Psychedelic and nutraceutical interventions as therapeutic strategies for military-related mild traumatic brain injuries

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REVIEW

Psychedelic and nutraceutical interventions as therapeutic strategies for military-related mild traumatic brain injuries

Amy C. Reichelt[a], Eric Vermetten[b] and Benjamin T. Dunkley[c]

ABSTRACT

Mild traumatic brain injury (mTBI), also referred to as concussion, is an acquired brain injury that is common in the military. mTBI results in alterations to brain function that are underpinned by a cascade of neuropathological and neurometabolic events that can result in excitotoxicity, oxidative stress, edema, neuroinflammation, and cell death. To date, traditional pharmaceutical therapies have been used with limited success to treat mTBI, leading to interest in the potential for psychedelic and nutraceutical therapies to alleviate the deleterious pathological sequelae that follow neurotrauma. An accumulating body of evidence supports research into the use of classic psychedelics and nutraceutical interventions for treating mTBI and concussion. This article highlights pre-clinical and clinical studies that show classic psychedelics are promising pharmacological interventions for mTBI because of their potent neuroplastic properties — including synaptogenesis and large-scale re-wiring, anti-inflammatory effects, and modulatory properties — on neural excitation and inhibition. The addition of nutraceutical interventions could also hasten recovery and improve general functioning along the spectrum from mild acute injury to long-term chronic issues (e.g., persistent post-concussive symptoms) and, potentially, to other forms of neurodegenerative disorders after neurotrauma and repetitive head injury.

Key words: concussion, military, mTBI, neuroinflammation, neuroplasticity, nutraceuticals, persistent post-concussive symptoms, psychedelics, TBI, traumatic brain injury

RÉSUMÉ

Le traumatisme craniocérébral léger (TCCL), également appelé commotion cérébrale, est une lésion cérébrale acquise, fréquemment observée chez les militaires. Le TCCL entraine des modifications de la fonction cérébrale qui sont renforcées par une cascade d'évènements neuropathologiques et neurométaboliques pouvant entrainer une excitotoxicité, un stress oxydatif, un œdème, une neuroinflammation et la mort cellulaire. À ce jour, le succès des thérapies pharmaceutiques classiques à traiter les TCCL demeure limité, ce qui suscite de l'intérêt pour le potentiel des thérapies psychotropes et nutraceutiques à soulager les séquelles pathologiques délétères qui suivent un neurotraumatisme. Des données toujours plus nombreuses encouragent la recherche sur l'utilisation des psychotropes et des interventions nutraceutiques dans le traitement des traumatismes craniocérébraux légers et des commotions cérébrales. Cet article signale des études précliniques et cliniques qui montrent que les psychotropes constituent des interventions pharmacologiques prometteuses pour les TCCL, en raison de leurs puissantes propriétés neuroplastiques – synaptogenèse et recâblage à grande échelle, effets antiinflammatoires et propriétés modulatrices, entre autres – agissant sur l'excitation et l'inhibition neuronales. Des interventions nutraceutiques complémentaires pourraient également accélérer le rétablissement et améliorer le fonctionnement général, dans le spectre allant des blessures aigües légères aux problèmes chroniques à long terme (p. ex. les symptômes postcommotionnels persistants) et, potentiellement, pour d'autres formes de troubles neurodégénératifs suivant un neurotraumatisme ou un traumatisme crânien répété.

Mots clés : commotion cérébrale, militaire, neuro-inflammation, neuroplasticité, produits nutraceutiques, psychotropes, symptômes postcommotionnels persistants, TCCL, traumatisme cérébral, traumatisme craniocérébral léger,

LAY SUMMARY

Concussion is a type of acquired brain injury that is common in the military, as well as among civilians and contact sport athletes, and is defined by a transient impairment in mental function. Nevertheless, concussion presents a considerable health burden, and a small minority of people suffer from continued impairment. Repetitive sub-concussive

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head injury is a known risk factor for neurodegenerative disease, including dementias. Concussions are difficult to treat because symptom profiles vary, but psychedelic therapies may help address some of the neurological issues that occur after brain injury. Classic psychedelics show promise as an emerging pharmacological intervention because they appear to help the brain to rewire, and they have anti-inflammatory effects. Nutraceutical interventions are widely available, cost-effective, and well tolerated, and they could also support recovery when combined with psychedelic compounds. Here, studies presenting classical psychedelics and nutraceuticals that may be combined with psychedelics as therapeutic strategies for the treatment of concussions and persistent symptoms are discussed.

