Published in final edited form as:

Curr Opin Neurobiol. 2014 December ; 29: 172–177. doi:10.1016/j.conb.2014.09.008.

Neuromodulation of the conscious state following severe brain injuries

Esteban A Fridman¹ and Nicholas D Schiff^{1,2}

¹Brain and Mind Research Institute, Weill Cornell Medical College, 1300 York Avenue, New York, NY 10065, United States

²Department of Neurology, Weill Cornell Medical College, 1300 York Avenue, New York, NY 10065, United States

Abstract

Disorders of consciousness (DOC) following severe structural brain injuries globally affect the conscious state and the expression of goal-directed behaviors. In some subjects, neuromodulation with medications or electrical stimulation can markedly improve the impaired conscious state present in DOC. We briefly review recent studies and provide an organizing framework for considering the apparently widely disparate collection of medications and approaches that may modulate the conscious state in subjects with DOC. We focus on neuromodulation of the anterior forebrain mesocircuit in DOC and briefly compare mechanisms supporting recovery from structural brain injuries to those underlying facilitated emergence from unconsciousness produced by anesthesia. We derive some general principles for approaching the problem of restoration of consciousness after severe structural brain injuries, and suggest directions for future research.

Introduction

Human disorders of consciousness (DOC) reflect a major alteration of the wakeful conscious state and typically arise from severe brain injuries that produce multi-focal neuronal cell death and disconnection (see [1,2•] for review). DOC include the conditions of vegetative state (VS), minimally conscious state (MCS) and confusional state (CS). Collectively, these disorders span a wide range of behavioral levels. VS, by definition, indicates a wakeful appearance without any signs of behavioral responsiveness. Demonstration of limited behavioral evidence of consciousness, such as visual tracking, is consistent with the lower boundary of MCS (labeled as MCS—, [3]). Recovery of command following, with or without an inconsistent communication system, sets the upper boundary of MCS (MCS+, [3]). CS reflects recovery of more complete communication systems, but lack of orientation and attentional control.

DOC are best considered in the context of basic mechanisms linking the internal state of neurons within the cerebral cortex, thalamus and striatum to the global network activation

Corresponding author: Schiff, Nicholas D (nds2001@med.cornell.edu).

Conflict of interest statement

Nothing declared.

patterns associated with different levels of consciousness. Severe brain injuries of all types produce widespread neuronal deafferentation and thus significantly reduce synaptic input across the corticothalamic system. In experimental studies, at the extreme boundary condition of removing all long-range inputs to the cerebral cortex only low-frequency electrical activity or a complete loss of signal is measurable in the scalp surface electroencephalogram (EEG) [4]. Typically, this level of deafferentation in the human brain only arises following very severe anoxic injuries and is invariably associated with permanent VS if subjects survive. Most DOC arise in the setting of a partially connected corticothalamic system with greater preservation of anatomical connectivity correlating with higher levels of observed behaviors [5].

Neurons in the cortex, thalamus and striatum are very sensitive to small changes in received synaptic background activity [6,7]. As a result, sharp changes in firing patterns of individual cell types and circuits probably explain large shifts in the conscious state that can be induced in some subjects with DOCs by exposure to pharmacologic agents or electrical brain stimulation [8–9,10••]. Moreover, examples of neuromodulation of the conscious state in DOC occurring very late in course of the recovery process (e.g., two decades following injury, see [11]) emphasize the crucial role of neuronal circuit mechanisms underpinning conscious state control after severe brain injury.

Normal brain function diurnally exhibits a wide range of states controlled by complex regulatory mechanisms involving many different brainstem, basal forebrain and hypothalamic neurons and neurotransmitter systems [12,13]. The awake conscious state is the most highly energy-demanding of these states [14] with these demands deriving from complex, high-frequency neuronal firing patterns associated with strong depolarization of neocortical, thalamic and striatal membrane potentials during wakeful states. Large reductions in arousal level progressively occurs across deeper stages of sleep in normal individuals and involves broad hyperpolarization of corticothalamic neurons via withdrawal of excitatory neuromodulatory influences from orexinergic, cholinergic, noradrenergic and other brainstem, basal forebrain and hypothalamic systems [12,13]. Importantly, along with their primary modulation of the neocortex, all of these endogenous neuromodulatory systems innervate and control activity in the central thalamus [15,16].

