Neurotherapeutics 21 (2024) e00374

Contents lists available at ScienceDirect

Neurotherapeutics

journal homepage: www.sciencedirect.com/journal/neurotherapeutics

Current Perspectives

Restoring consciousness with pharmacologic therapy: Mechanisms, targets, and future directions

Megan E. Barra [a,b], Ken Solt [c], Xin Yu [d], Brian L. Edlow [b,d,e,*]

[a] Department of Pharmacy, Massachusetts General Hospital, Boston, MA, USA
[b] Center for Neurotechnology and Neurorecovery, Massachusetts General Hospital, Boston, MA, USA
[c] Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, MA, USA
[d] Department of Radiology, Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Boston, MA, USA
[e] Department of Neurology, Massachusetts General Hospital, Boston, MA, USA

ARTICLE INFO

Keywords:
Consciousness
Stimulant
Recovery
Brain injury

ABSTRACT

Severe brain injury impairs consciousness by disrupting a broad spectrum of neurotransmitter systems. Emerging evidence suggests that pharmacologic modulation of specific neurotransmitter systems, such as dopamine, promotes recovery of consciousness. Clinical guidelines now endorse the use of amantadine in individuals with traumatic disorders of consciousness (DoC) based on level 1 evidence, and multiple neurostimulants are used off-label in clinical practice, including methylphenidate, modafinil, bromocriptine, levodopa, and zolpidem. However, the relative contributions of monoaminergic, glutamatergic, cholinergic, GABAergic, and orexinergic neurotransmitter systems to recovery of consciousness after severe brain injury are unknown, and personalized approaches to targeted therapy have yet to be developed. This review summarizes the state-of-the-science in the neurochemistry and neurobiology of neurotransmitter systems involved in conscious behaviors, followed by a discussion of how pharmacologic therapies may be used to modulate these neurotransmitter systems and promote recovery of consciousness. We consider pharmacologic modulation of consciousness at the synapse, circuit, and network levels, with a focus on the mesocircuit model that has been proposed to explain the consciousness-promoting effects of various monoaminergic, glutamatergic, and paradoxically, GABAergic therapies. Though fundamental questions remain about neurotransmitter mechanisms, target engagement and optimal therapy selection for individual patients, we propose that pharmacologic therapies hold great promise to promote recovery and improve quality of life for patients with severe brain injuries.

Introduction

Disorders of consciousness (DoC) are a continuum of states of impaired arousal and awareness, including coma, vegetative state/unresponsive wakefulness syndrome (VS/UWS), minimally conscious state (MCS), cognitive motor dissociation, and covert cortical processing [1–4]. Severe brain injury impairs consciousness through a broad spectrum of neuroanatomic lesions involving the bilateral cerebral hemispheres, rostral brainstem, diencephalon, or basal forebrain. Therapeutic approaches to restoring consciousness fundamentally depend on understanding how these anatomically diverse lesions cause reversible circuit and network changes that are amendable to modulation [5,6]. Advanced neuroimaging and electroencephalographic tools have been central to this effort, providing new opportunities to identify personalized targets for pharmacologic therapies [7]. Currently, a single pharmacologic therapy, amantadine, is recommended by clinical guidelines to promote recovery of consciousness in patients with traumatic DoC based on level 1 evidence [8,9]. However, multiple pharmacologic therapies are used off-label in clinical practice, including methylphenidate, modafinil, bromocriptine, levodopa, and zolpidem, among others [10]. For clinicians to select the optimal pharmacologic therapy for an individual patient, it is essential to consider each therapy's underlying mechanisms, intended targets, and safety profile.

This review summarizes the state-of-the-science in pharmacologic neurostimulant therapy to promote recovery of consciousness in patients with DoC after acquired brain injury. We begin with an update on the neurochemistry and neurobiology of brain circuits and networks that modulate human consciousness. Next, we discuss how neurochemical

* Corresponding author. Center for Neurotechnology and Neurorecovery, Massachusetts General Hospital, 101 Merrimac Street – Suite 310, Boston, MA 02114, USA.
E-mail address: bedlow@mgh.harvard.edu (B.L. Edlow).

https://doi.org/10.1016/j.neurot.2024.e00374
Received 1 December 2023; Received in revised form 16 April 2024; Accepted 3 May 2024

and neurobiological insights have been synthesized into a comprehensive mesocircuit model of DoC. Finally, we consider current evidence for clinical application of pharmacologic modulation of these circuits, and we propose future directions for promoting recovery of consciousness after severe brain injury.

Neurochemistry and Neurobiology of Consciousness: Identifying Treatment Targets

Numerous neurotransmitters have been identified as contributors to human consciousness over decades of investigation into sleep, anesthesia, and coma [11]. Alterations in the balance of GABA-mediated inhibitory neurotransmission and glutamate-mediated excitatory neurotransmission are well established to play an important role in generating a state of unconsciousness. Beyond GABA and glutamate, monoaminergic neurotransmitters, such as dopamine, have emerged as critical contributors to consciousness, while the contributions of norepinephrine, histamine, orexin, adenosine, and acetylcholine in the pathogenesis of DoC continue to be explored.

Understanding the pathophysiologic drivers of DoC is crucial to identifying targets for pharmacologic therapies that promote recovery of consciousness. Growing evidence from preclinical models and clinical trials indicates that multiple neurotransmitter systems can be stimulated to restore human consciousness. These neurotransmitter systems include amino acids, monoamines, orexin and acetylcholine, among others (Fig. 1 and Fig. 2A). However, there is currently a lack of animal models of DoC to investigate the relative contributions of these neurotransmitter systems to the two components of consciousness: arousal and awareness. Animal models have historically used a lesional approach to induce coma using invasive surgical procedures. Each animal model has limitations that are beyond the scope of this review but include preservation of purposeful behaviors [12–16], inability to distinguish the effects of lesional injury from global cerebral hypoperfusion at the time of coma induction [17], and uncertain neuroanatomic translation of lesional effects to humans with DoC [18]. Much of what we have learned has come from inducing transient coma with anesthetic agents and promoting reemergence of consciousness after anesthesia [11,19].

Below we consider the current state-of-the-science in neurotransmitter systems, recognizing that substantial additional work in preclinical models is required to determine the neurotransmitter systems that hold the greatest promise for pharmacologic modulation to restore consciousness.

Amino acid neurotransmission (glutamate, GABA)

Glutamate is the predominant excitatory neurotransmitter in the brain, while γ-aminobutyric acid (GABA) is the predominant inhibitory neurotransmitter. Glutamate binds to N-methyl-D-aspartate (NMDA) or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors to potentiate excitatory signaling, while GABA binds to $GABA_A$ or $GABA_B$ receptors to potentiate inhibitory signaling [21]. Alteration in neurotransmitter availability along with NMDA, AMPA, and GABA receptor subunit composition, expression, and function after acute brain injury may induce imbalance in excitatory and inhibitory circuits, causing widespread dysfunction in neural network connectivity [21]. Animal models indicate that even activating networks such as the subcortical ascending arousal network (i.e., ascending reticular activating system) require a delicate balance of inhibitory GABAergic signaling to sustain wakefulness [22–25].

It is also important to consider that enhancement of excitatory signaling is not always beneficial, as an increase of glutamate release in the hyperacute period after acquired brain injury may provoke secondary neuronal injury through excitotoxic mechanisms [26,27]. Glutamate excitotoxicity is thus a key consideration in the timing and selection of pharmacologic therapies to restore consciousness. While NMDA receptor antagonists dexanabinol and dizocilpine and AMPA receptor antagonist NBQX were found to be neuroprotective in preclinical models of traumatic brain injury, they have so far failed to improve outcomes in clinical trials [28,29]. Glutamate-activating NMDA receptors are diverse and may mediate either neuroprotective or neurotoxic effects depending on

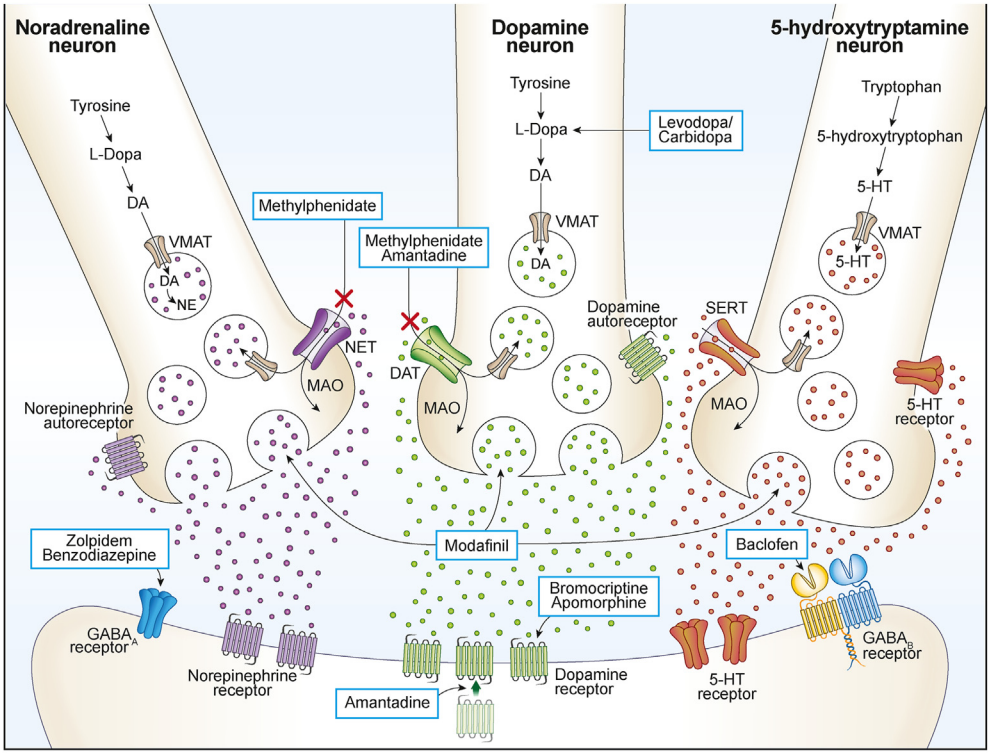

Fig. 1. Neurotransmitter and receptor targets of commonly prescribed pharmacologic neurostimulants
Three presynaptic neurons releasing noradrenaline, dopamine and 5-hydroxytryptamine, respectively, are shown synapsing with a single post-synaptic neuron for illustrative purposes. Abbreviations: 5-HT = 5-hydroxytryptamine; DA = dopamine; DAT = dopamine transporter; GABA = γ-aminobutyric acid; MAO = monoamine oxidase; NE = norepinephrine; NET = norepinephrine transporter; SERT = serotonin transporter; VMAT = vesicular monoamine transporter. Figure adapted from Barra et al. *Seminars in Neurology*, 2022 [10]. Artwork by Sarah Pyle.

subunit composition [30]. Non-discriminatory blockage of NMDA receptors or development of selective pharmacotherapies thus warrants further investigation.

