahydrocannabinol remains prohibited in competition due to its potential to impair performance, pose safety risks, and violate the 'spirit of sport', cannabidiol (CBD) has been permitted, as it lacks these properties. As research on psychedelics progresses, the regulatory status of specific compounds in sports may be reevaluated, potentially leading to updates similar to the removal of CBD from the prohibited list.

Conclusions and suggestions for future research

Several clinical studies have highlighted the mental health benefits of psychedelics and their potential role as therapeutic adjuncts to improve the quality of life, but significant considerations remain. A critical knowledge gap in evaluating these substances' effects on physical health in humans persists. Similarly, the impact of psychedelics on physiological responses relevant to athletic performance, such as muscular strength, motor coordination, locomotion, endurance, cardiorespiratory capacity, fluid and electrolyte balance, hormonal regulation, fatigue, and reflexes, remains largely unexplored scientifically. Moreover, it is worth noting the ethical and legal concerns associated with performance-enhancing substances and the importance of distinguishing

between the use of psychedelics within and outside the acute performance/sports context.

Rodent research can provide a valuable foundation for understanding the potential effects of psychedelic therapy on physical performance in humans (Fig. 2). The rotarod test has been used to assess motor coordination and balance in rodents. The gait analysis test provides a detailed assessment of movement patterns and gait symmetry, which is crucial for identifying motor coordination changes (Carter *et al.*, 2001; Deacon, 2013). Muscular strength is typically evaluated through the grip strength test, which measures the animal's grip force by stimulating traction of the forelimbs or hind limbs (Munier *et al.*, 2022). It provides a direct measure of muscle strength, relevant for assessing whether psychedelics could influence aspects of muscular endurance in humans, an essential factor in the performance of athletes. The treadmill running test (Dougherty *et al.*, 2016; Castro & Kuang, 2017) is a tool for exploring the effects of psychedelic substances on endurance and cardiorespiratory capacity. Rodents are encouraged to run on a treadmill, allowing for analysis of aerobic capacity, fatigue, and prolonged exercise tolerance. These data help understand the potential of psychedelics to enhance aerobic performance and to observe possible indirect cardiorespiratory impacts from their administration. Stress resilience is also essential for high-performance athletes, and the forced swim test is a tool for assessing stress-coping strategy in rodents (Slattery & Cryan, 2012; Commons *et al.*, 2017). In this test, the duration of immobility in a

forced swim scenario reflects the animal's ability to persist under adverse conditions. Several psychedelics have been shown to decrease immobility and increase active behaviours, including swimming and climbing (Cameron *et al.*, 2018; Hibicke *et al.*, 2020; Odland *et al.*, 2022; Rakoczy *et al.*, 2024). Metabolic parameters and overall physical condition can be monitored through assessments such as food and water intake (to evaluate impacts on basal metabolism and caloric needs) and body condition scoring, which provides a qualitative assessment of the animal's overall physical state by monitoring body composition and body mass index.

Overall, these methods could provide preclinical evidence to elucidate the influence of psychedelics on motor, metabolic, and cardiorespiratory functions, as well as their impact on stress resilience. This knowledge could inform the design of safer and more effective clinical protocols to explore the potential benefits of psychedelics as adjunctive therapies in enhancing the mental health and physical performance of athletes and non-athletes. Such studies could also illuminate the underlying mechanisms of action, identify potential effects on organs and tissues beyond the central nervous system, and investigate potential sex differences or genetic and metabolic influences (Rakoczy *et al.*, 2024; Werle & Bertoglio, 2024).

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Author contributions.

- M.A.M.P.: conception, methodology, data collection, writing, and editing of the text;
- I.W.: data collection, writing, and editing of the text;
- L.J.B.: conception, administration, project supervision, writing, and editing.

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