The highly interdependent and dynamic regulatory mechanisms underpinning brain arousal state control are vulnerable to many different types of dysfunction in the setting of severe brain injuries. For example, selective injuries to axon bundles containing key projections from brainstem arousal systems have been demonstrated to produce DOC. Interruption of the dopaminergic projection system via lesions near the lateral hypothalamus, where the medial forebrain bundle carries dopaminergic fibers to the frontal cortex and striatum, is correlated with DOC responsive to dopamine agonists [17]. Similarly, anatomical studies demonstrate isolated locations where selective interruption of white matter tracts carrying cholinergic projection fibers may lead to global functional impairments [53]. A more general circuit-level mechanism, however, is likely to play a role in all forms of severe brain injury as a result of disruption of the many long-range excitatory projections across the corticothalamic system [18].

Role of anterior forebrain mesocircuit

A common ‘mesocircuit’ mechanism has been proposed to arise across DOC following all types of severe brain injuries and to account for both the grading of the recovery process over time and the mechanism underlying often wide fluctuations in ongoing behavior observed in subjects with severe brain injuries [10•,18,19•]. The mesocircuit hypothesis posits that in all forms of severe brain injury, anterior forebrain function is markedly downregulated because of widespread cerebral deafferentation arising from a variety of mechanisms such as diffuse axonal injury, hypoxia, and ischemia that produce neuronal disconnection and induced cell death (Figure 1). A crucial role is proposed for neurons within the central thalamus based on their broad anatomical connectivity [20], functional role in forebrain arousal regulation [15,16], and pathological studies that demonstrate loss of these neurons in proportion to the severity of structural brain injuries and functional outcomes [21]. Two main effects are predicted: (1) the primary effect is a broad withdrawal of excitation across the corticothalamic system due to the functional consequence of disfacilitation [22] of central thalamic neurons arising via the integrated loss of their wide point-to-point connections [20]; and, (2) a closely related secondary effect is a further reduction of activity across the cortico-striatopallidal–thalamocortical loop system resulting from the loss of afferent input to the medium spiny neurons (MSNs) of the striatum from central thalamic and corticostriatal neurons, leading to the collapse of the level of synaptic background activity needed for the MSNs to reach their firing threshold [23]. Importantly, in addition to high levels of background activity, MSN firing also requires sufficient levels of dopaminergic modulation. As the MSNs provide an active inhibition of neurons within the globus pallidus interna that otherwise will actively inhibit some of the central thalamic neurons, the combined effect of both predicted mechanisms is a broad reduction in global cerebral synaptic activity with the strongest downregulation of activity occurring across the frontal/prefrontal cortex and striatum.

Recent studies support this hypothesis and include demonstrations that resting brain activity in DOC demonstrates patterns consistent with greater functional down-regulation in frontal structures [10•,24]), and evidence of reversal of the resting metabolic pattern of central thalamus and globus pallidus in DOC [19•]. Further supporting this hypothesis are findings that paired lesions of the central thalamus alone can produce enduring DOC [25]. The hypothesis predicts similar changes across the anterior forebrain mesocircuit are present in all settings of reduced synaptic activity; additionally, several phenomena observed in general anesthesia and sleep are consistent with the proposed mechanism [26•]. Importantly, recovery of function within the anterior forebrain mesocircuit covaries with activity in the precuneus, which also receives projections from the central thalamus [19•]. Measures of metabolic activity in precuneus and related structures of the posterior medial complex have demonstrated strong correlation with levels of expressed behavior across recovery from DOC [27]. Similarly, anatomical connectivity of thalamus *per se* and posterior medial complex correlate with levels of recovery across DOC [5]. Collectively, this hypothesis provides an economical first-order model for the patterns of restoration frontal cortical, striatal and thalamic activity seen in DOC with spontaneous recovery or effective neuromodulation as discussed below.

Neuromodulation of the conscious state in DOC

A surprisingly disparate set of medications and approaches have proven effective in some instances in modulating the conscious state in DOC. Primarily excitatory agents acting via receptor systems receiving ligands from the primary arousal system pathways, such as dopaminergic, noradrenergic and cholinergic agents have been traditionally used; however, strong agonists of the GABA receptor such as zolpidem have also proven effective in a subset of patients [28••]. In addition, there is evidence for the efficacy of direct electrical stimulation of the central nervous system [9].