$GABA_A$ receptors are heteropentamers with varied combinations of 19 known subunits resulting in numerous isoforms with distinct physiologic properties [31]. $GABA_A$ receptor surface expression is broadly represented throughout the brain, though some isoforms have selective expression in the thalamus, hypothalamus, cerebral cortex, cerebellum, or mesencephalon [32]. It is postulated that $GABA_B$ receptors modulate orexin A and B neurons in the hypothalamus and brainstem [33,34], as well as histaminergic neurons in the tuberomammillary nucleus [35], to promote wakefulness.

The role of GABA-mediated inhibition in modulating consciousness is clearly demonstrated in drug-induced coma with intravenous anesthetics [11]. Similarly, after acquired brain injury, alterations in GABA receptor function or GABA neurotransmitter release may result in prolonged brain suppression and neurodormancy in patients with DoC [20]. Whether this state of altered GABAergic signaling is a marker of irreversible neuronal injury, or a reversible and protective down-regulated state, is currently being debated and may differ among patients, or perhaps even among neuroanatomic regions in an individual patient's brain [36].

Although GABA is traditionally considered an inhibitory neurotransmitter and GABA receptor stimulation induces unconsciousness, paradoxical excitation of the cerebral cortex after GABAergic therapy has been reported in patients with and without severe brain injuries [37–40]. This paradoxical observation, which has been replicated with zolpidem and benzodiazepines, suggests that restoration of normal GABA signaling may reverse excessive inhibition, restore thalamocortical signaling within the mesocircuit, and promote functional recovery in a subset of patients with DoC [41]. The development of neuroimaging biomarkers to identify this subset of patients with DoC who respond to GABAergic therapy is an area of active inquiry [42–44].

Monoamine neurotransmission (dopamine, serotonin, norepinephrine, histamine)

Monoaminergic arousal circuits arise through norepinephrine release from the locus coeruleus, serotonin release from the median and dorsal raphe, histamine release from the tuberomammillary nucleus, and dopamine release from the ventral tegmental area (Fig. 2A) [11]. The dopaminergic system is thought to be a primary neurochemical driver of consciousness, based on pharmacologic [45,46], electrophysiologic [47], optogenetic [48,49], and chemogenetic [50] methods, as well as behavioral experiments in dopamine knock-out mice [51]. The ventral tegmental area is interconnected through dopaminergic neuromodulation with the posterior cingulate cortex and precuneus, a central node in the brain's default mode network [52–54]. In preclinical models of anesthetic-induced unconsciousness, pharmacologic stimulation of D1 receptors with amphetamine, chloro-APB, and methylphenidate induced emergence, highlighting the important role of dopamine signaling in higher levels of consciousness [45,46,55–58]. Stimulation of the ventral tegmental area but not the substantial nigra during general anesthesia activates emergence, further supporting the role of the ventral tegmental area and dopamine signaling in consciousness [47].

It has been postulated that depletion of monoamines or suppression of brain regions reliant on monoamines for function may play an important role in disorders of consciousness [20,59], a hypothesis that is supported by emerging evidence from human neuroimaging studies revealing presynaptic dopamine neurotransmitter deficits in the striatum and central thalamus [60]. In addition to dopamine, release of other monoamines, such as serotonin (5-hydroxytryptamine, 5-HT), norepinephrine, and histamine, promotes wakefulness in animal models [61]. Animal models also indicate that bilateral lesions in arousal-promoting noradrenergic neurons in the locus coeruleus reduced norepinephrine levels in the paleocortex, neocortex, thalamus, and midbrain that resulted in transient electroencephalogram (EEG) suppression with reactivation within 12–48 h post-injury [62]. Interestingly, behavioral arousal and EEG activation induced by amphetamine administration was not influenced by lesional injury in the locus coeruleus in cats or by anesthesia in rats [46,62]. The extent to which pharmacologically induced increases in extracellular norepinephrine augment dopaminergic stimulation of arousal in preclinical models of anesthetized animals is unknown [45,58]. Histaminergic pathways in the tuberomammillary nucleus also appear to play a role in modulation of arousal and emergence from anesthesia in pre-clinical models. Histamine levels are increased during awake states and decreased during sleep or anesthetized states [63]. Histamine is thought to modulate arousal through innervation of cholinergic and GABAergic neurons in the basal forebrain [64]. Administration of histamine into the nucleus basalis magnocellularis in the basal forebrain induced EEG activation and accelerated emergence from isoflurane-induced anesthesia in rat models [65]. The tuberomammillary nucleus likely exerts its effects in concert with other monoaminergic and orexinergic pathways, as histaminergic neurons do not necessary regulate global spontaneous wakefulness [66].

Serotonin plays an important role in promotion of wakefulness and regulation of the sleep wake cycle [67,68]. Serotonin levels have been reported to be markedly increased in postmortem evaluation of patients with hepatic and uremic coma, while decreased serotonin synthesis and serotonin transporters have been reported in rats with traumatic brain injury [69,70]. There are 14 different serotonin receptor subtypes, with varied localization and expression throughout the brain, that have been explored as therapeutic targets in a variety of disease states [71,72]. Serotonin receptors have a role in modulation of 5-HT, acetylcholine, norepinephrine, dopamine, glutamate, and GABA neurotransmission depending on receptor subtype and location. High density of $5\text{-}HT_{2A}$ receptors has been identified in association cortical areas of the default mode network and thalamo-cortical system [73–75]. Interestingly, various anesthetics have opposing effects on the $5\text{-}HT_3$ receptor, which is widely distributed throughout the central nervous system. Therefore, $5\text{-}HT_3$ contributions to anesthesia induction may occur through indirect mechanisms [76].

Other molecules (acetylcholine, orexin, adenosine)

Acetylcholine modulates arousal via cholinergic circuits emanating from the basal forebrain, lateral dorsal tegmental nuclei, and pedunculopontine tegmental nuclei [11,77]. Acetylcholine release is closely coupled with arousal state switching [78]. Different synchronization releasing patterns of acetylcholine (tonic versus phasic) are involved in regulating sleep stages and contribute to states of high-arousal [79,80]. Interruption of central cholinergic muscarinic neurotransmission may be a mechanism by which anesthetic agents contribute to loss of consciousness [11]. Cholinergic stimulation with carbachol, a mixed cholinergic agonist, in the prefrontal prelimbic cortex but not the parietal cortex reversed sevoflurane-induced anesthesia in rats [77]. However, physostigmine, a cholinesterase inhibitor that increases acetylcholine levels, has shown mixed results at reversing anesthesia-induced unconsciousness in preclinical models [81,82].

Orexinergic neurons also play a critical role in arousal. Increased orexinergic neuronal activity is observed during wakefulness, in contrast to the decreased discharge of orexin neurons during low vigilance states in animals [83,84]. Further, orexin interacts with other neuromodulatory systems in the locus coeruleus, ventral tegmental area, and basal forebrain to influence arousal state changes [85–87]. Recently, the orexin receptor 2 agonist danavorexton was found to accelerate recovery from general anesthesia and opioid-induced sedation in animal models [88]. Interestingly, stimulation of orexinergic neurons has only been shown to impact emergence from and not impede induction of anesthesia [89,90].

Lastly, adenosine is a ubiquitous signaling molecule that is essential to cellular activity throughout the body, including the central nervous system. Adenosine-facilitated inhibition of the locus coeruleus leads to downstream inhibition of ascending arousal circuits in non-REM sleep

[11]. In states of stress, such as hypoxic/anoxic conditions, adenosine may protect cells from metabolic stress through decreased excitatory neurotransmission, maintenance of intracellular calcium concentrations, and decreased membrane depolarization. While initially serving as a neuroprotectant, accumulation of adenosine may impede recovery through delayed return of synaptic transmission [91]. Caffeine, an adenosine receptor antagonist, was found to accelerate recovery from isoflurane and propofol anesthesia in preclinical and early clinical models [92,93].

Summary of neurobiological and neurochemical mechanisms of consciousness

In summary, numerous neurotransmitters contribute to wakefulness and to recovery of consciousness after anesthetic-induced unconsciousness or severe brain injury. Yet the neurotransmitter systems that are essential to sustaining human consciousness, and that are most important for recovery of consciousness after a severe brain injury, have yet to be fully identified. The roles of GABA-mediated inhibitory neurotransmission and glutamate-mediated excitatory neurotransmission are well established in the induction of coma or altered levels of consciousness. Dopaminergic signaling has emerged as a critical factor in consciousness and its disorders, while the contributions of norepinephrine, histamine, orexin, adenosine, and acetylcholine in the development of DoC after brain injury continue to be elucidated.

