Identification and neuromodulation of brain states to promote recovery of consciousness

Glenn J.M. van der Lande[1,2], Arnau Manasanch[3], Diana Casas-Torremocha[3], Leonardo Dalla Porta[3], Olivia Gosseries[1,2], Naji Alnagger[1,2], Alice Barra[1,2], Jorge F. Mejías[4], Rajanikant Panda[1,2], Fabio Riefolo[5,6,7], Aurore Thibaut[1,2], Vincent Bonhomme[8,9], Bertrand Thirion[10], Francisco Clasca[11], Pau Gorostiza[5,6,12], Maria V. Sanchez-Vives[3,12], Gustavo Deco[12,13], Steven Laureys[1,2,14,15], Gorka Zamora-López[13], Jitka Annen[1,2]

[1]GIGA-Consciousness, Coma Science Group, University of Liège, Liège, Belgium.
[2]Centre du Cerveau[2], University Hospital of Liège, Liège, Belgium.
[3]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona 08036, Spain.
[4]Swammerdam Institute for Life Sciences, University of Amsterdam, Science Park 904, 1098XH Amsterdam, Netherlands.
[5]Biomedical Institute for Bioengineering of Catalonia (IBEC), Barcelona Institute of Science and Technology, Barcelona 08028, Spain.
[6]InstituteBiomedical Research Networking Center in Bioengineering, Biomaterials, and Nanomedicine (CIBER-BBN), Madrid 28029, Spain.
[7]Teamit Institute, Barcelona.
[8]Department of Anesthesia and Intensive Care Medicine, Liege University Hospital, Liege, Belgium
[9]Anesthesia and Perioperative Neuroscience Laboratory, GIGA-Consciousness Thematic Unit, University of Liege, Liege, Belgium
[10]Inria, CEA, Université Paris-Saclay, Paris, France.
[11]Department of Anatomy and Neuroscience, School of Medicine, Universidad Autónoma de Madrid, Madrid 28029, Spain.
[12]Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain.
[13]Computational Neuroscience Group, Center for Brain and Cognition, Universitat Pompeu Fabra, Barcelona, Spain.
[14]Joint International Research Unit on Consciousness, CERVO Brain Research Centre, U Laval, Canada.
[15]International Consciousness Science Institute, Hangzhou Normal University, Hangzhou, China.

Abstract

Experimental and clinical studies of consciousness identify brain states (i.e., transient, relevant features of the brain associated with the state of consciousness) in a non-systematic manner and largely independent from the research into the induction of state changes. In this narrative review with a focus on patients with a disorder of consciousness (DoC), we synthesize advances on the identification of brain states associated with consciousness in animal models and physiological (sleep), pharmacological (anesthesia) and pathological (DoC) states of altered consciousness in human. We show that in reduced consciousness the frequencies in which the brain operates are slowed down and that the pattern of functional communication in the brain is sparser, less efficient, and less complex. The results also highlight damaged resting state networks, in particular the default mode network, decreased connectivity in long-range connections and in the thalamocortical loops. Next, we show that therapeutic approaches to treat DoC, through pharmacology (e.g., amantadine, zolpidem), and (non-)invasive brain stimulation (e.g., transcranial current stimulation, deep brain stimulation) have shown some effectiveness to promote consciousness recovery. It seems that these deteriorated features of conscious brain states may improve in response to these neuromodulation approaches, yet, targeting often remains non-specific and does not always lead to (behavioral) improvements. Furthermore, in silico model-based approaches allow the development of personalized assessment of the effect of treatment on brain-wide dynamics. Although still in infancy, the fields of brain state identification and neuromodulation of brain states in relation to consciousness are showing fascinating developments that, when united, might propel the development of new and better targeted techniques for DoC. For example, brain states could be identified in a predictive setting, and the theoretical and empirical testing (i.e., in animals, under anesthesia and patients with a DoC) of neuromodulation techniques to promote consciousness could be investigated. This review further helps to identify where challenges and opportunities lay for the maturation of brain state research in the context of states of consciousness.

Finally, it aids in recognizing possibilities and obstacles for the clinical translation of these diagnostic techniques and neuromodulation treatment options across both the multi-modal and multi-species approaches outlined throughout the review. This paper presents interactive figures, supported by the Live Paper initiative of the Human Brain Project, enabling the interaction with data and figures illustrating the concepts in the paper through EBRAINS (go to https://wiki.ebrains.eu/bin/view/Collabs/live-paper-states-altered-consciousness and get started with an EBRAINS account).

Keywords: Consciousness, brain states, neuromodulation, disorders of consciousness, anesthesia, animal models, humans, live paper

1. Introduction

Consciousness is the foundation of the human experience, yet a definition remains elusive. This is not necessarily a hindrance to the development of fundamental and clinically useful knowledge. The investigation of brain states, patterns of (surrogates of) neuronal activity (see Box 1), and their coupling to behavior and their dynamics across states of consciousness can help advance the field. Dynamic brain states form a rich repertoire associated with different states of consciousness, for instance clearly shown from the diversity of brain states in sleep. Brain states associated with states of (un)consciousness are usually regarded as whole-brain, with specific spatiotemporal dynamics. An exception of this whole-brain view is the phenomenon of local sleep, where only parts of the brain can display distinct sleep-like electrophysiological patterns, all in a behavioral state of wakefulness[1]. On the contrary, hypothetical islands of awareness in certain brain regions would allow preserved awareness in a behavioral state of unconsciousness [2]. As such, approaches to the identification of brain states can focus on the whole brain or single-out local dynamic patterns. We here focus on literature that has investigated brain states associated with (un)consciousness to give an overview of key elements of brain function that support normal consciousness.

Box 1 –What are brain states?

A brain state is a temporary configuration of activity within the brain. It is a quasi-stable state with minimal fluctuation within a state but with large fluctuations between states. Brain states are objective, as each brain state corresponds to a specific physical configuration of the brain. They are parallel to mental states, which represent the subjective experience at a given time, for example fear or excitement. All mental states have one or multiple associated brain state(s). However, with the brain operating on multiple spatial (e.g., single neurons to the whole brain) and temporal (e.g., action potentials to persistent functional connectivity networks) scales, it is in practice impossible to capture the entire brain state for every mental state. Moreover, investigation of the brain often resorts to proxies of neural activity (e.g., blood-oxygen level dependent (BOLD) signals). Therefore, the investigation of brain states relies on capturing vital parts of functional brain configurations to enable specific behaviors (e.g., connectivity to and specific activity within the motor cortex is required to make certain movements) or subjective experiences. As a result, the investigation of brain states is a potentially good proxy for approximating states of consciousness. These brain states need to be investigated across multiple timescales as behaviors, from deep sleep to greeting a friend, do not have the same temporal dynamics. The more short-lived the state, the harder it might be to capture.

Consciousness can be divided into an arousal component and an awareness component, which respectively refer to wakefulness (eye opening) and the subjective experience one can have[3]. The neural correlate of consciousness (NCC) is the brain state that supports these dimensions, with further distinction into the full NCC that captures both dimensions, and the specific NCC that supports specific conscious content. Some approaches to consciousness highlight the importance of, for instance, the temporo-parietal-occipital hot zone [4] that is mainly implicated in the collection of specific NCCs (i.e., motion perception). We can also consider facilitating background conditions like the ascending arousal network (AAN) (also referred to as ascending reticular activating system) and the thalamus [5]. Indeed, functional magnetic resonance imaging (fMRI) and electrophysiology studies suggest that consciousness depends on both large-scale thalamo-cortical and cortico-cortical interactions (e.g., [6,7]). These structures, their connections and their outputs shape brain states and their dynamics, for instance captured by whole-brain functional connectivity [8]. One successful way to study the brain state comprising a full NCC is the Perturbational Complexity Index (PCI), where the brain is perturbed by means of exogenous transcranial magnetic stimulation (TMS), and the subsequent cortical responses are assessed using electroencephalography (EEG [9]). While studying specific NCCs is a promising approach for many research questions, from a clinical point of view in the context of patients with a disorder of consciousness (DoC) after a coma following severe brain injury, the characterization and promotion of the full NCC seems the most urgent.

Consciousness can be lost by a disconnection from the outside world and the loss of the sense of self. Prolonged loss of consciousness can happen after severe brain injury, as shown by patients with a DoC [10]. These patients with a DoC show eye opening after coma (i.e., periods of, sometimes reduced, arousal), but do not recover (full) awareness. Several types of brain injury can lead to a DoC, including traumatic brain injury, cardiac arrest, hemorrhage or infection[11]. DoCs are considered a rare disease, affecting between 0.2 and 17 individuals per 100.000 in Europe and the US [12–18]. Behaviorally, patients with a DoC can be further split into those with a complete absence of awareness like patients with the unresponsive wakefulness syndrome (UWS) or vegetative state, or partially preserved awareness like patients in the minimally conscious state (MCS; Figure 1B). During recovery from a DoC, patients can transition between these states both in the acute phase (<28 days from onset), in the prolonged stage thereafter (>28 days), up to years after the initial injury [19], or might never transition to higher states of consciousness. Consciousness is usually assessed behaviorally, typically by means of the Coma Recovery Scale-Revised (CRS-R [20]). Misdiagnosis based on behavioral examination of patients with a DoC is common, especially when not performed repeatedly [21]. Therefore, the clinical need for complementary measures using various methods of neuroimaging, has been recognized [22]. As an example, capturing the metabolic brain state of patients with a DoC may safeguard against misdiagnosis, such as when brain states similar to those in MCS patients are identified in UWS patients, and refine the estimation of prognosis [23]. This implies that these possibly covertly aware patients, with a cognitive motor dissociation, might have a higher level of consciousness comparable to MCS, that does not manifest behaviorally[24,25].

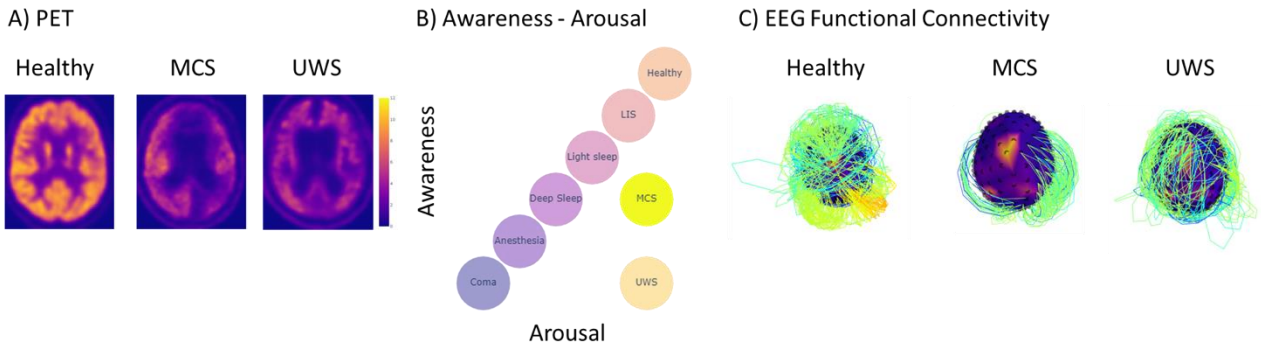

Figure 1 (Live). The arousal-awareness axes of consciousness and examples of metabolic and functional connectivity in patients with disorders of consciousness. Go to EBRAINS (t.ly/edVHU) to view the live version of this figure. **(A)** Transversal view of the standardized uptake value of the brain collected with glucose PET (fluorodeoxyglucose/FDG-PET) (see [23] for details about data processing). The glucose uptake values range from 1 to 12 (blue-yellow) where higher values are associated with more glucose consumption, as observed in a healthy brain. The displayed slice is from a healthy subject. The live version of the figure contains a slider that allows you to scroll through transversal slices of the healthy subject, a patient in the minimally conscious state and a patient in the unresponsive wakefulness syndrome. **(B)** Graphical depiction of states of consciousness alongside the dimensions of arousal and awareness. The live version of the figure contains 3 buttons ("Healthy", "MCS", "UWS") to select different states of consciousness. Panels A (FDG-PET) and C (EEG) will be updated accordingly, showing example data from subjects in these states. **(C)** Scalp mesh with EEG electrode locations indicated as black dots. Lines between electrodes depict the connectivity between functionally connected electrodes. Functional connectivity was determined by the weighted phase lag index[26] on preprocessed data (see [23] for details about the preprocessing). For clarity the top 5 strongest outgoing connections per electrode are shown. Strength of the connection is represented by the height and color of the line (i.e., weak connections are low and yellow, strong connections are high and red). The static image shows the posterior top left view of functional connectivity in a healthy subject. The live version of this image allows rotation of the 3D figure and inspection of all sides.