Dopaminergic agonists have been most commonly employed to attempt to improve the level of consciousness in patients with DOC. However, it is only recently that evidence for the general efficacy of any pharmacologic agent has emerged. In a double-blind, placebo controlled, randomized clinical trial, the drug amantadine was demonstrated to accelerate the speed and rate of recovery of patients in VS and MCS within the first year following severe traumatic brain injuries [29••]. In this study, the positive effects of the amantadine were proposed to derive from the modulatory effect on the nigrostriatal, mesolimbic, and frontostriatal dopaminergic systems. Nonetheless, it is not entirely clear which of several potential mechanisms may underlie amantadine's effects in DOC all can be framed in the context of the mesocircuit hypothesis as noted below. The cell bodies of dopaminergic neurons are located in the substantia nigra pars compacta and ventral tegmental area within the brainstem and project to the frontal cortex and striatum through the nigrostriatal, mesolimbic, and mesocortical dopaminergic pathways (Figure 1). Additionally, dopaminergic neurons within the ventral tegmental area project to the central thalamus [30]. Of note, the central thalamus demonstrates high levels of dopamine approximating those observed in the substantia nigra [31], and a preponderant distribution of 'D2-Like' (D2LR) type receptors [32]. Thus, dopaminergic modulatory effects of amantadine could directly facilitate increased neuronal activity within frontal cortex, striatum, and central thalamus.

At the presynaptic level, amantadine may increase the synthesis of endogenous dopamine by blocking NMDA- receptors that have a positive effect on the enzymedopamine decarboxylase increasing bioconversion of L-DOPA into dopamine [33]. This mechanism is unlikely to play a role in the effects observed in DOC unless exogenous L-DOPA is co-administered as hydroxylation of tyrosine into L-DOPA by the enzyme tyrosine hydroxylase is the rate limiting factor in the synthesis of dopamine. Thus, in the setting of a deficit in the substrate (i.e., endogenous L-DOPA), up-regulation of the enzyme L-DOPA decarboxylase cannot be effective [34]. In addition, it is possible at a presynaptic level that amantadine increases synaptic dopamine availability by blocking the dopamine transporter (DAT) [35]. Finally, there are some suggestions that amantadine acts at the postsynaptic level slightly increasing the expression of D2-like dopamine receptors [36].

Smaller studies have provided more direct evidence of dopaminergic effects in DOC using more powerful dopaminergic agonists such as levodopa [37], bromocriptine [38], apomorphine [39] and pramipexol [40], all of which have shown some successful responses. Unlike amantadine, levodopa may bypass a possible, but still uncharacterized, posttraumatic deficit of the enzyme tyrosine hydroxylase, increasing the biosynthesis of dopamine at a

presynaptic level. Conversely, dopaminergic agonists may also directly stimulate D2-like postsynaptic receptors to enhance the membrane excitability [41] or stimulate D1 receptors at the ventral tegmental area [42••]. Direct electrical stimulation of the ventral tegmental area, but not of the substantia nigra, induces emergence from anesthetic coma [43••].

Finally, the dopamine reuptake inhibitor methylphenidate has shown positive effects inducing emergence from anesthetic coma [44], and improving attention in longterm moderate to severe posttraumatic attention deficit disorders [45], but has failed to induce responses in patients in VS or MCS [46]. The contrasting results for emergence from anesthetic coma and posttraumatic attentional deficits with methylphenidate suggest that blockade of the dopamine transporter enhances a D1 receptor mediated response, possibly emanating from the VTA [42••]. By contrast, the lack of improvement with methylphenidate in patients in VS and MCS suggests that blockade of the dopamine transporter cannot increase dopamine background activity possibly as a result of a presynaptic deficit of dopamine biosynthesis resulting from the structural brain injuries.

It was recently demonstrated *in vitro* that amantadine can also strongly block the noradrenaline transporter [35]. Terminals of noradrenergic cells and norepinephrine transporter are found in the central thalamus [47], and modulation of these receptors and neocortical noradrenergic receptors in frontal and parietal cortices [48] may be a crucial aspect of amantadine's effects. This observation raises the further possibility that use of other agents producing strong reuptake blockade of the noradrenergic receptor (e.g., atomoxetine) might thus also have a role in DOC.