INTRODUCTION

Traumatic brain injury (TBI) is a major cause of death and disability worldwide, and it is common in the military,[1] often associated with falls, assaults, collisions, contact sports, whiplash, or an overpressure shockwave from a blast. The severities of TBI cover a broad continuum from mild, to moderate, to severe, with 80% to 95% being mild TBIs (mTBIs), commonly referred to as concussion. After the initial primary mechanical injury, a cascade of neurochemical and neurometabolic events occur in the brain, called secondary injury (Figure 1). Secondary injury is a potential therapeutic target.

Repeated concussions or sub-concussions are concerning for military personnel involved in training exercises and combat duty because they may precipitate deleterious neurobiological responses that can lead to pronounced neurofunctional changes.[2,3] The intense physical training routines of military personnel place high metabolic demands on the brain and body. In tandem with stress placed on the brain from physical

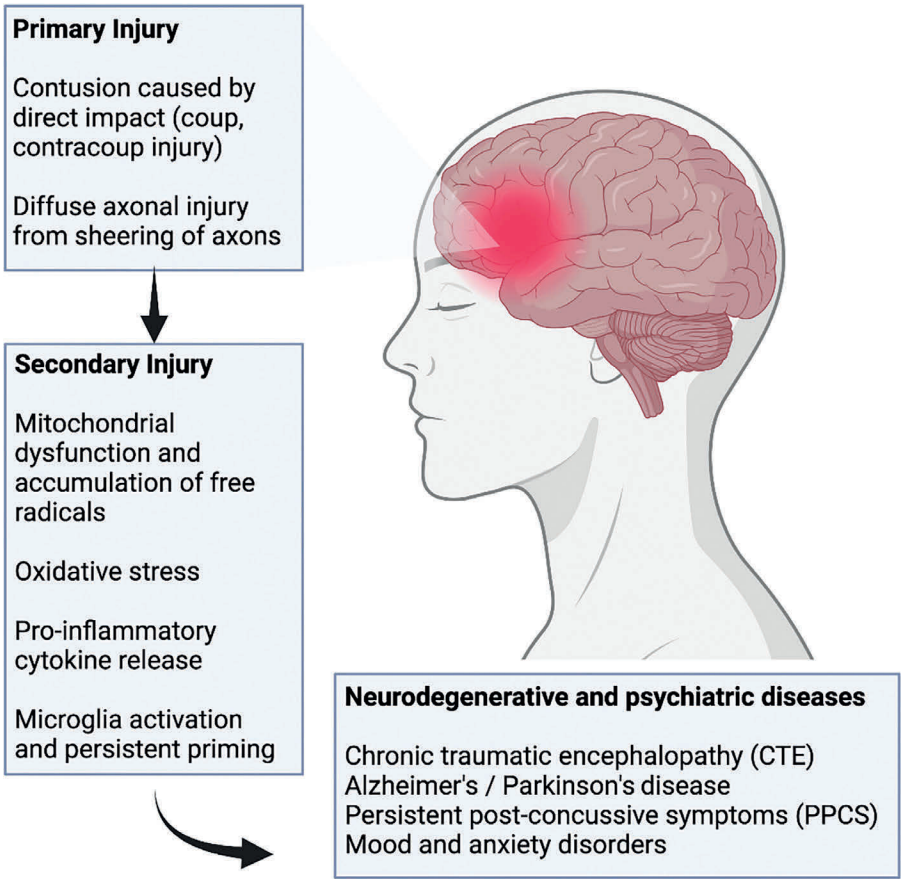

Figure 1. Primary traumatic injury typically occurs as a result of a direct impact to the brain from biomechanical forces
Note: This momentum causes the brain to collide with the inner skull (coup and contracoup injury), creating localised and distributed damage through compression or stretching, ranging from regional contusions to diffuse axonal injuries caused by the deformation and shearing of axons. In the secondary injury cascade, neuroactive molecules and immune response cause neuronal dysfunction and an enduring state of inflammation. This secondary neurochemical cascade can be more damaging than the primary insult and may be a potential target of therapeutic intervention with psychedelic-based drugs. Ameliorating secondary injury processes may mitigate enduring structural and functional damage to the brain, as well as neurodegenerative and psychiatric disorders. Image created in http://biorender.com.

activity, concussions and sub-concussions cause neurometabolic crises as a result of increased energy demands.[3]

Although most individuals recover from a concussion within 14 days, a significant proportion of individuals — up to 30% — experience persistent cognitive and behavioural impairment, termed persistent post-concussive symptoms.[4] Moreover, a single injury or the cumulative effects of repeated concussions pose a risk factor for secondary neuropsychiatric illness.[4] Cognitive impairments and mood shift after mTBI have negative implications for quality of life and, in a military context, significantly impair fighting and operational readiness.