While research with the DoC population has given new insights into the fundamentals of consciousness and improvement of care for those afflicted by it, clinical and ethical constraints rightfully limit the empirical possibilities. Therefore, there is a need for experimental control over the loss of consciousness, and over its recovery. Promoting recovery of consciousness is paramount in future research for both fundamental reasons and as a tool for clinical improvements. Behaviorally, pathological (e.g., DoC) and physiological (e.g., sleep) states of unconsciousness may have strong resemblance, but it is unsure how much the associated brain states are equal. Anesthesia, a pharmacologically induced state where agents reversibly modify brain functioning and reversibly alter consciousness, is another seemingly similar behavioral state. With its own challenges, the usefulness of anesthesia resides in the observation that a brain state with modified neuronal activity, and connectivity can corroborate the phenomenological changes in consciousness ([27–30]; see section 2.2).

Box 2 – Neuromodulation

With neuromodulation, we here refer to any exogenous intervention that changes neuronal activity. When transitions between states of consciousness do not occur in a natural way, neuromodulation can serve for defining a new line of treatment. Neuromodulation can be invasive or non-invasive, and neuronal processes can be targeted using various techniques. They can be grouped into two categories: chemical and electromagnetic physical stimulation. Chemical alterations can be made through pharmacological interventions, for instance targeting the ion channels that increase or decrease neurons' likelihood of producing action potentials, which in turn can change their behavior. Among possible physical stimulations, the electrical or magnetic ones can change neuronal behavior by inducing an extracellular flow of current, and an artificial neuronal hyper- or depolarization. The former is a more direct way of stimulation (invasive), while the latter can be done without impactful surgeries and with minimal side-effects. Radiofrequency, ultrasound, or infrared neural stimulation can also be used for neuromodulation, although they may not yet be considered conventional techniques. Neuromodulation techniques have already demonstrated their efficacy in other clinical areas, for instance with the use of transcranial direct current stimulation (tDCS) to treat central sensitization syndromes (fibromyalgia) and depression [239], and the use of deep brain stimulation (DBS) for Parkinson disease [240]. While neuromodulation is considered a safe and effective treatment for a multitude of diseases, its potential for the treatment of DoC is yet to be demonstrated.

Additionally, exogenous stimulation or neuromodulation (Box 2) techniques can be used to promote consciousness-supporting brain states, and as such might serve as a curative treatment for patients with a DoC. For example, transcranial direct current stimulation (tDCS) can reduce slow-wave activity usually associated with the absence of consciousness ([31]; see section 3.3). There is a variety of non-invasive approaches to modulate neuronal activity including magnetic and electrical stimulation, ultrasound and near-infrared laser light [32], as well as invasive methods such as deep brain stimulation (DBS), that have shown potential to induce brain state changes in both human and animal models ([33]; see section 3.4). Indeed, the way toward a better understanding can also be paved by the excellent experimental control that animal studies offer. The behavioral effects of induced brain state changes in these animal models can be assessed through the detection of increased movements and normalized vital signs, for instance [34]. Although the heterogeneity of brain injuries in patients with a DoC makes it challenging to create generalizable relevant animal models [35], they constitute important advances. In a recent study, coma was induced in rats by lesioning the tegmentum of the brain stem, and their recovery was described in terms of reactivation of thalamocortical functional connectivity[36]. Another approach is photopharmacology, that

allows to manipulate specific neuronal targets with great spatial and temporal precision, allowing precise control over brain states and, possibly, consciousness (see section 3.2). The development of such new neuromodulation tools in animals and their translation to the clinical reality also emphasizes the need to perform extensive efficacy and safety studies, as well as exhaustive evaluation of ethical concerns related to it (e.g., when and how can we utilize the proposed new technique in humans?).

The ability to promote recovery of consciousness in patients with a DoC will flow from two main research goals. First, identifying how brain states differ between consciousness and unconsciousness, and between pathological and healthy conditions. Second, developing theoretical and empirical tests for inducing transitions between different states of consciousness, or from pathological to healthy states. The second goal is often hindered by practical and ethical limitations. To see how the first goal can be achieved, we will first describe the known relationships between consciousness and brain states (section 2). We will first briefly review the evidence for the importance of investigating brain states (section 2.1) and then give an overview of the literature on brain states as observed during loss and recovery of consciousness (section 2.2). Section 3 discusses the induction of state changes through neuromodulation as potential curative treatments for DoC, where we discuss four options including pharmacology (section 3.1), photopharmacology (section 3.2), non-invasive brain stimulation (section 3.3), and finally deep brain stimulation (section 3.4). A comprehensive discussion highlights the limitations of the current state-of-the-art, and potential future perspectives. Specifically, we discuss future avenues of brain state identification (section 4.1) and then the future of inducing brain state transitions (section 4.2). A promising tool to understand the transitions between brain states, namely computational modelling, will be discussed (section 4.3), as well as the opportunities and challenges for clinical applicability (section 4.4).

2 Consciousness and brain states

The research on brain states opens the window to a common language and to toolboxes aiming at increasing the understanding of the brain in health and disease [37]. This is needed for the development of reliable biomarkers of consciousness, which can be used as diagnostic tools for patients with a DoC. Correct diagnosis has important implications regarding ethical considerations (e.g., end-of-life decisions[38]), pain treatment[39], curative treatment[40], and prognosis[41]. We here distill common features of brain states associated with conscious states.

2.1 Identification of brain states using electrophysiology and functional magnetic resonance imaging

Brain states can be studied with a high level of spatiotemporal details, potentially allowing for a fine-grained assessment of their link with subjective experience. However, this is not always necessary, as robust single feature-based classification of brain states using electrophysiology has been linked with behavior for a long time. Prominently, alterations in the amplitude of electrical activity as measured with electroencephalography (EEG) in different frequency bands, like delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12-30 Hz) and gamma (>30 Hz), have been used in sleep studies for that purpose [42,43]. According to the classical perspective on these oscillations, they follow a hierarchical organization with regard to brain states: lower frequency oscillations (e.g., delta) are associated with unconsciousness (although accumulating evidence now suggests the possibility for presence of dominant delta oscillations in conscious states [44]), while theta waves reflect drowsiness [45], alpha waves reflect attention [46], beta waves reflect normal waking consciousness [47], and gamma waves are associated with cognition [48]. Alongside the power spectrum, sleep stages, for instance, can be well characterized by features observed in the EEG

signal: during NREM sleep highly synchronous, low-frequency and high-amplitude oscillations are observed, along with features like spindles and K-complexes, while REM sleep is characterized by desynchronized wave-like activity [49]. Interestingly, the slow patterns of oscillatory electrical activity typically referred to as an "Up and Down" state are a hallmark of any situation where consciousness is absent, including sleep, anesthesia, and even focal epileptic seizures [50–52]. Yet, not all brain states, especially those encountered in heterogeneous syndromes such as DoC, can be as easily characterized by the aforementioned features. Indeed, the identification of classical sleep patterns in patients with a DoC is challenging, with large inter-individual variations [53]. Nonetheless, characterizing the brain states associated with unconsciousness in general, and in DoC in particular, can increase our understanding of brain physiology, and open a range of possibilities in the healthcare domain, just like the characterization of sleep stages has done for sleep medicine.

DoC patients display characteristic resting-state EEG features, which can be extracted using mathematical tools that estimate spectral, connectivity, or information theoretical aspects (see Figure 2B; [54]). These studies highlight that the features describing the dynamic fluctuations of brain activity are decisive elements among the sources of information that are used for the distinction between MCS and UWS patients. The accuracy of the classification predominantly depends on the presence of oscillations in the theta and alpha range. Moreover, by merely visually assessing the power spectrum distribution at specific frequency bands, one can define functional regimes (i.e., A, B, C, or D) that are rooted in the mesocircuit hypothesis of consciousness, which highlights the importance of thalamo-cortical loops [7]. There, the worst functioning category (A) is akin to complete deafferentation, corresponding to an absence of peaks in the power spectrum, while the highest functioning category (D) displays a healthy peak in the theta, alpha and beta range [55]. Progression of patients with an acute DoC along these regimes is predictive of their natural recovery [56,57]. Others have also shown the relevance of theta, alpha and beta activity. For example, several graph-theory measures of connectivity in the alpha frequency range follow the level of consciousness [58], while network centrality in the theta band is associated with a higher probability of a positive response to electrical stimulation (see section 3.3; [59]). Indeed, when comparing measures that capture different aspects of the EEG-recorded brain states, power in these frequency ranges along with the functional connectivity and complexity appear as a dependable marker of the state of consciousness [60].

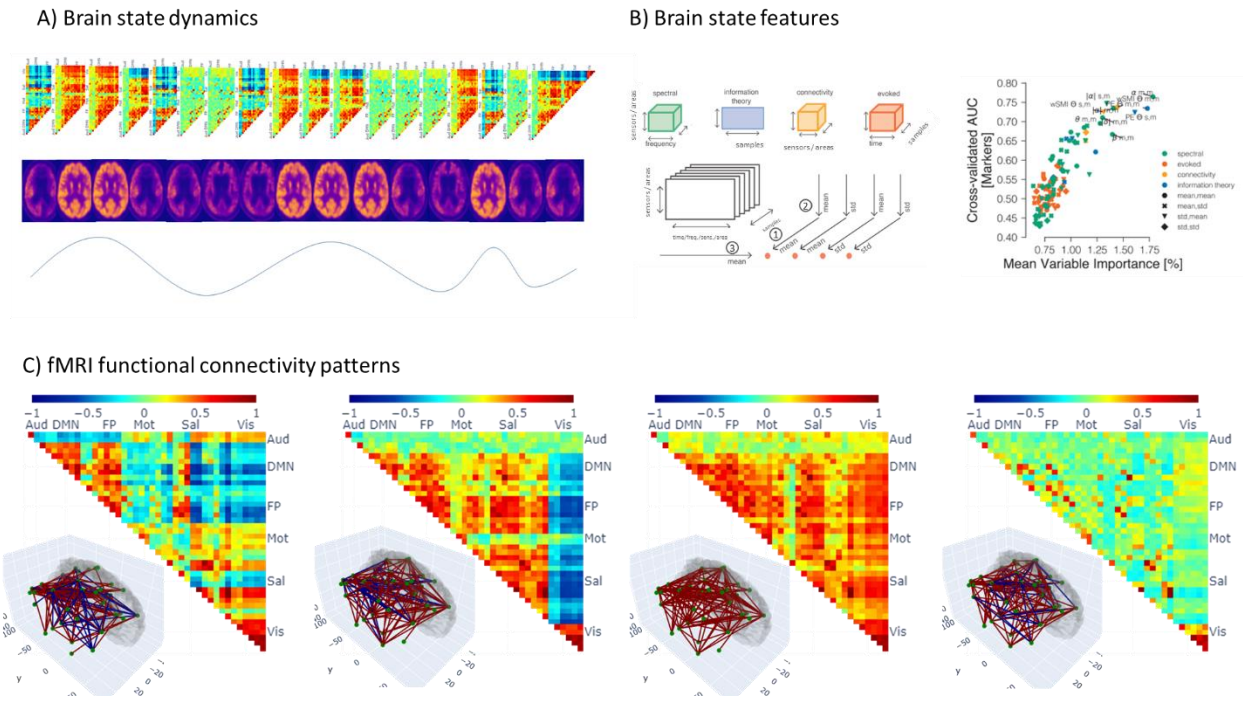

Figure 2 (Live). Methods for brain state identification and characterization of brain state dynamics illustrated through states of fMRI functional connectivity patterns. Go to EBRAINS (t.ly/xjoSy) to view the live version of this figure. **(A)** Illustration of the multi-modal dynamics of brain states showing how brain states can change on different timescales, while also displaying recurrences in a repertoire. The top shows an illustration of how brain states can be quantified (e.g., from bottom to top: through oscillatory EEG of fMRI activity, glucose metabolism or functional connectivity between regions) and how brain states fluctuate over time. **(B)** The wide range of features that can be used to describe brain states (adapted from [54]). The left figure displays these features in different categories, showing which dimensions they take into account (e.g., samples, time) and various ways to summarize them (e.g., mean, standard deviation). The right figure shows how this was applied on EEG data, with the plentitude of features now ordered based on their importance in predicting if a DoC patient is fully unaware (UWS) or has residual awareness (MCS) (see [54] for details). This illustrates that multifaceted brain state investigation is important, alongside the need for the selection of the most relevant features for the differentiation between brain states and parallel behavioral state. **(C)** Patterns of functional connectivity that occur in a quasi-stable manner and alternate dynamically. These could be considered brain states. Functional connectivity is defined between areas in the auditory network (Aud), Default Mode Network (DMN), Fronto-parietal network (FP), motor network (Mot), Salience network (Sal) Visual areas (Vis) defined as 10mm-diameter spheres around peak x,y,z coordinates selected from the literature. The top part shows 4 recurring patterns or brain states (for details on their extraction see [61]). The bottom shows a representation of the functional connectivity between brain regions for each of these brain states. Positive connections are shown in red and negative in blue. In the static version of the image, the 5% strongest connections are presented. The live version of this figure allows the user to vary this thresholding percentage dynamically, rotate the brain in 3D and to view the name of every brain area upon hovering to explore these brain states in more detail.