Whether impaired neurotransmitter synthesis, release or receptor function are the primary drivers of DoC in patients is unknown. As a result, there is currently a broad spectrum of therapeutic approaches being used in the investigational and clinical domains to target pre-synaptic and post-synaptic function (Fig. 1). Pharmacologic agents that modulate neurotransmitter release and/or re-uptake rely on the retained ability of the pre-synaptic neuron for neurotransmitter synthesis. Pharmacologic agents that act as positive allosteric modulators at neurotransmitter receptors also rely on preserved pre-synaptic neuronal function, augmenting neurotransmitter action on post-synaptic receptors. Finally, pharmacologic agents that act as direct agonists may reestablish post-synaptic neuronal function even in the presence of damaged pre-synaptic neurons that release decreased or absent levels of neurotransmitters. Future identification of pre-synaptic and/or post-synaptic neuronal dysfunction in individual patients with DoC will be a crucial step toward the development of novel, personalized therapeutic approaches.

Mesocircuit Model of Consciousness

The mesocircuit model of DoC is based on the broad withdrawal of excitatory neurotransmission across the frontoparietal cortical regions, central thalamus, brainstem, and striatum, leading to arousal dysregulation (Fig. 2B) [94]. Structural injury inducing forebrain neuronal death, deafferentation and disconnection, as well as functional disturbances of neuronal connections, may result in the large-scale forebrain dysfunction observed in DoC [95]. The anterior forebrain mesocircuit is interconnected with fronto-parietal networks that contribute to conscious awareness, including the default mode, executive control, and salience networks [3]. In DoC, loss of striatal inhibition of the globus pallidus results in excessive inhibition of a hypoactive thalamus, leading to reduced thalamocortical activation of frontoparietal regions [96]. As predicted by the mesocircuit model, disruptions in default mode network functional connectivity correlate with decreased level of consciousness [96–100]. Electrical stimulation of central thalamic nuclei (including intralaminar nuclei and mediodorsal thalamus) has aroused unconscious monkeys anesthetized with propofol [101,102], and has led to increased behavioral responsiveness in a patient with chronic minimally conscious state [103], strengthening the mechanistic link between thalamocortical signaling and consciousness. The development of neuroimaging and electrophysiologic biomarkers that measure the integrity of the mesocircuit in patients with DoC is an area of active inquiry that has the potential to guide selection of therapies aimed at upregulating mesocircuit function [42–44,104–106]. An extension of the mesocircuit model has recently been proposed to incorporate dysfunction of monoaminergic pathways from the brainstem as additional key contributors to the development of DoC [107].

Clinical Evidence for Pharmacologic Neurostimulation in the Treatment of DoC

Pharmacologic therapy offers an accessible and inexpensive pathway to modulate neurotransmitter systems that have been identified as key contributors to the pathophysiology of DoC (Figs. 1 and 2A). Pharmacologic therapy for the treatment of DoC aims to restore the functional integrity and homeostatic balance of neurotransmitter systems, thereby stimulating emergence of consciousness and maximizing rehabilitative efforts. Current therapeutic options modulate dopamine (amantadine, bromocriptine, levodopa, apomorphine), mixed monoamine neurotransmitters (methylphenidate, modafinil), or GABA receptors (zolpidem, benzodiazepine, baclofen), as detailed in Table 1 and Fig. 1. Amongst surveyed healthcare practitioners caring for patients with DoC in the acute, subacute, or chronic setting, amantadine was the most commonly prescribed neurostimulant (51%), followed by modafinil (37%), methylphenidate (30%), amphetamine salts (12%), levodopa (12%), and zolpidem (8%) [108].

Based on robust evidence for dopaminergic pathway disruption in preclinical and clinical models of DoC, pharmacologic neurostimulants that modulate dopaminergic transmission are currently the most widely utilized intervention to promote arousal. Amantadine is the only neurostimulant recommended by the 2018 practice guidelines for DoC in adults with traumatic DoC at 4–16 weeks post-injury [9]. Amantadine is currently the only therapy that has been shown in a randomized controlled trial to promote functional recovery in patients with severe brain injury [8]. In this double blind, randomized, placebo-controlled trial of patients in a VS/UWS or MCS 4–16 weeks after traumatic injury, amantadine treatment was associated with a higher proportion of patients who were moderately-severe-to-severely disabled (25.6% versus 16.8%), a lower proportion of patients in a vegetative state (18.6% versus 31.6%), and higher rates of recovery in all six domains of the Coma Recovery Scale-Revised at the end of the trial. The efficacy of amantadine in this study supports the hypothesis that dopaminergic pathway disruption plays a role in regulation of consciousness. Despite limited high-quality evidence, pharmacologic neurostimulation with amantadine continues to be reported in observational analysis and single-center studies in patients with acute traumatic DoC (i.e., before 4 weeks post-injury) and in non-traumatic DoC [109–118]. Case reports and case series have reported consciousness-promoting effects of dopaminergic stimulation with levodopa, apomorphine, and bromocriptine [119–124], but evidence from randomized controlled trials is currently lacking.

Methylphenidate inhibits dopamine reuptake, inhibits norepinephrine reuptake and is a weak agonist at the serotonin receptor [125]. Few studies have examined the effectiveness of methylphenidate in promoting recovery from DoC [7,126], and evidence from randomized controlled trials is similarly lacking. Nevertheless, methylphenidate therapy continues to be reported as a pharmacologic neurostimulant utilized off-label in clinical practice in patients with DoC [108,127,128]. Mechanistic support for this approach comes from a study of TBI patients without DoC, in whom methylphenidate administration increased connectivity between the ventral tegmental area and posteromedial complex (i.e., posterior cingulate cortex and precuneus) [52].

Modafinil is believed to have therapeutic effects in patients with DoC through stimulation of histamine, norepinephrine, serotonin, dopamine, and orexin neurotransmitters and potential anti-oxidative effects [129]. Neuroimaging studies found modafinil increased cerebral blood flow in the thalamus, locus coeruleus, limbic system, and insular cortex [129, 130]. However, observational reports of modafinil use in patients with DoC have revealed mixed results [130–132].

Table 1
Pharmacologic agents considered for the treatment of DoC.

Agent	Mechanism of Action	Suggested Dosing in DoC	Adverse Effects
Amantadine	↓ dopamine reuptake ↑ dopamine receptor density Modification of dopamine receptor conformation NMDA-receptor antagonism	Dose based on creatinine clearance: >50 mL/min: 100–200 mg twice daily 30–50 mL/min: 100 mg once daily 15–29 mL/min: 100 mg every other day <15 mL/min: 200 mg every 7 days Hemodialysis: 200 mg every 7 days	Agitation, anxiety, delirium, insomnia, dizziness, orthostatic hypotension, peripheral edema, livedo ritcularis, xerostomia, constipation, urinary retention
Bromocriptine	D2-receptor agonism	1.25–2.5 mg BID	Fatigue, headache, weakness, hypotension, xerostomia, nausea, vomiting, constipation, diarrhea, sialorrhea, hypoglycemia in combination with other antidiabetic agents
Levodopa/carbidopa	↑ dopamine	50mg/12.5 mg - 100/25 mg BID – TID[B]	Agitation, anxiety, delirium, insomnia, dizziness, headache, dyskinesia, psychosis, orthostatic hypotension, peripheral edema, hypertension, xerostomia, nausea, constipation, dyskinesia, rash
Methylphenidate	↓ dopamine reuptake ↓ norepinephrine reuptake	5–30 mg BID	Agitation, anxiety, delirium, insomnia, headache, tachycardia, hypertension, xerostomia, rash
Modafinil	↑ histamine, norepinephrine, serotonin, dopamine, and orexin Anti-oxidative effects	100 mg–400 mg daily	Agitation, anxiety, delirium, insomnia, headache, tachycardia, hypertension, edema, xerostomia, constipation, rash
Zolpidem	$GABA_A$ omega-1 receptor subtype agonism	10 mg QD – TID Hepatic impairment: Reduce dose by 50%	Agitation, anxiety, delirium, insomnia, headache, amnesia, disinhibition, tachycardia, hypertension, edema, orthostatic hypotension, xerostomia, diarrhea constipation, hiccups, urinary incontinence

[A] Limited evidence is available to guide appropriate apomorphine, baclofen, and benzodiazepine therapy with the goal of promoting recovery of consciousness.
[B] Utilization of levodopa/carbidopa 100 mg/25 mg tablets can decrease the risk of adverse effects from peripheral dopamine in patients with daily levodopa requirements ≤400 mg/day. Maximum daily dose carbidopa is 200 mg/day.

Paradoxical awakening after administration of $GABA_A$ receptor agonists zolpidem and benzodiazepines or the $GABA_B$ receptor agonist baclofen have been reported [133–137], leading to intense interest in identifying patients who are physiologically receptive to GABAergic therapy. Paradoxically increased conscious behaviors after zolpidem administration have been reported to occur in approximately 5% of patients with DoC [136,138–140]. Zolpidem's preferential binding to the $GABA_A$ omega-1 receptor subtype in the globus pallidus interna may in part explain the paradoxical effectiveness of zolpidem in patients with DoC and supports the mesocirciut model [134,138,141]. Baclofen has been theorized to promote emergence of consciousness either 1) through modulation of impulse transmission from spine to cortex, interfering with spasticity-induced proprioceptive outputs that may interfere with maintenance of alertness and awareness; or 2) through modulation of neurotransmission and functional restoration of cortico-thalamo-cortical connections [142].

Clinical Application of Pharmacologic Neurostimulant Therapy

Optimal timing of pharmacologic neurostimulant initiation after acquired brain injury remains controversial. When and which neurostimulant therapy is initiated is often clinician and patient specific. Recent international survey data indicate that amantadine is the most commonly prescribed stimulant worldwide [108], as it is currently the only neurostimulant recommended by clinical guidelines [9]. Prior to initiation, reversible etiologies of DoC should be evaluated and corrected or ruled out to reduce polypharmacy. Agent-specific interactions with comorbid conditions (e.g., renal dysfunction, hepatic dysfunction, cardiovascular disease, urologic disorders), drug-interactions, and adverse effect profiles (Table 1) should be considered when selecting the optimal agent.