Beyond acting as an agonist for classical arousal system neurotransmitter receptors, it is probable that amantadine's strong properties as an NMDA antagonist are linked to its broader activation properties. Paradoxical excitation of the cerebral cortex and striatum arises with the NMDA antagonist ketamine when used as an anesthesia [26•], and is associated with activation of the frontal cortex when ketamine is used in subanesthetic doses for resistant depression treatment [50]. In DOC subjects with structural brain injuries, paradoxical excitation with sedative agents such as zolpidem have been demonstrated to facilitate behavior in a small percentage of randomly selected and prospectively studied subjects [28••]. In detailed quantitative EEG investigations of a small number of such zolpidem responsive subjects with severe brain injuries, an initial burst of EEG activity consistent with effects in normal subjects (increased 15–30 Hz activity over frontocentral cortical regions) evolved into more narrowband activity lasting hours and replacing dominant low frequency EEG in subjects when behavioral improvements were observed [10••]. Zolpidem may directly bind to GABA-A alpha 1 receptor subtypes in the neocortex, where it may increase thalamocortical and thalamostriatal outflow indirectly, as a result of activation of cortical inhibitory interneuronal networks [51]. In addition, zolpidem may activate within the striatum where GABA-A currents facilitate alpha and beta (~8–30 Hz) rhythms within the striatum and normal MSN function [52]. An important additional proposed activating effect of zolpidem is suppression of increased firing of the GPI via a direct effect of zolpidem on the globus pallidus interna, which as noted above, is hypothesized to be overactive in the setting of the structurally deafferented brain.

No studies have systematically examined the role of cholinergic agonists in the treatment of DOC, but important evidence from studies of emergence from anesthesia suggest their possible role in the context of the mesocircuit hypothesis. Studies of human subjects receiving a systemic cholinergic agonist to initiate emergence from anesthetic coma showed statistically, significant increases in blood flow both in the thalamus and precuneus that selectively correlate with recovery of consciousness during otherwise stable anesthesia [49]. Similarly, in the same study, local decreases of regional blood flow in the same structures distinguished anesthetic coma compared with wakeful baselines. These observations are consistent with the key role of cholinergic innervation of the central thalamus and the correlation of the posterior medial complex and central thalamus in the anatomical and functional studies noted above.

Finally, direct neuromodulation of the outflow from the central thalamus has been demonstrated to improve level of consciousness and goal-directed behaviors in proof-of-concept study in a human subject after 6 years remaining in MCS [9]. Electrical activation of the central thalamus was causally linked in this study to the subjects transition from MCS to CS. The mesocircuit hypothesis predicts that broad activation of the central thalamic neuronal population is a final common pathway supporting a down-regulated anterior forebrain in severe brain injuries.

Summary

The above review emphasizes that neuromodulation of the conscious state in DOC can be linked to broad shifts in activity across the components of the anterior forebrain mesocircuit and its connections with the posterior medial complex. Effective neuromodulation is associated either with: (1) replacement of specific neurotransmitters by pharmacologic agents that are proposed to exert their effects via the release of thalamocortical outflow from central thalamic neurons to their targets in frontal cortex and striatum or at receptors on these targets, (2) via broader effects of bulk excitation via non-selective methods of paradoxical excitation (e.g., ketamine, zolpidem), or (3) by direct electrical stimulation of the central thalamus. Viewed from this perspective, approaches as seemingly disparate as zolpidem, amantadine and central thalamic brain stimulation all have a proposed main effect in restoring a threshold level of synaptic background activity to restore corticothalamic outflow from central thalamus and reestablish activity across the entire anterior forebrain. It is suggested that future research aims to identify a systematic polypharmacy approach to supporting the conscious state after structural brain injuries that build on this existing knowledge.

Acknowledgements

This work was supported by NIH-NICHD HD51912 and the James S. McDonnell Foundation (NDS, PI).