Emerging research and clinical trials using psychedelic-assisted psychotherapy led to initiation of larger-scale Phase 2 and 3 clinical trials for major depressive disorder,[5-7] a common comorbidity among people with chronic mTBI. Moreover, in this article, the authors propose that the neurobiological actions of psychedelics could address pathologies associated with neurological disorders, including mTBI.

Pre-clinical and clinical research with classic psychedelic compounds

Classic psychedelics include psilocybin, the prodrug form of psilocin, N,N-dimethyltryptamine (DMT), 5-MeO-DMT, mescaline, and lysergic acid diethylamide (LSD). Non-classic psychedelics are synthetic derivatives of these classic compounds and include 2,5-Dimethoxy-4-iodoamphetamine (DOI) and 4-Bromo-2,5-dimethoxyphenethylamine, as well as dissociative drugs such as ketamine and ibogaine.

The G-protein-coupled serotonin (5-hydroxytryptamine) 2A (5-HT2A) receptor is the common target of psychedelic compounds to elicit hallucinogenic effects. The 5-HT2A receptor is widely expressed in cortical brain regions and is also found in endocrine, endothelial, immune, and muscle tissue, thus providing multiple pharmacological targets.[8] Psychedelic drugs also activate other serotonin receptor subtypes, including 5-HT1A, 5-HT2B, and 5-HT2C.

Brain injuries can alter 5-HT2A receptor signalling in the brain, as shown in a recent pre-clinical study in mice in which blast-induced closed-head mTBI increased cortical 5-HT2A receptor sensitivity and ex vivo radioligand binding, corresponding with social behaviour deficits that were reversed by repeated administration of DOI.[9] However, if 5-HT2A receptor sensitivity is chronically altered, patients with mTBI may have different psychedelic dosing requirements to reach therapeutic efficacy.

Psychedelic drugs can promote neuroplasticity

Psychedelic drugs have been shown to have neurobiological effects that include altering neuronal structure,[10] brain activity,[11] and functional connectivity,[12,13] which may provide novel approaches for those experiencing prolonged effects of concussion. Pre-clinical studies using in vitro and in vivo models show that psychedelic drugs interact with neurogenic pathways, such as tropomyosin receptor kinase B and the mammalian target of rapamycin (mTOR), in a manner equivalent to brain-derived neurotrophic factor (BDNF), which is key for the repair, maintenance, and survival of neurons.[10]