After initiating a pharmacologic neurostimulant, close observation by clinicians and families for neurobehavioral changes is essential, and it is important to allow sufficient time (i.e., 4–6 weeks) to assess a therapeutic response. In the subacute-to-chronic setting, the Coma Recovery Scale-Revised (CRS-R) [143] and revised Motor Behavioral Tool (MBT-r) [144] may be used to optimize detection of subtle changes in behavior. In the acute ICU setting, the recently developed Coma Recovery Scale Revised For Accelerated Standardized Testing (CRSR-FAST) [145] may enhance opportunities to detect changes in behavior, given the insensitivity of the Glasgow Coma Scale at detecting changes in level of consciousness [146]. In patients with an inadequate or partial response to initial therapy selection, an alternative neurostimulant may be considered as monotherapy or in combination. Whether combination provides additive or synergistic effects is unknown and may depend upon patient-specific pathophysiologic factors.

Emerging Therapies in the Treatment of DoC

Elucidating the neurochemistry and neurobiology of consciousness and characterizing brain network disruptions with advanced imaging and electrophysiologic techniques are expected to pave the way for personalized pharmacotherapy approaches in patients with DoC. Given varying response to pharmacologic stimulant therapy in clinical practice, it is likely that the pathogenesis of DoC is not universally regulated by the same neurotransmitter alterations across all patients. Yet standardized diagnostic tools to detect patient-specific alterations in neurotransmitter pathways are not currently available, resulting in potentially inefficient treatment trials that enroll patients with a low likelihood of therapeutic target engagement.

The mesocircuit model provides a neurobiological basis for therapy selection to promote recovery of consciousness – both for investigation in clinical trials and for off-label use in clinical practice. The mesocircuit model further supports the use of dopaminergic therapy for initial selection in patients with DoC [44,52]. Cerebral spinal fluid sampling and microdialysis may identify neurotransmitter metabolites and thus surrogate markers of neurotransmitter deficits [147,148]. However, these invasive diagnostic approaches do not distinguish the cause of the neurotransmitter deficiency in DoC. New diagnostic tools are needed to identify whether synthesis, release, or reuptake pathways are impaired and to elucidate the functional integrity and expression of neurotransmitter receptors. Advanced neuroimaging tools such as functional MRI ("pharmacological MRI"), positron emission tomography (PET), and single photon emission computed tomography (SPECT) may identify alterations of neurotransmitter function but are not widely available, costly to implement, and no standardized biomarkers to guide therapy selection in patients with DoC currently exist [149–151].

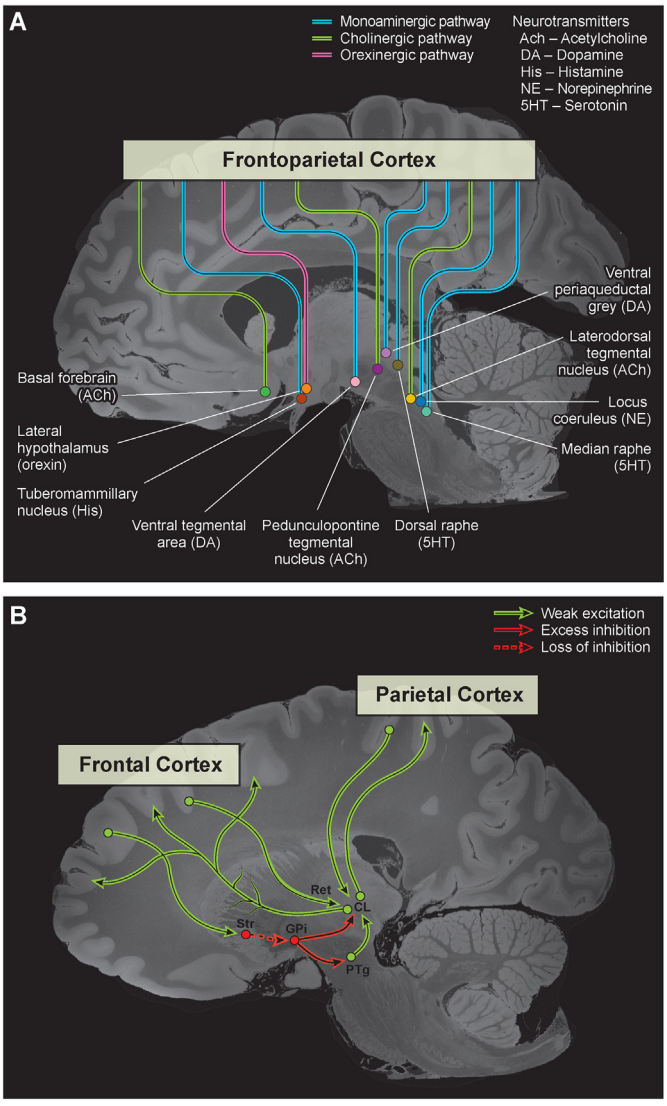

Fig. 2. Neurotransmitter systems and neural circuits of arousal
(A) Subcortical arousal circuits projecting from the brainstem, hypothalamus, and basal forebrain to the frontoparietal cortex are shown, color-coded by their primary neurotransmitter (inset, top right) for illustrative purposes. (B) A disrupted mesocircuit is shown, in which loss of striatal (Str) inhibition of the globus pallidus interna (GPi) leads to inhibition of the central thalamus, including the central lateral nucleus (CL). This type of mesocircuit disruption is hypothesized to cause decreased thalamocortical activation of the frontoparietal cortex in a subset of patients with disorders of consciousness. Artwork by Sarah Pyle is superimposed upon sagittal images from the 100 μm MRI dataset [164]. Abbreviations: PTg = pedunculo tegmental nucleus; Ret = reticular nucleus of the thalamus. Panel B is adapted from Ref. [3]. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

A connectome-based clinical trial platform has been proposed to identify predictive biomarkers that will facilitate enrollment in clinical trials based on a mechanistic assessment of a patient's potential for a therapeutic response [7]. A phase 1 clinical trial that leverages this connectome-based approach is evaluating the safety of intravenous methylphenidate in patients with acute traumatic DoC (NCT03814356) [7]. In addition, a prospective double-blind placebo-controlled trial (NCT03623828 and NCT05213169) is investigating the efficacy of apomorphine for patients with prolonged DoC.

New mechanistic targets are also being investigated in clinical trials of patients with DoC after acquired brain injury. Brain complexity has been used to describe the interplay between functional specialization of local areas and global integration during perception and behavior [152]. Patients with DoC and healthy individuals undergoing propofol anesthesia have both been reported to have decreased brain complexity, providing an empiric basis to use brain complexity as a pharmacodynamic biomarker to evaluate therapeutic target engagement [153]. Psychoactive therapies such as ketamine, lysergic acid, and psilocybin have been reported to increase neural complexity in healthy humans [154]. A double-blind, placebo-controlled, crossover randomized controlled trial (NCT05343507) is investigating whether subanesthetic ketamine promotes emergence of conscious behaviors and higher neural complexity in patients with VS/UWS or MCS. Ketamine, an NMDA receptor antagonist, induces aberrant excitatory activity in the cortex, hippocampus, and limbic system through inhibition of NMDA-mediated glutamatergic inputs to GABAergic interneurons – the proposed mechanism for dissociative anesthesia and hallucinations [11]. In patients with VS/UWS or MCS, investigators of this trial hypothesize that ketamine may facilitate increased neural complexity and thereby promote consciousness. Psylocibin predominately acts as a 5-HT_{2A} receptor agonist at cortical and thalamocortical areas and has been shown to increase brain complexity in healthy humans [154–156]. No trials to date have been performed evaluating psilocybin in DoC, and this therapy is only legal in select countries, complicating comprehensive investigation.

In Europe and South Korea, cerebrolysin, a neurotrophic peptidergic therapy, is being investigated in patients with prolonged DoC after ischemic or hemorrhagic stroke (NCT04427241, NCT04913831). Recovery from brain injury may involve the reemergence or creation of network connections. Cerebrolysin exhibits a multimodal pharmacologic profile, as it may mimic and modulate endogenous neurotrophic factors, promote neurogenesis and oligodendrogenesis through the sonic hedgehog pathway, protect against glutamate excitotoxicity, reduce free radical formation, inhibit apoptosis, modulate the inflammatory response, improve blood brain barrier integrity, and initiate and promote neuroplasticity [157]. Cerebrolysin may have more pronounced effects on neuroplasticity and neurorestoration than on neuroprotection, and thus cerebrolysin is a promising pharmacologic agent for the treatment of various types of brain injuries [158]. Cerebrolysin also modulates Akt/-glycogen synthase kinase3β (GSK3β) [159]. The GSK3β pathways and monoaminergic activity have been reported to be interconnected in preclinical models of various neuropsychiatric disorders. For example, impaired serotonergic activity may contribute to abnormally active GSK3β that imparts detrimental effects on neuronal structure, plasticity, and survival [160]. GSK3β may play an important role in the regulation of neurotransmitter vesicle exocytosis that induces pre-synaptic neurotransmitter release [161]. Activation of GSK3β in experimental models has also been found to reduce pre-synaptic glutamate release and lead to nigral dopaminergic neurodegeneration [162,163]. The precise mechanisms by which cerebrolysin may support restoration of neurotransmitter signaling in patients with DoC is yet to be elucidated and a key area of future exploration.

The field of DoC neurotherapeutics is an exciting frontier with tremendous potential to improve the lives of patients and their families. While optimal therapy selection based on patient-specific phenotypes requires further investigation, neurostimulant therapy is generally safe and inexpensive. Therapy selection can be informed by recent insights into the neuroanatomic networks and neurotransmitter systems that contribute to recovery of consciousness in patients with DoC. The mesocircuit model and dopamine neurostimulation have emerged as critical components of conscious behaviors, though other neurotransmitter systems and circuits are also key contributors. As such, dopaminergic therapy with various neurostimulants are frequently utilized off-label in clinical practice for patients with DoC. Pharmacologic neurostimulants offer the potential to accelerate recovery trajectory and support participation in rehabilitative efforts. In patients who do not respond to initial therapy, adjunct or alternative therapies that modulate other neurotransmitter systems may be considered. It is not currently known whether

short-term response to neurostimulant administration is predictive of functional recovery, and therefore stimulant responsiveness should not be used to guide decisions about withdrawal of life-sustaining therapy.