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest

•• of outstanding interest

1. Laureys S, Schiff ND: Coma and consciousness: paradigms (re)framed by neuroimaging. *Neuroimage* 2012, 61:478–491. [PubMed: 22227888]
2. Giacino J, Fins J, Laureys S, Schiff N: Disorders of consciousness after acquired brain injury: the state of the science. *Nat Rev Neurol* 2014, 10:2014. [PubMed: 24323054] • This is a comprehensive review of disorders of consciousness and possible mechanisms implicated in clinical expression of them. This paper reviews experimental and clinical evidence for mechanisms and current approaches for unconsciousness in humans.
3. Bruno M-A, Vanhaudenhuyse A, Thibaut A, Moonen G, Laureys S: From unresponsive wakefulness to minimally conscious PLUS and functional locked-in syndromes: recent advances in our understanding of disorders of consciousness. *J Neurol* 2011, 258:1373–1384. [PubMed: 21674197]
4. Timofeev I, Grenier F, Bazhenov M, Sejnowski T, Steriade M: Origin of slow cortical oscillations in deafferented cortical slabs. *Cereb Cortex* 2000, 10:1185–1199. [PubMed: 11073868]
5. Fernández-Espejo D, Soddu A, Cruse D, Palacios EM, Junque C, Vanhaudenhuyse A, Rivas E, Newcombe V, Menon DK, Pickard JD et al.: A role for the default mode network in the bases of disorders of consciousness. *Ann Neurol* 2012, 72:335–343. [PubMed: 23034909]
6. Steriade M: Impact of network activities on neuronal properties in corticothalamic systems. *J Neurophysiol* 2001, 86:1–39. [PubMed: 11431485]
7. Haider B, McCormick DA: Rapid neocortical dynamics: cellular and network mechanisms. *Neuron* 2009, 62:171–189. [PubMed: 19409263]
8. Brefel-Courbon C, Payoux P, Ory F, Sommet A, Slaoui T, Raboyeau G, Lemesle B, Puel M, Montastruc J-L, Demonet J-F et al.: Clinical and imaging evidence of zolpidem effect in hypoxic encephalopathy. *Ann Neurol* 2007, 62:102–105. [PubMed: 17357126]
9. Schiff ND, Giacino JT, Kalmar K, Victor JD, Baker K, Gerber M, Fritz B, Eisenberg B, Connor JO, Kobylarz EJ et al.: Behavioural improvements with thalamic stimulation after severe traumatic brain injury. *Nature* 2007, 448:3–7.
10. Williams ST, Conte MM, Goldfine AM, Noirhomme Q, Gosseries O, Thonnard M, Beattie B, Hersch J, Katz DI, Victor JD et al.: Common resting brain dynamics indicate a possible mechanism underlying zolpidem response in severe brain injury. *Elife* 2013, 2:e01157. [PubMed: 24252875] •• This quantitative EEG study provides the first evidence for a detailed neurophysiological mechanism underlying the paradoxical zolpidem response seen in some brain-injured subjects. It also discusses the possible mechanistic links of the zolpidem response to the mesocircuit hypothesis.
11. Voss HU, Ulu AM, Dyke JP, Watts R, Kobylarz EJ, McCandliss BD, Heier LA, Beattie BJ, Hamacher KA, Vallabhajosula S et al.: Possible axonal regrowth in late recovery from the minimally conscious state. *J Clin Invest* 2006, 116:2005–2012. [PubMed: 16823492]
12. Pace-Schott EF, Hobson JA: The neurobiology of sleep: genetics, cellular physiology and subcortical networks. *Nat Rev Neurosci* 2002, 3:591–605. [PubMed: 12154361]
13. Saper CB, Lu J, Chou TC, Gooley J: The hypothalamic integrator for circadian rhythms. *Trends Neurosci* 2005, 28:152–157. [PubMed: 15749169]
14. Raichle ME, MacLeod AM, Snyder aZ, Powers WJ, Gusnard DA, Shulman GL: A default mode of brain function. *Proc Natl Acad Sci USA* 2001, 98:676–682. [PubMed: 11209064]
15. Schiff ND: Central thalamic contributions to arousal regulation and neurological disorders of consciousness. *Ann NY Acad Sci* 2008, 1129:105–118. [PubMed: 18591473]
16. Mair RG, Onos KD, Hembrook JR: Cognitive activation by central thalamic stimulation: the yerkes-dodson law revisited. *Dose Response* 2011, 9:313–331. [PubMed: 22013395]
17. Ross E, Stewart R: Akinetic mutism from hypothalamic damage Successful treatment with dopamine agonists. *Neurology* 1981, 31:1981.
18. Schiff ND: Recovery of consciousness after brain injury: a mesocircuit hypothesis. *Trends Neurosci* 2010, 33:1–9. [PubMed: 19954851]
19. 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 USA* 2014, 111:6473–6478. [PubMed: 24733913] •• In this paper a theoretical

model of a mesocircuit mechanism arising across all forms severe brain injuries is tested by examining patterns of resting glucose metabolism within the central thalamus, striatum, and frontoparietal cortices. A predicted reversal of metabolic profile of the central thalamus and globus pallidus that characterizes and indexes the patients' behavioral level is observed.