However, especially in heterogeneous conditions such as DoC, the electrophysiological fingerprint of brain states can be challenging to interpret, as these physiological rhythms can be influenced by the presence of a pathological activity [62]. Ameliorating the spatiotemporal definition of brain states might help identifying the course of specific activity to characterize brain states more precisely. By considering the temporal patterns of the EEG with dynamic functional connectivity, it has been showed that reduced integration and increased network segregation characterize patients with a DoC [63]. EEG microstates also consider the spatial distribution of activity, as they are transient (millisecond to second range), patterned (dipole over the scalp), and quasi-stable (extended periods during which there is small variance) states or patterns over the scalp. They are considered global functional states that function as elementary building blocks of the content of consciousness [64]. As recently shown, the temporal dynamics of these microstates is predictive of outcomes in patients with a DoC [65,66]. Also after external perturbation, spatiotemporal patterns of brain responses are informative for states of consciousness. The perturbational complexity index (PCI) evaluates the brain-wide spatiotemporal patterns of activity elicited –and measured via EEG– as a response to focal perturbation applied with TMS [9]. At its foundation, PCI aims at identifying whether a focal perturbation elicits widespread responses (representative of conscious wakefulness) or, on the contrary, triggers no notable or stereotypical responses (representative of unconsciousness). The PCI has been shown to reliably distinguish states of high and low consciousness in patients with DoC, and also in benchmark populations of healthy volunteers during sleep or anesthesia [9,67]. Further developments with the ECI have made it possible to not only distinguish the level of awareness, but also of arousal[68].

Another way to increase the spatial resolution for the identification of brain states is using neuroimaging. Functional connectivity between brain regions, commonly assessed using fMRI is an important tool which can identify fluctuating brain states characterized by networks of functional connectivity at rest. These resting state networks are important for consciousness. For example, the preservation of connectivity in networks that have been associated with “internal” and “external” awareness is associated with the level of consciousness [69]. Especially the default mode network’s functional connectivity is reduced in patients with a DoC [70,71], and can be associated with reduced thalamic function [72]. Other traits of the functional networks of the brain, like the connections in sensory, auditory and motor networks and interhemispheric connectivity are also reduced [71,73,7471,73]. More recently, the importance of dynamics within these networks has been emphasized repeatedly. Indeed, increasingly complex functional connectivity patterns are shown more often in controls and to some extent in MCS patients while this is greatly reduced in UWS patients ([61]; Figure 2). The decrement in these arousal and awareness supporting dynamics is linked to a global reduction in functional connections, their diversity and recurrent inputs coupled with more homogenous local dynamics [75]. The importance of functional diversity and its interaction with integration in supporting consciousness has been supported by others [76]. In addition, patterns of global brain communication in DoC are characterized by reduced transitions between states of functional connectivity [77]. The amount and occupancy of states in the dynamic functional connectivity repertoire, for instance in the default mode network, of patients with a DoC is reduced in UWS compared to MCS patients [78].

2.2 Anesthesia as a model for pathological loss and recovery of consciousness

Anesthesia can be used as a powerful model for loss of consciousness that propels research into its recovery [79,80]. Its applicability in preclinical investigation facilitates research even more [81–86]. Moreover, mechanisms of action through these manipulations can be studied in greater detail, allowing the generation of hypotheses for loss and recovery of consciousness in DoC (e.g., see [87–91]).

Anesthesia induces states with a prominence of low-frequency oscillations [92–95] and a reduction in high frequency functional connectivity (85-155 Hz; [96]). It has been suggested that local connectivity increases, whereas global alpha connectivity decreases [93]. Another study showed decreased frontal-parietal connectivity, while thalamo-cortical connectivity remained unchanged [97]. The difference in PCI between propofol, xenon or midazolam anesthesia and wakefulness is comparable to the one observed when comparing UWS and, slightly less so, MCS patients in comparison with healthy wakefulness [9]. In non-human primates, anesthesia led to the attenuation of high frequencies and to a decreased spiking activity, paired with synchronized slow activity, putatively disrupting global dynamics, similarly to the observations in humans [84]. More fine-grained, in vitro experimentation of mice brain slices showed decreased bursts of neuronal spikes and decreased spread under isoflurane anesthesia [98]. In vivo rat experiments have identified that these focal bursts propagate throughout the brain orchestrated by the thalamo-cortical loops [99].

Thalamo-cortical connections, which play a key role in the brain state of patients with a DoC, are also altered after the application of most anesthetic agents [91,100,101]. As in DoC [102], the AAN is affected [103]. Similar reductions in dynamics of global brain communication in both anesthesia and DoC have been found [77]. Although not directly compared, a reduction in global connectivity, dynamic repertoire, network topological properties (i.e., integration and segregation) and regional heterogeneity of healthy controls under anesthesia was similar to the one that distinguished patients with a DoC from healthy controls [75]. A direct comparison matched these findings with reduced integration and functional diversity in overlapping brain regions of posterior cingulate cortex and precuneus in both DoC and under anesthesia compared to healthy wakefulness [76]. In addition, the occupancy of dynamic connectivity patterns of low complexity, which increases from MCS to UWS, has similar rates in DoC compared to anesthetized volunteers (Figure 2C for DoC; [61]). Anesthesia reduces a wide range of brain state properties like cortico-cortical and thalamo-cortical connectivity within and between default mode and executive-control networks [104], thalamic connectivity with key arousal nodes[105], connectivity of the posterior cingulate cortex, part of the default mode network [106], flexibility of networks [107], decoupling from anatomical networks as studied in macaques [108], interhemispheric cortical functional connectivity in mice [109] or different whole brain connectivity patterns in rats [101]. It should be noted that different pharmacological agents have different, sometimes not completely understood, mechanisms of action [110], and some of the research found the presented effects only for specific anesthetic agents (e.g., thalamic connectivity to arousal structures is only reduced under propofol, not under dexmedetomidine [101,105,109] and the Lempel-Ziv complexity of spontaneous EEG in healthy volunteers is higher under ketamine than baseline at sub-anesthetic dosages [111]). Furthermore, unresponsiveness during anesthesia does not necessarily mean absence of mental content. Episodes of intraoperative awareness without explicit recall have been estimated to occur in up to 5% of the cases immediately after tracheal intubation[112] and even more frequently in younger and female patients (up to 13%)[113], in experimental settings using the isolated forearm technique to allow voluntary motor responses to command in otherwise paralyzed patients. Dreams can also occur during anesthesia. Consequently, by reversibly and selectively altering some aspects of consciousness [presence of a mental content with (connected consciousness) or without (disconnected consciousness or dream) perception of the environment, or absence of mental content (unconsciousness)], anesthesia can be seen as a very useful tool to identify the functional tenets of these aspects of consciousness. Scientific work is underway in that direction[114].

3. Induction of brain state changes

Recovery of consciousness can occur at any time during the course of a DoC, from the acute to the subacute and chronic phase. Recovery can occur spontaneously or be promoted by treatment. A barrier to developing targeted, consciousness-promoting neuromodulation therapies has been the lack of biomarkers, such as the precise identification and characterization of brain states, which would allow a better assessment of the therapeutic responses[115]. With recent advances in this field, we here discuss the induction of state changes through pharmacology, photopharmacology, non-invasive brain stimulation, and deep brain stimulation. These act on different targets, from the cortical, for example with tDCS [115], to the subcortical level, where for instance thalamic and brainstem nuclei are critical targets [36,81,116], and the whole brain for pharmacological approaches [40]. Despite the fact that only few randomized controlled clinical trials have been performed in large samples, novel electrophysiological and pharmacological therapies have shown a potential to reactivate injured neural networks and promote re-emergence of consciousness (reviewed in [115]). Curative treatments for patients with a DoC will be discussed here in light of the mesocircuit model[7]. In short, this model describes cerebral malfunction in DoC as related to the widespread disruption of cortical neurons, causing a decrease in striatal activity due to the loss of thalamo-striatal and cortico-striatal connections. This reduction in striatal activity then inhibits thalamic function and leads to a decrease in both thalamo-cortical connectivity and cortical activation (Figure 3). Each of the presented treatments attempts to normalize activity somewhere in the thalamo-cortical circuit, with the aim of increasing activity of the whole circuit and facilitating functional recovery. To support this theory, the anticipated changes in the globus pallidus, striatum and frontal cortex measured with $GABA_A$ ligand precedes functional recovery in patients with a traumatic brain injury[117].

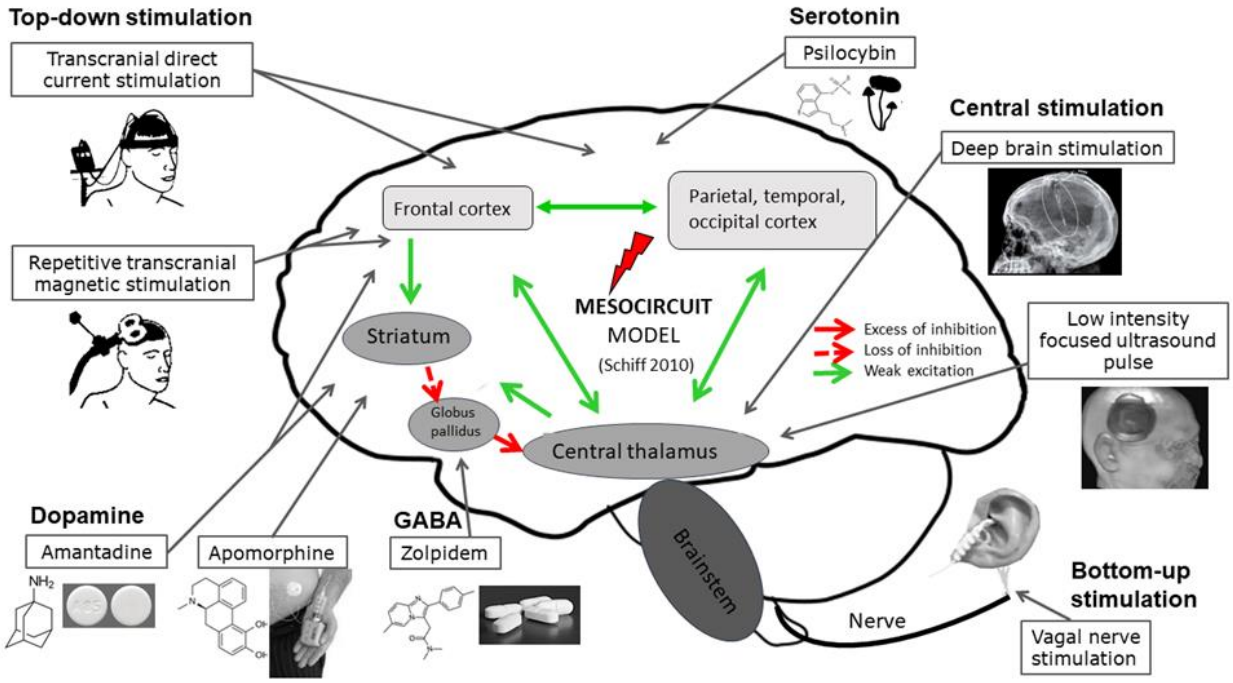

Figure 3. Available treatments and treatments currently being tested for the treatment of patients with disorders of consciousness and their effect on the mesocircuit. Pathways of weakened excitation (green) and excessive (red, solid) or loss (red, dashed) of inhibition that characterize patients with a DoC are

shown in the mesocircuit model. From top right, going clock-wise, is shown: the serotonin system that is affected by psilocybin and acts cortically; central stimulation through deep brain stimulation (DBS) acts mostly on the thalamus; low intensity focused ultrasound also affects the thalamus; vagal nerve stimulation stimulates the brainstem by nerve stimulation (latter three are bottom-up processes); the GABAergic drug zolpidem targets the globus pallidus; dopaminergic drugs amantadine and apomorphine act on the striatum, while the former also affects the frontal cortex; repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) act cortically and stimulate activity in a top-down fashion. Figure adapted from [118].

3.1 Pharmacological curative treatments for DoC

Most pharmacological trials in patients with subacute-to-chronic DoC have tested stimulants that promote dopamine signaling, such as amantadine [119], methylphenidate [120], and subcutaneous apomorphine [121]. However, up to date, the only therapy that has shown benefit in a randomized placebo-controlled trial is amantadine [115], which was associated with accelerated functional recovery in patients with a DoC [122,123]. The mechanism behind it is still unclear, yet it appears to act as both a N-methyl-D-aspartate glutamate receptor subtype antagonist and indirect dopamine agonist [119]. Although the action of action of dopaminergic agents on the recovery of consciousness remain unclear, based on the mesocircuit hypothesis, dopamine could regulate the activity of the striatum to the globus pallidus, which will, in turn reduce the inhibition of the thalamus, as well as promote the activity of the mesiofrontal cortex, thus acting on the fronto-striatal-thalamic loop[7]. Sedative drugs, such as Zolpidem, a GABAergic is a gamma-aminobutyric acid (GABA)ergic agonist, have shown promising effects with a paradoxical arousing effect in some patients with subacute-to-chronic DoC [124], or showing emergence of functional communication [125]. This GABAergic drug is thought to act on the globus pallidus interna, reducing its inhibitory effect on the thalamus. Other pharmacological therapies that promote consciousness and neuronal function have been investigated with varying results[40] while others (e.g., levodopa, bromocriptine, modafinil, ketamine (e.g., ClinicalTrials.gov: NCT05343507), selegiline and baclofen) are now also being tested in patients with (acute) DoC[126]. Despite these modest successes, the gap between brain states and pharmacological treatments has not received sufficient attention. This could be due to the challenge of assessing how the microscale mechanisms of action of these drugs affect the global dynamics, for instance the brains' functional connectivity on a macroscale.