Author contributions

Drs. Barra, Solt, Yu, and Edlow all contributed to drafting the manuscript. Dr. Barra created the Table. Drs. Barra and Edlow created the Figures. All authors performed critical review and revision of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was funded by the National Institutes of Health (NIH) Director's Office (DP2HD101400), NIH National Institute of Neurologic Disorders and Stroke (R01NS122904), NIH National Institute of General Medical Sciences (R01GM126155), the MIT/MGH Brain Arousal State Control Innovation Center (BASCIC), and the Chen Institute MGH Research Scholar Award.

References

[1] Kondziella D, Menon DK, Helbok R, Naccache L, Othman MH, Rass V, et al. A precision medicine framework for classifying patients with disorders of consciousness: advanced classification of consciousness endotypes (ACCESS). Neurocritical Care 2021 Jul;35(Suppl 1):27–36.
[2] Schiff ND. Cognitive motor dissociation following severe brain injuries. JAMA Neurol 2015 Dec;72(12):1413–5.
[3] Edlow BL, Claassen J, Schiff ND, Greer DM. Recovery from disorders of consciousness: mechanisms, prognosis and emerging therapies. Nat Rev Neurol 2021 Mar;17(3):135–56.
[4] Young MJ, Fecchio M, Bodien YG, Edlow BL. Covert cortical processing: a diagnosis in search of a definition. Neurosci Conscious 2024;2024(1):niad026.
[5] Thibaut A, Schiff N, Giacino J, Laureys S, Gosseries O. Therapeutic interventions in patients with prolonged disorders of consciousness. Lancet Neurol 2019 Jun;18(6):600–14.
[6] Edlow BL, Sanz LRD, Polizzotto L, Pouratian N, Rolston JD, Snider SB, et al. Therapies to restore consciousness in patients with severe brain injuries: a gap analysis and future directions. Neurocritical Care 2021 Jul;35(Suppl 1):68–85.
[7] Edlow BL, Barra ME, Zhou DW, Foulkes AS, Snider SB, Threlkeld ZD, et al. Personalized connectome mapping to guide targeted therapy and promote recovery of consciousness in the intensive care unit. Neurocritical Care 2020 Oct;33(2):364–75.
[8] Giacino JT, Whyte J, Bagiella E, Kalmar K, Childs N, Khademi A, et al. Placebo-controlled trial of amantadine for severe traumatic brain injury. N Engl J Med 2012 Mar 1;366(9):819–26.
[9] Giacino JT, Katz DI, Schiff ND, Whyte J, Ashman EJ, Ashwal S, et al. Practice guideline update recommendations summary: disorders of consciousness: report of the guideline development, dissemination, and implementation subcommittee of the American academy of Neurology; the American congress of rehabilitation medicine; and the national Institute on disability, independent living, and rehabilitation research. Neurology 2018 Sep 4;91(10):450–60.
[10] Barra ME, Edlow BL, Brophy GM. Pharmacologic therapies to promote recovery of consciousness. Semin Neurol 2022 Jun;42(3):335–47.
[11] Brown EN, Lydic R, Schiff ND. General anesthesia, sleep, and coma. N Engl J Med 2010 Dec 30;363(27):2638–50.
[12] Bell DJ, Horne EA, Magee HE. The decerebrate rat. J Physiol 1933 May 23;78(2):196–207.
[13] Woods JW. Behavior of chronic decerebrate rates. J Neurophysiol 1964 Jul;27:635–44.
[14] Bignall KE, Schramm L. Behavior of chronically decerebrated kittens. Exp Neurol 1974 Mar;42(3):519–31.
[15] Tonkovic-Capin M, Krolo M, Stuth EA, Hopp FA, Zuperku EJ. Improved method of canine decerebration. J Appl Physiol Bethesda Md 1985. 1998 Aug;85(2):747–50.
[16] Fuller PM, Sherman D, Pedersen NP, Saper CB, Lu J. Reassessment of the structural basis of the ascending arousal system. J Comp Neurol 2011 Apr 1;519(5):933–56.
[17] Pais-Roldán P, Edlow BL, Jiang Y, Stelzer J, Zou M, Yu X. Multimodal assessment of recovery from coma in a rat model of diffuse brainstem tegmentum injury. Neuroimage 2019 Apr 1;189:615–30.
[18] Fischer DB, Boes AD, Demertzi A, Evrard HC, Laureys S, Edlow BL, et al. A human brain network derived from coma-causing brainstem lesions. Neurology 2016 Dec 6;87(23):2427–34.
[19] Kelz MB, García PS, Mashour GA, Solt K. Escape from oblivion: neural mechanisms of emergence from general anesthesia. Anesth Analg 2019 Apr;128(4):726–36.
[20] Clauss RP. Neurotransmitters in coma, vegetative and minimally conscious states, pharmacological interventions. Med Hypotheses 2010 Sep;75(3):287–90.
[21] Guerriero RM, Giza CC, Rotenberg A. Glutamate and GABA imbalance following traumatic brain injury. Curr Neurol Neurosci Rep 2015 May;15(5):27.
[22] Ford B, Holmes CJ, Mainville L, Jones BE. GABAergic neurons in the rat pontomesencephalic tegmentum: codistribution with cholinergic and other tegmental neurons projecting to the posterior lateral hypothalamus. J Comp Neurol 1995 Dec 11;363(2):177–96.
[23] Steriade M, McCormick DA, Sejnowski TJ. Thalamocortical oscillations in the sleeping and aroused brain. Science 1993 Oct 29;262(5134):679–85.
[24] Bickford M, Gunluk A, Van Horn S, Sherman S. GABAergic projection from the basal forebrain to the visual sector of the thalamic reticular nucleus in the cat. J Comp Neurol 1994 Oct 22;348(4):481–510.
[25] Xi MC, Morales FR, Chase MH. Interactions between GABAergic and cholinergic processes in the nucleus pontis oralis: neuronal mechanisms controlling active (rapid eye movement) sleep and wakefulness. J Neurosci Off J Soc Neurosci 2004 Nov 24;24(47):10670–8.
[26] Yi JH, Hazell AS. Excitotoxic mechanisms and the role of astrocytic glutamate transporters in traumatic brain injury. Neurochem Int 2006 Apr;48(5):394–403.
[27] Shen Z, Xiang M, Chen C, Ding F, Wang Y, Shang C, et al. Glutamate excitotoxicity: potential therapeutic target for ischemic stroke. Biomed Pharmacother Biomedecine Pharmacother 2022 Jul;151:113125.
[28] Maas AIR, Murray G, Henney H, Kassem N, Legrand V, Mangelus M, et al. Efficacy and safety of dexanabinol in severe traumatic brain injury: results of a phase III randomised, placebo-controlled, clinical trial. Lancet Neurol 2006 Jan;5(1):38–45.
[29] Ng SY, Lee AYW. Traumatic brain injuries: pathophysiology and potential therapeutic targets. Front Cell Neurosci 2019;13:528.
[30] Paoletti P, Bellone C, Zhou Q. NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease. Nat Rev Neurosci 2013 Jun;14(6):383–400.
[31] Ghit A, Assal D, Al-Shami AS, Hussein DEE. GABAA receptors: structure, function, pharmacology, and related disorders. J Genet Eng Biotechnol 2021 Aug 21;19(1):123.
[32] Sequeira A, Shen K, Gottlieb A, Limon A. Human brain transcriptome analysis finds region- and subject-specific expression signatures of GABAAR subunits. Commun Biol 2019;2:153.
[33] Xie X, Crowder TL, Yamanaka A, Morairty SR, Lewinter RD, Sakurai T, et al. GABA(B) receptor-mediated modulation of hypocretin/orexin neurones in mouse hypothalamus. J Physiol 2006 Jul 15;574(Pt 2):399–414.
[34] Matsuki T, Nomiyama M, Takahira H, Hirashima N, Kunita S, Takahashi S, et al. Selective loss of GABA(B) receptors in orexin-producing neurons results in disrupted sleep/wakefulness architecture. Proc Natl Acad Sci U S A. 2009 Mar 17;106(11):4459–64.
[35] Stevens DR, Kuramasu A, Haas HL. GABAB-receptor-mediated control of GABAergic inhibition in rat histaminergic neurons in vitro. Eur J Neurosci 1999 Apr;11(4):1148–54.
[36] Schiff ND, Brown EN. Protective down-regulated states in the human brain: a possible lesson from COVID-19. Proc Natl Acad Sci U S A 2022 Nov 16;119(46):e2120221119.
[37] Whyte J, Rajan R, Rosenbaum A, Katz D, Kalmar K, Seel R, et al. Zolpidem and restoration of consciousness. Am J Phys Med Rehabil 2014 Feb;93(2):101–13.
[38] Zaal IJ, Devlin JW, Hazelbag M, Klein Klouwenberg PMC, van der Kooi AW, Ong DSY, et al. Benzodiazepine-associated delirium in critically ill adults. Intensive Care Med 2015 Dec;41(12):2130–7.
[39] Tae CH, Kang KJ, Min BH, Ahn JH, Kim S, Lee JH, et al. Paradoxical reaction to midazolam in patients undergoing endoscopy under sedation: incidence, risk factors and the effect of flumazenil. Dig Liver Dis Off J Ital Soc Gastroenterol Ital Assoc Study Liver 2014 Aug;46(8):710–5.
[40] Jeong S, Lee HG, Kim WM, Jeong CW, Lee SH, Yoon MH, et al. Increase of paradoxical excitement response during propofol-induced sedation in hazardous and harmful alcohol drinkers. Br J Anaesth 2011 Dec;107(6):930–3.
[41] Arnts H, van Erp WS, Boon LI, Bosman CA, Admiraal MM, Schrantee A, et al. Awakening after a sleeping pill: restoring functional brain networks after severe brain injury. Cortex J Devoted Study Nerv Syst Behav 2020 Nov;132:135–46.
[42] Fridman EA, Beattie BJ, Broft A, Laureys S, Schiff ND. Regional cerebral metabolic patterns demonstrate the role of anterior forebrain mesocircuit dysfunction in the severely injured brain. Proc Natl Acad Sci U S A 2014 Apr 29;111(17):6473–8.
[43] Li J, Curley WH, Guerin B, Dougherty DD, Dalca AV, Fischl B, et al. Mapping the subcortical connectivity of the human default mode network. Neuroimage 2021 Dec 15;245:118758.
[44] Fridman EA, Schiff ND. Organizing a rational approach to treatments of disorders of consciousness using the anterior forebrain mesocircuit model. J Clin Neurophysiol Off Publ Am Electroencephalogr Soc 2022 Jan 1;39(1):40–8.
[45] Solt K, Cotten JF, Cimenser A, Wong KFK, Chemali JJ, Brown EN. Methylphenidate actively induces emergence from general anesthesia. Anesthesiology 2011 Oct;115(4):791–803.
[46] Kenny JD, Taylor NE, Brown EN, Solt K. Dextroamphetamine (but not atomoxetine) induces reanimation from general anesthesia: implications for the roles of dopamine and norepinephrine in active emergence. PLoS One 2015;10(7):e0131914.