20. Van der Werf Y, Witter M, Groenewegen H: The intralaminar and midline nuclei of the thalamus. Anatomical and functional evidence for participation in processes of arousal and awareness. *Brain Res Rev* 2002, 39:107–140. [PubMed: 12423763]
21. Maxwell WL, MacKinnon MA, Smith DH, McIntosh TK, Graham DI: Thalamic nuclei after human blunt head injury. *J Neuropathol Exp Neurol* 2006, 65:478–488. [PubMed: 16772871]
22. Gold L, Lauritzen M: Neuronal deactivation explains decreased cerebellar blood flow in response to focal cerebral ischemia or suppressed neocortical function. *Proc Natl Acad Sci U S A* 2002, 99:7699–7704. [PubMed: 12032346]
23. Grillner S, Hellgren J, Menard A, Saitoh K, Wikstrom MA: Mechanisms for selection of basic motor programs — roles for the striatum and pallidum. *Trends Neurosci* 2005, 28:364–370. [PubMed: 15935487]
24. Boly M, Garrido MI, Gosseries O, Bruno M-A, Boveroux P, Schnakers C, Massimini M, Litvak V, Laureys S, Friston K: Preserved feedforward but impaired top-down processes in the vegetative state. *Science* 2011, 332:858–862. [PubMed: 21566197]
25. Castaigne P, Lhermitte F, Buge A, Escourolle R, Hauw J, Lyon- Caen O: Paramedian thalamic and midbrain infarct: clinical and neuropathological study. *Ann Neurol* 1981, 10:127–148. [PubMed: 7283400]
26. Brown E, Lydic R, Schiff ND: General anesthesia, sleep, and coma. *N Engl J Med* 2010, 363:2638–2650. [PubMed: 21190458] • This is a comprehensive review of anesthesia mechanisms, and focuses on a comparison of the anesthetic state, coma, and sleep. The review develops the evidence that anesthesia and coma result from similar large- scale circuit mechanisms.
27. Vanhaudenhuyse A, Noirhomme Q, Tshibanda L, Bruno M, Boveroux P, Schnakers C, Soddu A, Perlberg V, Ledoux D, Brichant J et al.: Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients. *Brain* 2010, 133:161–171. [PubMed: 20034928]
28. Whyte J, Rajan R, Rosenbaum A, Katz D, Kalmar K, Seel R, Greenwald B, Zafonte R, Demarest D, Brunner R et al.: Zolpidem and Restoration of Consciousness. *Am J Phys Med Rehabil* 2014, 93:101–113. [PubMed: 24434886] •• This study is a double-blind, placebo controlled, crossover, single dose clinical trial to evaluate the prevalence of zolpidem responders in a large group of patients with DOC.
29. Giacino JT, Whyte J, Bagiella E, Kalmar K, Childs N, Khademi A, Eifert B, Long D, Katz DI, Cho S et al.: Placebo-controlled trial of amantadine for severe traumatic brain injury. *N Engl J Med* 2012, 366:819–826. [PubMed: 22375973] •• This study is the first double-blind, placebo controlled, randomized clinical trial to demonstrate a therapeutic benefit in disorders of consciousness. In the study subjects with severe brain injuries in vegetative state and minimally conscious state received the drug amantadine or placebo. The treated group demonstrated an accelerated speed and rate of recovery.
30. Volkow ND, Wang G-J, Ma Y, Fowler JS, Wong C, Ding Y-S, Hitzemann R, Swanson JM, Kalivas P: Activation of orbital and medial prefrontal cortex by methylphenidate in cocaine- addicted subjects but not in controls: relevance to addiction. *J Neurosci* 2005, 25:3932–3939. [PubMed: 15829645]
31. Hornykiewicz O: Dopamine (3-hydroxytyramine) and brain function. *Pharmacol Rev* 1966, 18:925–964. [PubMed: 5328389]
32. Rieck RW, Ansari MS, Whetsell WO, Deutch AY, Kessler RM: Distribution of dopamine D2-like receptors in the human thalamus: autoradiographic and PET studies. *Neuropsychopharmacology* 2004, 29:362–372. [PubMed: 14627996]
33. Deep P, Dagher A, Sadikot A, Gjedde A, Cumming P: Stimulation of dopa decarboxylase activity in striatum of healthy human brain secondary to NMDA receptor antagonism with a low dose of amantadine. *Synapse* 1999, 34:313–318. [PubMed: 10529725]