3.2 Photopharmacology

Although currently not used in humans, localized drug administration has the potential to dramatically improve treatment effects. Since the use of exogenous neurotransmitters, as in the section above, could be problematic at the systemic level, localized drug action has been pursued by means of light using photopharmacology [127,128]. Neuronal activity can be controlled with light by (opto)genetic expression of photo-switchable microbial proteins [129]. Optogenetics has been used to transition the brain to a state of arousal both in awake and asleep rodents ([130,131]; Figure 4A-B), yet its clinical translation to humans is hampered by the need for gene manipulation. This problem and potential immune-reactivity are overcome by photo-pharmacology, which uses synthetic light-sensitive drugs targeting endogenous proteins [132]. Several photo-switchable inhibitory ligands have been studied, including derivatives of the anesthetic propofol [133,134], fomocaine [135], and benzodiazepines modulating both $GABA_A$ receptors [136] and glycine receptors [137]. The potentiation of $GABA_A$ receptors with light has also been demonstrated using

diazepam [138]. In addition, photo-switchable blockers of potassium channels have been developed [139]. Photo-switchable tethered propofol derivatives have been used to investigate the propofol binding site in $GABA_A$ receptors [140]. Localized $GABA_A$ administration to the globus pallidum might decrease its inhibitory effect on the thalamus[7], while avoiding the depressing effect of $GABA_A$ on the rest of the brain. Recently, several photo-switchable derivatives of the mild sedative clonidine (termed adreno-switches) have been reported [141], as well as a photo-switchable dopaminergic agonist (azodopa) resembling apomorphine. All these compounds display pharmacological profiles that offer the potential to control arousal with light in mammals. Drug-based light-mediated control on a brain network has been demonstrated recently using a photo-switchable muscarinic agonist that controls cholinergic-dependent brain state transitions in anesthetized mice ([142,143]; Figure 4C-G). Synchronous emergent cortical activity, similar to slow-wave sleep, was transformed into a higher frequency pattern both in vitro and in vivo, by activation of a muscarinic agonist with light. These results pave the way to study neuromodulation by cholinergic ligands (including recently developed photo-switchable antagonists; [144]). Together, they offer the promise of controlling spatiotemporal patterns of activity in different brain states and facilitate their transitions to wake-like patterns, which could be linked to cognition and behavior. Thus, photo-pharmacology is a promising tool to achieve high spatiotemporal control of drug actions (Figure 4) without genetic manipulation. Advances in the use of red [145] and pulsed infrared light (two-photon excitation, [146]) make photo-pharmacology compatible with transcranial non-invasive illumination that, in the long term, could be used in humans.

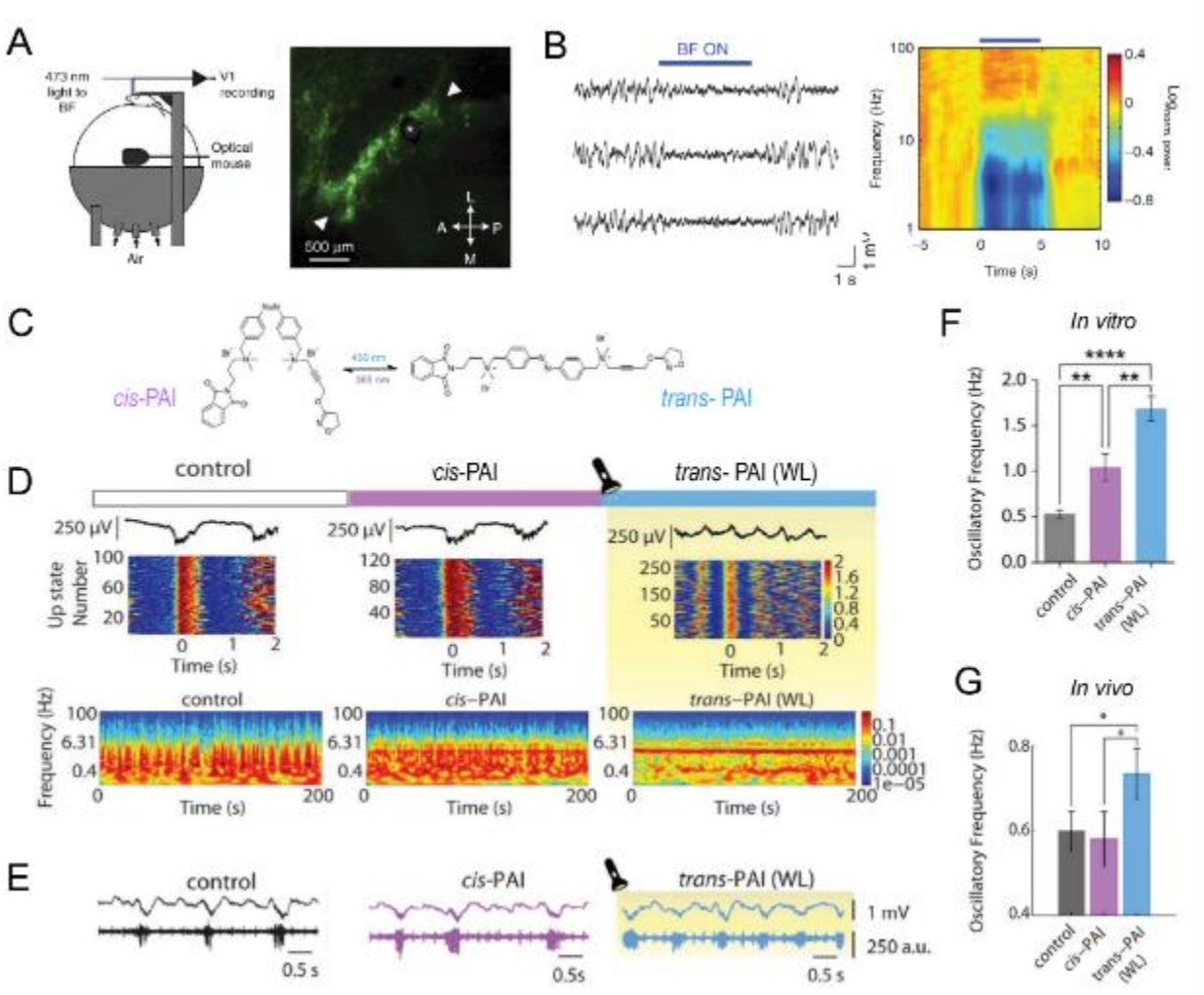

Figure 4 (Live). Pharmacological neuromodulation induced consciousness state changes in animal models. Go to EBRAINS (t.ly/qSE8b) to view the live version of this figure. **(A, B)** Optogenetic activation of basal forebrain cholinergic neurons desynchronize cortical activity in awake mice. Light activation of basal forebrain cholinergic neurons reliably desynchronized cortical activity by reducing the power at low frequencies (1–5 Hz) and increasing the power at high frequencies (60–100 Hz). **(A)** Schematic illustration of experimental setup and fluorescence microscopy image of basal forebrain cholinergic cells. **(B)** Three example local field potential (LFP) traces show the effect of basal forebrain stimulation (blue bar; average of all experiments in the right panel). Figure modified from [130]. **(C-F)** Control of brain state transitions with a photoswitchable muscarinic agonist (Phthalimide-Azo-Iper (PAI)) *in vitro* and *in vivo*, and the effect on the brain network is studied Physiological synchronous emergent cortical activity consisting of slow oscillations is transformed into a higher frequency pattern in the cerebral cortex, both *in vitro* and *in vivo*, as a consequence of PAI activation with light. **(C)** Chemical structures of trans- and cis-PAI photoisomers are shown. **(D)** Photocontrol of brain waves *in vitro* using PAI and direct illumination with white light. Representative LFP traces (top), raster plots of firing rate during the Up-states (middle) and spectrograms (bottom) under control conditions, Mcis-PAI and Mtrans-PAI after photoconversion with white light (WL). The live version of this figure allows the user to inspect the LFP (Local Field Potential) and MUA (Multi-Unit Activity) traces for 3 different brain slices and for control, cis and trans conditions. The user can then select the channel (based on the electrode location provided) and visualize how the frequency of the slow oscillation changes along with the corresponding rastergrams. **(E)** In vivo photomodulation of brain waves. Representative raw traces of LFP (top) and multiunit activity (bottom), showing the differences in oscillatory frequency and firing rate during the Up-states between the control, cis-PAI, and trans-PAI after photoswitching with WL. **(F, G)** Changes in oscillatory frequency in vitro **(F)** and in vivo **(G)** by PAI photoisomerization. Comparison of the different conditions analyzed in this study: control, cis-PAI and trans-PAI. Figures C-F have been adapted from [142].

3.3 Non-invasive brain stimulation for curative treatment of DoC

Electromagnetic stimulation techniques are proven useful in clinical practice for the treatment of specific diseases such as major depressive disorders[147]. Research in the past decades has explored several non-invasive brain stimulation techniques as therapeutic options for promoting consciousness in patients with DoC. The first studies employed electromagnetic techniques to stimulate brain activity and promote consciousness recovery, such as transcranial direct current stimulation (tDCS) or repeated transcrianial magnetic stimulation (rTMS). ¹⁴⁸Treatment protocols for rTMS have been developed, which by top-down stimulation of the cortex could directly increase neuronal excitability of specific brain regions or networks, indirectly. One study showed increases in cerebral blood flow in MCS, but not in UWS patients [149]. rTMS applied over the motor cortex have shown little behavioural effects[150–152]. However, more recently the effects of rTMS have improved, by optimizing target locations (left prefrontal cortex), using high-frequency stimulation (10-20Hz) and multiple sessions (10-30 sessions)[153–155]. Stimulation over the left parietal cortex has shown promising improvements in behavioral scores in MCS[156] and even UWS patients[157]. Interestingly, rTMS has been shown to increase levels of the estradiol hormone in responders [154], which in turn has been shown to be capable of influencing brain states by restoring interhemispheric balance [158]. These studies collectively show that rTMS is a valid and safe treatment option in DoC patients, that, by optimizing stimulation protocols, can normalize brain activity and improve behavioral responsiveness.

Among these non-invasive brain stimulation techniques acting in a top-down manner, the easy-to-apply and inexpensive transcranial direct-current stimulation (tDCS) is, currently, one of the most popular and

well-studied[159,160] .During the stimulation, tDCS modulates membrane polarity and neuronal excitability, while after-effects are also observed through LTD or LTP-like mechanisms[161]. Insightful animal studies contributed that tDCS could also stimulate gene expression, in particular that of brain-derived neurotrophic factor and glial fibrillary acidic protein[162], which are, respectively, involved in the prevention of cell death [163] and promotion of plasticity [164], that might be crucial for patients with a DoC. In a pivotal randomized placebo controlled cross-over trial of tDCS over left dorsolateral prefrontal cortex (dlPFC) as a therapeutic tool to enhance consciousness in patients with DoC it was found that 43% of MCS patients (i.e., 13 out of 30) showed significant behavioral improvement[165]. This might be a result of increased functional connectivity from the site of tDCS stimulation (dlPFC) to frontal and parietal brain regions [166]. In an effort to understand and reproduce this outcome, the associated brain states needed to be investigated, along with a protocol and stimulation-site optimization (for more extensive discussion, see [32]). Repeated stimulation sessions, compared to single session protocols, have resulted in more patients showing behavioral improvement and effects lasting up to 3 months [167–169]. In an exploration of brain areas other than the dlPFC as target, the precuneus [170], and primary somatosensory area [171] have been found successful, while the primary motor cortex [172] or the fronto-parietal network [173] are not associated with improvement. Besides the stimulated area, more parameters seem to influence the effectiveness of tDCS. Patients that respond to stimulation show more preserved grey matter in areas that are considered critical for consciousness (e.g., precuneus and thalamus) and greater overall metabolism than non-responders [174]. Differential effects between behavioral responders and non-responders were also found in UWS patients when objective EEG metrics as power and connectivity did not change, while for MCS patients tDCS usually induced alterations of the ongoing EEG [175–177]. Also, at rest before tDCS, responders could be characterized by higher theta connectivity and network centrality as compared to non-responders [59]. Even in the absence of behavioral improvement, tDCS can cause changes in the brain states as evidenced by EEG[178,179]. One study ([31]; Figure 5) explored the effects of tDCS on TMS-evoked potentials and found that tDCS significantly reduced the amount of slow-wave activity but did not produce an increase in high frequency suppression. As the patients in this study did not show any behavioral improvement it has been suggested that reduced slow wave activity is not sufficient alone, without an increase in high frequency suppression. Alternatively, these findings might suggest that conscious brain states could be stimulated with tDCS, but that behavior is limited by physical impairments, leading to the presence of covert consciousness[23,25]. Although the effects of tDCS are consistent[32,180], a recent translational multicentric study debates this as at the group level no treatment effect was found, even if the 3 months' follow-up revealed a significant improvement for patients in MCS and with traumatic aetiology[181]. Given its relative ease of use, limited costs, and potential future developments (Section 4) it remains an appealing option for the treatment of patients with a DoC.