The plasticity-enhancing effects of psychedelic drugs may provide therapeutic avenues for people with neurodegenerative conditions,[10,14] including mTBI (Figure 2). Pre-clinical studies show that DMT can increase dendritic spine density and hippocampal neurogenesis and reduce cytokine expression, mediated in part by its affinity for sigma-1 receptors.[10,15] However, currently no clear evidence exists that physiological doses of DMT in humans lead to concentrations in the brain high enough to engage sigma-1 receptors. In addition, a single psilocybin treatment has been shown to rapidly increase dendritic spine density in the mouse prefrontal cortex, an effect that was observed 24 hours after treatment and persisted for a month.[16] Psychedelic-evoked spineogenesis is proposed to result from indirect modulation of synaptic architecture by elevated glutamate levels acting through BDNF/tropomyosin receptor kinase B and mTOR signalling, leading to protein synthesis and synapse formation.[17] mTBI is associated with the loss of functional N-methyl-D-aspartate (NMDA) receptors, which persists for weeks after initial injury;[18] therefore, the elevation of glutamate by psychedelics may restore aspects of structural and functional plasticity. In addition, one study established an association between ayahuasca-induced increases in BDNF and decreased depression symptoms in people with major depressive disorder.[19]

Psychedelic drugs can decrease inflammation

The initial oxidative stress and neuroinflammation that follow a TBI play a beneficial role in recovery; however, chronic activation of microglia affects neuronal regeneration, including neurogenesis.[20] The strain on mitochondrial capacity to scavenge reactive oxygen species (ROS) that results in heightened oxidative stress is a key contributor to neuron damage and death after trauma.[21]

As shown in Figure 2, psychedelics might elicit neuroprotective activity by decreasing apoptotic protease activating factor 1 and pro-inflammatory cytokines (e.g., interleukin [IL]-1 β, IL-6) while up-regulating the expression of neurogenic and anti-inflammatory factors (e.g., BDNF, glial-derived neurotrophic factor, IL-10).[22]

The anti-inflammatory capacity of psychedelics on mouse neural tissue in vivo has recently been shown after pre-treatment with psilocybin (0.88 mg/kg), which decreased lipopolysaccharide (LPS)-induced messenger RNA (mRNA) expression of IL-6, cyclooxygenase-2, and tumour necrosis factor (TNF)-α, and post-treatment psilocybin reduced LPS-induced mRNA expression of IL-6 and TNF-α.[23] In vitro, DOI has been shown to decrease inflammation markers in tissue and cell cultures stimulated with TNF-α,[24,25] which activates nuclear factor kappa B (NF-κB) signalling cascades to evoke inflammation.

The translatability from rodent cells to human immune cells is still in question, because a recent study demonstrated that the 5-HT2A partial agonists LSD, psilocin, DMT, and mescaline did not attenuate lipopolysaccharide (LPS)-triggered NF-κB induction in human monocytes.[26] However, studies examining the anti-inflammatory effects of the full 5-HT2A agonist R-DOI on non-human cells have used TNF-α as an inflammatory stimulus,[24,25] which induces inflammation via different pathways to LPS.

Gastrointestinal (GI) dysfunction is one of several complications among TBI patients that may contribute to systemic inflammation (Figure 3). Neurotrauma can damage gut mucosa and alter gut microbiome composition.[27,28] Because of the expression of serotonin receptors in the gut, orally ingested psychedelic drugs may affect the GI tract, and a recent study showed that repeated LSD treatment altered gut microbiome composition in mice.[29] In smooth muscle cell culture models of inflammation, psychedelic drugs have potent anti-inflammatory effects,[24] and, as such, development of low-dose psychedelics to treat peripheral inflammation may be harnessed as a therapeutic approach in mTBI, as well as in other psychiatric and GI disorders.