[47] Solt K, Van Dort CJ, Chemali JJ, Taylor NE, Kenny JD, Brown EN. Electrical stimulation of the ventral tegmental area induces reanimation from general anesthesia. Anesthesiology 2014 Aug;121(2):311–9.

[48] Taylor NE, Van Dort CJ, Kenny JD, Pei J, Guidera JA, Vlasov KY, et al. Optogenetic activation of dopamine neurons in the ventral tegmental area induces reanimation from general anesthesia. Proc Natl Acad Sci U S A. 2016 Nov 8;113(45):12826–31.

[49] Eban-Rothschild A, Rothschild G, Giardino WJ, Jones JR, de Lecea L. VTA dopaminergic neurons regulate ethologically relevant sleep-wake behaviors. Nat Neurosci 2016 Oct;19(10):1356–66.

[50] Oishi Y, Suzuki Y, Takahashi K, Yonezawa T, Kanda T, Takata Y, et al. Activation of ventral tegmental area dopamine neurons produces wakefulness through dopamine D2-like receptors in mice. Brain Struct Funct 2017 Aug;222(6):2907–15.

[51] Palmiter RD. Dopamine signaling as a neural correlate of consciousness. Neuroscience 2011 Dec 15;198:213–20.

[52] Spindler LRB, Luppi AI, Adapa RM, Craig MM, Coppola P, Peattie ARD, et al. Dopaminergic brainstem disconnection is common to pharmacological and pathological consciousness perturbation. Proc Natl Acad Sci U S A. 2021 Jul 27;118(30):e2026289118.

[53] Edlow BL. Dopaminergic modulation of human consciousness via default mode network connectivity. Proc Natl Acad Sci U S A. 2021 Aug 3;118(31):e2111268118.

[54] Edlow BL, Olchanyi M, Freeman HJ, Li J, Maffei C, Snider SB, et al. Multimodal MRI reveals brainstem connections that sustain wakefulness in human consciousness. Sci Transl Med 2024;16(745):eadj4303.

[55] Kato R, Zhang ER, Mallari OG, Moody OA, Vincent KF, Melonakos ED, et al. D-amphetamine rapidly reverses dexmedetomidine-induced unconsciousness in rats. Front Pharmacol 2021 May 18;12:668285.

[56] Taylor NE, Chemali JJ, Brown EN, Solt K. Activation of D1 dopamine receptors induces emergence from isoflurane general anesthesia. Anesthesiology 2013 Jan;118(1):30–9.

[57] Moody OA, Zhang ER, Arora V, Kato R, Cotten JF, Solt K. D-amphetamine accelerates recovery of consciousness and respiratory drive after high-dose fentanyl in rats. Front Pharmacol 2020;11:585356.

[58] Chemali JJ, Van Dort CJ, Brown EN, Solt K. Active emergence from propofol general anesthesia is induced by methylphenidate. Anesthesiology 2012 May;116(5):998–1005.

[59] Fukuda T, Araki Y, Takishita S, Koga T. Correlation between brain monoamine levels and postictal coma following electroshock. Arch Int Pharmacodyn Ther 1975 Jan;213(1):58–63.

[60] Fridman EA, Osborne JR, Mozley PD, Victor JD, Schiff ND. Presynaptic dopamine deficit in minimally conscious state patients following traumatic brain injury. Brain J Neurol 2019 Jul 1;142(7):1887–93.

[61] Watson CJ, Baghdoyan HA, Lydic R. Neuropharmacology of sleep and wakefulness. Sleep Med Clin 2010 Dec;5(4):513–28.

[62] Jones BE, Harper ST, Halaris AE. Effects of locus coeruleus lesions upon cerebral monoamine content, sleep-wakefulness states and the response to amphetamine in the cat. Brain Res 1977 Apr 1;124(3):473–96.

[63] Strecker RE, Nalwalk J, Dauphin LJ, Thakkar MM, Chen Y, Ramesh V, et al. Extracellular histamine levels in the feline preoptic/anterior hypothalamic area during natural sleep-wakefulness and prolonged wakefulness: an in vivo microdialysis study. Neuroscience 2002;113(3):663–70.

[64] Xu C, Michelsen KA, Wu M, Morozova E, Panula P, Alreja M. Histamine innervation and activation of septohippocampal GABAergic neurones: involvement of local ACh release. J Physiol 2004 Dec 15;561(Pt 3):657–70.

[65] Basal forebrain histaminergic transmission modulates electroencephalographic activity and emergence from isoflurane anesthesia - PubMed [Internet]. [cited 2023 Nov 20]. Available from: https://pubmed.ncbi.nlm.nih.gov/19741500/#.

[66] Luo T, Leung LS. Involvement of tuberomamillary histaminergic neurons in isoflurane anesthesia. Anesthesiology 2011 Jul;115(1):36–43.

[67] Monti JM. Serotonin control of sleep-wake behavior. Sleep Med Rev 2011 Aug;15(4):269–81.

[68] Haynes RL, Trachtenberg F, Darnall R, Haas EA, Goldstein RD, Mena OJ, et al. Altered 5-HT2A/C receptor binding in the medulla oblongata in the sudden infant death syndrome (SIDS): Part I. Tissue-based evidence for serotonin receptor signaling abnormalities in cardiorespiratory- and arousal-related circuits. J Neuropathol Exp Neurol 2023 May 25;82(6):467–82.

[69] Jellinger K, Riederer P. Brain monoamines in metabolic (endotoxic) coma. A preliminary biochemical study in human postmortem material. J Neural Transm 1977;41(4):275–86.

[70] Abe K, Shimada R, Okada Y, Kibayashi K. Traumatic brain injury decreases serotonin transporter expression in the rat cerebrum. Neurol Res 2016 Apr 2;38(4):358–63.

[71] Nichols DE, Nichols CD. Serotonin receptors. Chem Rev 2008 May;108(5):1614–41.

[72] Tsuiki K, Takada A, Nagahiro S, Grdiša M, Diksic M, Pappius HM. Synthesis of serotonin in traumatized rat brain. J Neurochem 1995;64(3):1319–25.

[73] Beliveau V, Ganz M, Feng L, Ozenne B, Højgaard L, Fisher PM, et al. A high-resolution in vivo atlas of the human brain's serotonin system. J Neurosci Off J Soc Neurosci 2017 Jan 4;37(1):120–8.

[74] Guldenmund P, Vanhaudenhuyse A, Boly M, Laureys S, Soddu A. A default mode of brain function in altered states of consciousness. Arch Ital Biol 2012;150(2–3):107–21.

[75] Barre A, Berthoux C, De Bundel D, Valjent E, Bockaert J, Marin P, et al. Presynaptic serotonin 2A receptors modulate thalamocortical plasticity and associative learning. Proc Natl Acad Sci U S A 2016 Mar 8;113(10):E1382–91.

[76] Jenkins A, Franks NP, Lieb WR. Actions of general anaesthetics on 5-HT3 receptors in N1E-115 neuroblastoma cells. Br J Pharmacol 1996 Apr;117(7):1507–15.

[77] Pal D, Dean JG, Liu T, Li D, Watson CJ, Hudetz AG, et al. Differential role of prefrontal and parietal cortices in controlling level of consciousness. Curr Biol CB 2018 Jul 9;28(13):2145–2152.e5.

[78] Saper CB, Fuller PM, Pedersen NP, Lu J, Scammell TE. Sleep state switching. Neuron 2010 Dec 22;68(6):1023–42.

[79] Sarter M, Parikh V, Howe WM. Phasic acetylcholine release and the volume transmission hypothesis: time to move on. Nat Rev Neurosci 2009 May;10(5):383–90.

[80] Teles-Grilo Ruivo LM, Baker KL, Conway MW, Kinsley PJ, Gilmour G, Phillips KG, et al. Coordinated acetylcholine release in prefrontal cortex and Hippocampus is associated with arousal and reward on distinct timescales. Cell Rep 2017 Jan 24;18(4):905–17.

[81] Meuret P, Backman SB, Bonhomme V, Plourde G, Fiset P. Physostigmine reverses propofol-induced unconsciousness and attenuation of the auditory steady state response and bispectral index in human volunteers. Anesthesiology 2000 Sep;93(3):708–17.