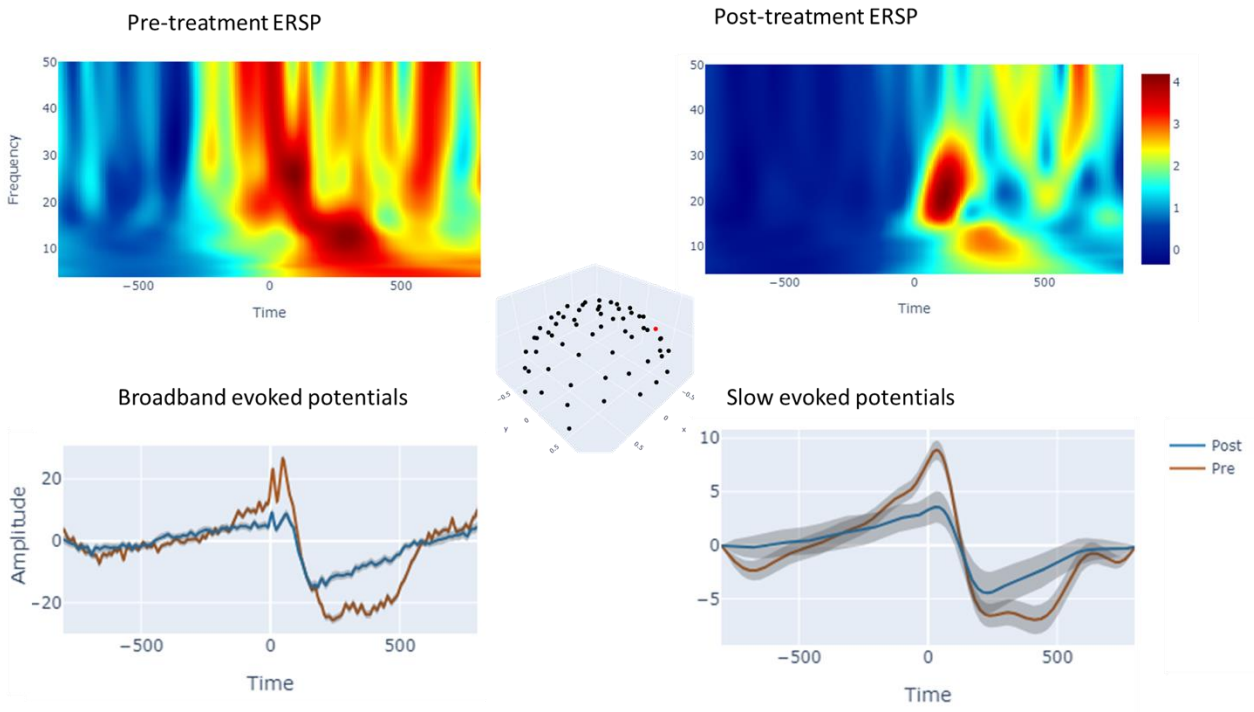

Figure 5 (Live). Neurophysiological effects of tDCS over the dorsolateral prefrontal cortex in a patient in the minimally conscious state. Go to EBRAINS (t.ly/kqi9M) to view the live version of this figure. EEG data evoked by a TMS pulse (-800ms before to 800ms after, on each x-axis) before and after tDCS treatment (see Mensen ref for experimental details). The top left figure shows the event-related spectral perturbation (ERSP; frequency on the y-axis, color indicating increasing power blue->red) pre-treatment while the right figure shows the ERSP post-treatment. A marked decrease in the slow wave induced by the TMS pulse can be observed. The top middle figure displays the electrode configuration, with a red dot indicating the electrode for which the responses are displayed. In the live version of this figure, a dropdown menu allows you to select different electrodes and view their responses. Electrode configuration is rotatable and electrode names are displayed upon hovering over them. The bottom figures show the amplitude response (y-axis) for both the broadband and the filtered (2-6Hz) signals on the left and right, respectively.

Interestingly, both for rTMS and tDCS, the top-down targeting the prefrontal cortex seems to be the most promising area to stimulate. This is in line with the mesocircuit model, as the prefrontal cortex as direct projection to the striatum, which could in turn, promote the fronto-striatal-thalamic loop. More recently, studies have employed a variety of techniques to act on the brain in a bottom-up manner, such as ultrasound stimulation [148] which could act directly on the thalamus to restore brain activity. Transcutaneous vagal nerve stimulation provides another promising outlook, as it could stimulate cerebral activity through the modulation of brainstem activity [182]. In brief, vagus nerve stimulation, through its connection to the locus coeruleus and the raphe nuclei (via the trigeminal nucleus and the nucleus of the solitary tract located in the lower brainstem areas) could promote norepinephrine and serotonin release which act on specific brain regions, but most importantly on the thalamus[116]. Both techniques have shown promising effects in small sample open-label studies.

3.4 Deep brain stimulation

While non-invasive techniques are generally less risky and easier to try, invasive neuromodulation techniques can reach deeper structures and induce stronger beneficial effects. The thalamus and its role in the thalamo-cortical loops have repeatedly been mentioned as an influential regulator of brain states. This main component of the diencephalon is located between the cortex and the midbrain, and consists of a left and right hemisphere part, divided by the third ventricle. However, the thalamus is not a single entity but consists of a great number of sub-nuclei. Broadly, the thalamus can be divided into an anterior, a lateral and a medial part, separated by the white matter tracts of the medial medullary lamina [183]. Inside the medial medullary lamina are the intralaminar nuclei, with, importantly in the caudal part, the centromedian parafascicular nuclei complex (CM-PF) that has glutamatergic afferents to the striatum beside some output to the nucleus accumbens, other parts of the basal ganglia, midbrain and cortex [184,185]. The thalamic axonal projections of these nuclei to the cortex have been considered as "non-specific" since they innervate different cortical areas in a diffuse way (reviewed in [186]). These diffuse projections allow the nuclei to influence the overall excitability of the cortex and are implicated in consciousness ([187]; see below, Figure 6). On the other hand, a small lesion in the intralaminar thalamic nuclei can cause loss of consciousness [188]. In addition, studies with patients with a DoC have reported reductions in functional connectivity restricted to the cortico-thalamo-cortical networks from the intralaminar nuclei [189]. The DBS of different intralaminar nuclei and adjacent portions of the mediodorsal, ventral lateral and anterior pulvinar nuclei has been demonstrated to 'awaken' anesthetized non-human primates and reverse electrophysiological features of unconsciousness, restoring both the signatures of arousal and awareness ([34,84,190]; Figure 6A-D). In addition, DBS of this "central thalamus" has been used successfully to restore cognitive functions and obtaining the impressive recovery of consciousness in DoC patients [191–194] (Figure 6E,F). It has also been shown to be effective in facilitating memory and attention in rats [195]. This heterogeneous collection of nuclei together innervates the dorsolateral prefrontal, premotor, posterior parietal and cingulate cortices and the dorsal striatum, which are key nodes of the brain's attention, executive control, and working-memory networks[196]. Clinical DBS in the thalamus focuses on the central-lateral (CL) nucleus, with the aim to restore arousal regulation sufficiently to support communication or to restore executive cognitive function [192,197,198]. Ushering caution, recent studies in rodents and non-human primates have shown that the electrical activation of the central thalamus can either drive the brain to an "awake" state or promote a state of unconsciousness, depending on the parameters of the stimulation [131,199]. Recently, Redinbaugh and colleagues provided evidence that the CL nucleus supports consciousness through modulation of neocortical intra-columnar and inter-regional interactions in macaques [34], specifically showing an enhancement of cortico-cortical synchrony in the gamma range.

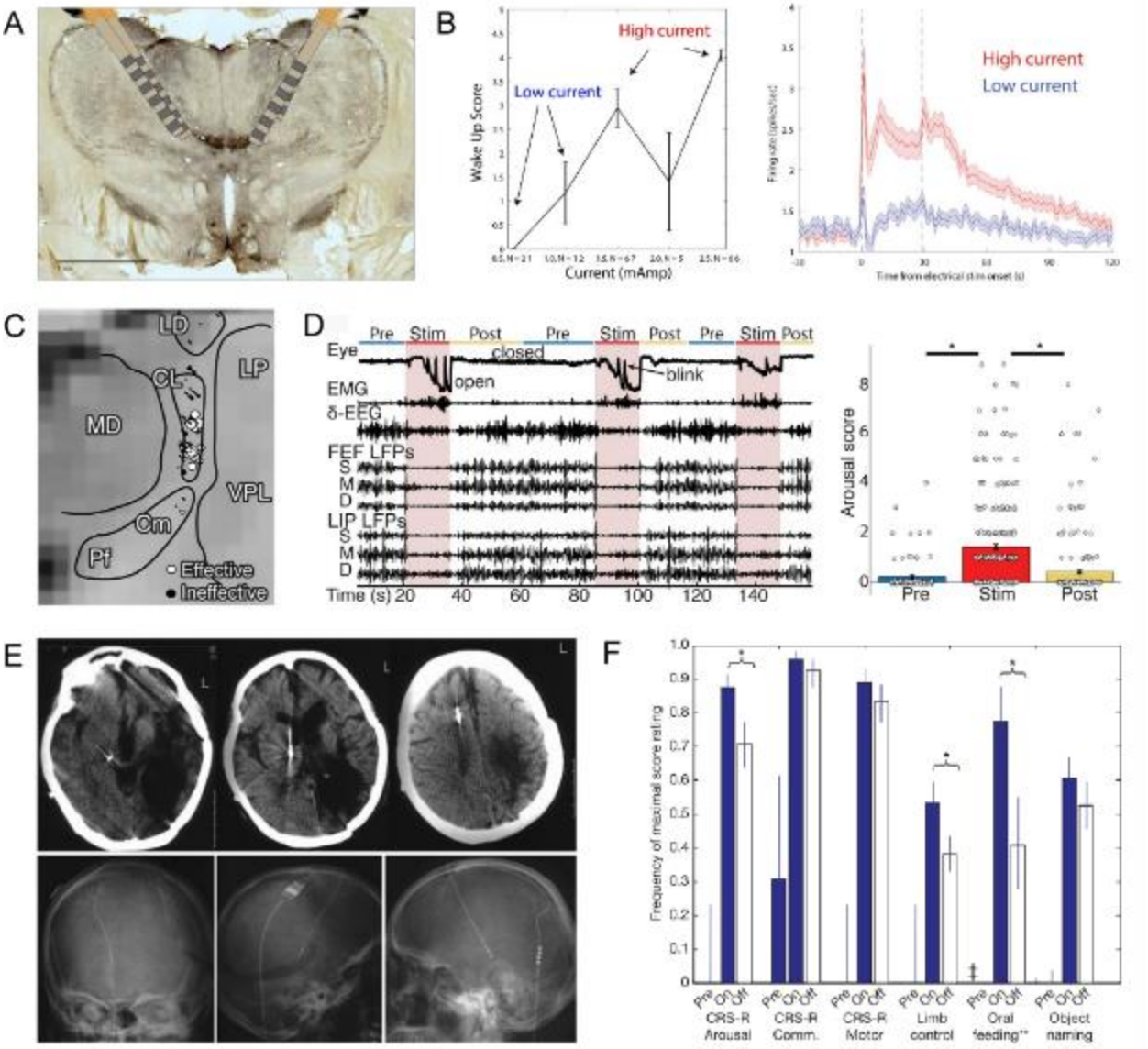

Figure 6. **Electrical induced state changes to promote consciousness in animals and humans by means of thalamic stimulation.** Consciousness depends on large-scale thalamocortical and corticocortical interactions. Many studies support non-specific thalamic nuclei (intralaminar nuclei) as critical structures. **(A-B)** Thalamic electrical stimulation in central thalamus arouses monkeys (adapted from [84]). **(A)** The histological images show the thalamic stimulation leads in the central thalamus. **(B)** The effects of thalamic electrical stimulation on cortical state in monkeys are shown by an example of the behavioral wake-up score as a function of thalamic current (left) and the mean firing rates with respect to electrical stimulation onset (at time zero) and offset across all cortical areas (right)[84]. **(C-D)** Central lateral thalamic stimulation arouses macaques from stable anesthesia (adapted from [34]). **(C)** Stimulation sites (n=90) in one subject collapsed along the antero-posterior axis are shown in the image. Circles represent the middle contact in the stimulation array, diameter scales with induced arousal. **(D)** An example of the behavioral and neural recordings during 50-Hz stimulation is shown in the left panel. The population mean arousal score before, during and after stimulations is represented in the right panel. **(E-F)** The electrical stimulation of different intralaminar nuclei has been demonstrated to restore consciousness in patients with disorders of

consciousness. **(E)** Example of deep brain stimulation (DBS) for treatment of a patient with the unresponsive wakefulness syndrome. The stimulating electrode was implanted for stimulation of the CM-PF. Computerized tomography (upper) and radiography (lower) show the trajectory and location of DBS electrode (adapted from [200]). **(F)** Bilateral DBS of the central thalamus modulates behavioral responsiveness in a patient who remained in minimally conscious state for 6 years following traumatic brain injury before the intervention. Comparison of pre-surgical baselines of achieving the maximal obtained behavioral score with this same metric with DBS on and DBS off periods during the crossover phase (adapted from [192]).