Psychedelics may restore brain network connectivity disrupted by traumatic brain injury

After mTBI, damage to neurons and synaptic loss result in reduced neural dynamics and functional complex-

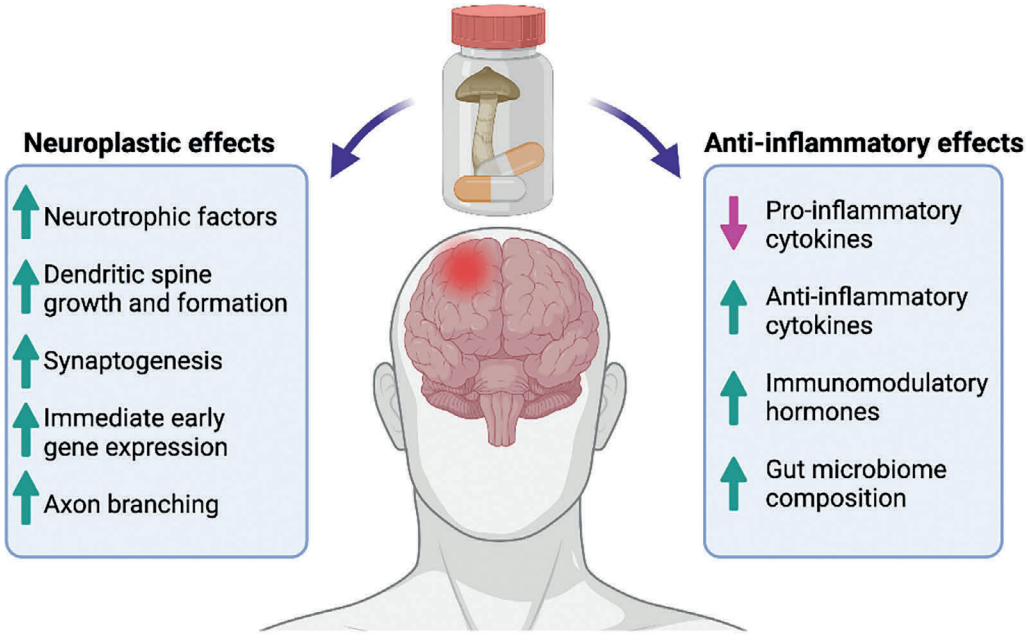

Figure 2. Psychedelic compounds can elicit both neuroplastic and anti-inflammatory effects that may attenuate or counter neuropathological events caused by mild traumatic brain injury.

Note: Psychedelic drugs can increase protein and gene expression of neurotrophic factors, including brain-derived neurotrophic factor, glial-cell-derived neurotrophic factor, and nerve growth factor, as well as increasing expression of immediate early genes such as c-Fos, early growth response protein 1/2, and homer1, which can alter synaptic plasticity. Reduced gene and protein expression of pro-inflammatory cytokines include interleukin (IL)-1β, IL-6, and tumour necrosis factor-α, and increased anti-inflammatory cytokines include IL-10 and transforming growth factor-β. Immunomodulatory hormones include prolactin, cortisol, and prolactin. Image created in http://biorender.com.

ity.[30] An objective measure of neural network dynamics can be calculated from resting-state functional imaging with electroencephalography or magnetoencephalography (MEG). It has been shown that neural complexity is reduced across multiple brain regions among military Veterans who experienced mTBIs relative to healthy controls.[31] In addition, performance of motor responses, visual perception, and memory correlated with functional complexity, and, as such, the decreased repertoire of neural states measured in MEG signals in TBI is likely the result of injured neurons and damaged network connectivity.[32] The acute administration of psilocybin, LSD, or ketamine increased spontaneous neural complexity measured by MEG,[32] and psilocybin globally increased brain network integration measured with functional MRI.[33] This observation suggests that psychedelic therapies may restore the impaired dynamic neural repertoire and improve cognitive flexibility;[34] however, this needs to be tested with patients with mTBI, and the durability of such brain state changes is as yet unknown.