[82] Kenny JD, Chemali JJ, Cotten JF, Van Dort CJ, Kim SE, Ba D, et al. Physostigmine and methylphenidate induce distinct arousal states during isoflurane general anesthesia in rats. Anesth Analg 2016 Nov;123(5):1210–9.

[83] Lee MG, Hassani OK, Jones BE. Discharge of identified orexin/hypocretin neurons across the sleep-waking cycle. J Neurosci Off J Soc Neurosci 2005 Jul 13;25(28):6716–20.

[84] Mileykovskiy BY, Kiyashchenko LI, Siegel JM. Behavioral correlates of activity in identified hypocretin/orexin neurons. Neuron 2005 Jun 2;46(5):787–98.

[85] Horvath TL, Peyron C, Diano S, Ivanov A, Aston-Jones G, Kilduff TS, et al. Hypocretin (orexin) activation and synaptic innervation of the locus coeruleus noradrenergic system. J Comp Neurol 1999 Dec 13;415(2):145–59.

[86] Vittoz NM, Berridge CW. Hypocretin/orexin selectively increases dopamine efflux within the prefrontal cortex: involvement of the ventral tegmental area. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol 2006 Feb;31(2):384–95.

[87] Fadel J, Burk JA. Orexin/hypocretin modulation of the basal forebrain cholinergic system: role in attention. Brain Res 2010 Feb 16;1314:112–23.

[88] Suzuki M, Shiraishi E, Cronican J, Kimura H. Effects of the orexin receptor 2 agonist danavorexton on emergence from general anaesthesia and opioid-induced sedation, respiratory depression, and analgesia in rats and monkeys. Br J Anaesth 2024 Mar;132(3):541–52.

[89] Kelz MB, Sun Y, Chen J, Cheng Meng Q, Moore JT, Veasey SC, et al. An essential role for orexins in emergence from general anesthesia. Proc Natl Acad Sci U S A 2008 Jan 29;105(4):1309–14.

[90] Zhang LN, Li ZJ, Tong L, Guo C, Niu JY, Hou WG, et al. Orexin-A facilitates emergence from propofol anesthesia in the rat. Anesth Analg 2012 Oct;115(4):789–96.

[91] Van Dusen RA, Lanz C, Robertson RM. Role of adenosine in functional recovery following anoxic coma in Locusta migratoria. J Insect Physiol 2020 Jul;124:104057.

[92] Wang Q, Fong R, Mason P, Fox AP, Xie Z. Caffeine accelerates recovery from general anesthesia. J Neurophysiol 2014 Mar 15;111(6):1331–40.

[93] Fong R, Wang L, Zacny JP, Khokhar S, Apfelbaum JL, Fox AP, et al. Caffeine accelerates emergence from isoflurane anesthesia in humans: a randomized, double-blind, crossover study. Anesthesiology 2018 Nov 1;129(5):912–20.

[94] Schiff ND. Mesocircuit mechanisms in the diagnosis and treatment of disorders of consciousness. Presse Medicale Paris Fr 1983. 2022 Dec 20;52(2):104161.

[95] Schiff ND. Recovery of consciousness after brain injury: a mesocircuit hypothesis. Trends Neurosci 2010 Jan;33(1):1–9.

[96] Coulborn S, Taylor C, Naci L, Owen AM, Fernández-Espejo D. Disruptions in effective connectivity within and between default mode network and anterior forebrain mesocircuit in prolonged disorders of consciousness. Brain Sci 2021 Jun 4;11(6):749.

[97] Vanhaudenhuyse A, Noirhomme Q, Tshibanda LJF, Bruno MA, Boveroux P, Schnakers C, et al. Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients. Brain J Neurol 2010 Jan;133(Pt 1):161–71.

[98] Demertzi A, Antonopoulos G, Heine L, Voss HU, Crone JS, de Los Angeles C, et al. Intrinsic functional connectivity differentiates minimally conscious from unresponsive patients. Brain J Neurol 2015 Sep;138(Pt 9):2619–31.

[99] Di Perri C, Bahri MA, Amico E, Thibaut A, Heine L, Antonopoulos G, et al. Neural correlates of consciousness in patients who have emerged from a minimally conscious state: a cross-sectional multimodal imaging study. Lancet Neurol 2016 Jul;15(8):830–42.

[100] Threlkeld ZD, Bodien YG, Rosenthal ES, Giacino JT, Nieto-Castanon A, Wu O, et al. Functional networks reemerge during recovery of consciousness after acute severe traumatic brain injury. Cortex J Devoted Study Nerv Syst Behav. 2018 Sep;106:299–308.

[101] Redinbaugh MJ, Phillips JM, Kambi NA, Mohanta S, Andryk S, Dooley GL, et al. Thalamus modulates consciousness via layer-specific control of cortex. Neuron 2020 Apr 8;106(1):66–75.e12.

[102] Bastos AM, Donoghue JA, Brincat SL, Mahnke M, Yanar J, Correa J, et al. Neural effects of propofol-induced unconsciousness and its reversal using thalamic stimulation. Elife 2021 Apr 27;10:e60824.

[103] Schiff ND, Giacino JT, Kalmar K, Victor JD, Baker K, Gerber M, et al. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. Nature 2007 Aug 2;448(7153):600–3.

[104] Forgacs PB, Frey HP, Velazquez A, Thompson S, Brodie D, Moitra V, et al. Dynamic regimes of neocortical activity linked to corticothalamic integrity correlate with outcomes in acute anoxic brain injury after cardiac arrest. Ann Clin Transl Neurol 2017 Feb;4(2):119–29.

[105] Frohlich J, Crone JS, Johnson MA, Lutkenhoff ES, Spivak NM, Dell'Italia J, et al. Neural oscillations track recovery of consciousness in acute traumatic brain injury patients. Hum Brain Mapp 2022 Apr 15;43(6):1804–20.

[106] Curley WH, Bodien YG, Zhou DW, Conte MM, Foulkes AS, Giacino JT, et al. Electrophysiological correlates of thalamocortical function in acute severe traumatic brain injury. Cortex J Devoted Study Nerv Syst Behav 2022 Jul;152:136–52.

[107] Spindler LR. Where Does it Stem From? Functional Neuroimaging of Monoaminergic Brainstem Nuclei in Altered States of Consciousness: Translational, Diagnostic and Therapeutic Implications [doctor of philosophy, Queens' College]. 2022. https://api.repository.cam.ac.uk/server/api/core/bitstreams/e76c629f-b308-446f-b176-7f57e700af9b/content.

[108] Helbok R, Rass V, Beghi E, Bodien YG, Citerio G, Giacino JT, et al. The curing coma campaign international survey on coma epidemiology, evaluation, and therapy (COME TOGETHER). Neurocritical Care 2022 Aug;37(1):47–59.

[109] Rühl L, Kuramatsu JB, Sembill JA, Kallmünzer B, Madzar D, Gerner ST, et al. Amantadine treatment is associated with improved consciousness in patients with non-traumatic brain injury. J Neurol Neurosurg Psychiatry 2022 Jun;93(6):582–7.

[110] Ghalaenovi H, Fattahi A, Koohpayehzadeh J, Khodadost M, Fatahi N, Taheri M, et al. The effects of amantadine on traumatic brain injury outcome: a double-blind, randomized, controlled, clinical trial. Brain Inj 2018;32(8):1050–5.

[111] Abbasivash R, Valizade Hasanloei MA, Kazempour A, Mahdkhah A, Shaaf Ghoreishi MM, Akhavan Masoumi G. The effect of oral administration of amantadine on neurological outcome of patients with diffuse axonal injury in ICU. J Exp Neurosci 2019;13:1179069518824851.

[112] Wu TS, Garmel GM. Improved neurological function after Amantadine treatment in two patients with brain injury. J Emerg Med 2005 Apr;28(3):289–92.

[113] Hughes S, Colantonio A, Santaguida PL, Paton T. Amantadine to enhance readiness for rehabilitation following severe traumatic brain injury. Brain Inj 2005 Dec 20;19(14):1197–206.

[114] Avecillas-Chasín JM, Barcia JA. Effect of amantadine in minimally conscious state of non-traumatic etiology. Acta Neurochir (Wien) 2014 Jul;156(7):1375–7.

[115] Lehnerer SM, Scheibe F, Buchert R, Kliesch S, Meisel A. Awakening with amantadine from a persistent vegetative state after subarachnoid haemorrhage. BMJ Case Rep 2017 Jul 24;2017. bcr-2017-220305.

[116] Gao Y, Ma L, Liang F, Zhang Y, Yang L, Liu X, et al. The use of amantadine in patients with unresponsive wakefulness syndrome after severe cerebral hemorrhage. Brain Inj 2020 Jul 2;34(8):1084–8.

[117] Zafonte RD, Watanabe T, Mann NR. Amantadine: a potential treatment for the minimally conscious state. Brain Inj 1998 Jul;12(7):617–21.

[118] Barra ME, Izzy S, Sarro-Schwartz A, Hirschberg RE, Mazwi N, Edlow BL. Stimulant therapy in acute traumatic brain injury: prescribing patterns and adverse event rates at 2 level 1 trauma centers. J Intensive Care Med 2020 Nov;35(11):1196–202.

[119] Matsuda W, Komatsu Y, Yanaka K, Matsumura A. Levodopa treatment for patients in persistent vegetative or minimally conscious states. Neuropsychol Rehabil 2005 Sep;15(3–4):414–27.

[120] Haig AJ, Ruess JM. Recovery from vegetative state of six months' duration associated with Sinemet (levodopa/carbidopa). Arch Phys Med Rehabil 1990 Dec;71(13):1081–3.

[121] Di Rocco C, Maira G, Meglio M, Rossi GF. L-DOPA treatment of comatose states due to cerebral lesions. Preliminary findings. J Neurosurg Sci 1974 Sep;18(3):169–76.

[122] Chajek T, Berry EM, Friedman G, Abramsky O. Treatment of acute hepatic encephalopathy with L-dopa. Postgrad Med 1977 May;53(619):262–5.