34. Arai A, Kannari K, Shen H, Maeda T, Suda T: Amantadine increases L-DOPA-derived extracellular dopamine in the striatum of 6-hydroxydopamine-lesioned rats. *Brain Res* 2003, 972:229–234. [PubMed: 12711097]
35. Sommerauer C, Rebernik P, Reither H, Nanoff C, Pifl C: The noradrenaline transporter as site of action for the antiParkinson drug amantadine. *Neuropharmacology* 2012, 62:1708–1716. [PubMed: 22155208]
36. Volonté MA, Moresco RM, Gobbo C, Messa C, Carpinelli A, Rizzo G, Comi G, Fazio F: A PET study with raclopride in Parkinson's disease: preliminary results on the effect of amantadine on the dopaminergic system. *Neurol Sci* 2001, 22:107–108. [PubMed: 11487182]
37. Matsuda W, Matsumura A, Komatsu Y, Yanaka K, Nose T: Awakenings from persistent vegetative state: report of three cases with parkinsonism and brain stem lesions on MRI. *J Neurol Neurosurg Psychiatry* 2003, 74:1571–1573. [PubMed: 14617720]
38. Passler M, Riggs R: Positive outcomes in traumatic brain injuryvegetative state: patients treated with bromocriptine. *Arch Phys Med Rehabil* 2001, 82:311–315 [Internet]. [PubMed: 11245751]
39. Fridman EA, Krimchansky BZ, Bonetto M, Galperin T, Gamzu ER, Leiguarda RC, Zafonte R: Continuous subcutaneous apomorphine for severe disorders of consciousness after traumatic brain injury. *Brain Inj* 2010, 24:636–641. [PubMed: 20235766]
40. Patrick P, Blackman J, Mabry J: Dopamine agonist therapy in low-response children following traumatic brain injury. *J Child Neurol* 2006, 21:879–886. [PubMed: 17005105]
41. Lavin a, Grace a a: Dopamine modulates the responsivity of mediodorsal thalamic cells recorded in vitro. *J Neurosci* 1998, 18:10566–10578. [PubMed: 9852593]
42. Taylor N, Chemali J, Brown E, Solt K: Activation of D1 dopamine receptors induces emergence from isoflurane general anesthesia. *Anesthesiology* 2013, 118:30–39. [PubMed: 23221866] •• This is pharmacological study in rats that evaluated the selectivity of dopamine receptors during emergence from anesthesia. Activation of D1 receptors but not D2 decreased the time to emergence from anesthesia and produced behavioral and neurophysiologic evidence of arousal.
43. 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 10.1097/ALN.000000000000117. •• This is a study in rats that evaluated the selectivity of electrical stimulation of the VTA and SNc during emergence from anesthesia. Electrical stimulation of the VTA but not SNc induced reanimation during general anesthesia.
44. Chemali JJ, Van Dort CJ, Brown EN, Solt K: Active emergence from propofol general anesthesia is induced by methylphenidate. *Anesthesiology* 2012, 116:998–1005. [PubMed: 22446983]
45. Willmott C, Ponsford J: Efficacy of methylphenidate in the rehabilitation of attention following traumatic brain injury: a randomised, crossover, double blind, placebo controlled inpatient trial. *J Neurol Neurosurg Psychiatry* 2009, 80:552–557. [PubMed: 19060022]
46. Martin RT, Whyte J: The effects of methylphenidate on command following and yes/no communication in persons with severe disorders of consciousness: a meta-analysis of n- of-1 studies. *Am J Phys Med Rehabil* 2007, 86:613–620. [PubMed: 17667191]
47. Gallezot J-D, Weinzimmer D, Nabulsi N, Lin S-F, Fowles K, Sandiego C, McCarthy TJ, Maguire RP, Carson RE, Ding Y-S: Evaluation of [(11)C]MRB for assessment of occupancy of norepinephrine transporters: studies with atomoxetine in nonhuman primates. *Neuroimage* 2011, 56:268–279. [PubMed: 20869448]
48. Arnsten AFT: Catecholamine influences on dorsolateral prefrontal cortical networks. *Biol Psychiatry* 2011, 69:e89–e99. [PubMed: 21489408]
49. Xie G, Deschamps A, Backman SB, Fiset P, Chartrand D, Dagher A, Plourde G: Critical involvement of the thalamus and precuneus during restoration of consciousness with physostigmine in humans during propofol anaesthesia: a positron emission tomography study. *Br J Anaesth* 2011, 106:548–557. [PubMed: 21285081]
50. Långsjö JW, Salmi E, Kaisti KK, Aalto S, Sc M, Hinkka S, Lic P, Scheinin H: Effects of subanesthetic ketamine on regional cerebral glucose metabolism in humans. *Anesthesiology* 2004, 100:1065–1071. [PubMed: 15114201]