Entourage effects in naturally derived psychedelics

The term entourage effect refers to the synergistic interaction of two or more co-administered compounds. In the case of the psychedelic preparation ayahuasca, β-carboline derivative harmala alkaloids are monoamine oxidase inhibitors that allow DMT to enter the systemic circulation and central nervous system but may also enhance neuroplastogenic effects.[35] Harmine, tetrahydroharmine, and harmaline, the three main alkaloids, and the harmine metabolite harmol stimulate adult neurogenesis in vitro and increase neural stem cell pro-

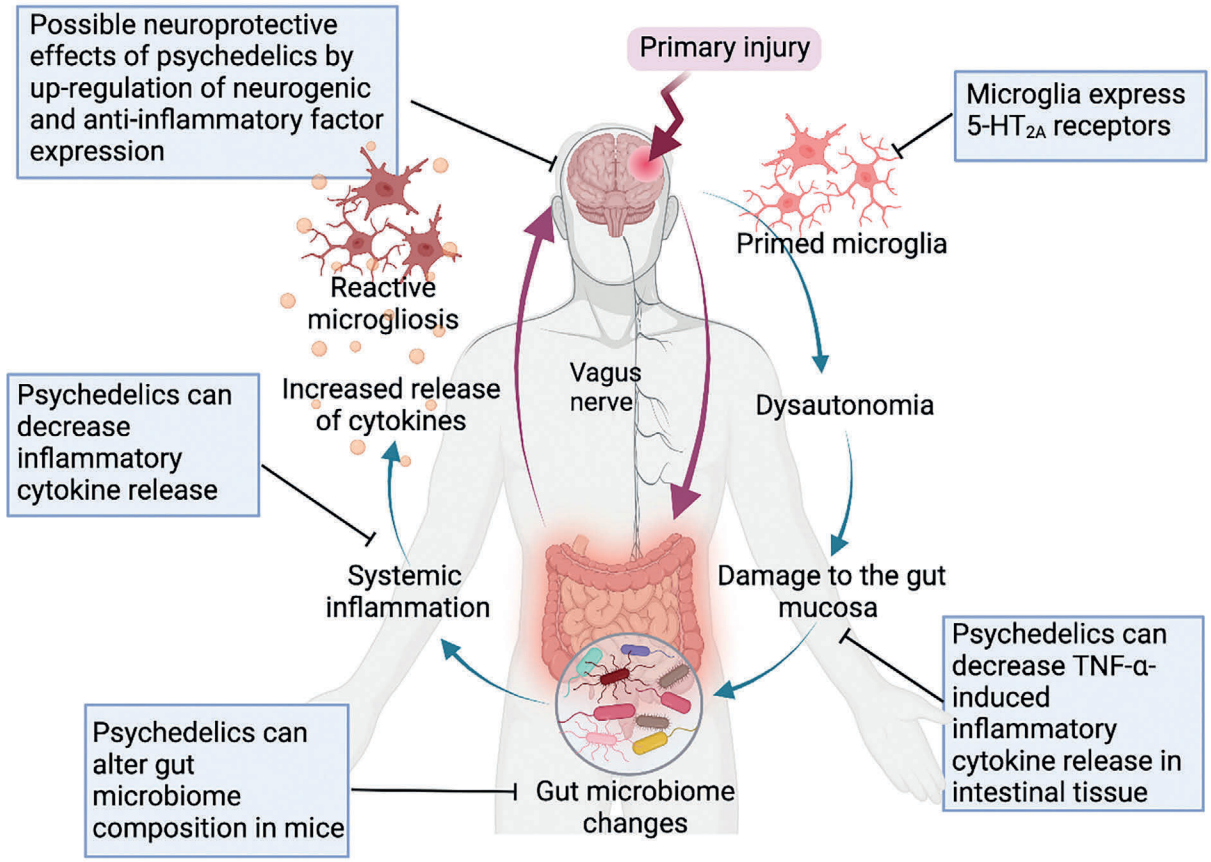

Figure 3. How TBI can cause systemic inflammation and alter gastrointestinal tract function and how psychedelics may diminish these effects

Note: Altered gut microbiome composition can follow brain injury, including increases in populations of pathological microbes, such as *Helicobacter*, *Campylobacter*, and *Escherichia coli*. This can influence neurological health via the gut-microbiome-brain axis — changing neurotransmission, neuroplasticity, microglial activation, and behaviour. Accordingly, therapeutic alterations to the gut microbiota, or attenuating microglia priming or reduced systemic inflammation by psychedelics, may temper the neuropsychiatric consequences of mild TBI. Red arrows indicate the bidirectional gut-microbiome-brain axis. Image created in http://biorender.com.