Apart from the thalamus, other studies in rodents demonstrated recovery from anesthesia induced by site-specific electrical stimulation in different subcortical structures that are part of the AAN distributed across the brainstem [201]. Stimulation of the parabrachial nucleus of the pons has been proposed to regulate arousal [202] and has been shown to cause awakening from anesthesia [203]. In parallel, the stimulation decreases EEG delta oscillations. Electrical stimulation of the pontine reticular nucleus also decreases delta and theta power under anesthesia and increases the integration of cortical information, both spontaneous and stimulus-evoked [204]. Finally, stimulating the ventral tegmental area, a main source of dopamine in the brain, thus important for regulating arousal [205], increased responsiveness [206], and was accompanied by a shift in peak frequency from delta to theta range [207].

4. Limitations of current state-of-the-art and future perspectives

4.1 Current and future approaches for brain states identification

Till now, research on the identification of brain states lacks clear definitions on what a brain state precisely is [208]. Going forward, brain states should quantify and clearly describe which multi-dimensional perspective is the most adapted to consciousness research. Here, we employed a rather broad definition, incorporating a large array of features extracted from the brain. The frequency ranges in which the brain operates are important, with slow delta oscillation being associated with unconsciousness, while alpha and, to a lesser extent, theta, beta and gamma oscillations being related to states of consciousness. Well-organized yet flexible functional communication between brain regions, and the loose coupling of functional connectivity to structural connectivity, is crucial for the emergence of conscious states. The ability to orchestrate complex temporal dynamics, by dynamically crossing a wide range of network configurations to allow for appropriate multisensory integration is paramount for consciousness. Perturbation-based tools like the PCI or dynamic analysis tools investigating the complexity of functional connectivity patterns (e.g., [61], Figure 2A,C) bring along promising opportunities to not only describe a single state but to explore the importance of their temporal dynamics.

The precise experimental control that can be achieved with animal models and the use of anesthesia could pave the way for future clinical and fundamental knowledge, given broad similarities in their findings to human research. Although from an outsider's perspective, these different ways of losing consciousness may appear similar, it has been argued that the mental state of sleep and anesthesia are different [209]. In this sense, care should be taken in aggregating data across multiple domains and should put additional effort into comparative research across different states of (un)consciousness. For example, anesthetics have been shown to alter neurovascular coupling, complicating the interpretation of how these changes might be related to brain states and consciousness specifically [210]. Despite these differences, the onset of consciousness (or maintaining a conscious state) requires some minimal conditions to happen. Thus, although anesthesia, sleep and DoC might follow different mechanisms, they all affect those minimal

conditions required for consciousness. Simple measures to uncover some of those minimal conditions that allow the recovery of (partial) consciousness, as demonstrated in MCS patients[211], could be useful in all altered states of consciousness.

From a methodological perspective, it is important to consider brain state identification tools in a predictive setting: extract as many features as possible from the data and identify the ones that are more representative and meaningful to predict brain states. Moreover, the use of generalization-based assessment metrics (cross-validation-based prediction accuracy, sometimes, cross-cohort validation) is the only way to guarantee the external validity of these measurements. There remain several challenges regarding such predictive modeling. The first one consists of generalization problems due to the variety of devices used (e.g., number, position and characteristic of electrodes, scanner type, MRI acquisition sequence), as well as the different protocols or different ways to record the signal in each dataset. Consequently, naive models that simply predict the behavioral features from raw signals are suboptimal. Robust methods should be favored, and explicit domain adaptation techniques should be used to bridge across datasets [212]. With such approaches, the decoding of cognitive tasks from functional neuroimaging data is possible [213], making it a promising avenue for discerning the specific NCCs. For the exploration of the full NCC, black box predictive models can be suboptimal as it is challenging to match signatures of brain states with a given behavioral state. Isolation analysis can be carried out using for example cross-validated univariate forests to assess variable importance in order to discriminate UWS and MCS patients ([54], Figure 2B).

While more and more data has become accessible to facilitate fine-grained assessment of phenomenology, expert annotations necessary for predictive settings are often unavailable. In such cases, self-supervised learning is a recently developed area of research that provides a compelling approach to make use of large unlabeled datasets. With self-supervised learning, the structure of the data is used to turn an unsupervised learning problem into a supervised learning problem. The power of this approach has been shown in [214], where sleep data analysis was enhanced by such a procedure, revealing age- and diseases-related features without observing them directly in the first place. In the context of consciousness research, this approach can be powerful, as patients with a DoC are usually unable to provide a subjective report of their mental state. The level of consciousness possessed by these patients is thus inferred from a third-person perspective, and by nature poses a non-supervised learning task. While remaining vigilant to physiological and phenomenological differences of various altered states of consciousness, benchmark populations comprised of healthy volunteers under anesthesia with no report of conscious experience or non-dreaming sleep could serve as labeled examples to which the states of consciousness in patients with a DoC can be compared, much like what was done for the validation of the PCI [67].

4.2 Future of brain state transitions

There are different ways to regulate consciousness. First, neurotransmitters play a key role in the regulation of arousal and awareness and are therefore a good target to achieve unconsciousness (e.g., as often is the case through anesthesia), but also to facilitate its recovery. The most dramatic pharmacological improvements in patients with a DoC are achieved through the GABAergic zolpidem, but these effects are rare (~5% [124]). While several other drugs are being investigated (e.g., apomorphine [215]), currently amantadine is the only one supported by class II evidence[119,216]. The future development of pharmacological curative treatments can be aided through photo-pharmacology. Various photo-switchable drugs have been developed and their deployment has been shown to be capable of altering brain states. Reversibility with light, drug-likeness, and administration routes are aspects to be improved.

On the other hand, non-invasive brain stimulation through, for instance, tDCS is considered an acceptable manner to modify the brain state, sometimes coupled with behavioral improvements in patients with a DoC. With increased precision at the cost of invasiveness, DBS, especially to nuclei of the thalamus but also to parts of the AAN, has been successful in manipulating brain states and even inciting recovery from anesthetically induced unconsciousness. In most of the fruitful approaches, brain state changes followed the same divergence between conscious and unconscious states that are described above in the investigation of brain state identification, reducing slow oscillations and increasing faster ones, increasing functional connectivity patterns and complexity.

Crucially in this review, we see that treatment options to increase consciousness in patients with a DoC target aspects of the brain states associated with unconsciousness (e.g., tDCS to the prefrontal cortex to normalize DMN connectivity[217], or DBS in the thalamus to increase cortical function[191–194]. We believe that tracking brain states more carefully and systematically allows to fine-tune treatment protocols to improve behavioral effectiveness. Novel therapeutic interventions allowing for a change in brain states and behavioral improvement, will help to better understand the mechanisms of consciousness and its recovery. At the same time, a better characterization of the NCC would allow to capture sub-clinical changes following an intervention and help to re-evaluate treatment efficacy, even in the absence of behavioral evidence for improvement of consciousness and help avoid the misdiagnosis of covert consciousness. In this way, the fields of brain state identification and the induction of brain state transitions can be mutually beneficial. Within the application of each neuromodulation tool, many parameters must be chosen, and, consequently, optimized. Amongst others, the target of stimulation (be it (photo)pharmacological, electrical, or magnetic), as well as the number of sessions, duration and dosage, play a big role in determining the success of a therapy. For instance, for tDCS the left dlPFC is the most explored target and also the one that seems to produce the strongest effects. Repeated sessions of stimulation would also need to be preferred to single session protocols, as not all patients show improvement after the first session. For DBS, stimulation of different thalamic nuclei, e.g., CM-PF and CL nucleus of the thalamus, have been shown to affect the brain state, and other choices in the stimulation paradigm could likely be made. Pharmacological stimulation may be useful through different neurotransmitter systems (e.g., GABAergic system through zolpidem, dopaminergic system through amantadine), but both have their dosage challenges. Solutions can be found in tailoring approaches at the individual level, while performing systematic comparisons across parameters hypothesized to be relevant.

To conclude, the developments in the identification of brain states make it now possible to go beyond exploratory approaches and embrace an open science framework of confirmatory testing. Here, the field could start by defining a target brain state, formulating hypotheses about which procedures may lead to it and in what way, choosing the appropriate methodology and pre-registering this prior to the conduction of the experiment. By adopting a more coherent framework that integrates single-feature approaches to brain state research, this could form the foundation to take the field into a more mature path.

4.3 How can whole-brain modelling approaches help?

The development of computational models can help understanding the dynamics of different brain states. For example, EEG data can be modeled using neural field models that allow fitting the power spectrum distribution by tuning thalamo-cortical connectivity and regional properties, which can differentiate between levels of consciousness in DoC and sleep [218]. Networks of coupled dynamical equations describing the activity of different brain regions have been used to get insight into the mechanisms underlying

different brain states. These models are built considering the long-range, white matter fibers connecting different brain regions and impose some hypothesized dynamics for the activity of the individual regions. Computational modelling is becoming a promising approach to the investigation of brain states and their dynamics with respect to states of consciousness. For example, models of sleep, anesthesia and DoC have been employed to probe the effects of perturbations during those states, reflecting the empirical observation according to the level of consciousness [219]. Moreover, previous studies in animals under anesthesia demonstrated high constraints of functional connectivity on structural connectivity [108]. These constraints can also be shown through computational modelling in humans under anesthesia and in patients with a DoC [220,221]. Modelling work also highlights reduced network interactions [75], and reduced long-range connectivity in frontotemporal regions [221].

Modelling has also been shown to be effective at capturing the essential dynamics underlying sleep-wake transitions. This is also the case for simulation of lesions and their effect on the brain-wide dynamics [222]. Another approach could be perturbing the model to result in a state change from sleep to wakefulness and back [208], serving as promising building ground for the modeling of state transitions in patients with a DoC. Modelling has even been used to show that sleep-wake transitions across 17 animal species share a common physiological background [223]. In line with a recent review, it seems that computational modeling is a reliable and robust way to characterize brain states and induce changes regardless of their context [224]. Data-constrained computational brain models have also contributed to explore neurobiological mechanisms of conscious perception, for example the potential origin of ignition thresholds in prefrontal areas[225,226], and they constitute a promising tool to approach DoC in this context. Computational modeling of the brain-wide activity is particularly promising in the investigation of DoC since the lesion every patient suffers is unique. The possibility of adapting the models for each patient opens the door to personalized investigations[227].

Models without hypothesized structure or dynamics such as maximum entropy models that match certain measured observables can distinguish between awake and anesthetized states and derive macroscopic properties that quantify the system's capabilities for information processing [228]. Such data-driven approaches might be powerful in the context of DoC, where hypothesized parameters values might be unreliable due to brain injury, and where the ground truth of the patients' state is lacking. Consistently adding modelling approaches to the common toolbox of those interested in consciousness can be beneficially implemented by creating adherence of generative models to rules derived from theories of consciousness that lean on their empirical observations [229].

4.4 Opportunities and challenges for the clinical translation of these findings

Challenges in DoC care and treatment include translatability. EEG at the bedside may be feasible on a large scale [54], while this is more limited for e.g., fMRI. Each technique has its own practical considerations too, with for instance EEG showing its strength of widespread availability by utilizing a large sample collected across multiple sites, and relative insensitivity to the numbers of trials and electrodes [54]. Benefits like this, of course, need to be weighed against the potential for accurately capturing the relevant features of the brain state under investigation. An important remark is that up to now, no study has directly compared the usefulness of brain state investigation using different techniques in the same population.