[123] Fridman EA, Krimchansky BZ, Bonetto M, Galperin T, Gamzu ER, Leiguarda RC, et al. Continuous subcutaneous apomorphine for severe disorders of consciousness after traumatic brain injury. Brain Inj 2010;24(4):636–41.

[124] Passler MA, Riggs RV. Positive outcomes in traumatic brain injury-vegetative state: patients treated with bromocriptine. Arch Phys Med Rehabil 2001 Mar;82(3):311–5.

[125] Challman TD, Lipsky JJ. Methylphenidate: its pharmacology and uses. Mayo Clin Proc 2000 Jul;75(7):711–21.

[126] Kim YW, Shin JC, An Y sil. Effects of methylphenidate on cerebral glucose metabolism in patients with impaired consciousness after acquired brain injury. Clin Neuropharmacol 2009;32(6):335–9.

[127] Moein H, Khalili HA, Keramatian K. Effect of methylphenidate on ICU and hospital length of stay in patients with severe and moderate traumatic brain injury. Clin Neurol Neurosurg 2006 Sep;108(6):539–42.

[128] Plenger PM, Dixon CE, Castillo RM, Frankowski RF, Yablon SA, Levin HS. Subacute methylphenidate treatment for moderate to moderately severe traumatic brain injury: a preliminary double-blind placebo-controlled study. Arch Phys Med Rehabil 1996 Jun;77(6):536–40.

[129] Gerrard P, Malcolm R. Mechanisms of modafinil: a review of current research. Neuropsychiatric Dis Treat 2007 Jun;3(3):349–64.

[130] Dhamapurkar SK, Wilson BA, Rose A, Watson P, Shiel A. Does Modafinil improve the level of consciousness for people with a prolonged disorder of consciousness? a retrospective pilot study. Disabil Rehabil 2017 Dec;39(26):2633–9.

[131] Leclerc AM, Riker RR, Brown CS, May T, Nocella K, Cote J, et al. Amantadine and modafinil as neurostimulants following acute stroke: a retrospective study of intensive care unit patients. Neurocritical Care 2021 Feb;34(1):102–11.

[132] Hintze TD, Small CE, Montgomery J, Reveles KR, Hafeez S, Barthol CA. Comparison of amantadine, modafinil, and standard of care in the acute treatment of disorders of consciousness after severe traumatic brain injury. Clin Neuropharmacol 2022 Feb 1;45(1):1–6.

[133] Margetis K, Korfias SI, Gatzonis S, Boutos N, Stranjalis G, Boviatsis E, et al. Intrathecal baclofen associated with improvement of consciousness disorders in spasticity patients. Neuromodulation J Int Neuromodulation Soc 2014 Oct;17(7):699–704. : discussion 704.

[134] Zhang B, O'Brien K, Won W, Li S. A retrospective analysis on clinical practice-based approaches using zolpidem and lorazepam in disorders of consciousness. Brain Sci 2021 May 29;11(6):726.

[135] Calabrò RS, Aricò I, De Salvo S, Conti-Nibali V, Bramanti P. Transient awakening from vegetative state: is high-dose zolpidem more effective? Psychiatr Clin Neurosci 2015 Feb;69(2):122–3.

[136] Whyte J, Myers R. Incidence of clinically significant responses to zolpidem among patients with disorders of consciousness: a preliminary placebo controlled trial. Am J Phys Med Rehabil 2009 May;88(5):410–8.

[137] Nardone R, Sebastianelli L, Brigo F, Golaszewski S, Trinka E, Pucks-Faes E, et al. Effects of intrathecal baclofen therapy in subjects with disorders of consciousness: a reappraisal. J Neural Transm Vienna Austria 1996 2020 Sep;127(9):1209–15.

[138] Cohen SI, Duong TT. Increased arousal in a patient with anoxic brain injury after administration of zolpidem. Am J Phys Med Rehabil 2008 Mar;87(3):229–31.

[139] Clauss R, Nel W. Drug induced arousal from the permanent vegetative state. NeuroRehabilitation 2006;21(1):23–8.

[140] Kim C, Kwon BS, Nam KY, Park JW, Lee HJ. Zolpidem-induced arousal by paradoxical GABAergic stimulation: a case report with F-18 flumazenil positron emission tomography and single photon emission computed tomography study. Ann Rehabil Med 2016 Feb;40(1):177–81.

[141] Tucker C, Sandhu K. The effectiveness of zolpidem for the treatment of disorders of consciousness. Neurocritical Care 2016 Jun;24(3):488–93.

[142] Pistoia F, Mura E, Govoni S, Fini M, Sarà M. Awakenings and awareness recovery in disorders of consciousness: is there a role for drugs? CNS Drugs 2010 Aug;24(8):625–38.

[143] Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil 2004 Dec;85(12):2020–9.

[144] Pincherle A, Jöhr J, Chatelle C, Pignat JM, Du Pasquier R, Ryvlin P, et al. Motor behavior unmasks residual cognition in disorders of consciousness. Ann Neurol 2019 Mar;85(3):443–7.

[145] Bodien YG, Vora I, Barra A, Chiang K, Chatelle C, Goostrey K, et al. Feasibility and validity of the coma recovery scale-revised for accelerated standardized testing: a practical assessment tool for detecting consciousness in the intensive care unit. Ann Neurol 2023 Nov;94(5):919–24.

[146] Bodien YG, Barra A, Temkin NR, Barber J, Foreman B, Vassar M, et al. Diagnosing level of consciousness: the limits of the Glasgow coma scale total score. J Neurotrauma 2021 Dec;38(23):3295–305.

[147] Rodan LH, Gibson KM, Pearl PL. Clinical use of CSF neurotransmitters. Pediatr Neurol 2015 Oct;53(4):277–86.

[148] Chefer VI, Thompson AC, Zapata A, Shippenberg TS. Overview of brain microdialysis. Curr Protoc Neurosci 2009 Apr. Chapter 7:Unit7.1.

[149] Jenkins BG. Pharmacologic magnetic resonance imaging (phMRI): imaging drug action in the brain. Neuroimage 2012 Aug 15;62(2):1072–85.

[150] Finnema SJ, Scheinin M, Shahid M, Lehto J, Borroni E, Bang-Andersen B, et al. Application of cross-species PET imaging to assess neurotransmitter release in brain. Psychopharmacology (Berl) 2015 Nov;232(21–22):4129–57.

[151] Bajaj N, Hauser RA, Grachev ID. Clinical utility of dopamine transporter single photon emission CT (DaT-SPECT) with (123I) ioflupane in diagnosis of parkinsonian syndromes. J Neurol Neurosurg Psychiatry 2013 Nov;84(11):1288–95.

[152] Tononi G, Sporns O, Edelman GM. A measure for brain complexity: relating functional segregation and integration in the nervous system. Proc Natl Acad Sci U S A 1994 May 24;91(11):5033–7.

[153] López-González A, Panda R, Ponce-Alvarez A, Zamora-López G, Escrichs A, Martial C, et al. Loss of consciousness reduces the stability of brain hubs and the heterogeneity of brain dynamics. Commun Biol 2021 Sep 6;4(1):1037.

[154] Schartner MM, Carhart-Harris RL, Barrett AB, Seth AK, Muthukumaraswamy SD. Increased spontaneous MEG signal diversity for psychoactive doses of ketamine, LSD and psilocybin. Sci Rep 2017 Apr 19;7:46421.

[155] Scott G, Carhart-Harris RL. Psychedelics as a treatment for disorders of consciousness. Neurosci Conscious 2019;2019(1):niz003.

[156] Carhart-Harris RL, Roseman L, Haijen E, Erritzoe D, Watts R, Branchi I, et al. Psychedelics and the essential importance of context. J Psychopharmacol Oxf Engl 2018 Jul;32(7):725–31.

[157] Fiani B, Covarrubias C, Wong A, Doan T, Reardon T, Nikolaidis D, et al. Cerebrolysin for stroke, neurodegeneration, and traumatic brain injury: review of the literature and outcomes. Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol 2021 Apr;42(4):1345–53.

[158] Mureşanu DF, Livinț Popa L, Chira D, Dăbală V, Hapca E, Vlad I, et al. Role and impact of cerebrolysin for ischemic stroke care. J Clin Med 2022 Feb 25;11(5):1273.

[159] Tao Y, Xu Y, Shen M, Feng X, Wu Y, Wu Y, et al. The neuroprotection of cerebrolysin after spontaneous intracerebral hemorrhage through regulates necroptosis via Akt/GSK3β signaling pathway. Acta Cir Bras 2021;36(10): e361002.
[160] Li X, Zhu W, Roh MS, Friedman AB, Rosborough K, Jope RS. In vivo regulation of glycogen synthase kinase-3beta (GSK3beta) by serotonergic activity in mouse brain. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. 2004 Aug;29(8):1426–31.
[161] Zhu LQ, Liu D, Hu J, Cheng J, Wang SH, Wang Q, et al. GSK-3 beta inhibits presynaptic vesicle exocytosis by phosphorylating P/Q-type calcium channel and interrupting SNARE complex formation. J Neurosci Off J Soc Neurosci 2010 Mar 10;30(10):3624–33.
[162] Zhu LQ, Wang SH, Liu D, Yin YY, Tian Q, Wang XC, et al. Activation of glycogen synthase kinase-3 inhibits long-term potentiation with synapse-associated impairments. J Neurosci Off J Soc Neurosci 2007 Nov 7;27(45):12211–20.
[163] Li J, Ma S, Chen J, Hu K, Li Y, Zhang Z, et al. GSK-3β contributes to parkinsonian dopaminergic neuron death: evidence from conditional knockout mice and tideglusib. Front Mol Neurosci 2020;13:81.
[164] Edlow BL, Mareyam A, Horn A, Polimeni JR, Witzel T, Tisdall MD, et al. 7 Tesla MRI of the ex vivo human brain at 100 micron resolution. Sci Data 2019 Oct 30;6(1):244.