TBI = traumatic brain injury.

liferation, migration, and differentiation into adult neurons,[36] and harmine and harmaline possess antioxidant properties.[36] Pharmahuasca, a form of DMT co-dosed with defined quantities of specific β-carbolines, may be used to reduce the confounds of heterogeneous ayahuasca preparations.

Psilocybin, baeocystin, norbaeocystin, and aeruginascin are tryptamines present in *psilocybe* mushrooms. Although less studied than psilocybin and psilocin, in vitro assessment of baeocystin, norbaeocystin, and aeruginascin shows that they display affinity for 5-HT2A and 5-HT1A in mouse brain tissue and exhibit agonist efficacy in assays examining 5-HT2A-mediated calcium mobilization and β-arrestin 2 recruitment while not evoking head-twitch response in mice in vivo,[37] a proxy for 5-HT2A-induced hallucinogenic effects. Moreover, botanical *psilocybe* extracts were 10 times as potent as synthetic psilocin at inducing head-twitch responses in mice,[38] further suggesting synergistic effects. Although clinical trials can use both synthetic and naturally derived psilocybin, whole *psilocybe* extracts may have some advantages because they contain a spectrum of tryptamines, although these require further characterization and likely must be delivered in defined quantities, similar to pharmahuasca in clinical studies.

Nutraceutical compounds

Non-psychedelic functional mushrooms fall into the category of nutraceutical compounds — food or dietary supplements with potential physiological benefits. Lion's mane (*Hericium erinaceus*) and reishi (*Ganoderma lucidum*) have a long history of use in traditional Eastern medicines and are becoming recognized as nutraceutical approaches to neurological health through neuroprotective and anti-inflammatory mechanisms. The putative neuroregenerative mechanism of *H. erinaceus* has been examined pre-clinically, and it has recently been shown that the bioactive compounds N-dephenylethyl isohericerin and hericene A promote extensive axon outgrowth and neurite branching, enhanced hippocampal memory, and increased neurotrophin expression and downstream signalling.[39]

Extracts from *G. lucidum* have been shown to downregulate pro-inflammatory cytokine expression in microglia cell culture via attenuation of NF-κB and mitogen-activated protein kinase signalling pathways after stimulation with lipopolysaccharide.[40] *Ganoderma microsporum* (another species of *Ganoderma* mushrooms native to Taiwan) supplementation has been explored in a penetrating cortical damage model of TBI in rats that reduced astrogliosis, increased anti-oxidative superoxide dismutase type 1 expression, and improved spatial memory deficits.[41]

Synergistic interactions between psychedelic and non-psychedelic compounds

The combination of functional mushrooms, particularly lion's mane and niacin with sub-perceptual micro-doses of psilocybin or LSD, which refers to the administration of doses equal to approximately 10% of the hallucinogenic doses used recreationally, is a growing practice in individuals. The micro-dosing literature remains early and exploratory, with clear limitations on existing study designs, such as lack of randomized placebo-controlled trials,[42] and therapeutic margins of receptor occupancy have yet to be determined. Citizen science studies of micro-dosing have shown some mental health benefits in humans, as well as improvements in psychomotor performance among older adults.[43] Further research, including the examination of objective biomarkers of inflammation and neuroplasticity in humans and rodents, is needed to establish whether there are synergistic effects of low doses of psilocybin combined with lion's mane or niacin.