Studies investigating the effects of anesthetics on brain states and consciousness are of special interest regarding DoC. Indeed, there are important commonalities between the observed brain state changes in

pathological and pharmacologically altered consciousness, with the important difference that the healthy volunteers undergoing anesthesia can provide subjective reports after recovery. These studies therefore can serve as benchmark, and the findings could be extrapolated to the DoC population. However, several remarks should be made. Although anesthetic agents act on different neurotransmitter receptors, they affect whole brain dynamics. Therefore, it is challenging to disentangle whether the observed cerebral changes are the cause or the effect of loss of consciousness. Furthermore, their effects are usually studied in healthy volunteers without brain damage. It has been argued before to carefully design benchmark groups that include such relevant conditions as though with brain damage without an affected consciousness [230]. To date, given this heterogeneity in the etiologies and brain lesions, it is challenging to make group level predictions from patients with a DoC regarding brain regional involvement in consciousness. Moreover, predictions on how state changes could be induced to help patients improve their consciousness is still not possible. The likely limiting factor of widespread, unpredictable brain damage should be taken into account when trying to foresee the results of invasive curative treatments.

With regards to the investigation of state transitions in DoC, treatment responses are often relatively small in comparison to, for instance, the paradoxical but dramatic changes following zolpidem. Moreover, responders to any treatment are mostly MCS patients, whereas patients in UWS do not often show significant improvement. This poses the question if, up to now, it had not yet been possible to induce brain state changes, or if some patients' curative treatment would be forever futile. The heterogeneity observed amongst patients might skew research towards more personalized brain stimulation protocols. Montages and stimulation settings are varied and far from being exhaustively explored. Furthermore, other personal and contextual factors such as the vigilance state of the patient at the moment of stimulation could be a crucial factor. For this reason, an ongoing study [231] is exploring the effects of tDCS according to the patient's vigilance level and explores the effect of stimulation during high or low levels of vigilance [232]. Other factors to consider for the positive outcome of the treatment could be the subjects' brain lesions and brain state when the stimulation is delivered. Certainly, if the stimulation electrode is placed on a skull area that is above a brain lesion, the stimulation might not be effectively delivered, similarly to the observation that the PCI is not representative of the level of consciousness if stimulation is provided over a brain lesion [233]. Computational models to simulate the effects of specific treatments might provide a way forward here. Ideally, they should be developed at the single subject level, accounting for specific lesions, to tune and estimate the desired effects *in vitro* before subjecting patients to the actual treatment. This could improve treatment, but also open doors to the use of more experimental treatment options including the use of psychedelics [234]. Indeed, in that case, the potential effects could be studied beforehand. Such an approach would limit the number of potential ethical problems with more exploratory treatment options, as well as provide a way to deal with the limited available data to empirically test predictions.

Animal studies also provide possibilities to test specific hypotheses regarding the role of specific brain regions in sustaining brain states of reduced or normal consciousness. This can be done by performing lesion studies, but also by the application of (local) (photo)pharmacology or brain stimulation, in an attempt to activate brain regions. Alternatively, photosensitive muscarinic receptors could be used to functionally "lesion" one single brain region at a time in vivo. This could be employed as a proxy for a localized lesion at a specific brain location, and to measure the effect of that lesion on brain states. Such an approach would allow investigating how the thalamo-cortical loops and specific resting-state networks such as the default mode network's influence on whole-brain dynamics and brain states. Although techniques like near-infrared spectroscopy (NIRS; [235]) and photobiomodulation do allow sending light pulses into the human brain non-invasively[236], the clinical translation of photo-pharmacology is yet to be done. Furthermore, different protocols of tDCS in human and animal analogs (e.g., stimulation intensity differing in magnitude; [237]) are being used. This may have resulted in conflicting results in human and

animal research on the mechanisms of DBS[238]. The clinical translation of animal research is unsure, and will require careful investigation, but these preclinical trials allow the development of promising tools for the promotion of conscious brain states.

5. Conclusions

A large body of research shows that crucial features of conscious brain states are lost during unconsciousness. In the frequency domain of the EEG, higher frequencies are associated with conscious states, and, in the domain of functional connectivity, a rich dynamic repertoire of resting state networks is crucial for supporting consciousness. Overall, complex brain states seem to reliably indicate consciousness. Promoting these consciousness-associated brain states through various specific targets is the main avenue for neuromodulation, which paves the way to improvements in the level of consciousness of patients with a DoC. By matching both the brain state and neuromodulation fields, we believe that it is now possible to further develop rigorous, theory-driven, large-scale confirmatory research, utilizing the outlined methods, to end up with a fundamental understanding of consciousness, its alteration, and associated clinical conditions.

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6. References

1. Vyazovskiy V V, Olcese U, Hanlon EC, Nir Y, Cirelli C, Tononi G. Local sleep in awake rats. *Nature*. 2011;472(7344):443-447. doi:10.1038/nature10009

2. Bayne T, Seth AK, Massimini M. Are There Islands of Awareness? *Trends Neurosci*. 2020;43(1):6-16. doi:10.1016/j.tins.2019.11.003

3. Laureys S, Boly M, Moonen G, Maquet P. Two Dimensions of Consciousness: Arousal and Awareness. In: *Encyclopedia If Neuroscience*. Vol 2. ; 2009:1133-1142.

4. Koch C, Massimini M, Boly M, Tononi G. Neural correlates of consciousness: Progress and problems. *Nat Rev Neurosci*. 2016;17(5):307-321. doi:10.1038/nrn.2016.22

5. Moruzzi G, Magoun HW. Brain Stem Reticular Formation and Activation of the EEG. *Electroencephalogr Clin Neurophysiol*. 1949;1(1):455-473.

6. Monti MM, Rosenberg M, Finoia P, Kamau E, Pickard JD, Owen AM. Thalamo-frontal connectivity mediates top-down cognitive functions in disorders of consciousness. *Neurology*. 2015;84(2):167-173. doi:10.1212/wnl.0000000000001123

7. Schiff ND. Recovery of consciousness after brain injury: a mesocircuit hypothesis. *Trends Neurosci*. 2010;33(1):1-9. doi:10.1016/j.tins.2009.11.002

8. Deco G, Ponce-Alvarez A, Mantini D, Romani GL, Hagmann P, Corbetta M. Resting-state functional connectivity emerges from structurally and dynamically shaped slow linear fluctuations. *J Neurosci*. 2013;33(27):11239-11252. doi:10.1523/JNEUROSCI.1091-13.2013

9. Casali AG, Gosseries O, Rosanova M, et al. A Theoretically Based Index of Consciousness Independent of Sensory Processing and Behavior. *Sci Transl Med*. 2013;5(198):198ra105-198ra105. doi:10.1126/scitranslmed.3006294

10. Giacino JT, Fins JJ, Laureys S, Schiff ND. Disorders of consciousness after acquired brain injury: The state of the science. *Nat Rev Neurol*. 2014;10(2):99-114. doi:10.1038/nrneurol.2013.279

11. Laureys S, Owen AM, Schiff ND. Brain function in brain death, coma, vegetative state, minimally conscious state and locked-in syndrome. *Lancet Neurol*. 2004;3(9):537-546.

12. Van Erp WS, Lavrijsen JCM, Vos PE, Bor H, Laureys S, Koopmans TCM. The Vegetative State : Prevalence , Misdiagnosis , and Treatment Limitations. *J Am Med Dir Assoc*. 2015;16(1). doi:10.1016/j.jamda.2014.10.014

13. Pisa F, Biasutti E, Drigo D, Barbone F. The Prevalence of Vegetative and Minimally Conscious States : A Systematic Review and Methodological Appraisal. *J Head Trauma Rehabil*. 2014;(September). doi:10.1097/HTR.0b013e3182a4469f

14. Klingshirn H, Mittrach R, Braitmayer K, et al. RECAPDOC - a questionnaire for the documentation of rehabilitation care utilization in individuals with disorders of consciousness in long-term care in Germany : development and pretesting. *BMC Health Serv Res*. 2018;18(329):1-9.

15. Donis J, Kräftner B. The prevalence of patients in a vegetative state and minimally conscious state in nursing homes in Austria. *Brain Inj*. 2011;25(11):1101-1107. doi:10.3109/02699052.2011.577047

16. Lavrijsen JCM, Koopmans RTCM, Weel C Van. Prevalence and characteristics of patients in a vegetative state in Dutch nursing homes. *J Neurol Neurosurg Psychiatry*. 2005;76(10):1420-1424. doi:10.1136/jnnp.2004.058198

17. Beaumont JG, Kenealy PM. Incidence and prevalence of the vegetative and minimally conscious states. *Neuropsychol Rehabil*. 2011;15(3):184-189. doi:10.1080/09602010443000489

18. Saout V, Ombredane M-P, Mouille J-M, Marteau C, Mathe J-F, Richard I. Patients in a permanent vegetative state or minimally conscious state in the Maine-et-Loire county of France : A cross-sectional , descriptive study Situation des patients en état végétatif chronique et en état paucirelationnel en. *Ann or Phys Rehabil Med*. 2010;53:96-104. doi:10.1016/j.rehab.2010.01.002

19. Voss HU, Ulŭg AM, Dyke JP, et al. Possible axonal regrowth in late recovery from the minimally

conscious state. *J Clin Invest*. 2006;116(7):2005-2011. doi:10.1172/JCI27021

20. Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: Measurement characteristics and diagnostic utility. *Arch Phys Med Rehabil*. 2004;85(12):2020-2029. doi:10.1016/j.apmr.2004.02.033

21. Wannez S, Heine L, Thonnard M, Gosseries O, Laureys S. The repetition of behavioral assessments in diagnosis of disorders of consciousness. *Ann Neurol*. 2017;81(6):883-889. doi:10.1002/ana.24962

22. Kondziella D, Bender A, Diserens K, et al. European Academy of Neurology guideline on the diagnosis of coma and other disorders of consciousness. *Eur J Neurol*. 2020;27(5):741-756. doi:10.1111/ene.14151

23. Thibaut A, Panda R, Annen J, et al. Preservation of Brain Activity in Unresponsive Patients Identifies MCS Star. *Ann Neurol*. 2021;90(1):89-100. doi:10.1002/ana.26095

24. Schnakers C, Bauer C, Formisano R, et al. What names for covert awareness? A systematic review. *Front Hum Neurosci*. 2022;16. doi:10.3389/fnhum.2022.971315

25. Claassen J, Kondziella D, Alkhachroum A, et al. Cognitive Motor Dissociation: Gap Analysis and Future Directions. *Neurocrit Care*. Published online 2023. doi:10.1007/s12028-023-01769-3

26. Vinck M, Oostenveld R, Van Wingerden M, Battaglia FP, Pennartz CMA. An improved index of phase-synchronization for electrophysiological data in the presence of volume-conduction, noise and sample-size bias. *Neuroimage*. 2011;55(4):1548-1565. doi:10.1016/j.neuroimage.2011.01.055

27. Alkire MT, Hudetz AG, Tononi G. Consciousness and Anesthesia. *Science (80-)*. 2008;322(November):876-881.

28. Gao Y, Ma Y, Zhang Q, Winder AT, Liang Z. Time to wake up : Studying neurovascular coupling and brain-wide circuit function in the un-anesthetized animal. *Neuroimage*. 2017;153(November 2016):382-398. doi:10.1016/j.neuroimage.2016.11.069

29. Lee U, Arbor A, Ku S, et al. Disruption of Frontal-Parietal Communication by Ketamine, Propofol, and Sevoflurane. *Anesthesiology*. 2013;118(6):1264-1275. doi:10.1097/ALN.0b013e31829103f5.Disruption

30. Mashour GA. Neuroscience and Biobehavioral Reviews Cognitive unbinding : A neuroscientific paradigm of general anesthesia and related states of unconsciousness. *Neurosci Biobehav Rev*. 2013;37(10):2751-2759. doi:10.1016/j.neubiorev.2013.09.009

31. Mensen A, Bodart O, Thibaut A, et al. Decreased Evoked Slow-Activity After tDCS in Disorders of Consciousness. *Front Syst Neurosci*. 2020;14(September). doi:10.3389/fnsys.2020.00062

32. Barra A, Monti MM, Thibaut A. Noninvasive Brain Stimulation Therapies to Promote Recovery of Consciousness: Where We Are and Where We Should Go. *Semin Neurol*. 2022;42:348-362. doi:10.1055/s-0042-1755562

33. Kundu B, Brock AA, Englot DJ, Butson CR, Rolston JD. Deep brain stimulation for the treatment of disorders of consciousness and cognition in traumatic brain injury patients: a review. *Neurosurg Focus*. 2018;45(August):1-8. doi:10.3171/2018.5.FOCUS18168.