51. McCarthy MM, Brown EN, Kopell N: Potential network mechanisms mediating electroencephalographic beta rhythm changes during propofol-induced paradoxical excitation. *J Neurosci* 2008, 28:13488–13504. [PubMed: 19074022]
52. McCarthy MM, Moore-Kochlacs C, Gu X, Boyden ES, Han X, Kopell N: Striatal origin of the pathologic beta oscillations in Parkinson's disease. *Proc Natl Acad Sci USA* 2011, 108:11620–11625. [PubMed: 21697509]
53. Selden NR, Gitelman DR, Salamon-Murayama N, Parrish TB, Mesulam MM: Trajectories of cholinergic pathways within the cerebral hemispheres of the human brain. *Brain* 1998, 121(Pt 12): 2249–2257. [PubMed: 9874478]

Figure 1.

(a) Anterior forebrain 'mesocircuit'. Image displays key cortical and subcortical components of the anterior forebrain mesocircuit vulnerable to effects of severe brain injuries and widespread cerebral deafferentation. Lines in black represent the direction of the projections for branching axons. Lines in blue represent the direction of the four main dopamine projections from SNc (nigrostriatal) and VTA (mesolimbic, mesocortical and mesothalamic). (+) denotes 'excitatory' projections and (-) denotes 'inhibitory' projections. Following multi-focal brain injuries that produce widespread deafferentation and neuronal cell loss the deafferentation and functional disfacilitation of the central thalamus reduces or removes activity from these thalamocortical projections to the frontal cortex, posterior medial parietal cortex and striatum [1,15,19••]. Downregulation across these structures is further generated by release of inhibition of the globus pallidus, with an overall result of marked reduction of cerebral metabolism across the mesocircuit following different mechanisms of brain injury. (ST: striatum; GP: globus pallidus; c-TH: central thalamus; LC: locus coeruleus; SNc: substantia nigra pars compacta; VTA: ventral tegmental area). **(b)** Mesocircuit component downregulation correlates with clinical impairment in DOC. Group data displaying mean normalized uptake values of glucose metabolism in deep brain structures measured with [¹⁸F]-FDG PET in NV and BI subjects. Above, the bivariate scattergram demonstrates an inverse linear correlation between glucose metabolic rate of the c-TH (x axis) and the GP (y axis), $P < 0.001$. Below, the bivariate scattergram demonstrates a linear correlation between glucose metabolic rate of the left precuneus (x axis) and the c-TH (y axis), $P < 0.001$. (GP: globus pallidus; c-TH: central thalamus; NV: normal volunteer; MCS(+): minimally conscious state 'plus', and MCS(-): minimally conscious state 'minus', according to [6]; VS: vegetative state). **(c)** Pharmacological mesocircuit dopaminergic neuromodulation. Bodies of dopaminergic neurons located in the SNc and VTA (presynaptic level) project to target postsynaptic neurons in the sensorimotor (SNc) and limbic striatum, prefrontal cortex and central thalamus (VTA). Dopaminergic neuromodulation can be achieved using drugs that target the selective mechanisms at the presynaptic level (A, B, C), and/or with drugs targeting the postsynaptic level (D). (AMT: amantadine; MPH: methylphenidate; dAMPH: dextroamphetamine; DAT: dopamine transporter; APO: apomorphine; Bro: bromocriptine; Ppx: pramipexole).