N-acetyl-cysteine (NAC) has been shown to have antioxidant and neurovascular-protective effects after TBI.[44] NAC administration has been shown to protect against oxidative injury mediated by ROS and to reduce inflammatory markers in a rat model of TBI,[45] as well as to enhance cognitive recovery.[46] In a human study, blast-exposed military personnel who received NAC supplementation within 24 hours of TBI exposure had a greater resolution of symptoms than controls who received placebo.[47] The potential synergy between NAC and psilocybin is currently being investigated in a Phase 1 clinical trial for posttraumatic stress disorder.

Conclusions, limitations, and future research

To be an effective moderator of neurological outcomes at multiple points along the mTBI continuum, a therapeutic intervention needs to restore cognitive reserve, attenuate or modify signalling inflammatory cascades in the brain and other organ systems, such as the GI tract, and support neural compensation and repair. Moreover, the experimental models of mTBI differ greatly from the biomechanics of mTBIs experienced by humans (Figure 4). If pre-clinical studies do translate to humans, the neuroplasticity-enhancing and anti-inflammatory capacity of psychedelic compounds may provide a two-pronged approach to therapies for mTBI.

Whether psychedelic compounds can address mTBI neuropathologies in humans is currently unknown, and currently no clinical trials are investigating psychedelic compounds with TBI as a direct indication. Moreover, the therapeutic parameters of 5-HT2A receptor occupancy and duration of activation are still to be determined, and if both 5-HT2A and NMDA receptor sensitivity are altered by mTBI, this may alter the therapeutic dose and increase potential side effects of psychedelic-based compounds. Nevertheless, pre-clinical data that suggest psychedelics could potentially ameliorate some of the negative neurobiological effects of brain injury are promising.

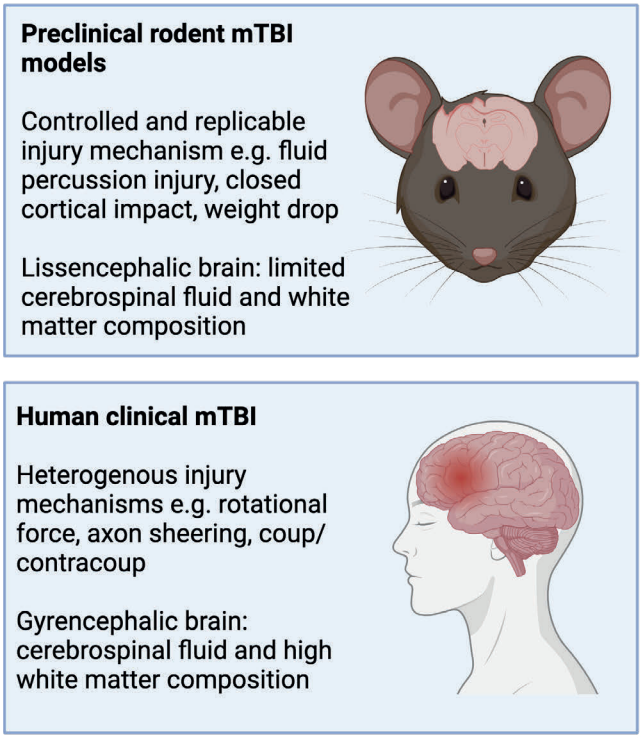

Figure 4. Preclinical models of TBI can inform about the neurological, morphological, biochemical, and behavioural outcomes of injury in a controlled and replicable setting, but there are translational limitations.

Note: Rodents have small, lissencephalic brains with less cerebrospinal fluid and white matter than the large, gyrencephalic human brains; thus, the biomechanics of TBIs differ substantially. The consequences of the controlled experimental injury mechanisms used in rodent studies (e.g., fluid percussion injury, closed cortical impact, weight drop) differ from the heterogeneous injury mechanisms in human TBIs, so success with interventions in rodents might not always be translatable to humans. Nonetheless, rodent models can help reveal therapeutic mechanisms and provide proof-of-concept information to drive clinical investigations.

TBI = traumatic brain injury; mTBI = mild traumatic brain injury.

AUTHOR INFORMATION

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COMPETING INTERESTS

The authors have nothing to disclose.

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