34. Redinbaugh MJ, Phillips JM, Kambi NA, et al. Thalamus modulates consciousness via layer-specific control of cortex. *Neuron*. 2020;106(1):66-75. doi:10.1016/j.neuron.2020.01.005.Thalamus

35. Morales DM, Marklund N, Lebold D, et al. Experimental models of traumatic brain injury: Do we really need to build a better mousetrap? *Neuroscience*. 2005;136(4):971-989. doi:10.1016/j.neuroscience.2005.08.030

36. 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;189(January):615-630. doi:10.1016/j.neuroimage.2019.01.060

37. Greene AS, Horien C, Barson D, Scheinost D, Constable RT. Why is everyone talking about brain state? *Trends Neurosci*. 2023;46(7):508-524. doi:10.1016/j.tins.2023.04.001

38. Demertzi A, Ledoux D, Bruno MA, et al. Attitudes towards end-of-life issues in disorders of consciousness: A European survey. *J Neurol*. 2011;258(6):1058-1065. doi:10.1007/s00415-010-5882-z

39. Chatelle C, Thibaut A, Whyte J, De Val MD, Laureys S, Schnakers C. Pain issues in disorders of consciousness. *Brain Inj*. 2014;9052(9):1202-1208. doi:10.3109/02699052.2014.920518

40. Thibaut A, Schiff N, Giacino JT, Laureys S, Gosseries O. Therapeutic interventions in patients with prolonged disorders of consciousness. *Lancet Neurol*. 2019;18(6):600-614. doi:10.1016/S1474-4422(19)30031-6

41. Edlow BL, Claassen J, Schiff ND, Greer DM. Recovery from disorders of consciousness: mechanisms, prognosis and emerging therapies. *Nat Rev Neurol*. 2021;17(3):135-156. doi:10.1038/s41582-020-00428-x

42. Simon CW, Emmons WH. Responses to material presented during various levels of sleep. *J Exp Psychol*. 1956;51(2):89-97. doi:10.1037/h0043637

43. Rosenberg GA, Johnson SF, Brenner RP. Recovery of cognition after prolonged vegetative state. *Ann Neurol*. 1977;2(2):167-168. doi:10.1002/ana.410020215

44. Frohlich J, Toker D, Monti MM. Consciousness among delta waves: A paradox? *Brain*. 2021;144(8):2257-2277. doi:10.1093/brain/awab095

45. Wascher E, Rasch B, Sänger J, et al. Frontal theta activity reflects distinct aspects of mental fatigue. *Biol Psychol*. 2014;96(1):57-65. doi:10.1016/j.biopsycho.2013.11.010

46. Klimesch W. Alpha-band oscillations, attention, and controlled access to stored information. *Trends Cogn Sci*. 2012;16(12):606-617. doi:10.1016/j.tics.2012.10.007

47. Uhlhaas PJ, Haenschel C, Nikolić D, Singer W. The role of oscillations and synchrony in cortical networks and their putative relevance for the pathophysiology of schizophrenia. *Schizophr Bull*. 2008;34(5):927-943. doi:10.1093/schbul/sbn062

48. Wang XJ. Neurophysiological and computational principles of cortical rhythms in cognition. *Physiol Rev*. 2010;90(3):1195-1268. doi:10.1152/physrev.00035.2008

49. American Academy Of Sleep Medicine. *The AASM Manual for the Scoring of Sleep and Associated Events*.; 2007.

50. Ruiz-Mejias M, Ciria-Suarez L, Mattia M, Sanchez-Vives M V. Slow and fast rhythms generated in the cerebral cortex of the anesthetized mouse. *J Neurophysiol*. 2011;106(6):2910-2921. doi:10.1152/jn.00440.2011

51. Sanchez-Vives M V., Massimini M, Mattia M. Shaping the Default Activity Pattern of the Cortical Network. *Neuron*. 2017;94(5):993-1001. doi:10.1016/j.neuron.2017.05.015

52. Yue Z, Freedman IG, Vincent P, et al. Up and Down States of Cortical Neurons in Focal Limbic Seizures. *Cereb Cortex*. 2020;30(5):3074-3086. doi:10.1093/cercor/bhz295

53. Van der Lande GJM, Blume C, Annen J. *Sleep and Circadian Disturbance in Disorders of Consciousness: Used Methods and the Underlying Role of Cerebral Integrity and Slow Waves*.; 2022.

54. Engemann DA, Raimondo F, King JR, et al. Robust EEG-based cross-site and cross-protocol classification of states of consciousness. *Brain*. 2018;141(11):3179-3192. doi:10.1093/brain/awy251

55. Schiff ND. Mesocircuit Mechanisms Underlying Recovery of Consciousness Following Severe Brain Injuries: Model and Predictions. In: Monti MM, Sannita WG, eds. *Brain Function and Responsiveness in Disorders of Consciousness*. Springer International Publishing; 2016:195-204. doi:10.1007/978-3-319-21425-2_15

56. Frohlich J, Crone JS, Johnson MA, et al. Neural oscillations track recovery of consciousness in acute traumatic brain injury patients. *Hum Brain Mapp*. 2022;43(6):1804-1820. doi:10.1002/hbm.25725

57. Forgacs PB, Frey HP, Velazquez A, 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;4(2):119-129. doi:10.1002/acn3.385

58. Chennu S, Annen J, Wannez S, et al. Brain networks predict metabolism, diagnosis and prognosis at the bedside in disorders of consciousness. *Brain*. 2017;140(8):2120-2132. doi:10.1093/brain/awx163

59. Thibaut A, Chennu S, Chatelle C, et al. Theta network centrality correlates with tDCS response in disorders of consciousness. *Brain Stimul*. 2018;11(6):1407-1409. doi:10.1016/j.brs.2018.09.002

60. Sitt JD, King JR, El Karoui I, et al. Large scale screening of neural signatures of consciousness in patients in a vegetative or minimally conscious state. *Brain*. 2014;137(8):2258-2270. doi:10.1093/brain/awu141

61. Demertzi A, Tagliazucchi E, Dehaene S, et al. Human consciousness is supported by dynamic complex patterns of brain signal coordination. *Sci Adv*. 2019;5:1-12. doi:10.1126/sciadv.aat7603

62. Annen J, Frasso G, van der Lande GJM, et al. Cerebral electrometabolic coupling in disordered and normal states of consciousness. *Cell Rep*. 2023;42(8):112854. doi:10.1016/j.celrep.2023.112854

63. Rizkallah J, Annen J, Modolo J, et al. Clinical Decreased integration of EEG source-space networks in disorders of consciousness. *NeuroImage Clin*. 2019;23:1-9. doi:10.1016/j.nicl.2019.101841

64. Changeux J-P, Michel CM. Mechanisms of Neural Integration at the Brain-scale Level: The

Neuronal Workspace and Microstate Models. In: Grillner S, Graybiel AM, eds. *Microcircuits: The Interface between Neurons and Global Brain Function*. 1st ed. MIT Press; 2004:347-370.

65. Fingelkurts AA, Fingelkurts AA, Bagnato S, Boccagni C, Galardi G. EEG oscillatory states as neuro-phenomenology of consciousness as revealed from patients in vegetative and minimally conscious states. *Conscious Cogn*. 2012;21(1):149-169. doi:10.1016/j.concog.2011.10.004

66. Stefan S, Schorr B, Lopez-Rolon A, et al. Consciousness Indexing and Outcome Prediction with Resting-State EEG in Severe Disorders of Consciousness. *Brain Topogr*. 2018;31(5):848-862. doi:10.1007/s10548-018-0643-x

67. Sarasso S, Rosanova M, Casali AG, et al. Quantifying cortical EEG responses to TMS in (Un)consciousness. *Clin EEG Neurosci*. 2014;45(1):40-49. doi:10.1177/1550059413513723

68. Lee M, Sanz LRD, Barra A, et al. Quantifying arousal and awareness in altered states of consciousness using interpretable deep learning. *Nat Commun*. 2022;13(1):1-14. doi:10.1038/s41467-022-28451-0

69. Demertzi A, Soddu A, Laureys S. Consciousness supporting networks. *Curr Opin Neurobiol*. 2013;23(2):239-244. doi:10.1016/j.conb.2012.12.003

70. Heine L, Soddu A, Gómez F, et al. Resting state networks and consciousness Alterations of multiple resting state network connectivity in physiological, pharmacological, and pathological consciousness states. *Front Psychol*. 2012;3(AUG):1-12. doi:10.3389/fpsyg.2012.00295

71. Amico E, Marinazzo D, Di Perri C, et al. Mapping the functional connectome traits of levels of consciousness. *Neuroimage*. 2017;148:201-211. doi:10.1016/j.neuroimage.2017.01.020

72. 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*. 2014;111(17). doi:10.1073/pnas.1320969111

73. Cao B, Chen Y, Yu R, et al. Abnormal dynamic properties of functional connectivity in disorders of consciousness. *NeuroImage Clin*. 2019;24(June):102071. doi:10.1016/j.nicl.2019.102071

74. Demertzi A, Antonopoulos G, Heine L, et al. Intrinsic functional connectivity differentiates minimally conscious from unresponsive patients. *Brain*. 2015;138(9):2619-2631. doi:10.1093/brain/awv169

75. López-González A, Panda R, Ponce-Alvarez A, et al. Loss of consciousness reduces the stability of brain hubs and the heterogeneity of brain dynamics. *Commun Biol*. 2021;4(1). doi:10.1038/s42003-021-02537-9

76. Luppi AI, Craig MM, Pappas I, et al. Consciousness-specific dynamic interactions of brain integration and functional diversity. *Nat Commun*. 2019;10(4616):1-12. doi:10.1038/s41467-019-12658-9

77. Golkowski D, Willnecker R, Rösler J, et al. Dynamic Patterns of Global Brain Communication Differentiate Conscious From Unconscious Patients After Severe Brain Injury. *Front Syst Neurosci*. 2021;15(September):1-9. doi:10.3389/fnsys.2021.625919

78. Panda R, Thibaut A, Lopez-Gonzalez A, et al. Disruption in structural–functional network repertoire and time-resolved subcortical fronto-temporoparietal connectivity in disorders of

consciousness. *Elife*. 2022;11:1-19. doi:10.7554/eLife.77462

79. Purdon PL, Sampson A, Pavone KJ, Brown EN. Clinical Electroencephalography for Anesthesiologists: Part I: Background and Basic Signatures. *Anesthesiology*. 2015;123(4):937-960. doi:10.1097/ALN.0000000000000841

80. Brown EN, Pavone KJ, Naranjo M. Multimodal general anesthesia: Theory and practice. *Anesth Analg*. 2018;127(5):1246-1258. doi:10.1213/ANE.0000000000003668

81. Calderon DP, Schiff ND. Objective and graded calibration of recovery of consciousness in experimental models. *Curr Opin Neurol*. 2021;34(1):142-149. doi:10.1097/WCO.0000000000000895

82. Dasilva M, Camassa A, Navarro-Guzman A, et al. Modulation of cortical slow oscillations and complexity across anesthesia levels. *Neuroimage*. 2021;224(September 2020):117415. doi:10.1016/j.neuroimage.2020.117415

83. Torao-Angosto M, Manasanch A, Mattia M, Sanchez-Vives M V. Up and Down States During Slow Oscillations in Slow-Wave Sleep and Different Levels of Anesthesia. *Front Syst Neurosci*. 2021;15(February):1-9. doi:10.3389/fnsys.2021.609645

84. Bastos AM, Donoghue JA, Brincat SL, et al. Neural effects of propofol-induced unconsciousness and its reversal using thalamic stimulation. *Elife*. 2021;10:1-28. doi:10.7554/ELIFE.60824

85. Bettinardi RG, Tort-colet N, Ruiz-mejias M, Sanchez-vives M V, Deco G. Gradual emergence of spontaneous correlated brain activity during fading of general anesthesia in rats : Evidences from fMRI and local field potentials. *Neuroimage*. 2015;114:185-198. doi:10.1016/j.neuroimage.2015.03.037

86. Tort-Colet N, Capone C, Sanchez-Vives M V., Mattia M. Attractor competition enriches cortical dynamics during awakening from anesthesia. *Cell Rep*. 2021;35(12). doi:10.1016/j.celrep.2021.109270

87. Rudolph U, Antkowiak B. Molecular and neuronal substrates for general anaesthetics. *Nat Rev Neurosci*. 2004;5(9):709-720. doi:10.1038/nrn1496

88. Van Dort CJ, Baghdoyan HA, Lydic R. Neurochemical modulators of sleep and anesthetic states. *Int Anesthesiol Clin*. 2008;46(3):75-104. doi:10.1097/AIA.0b013e318181a8ca

89. Brown EN, Purdon PL, Van Dort CJ. General anesthesia and altered states of arousal: A systems neuroscience analysis. *Annu Rev Neurosci*. 2011;34:601-628. doi:10.1146/annurev-neuro-060909-153200

90. Steinberg EA, Wafford KA, Brickley SG, Franks NP, Wisden W. The role of K2P channels in anaesthesia and sleep. *Pflugers Arch Eur J Physiol*. 2015;467(5):907-916. doi:10.1007/s00424-014-1654-4

91. Franks NP. General anaesthesia: From molecular targets to neuronal pathways of sleep and arousal. *Nat Rev Neurosci*. 2008;9(5):370-386. doi:10.1038/nrn2372

92. Huupponen E, Maksimow A, Lapinlampi P, et al. Electroencephalogram spindle activity during dexmedetomidine sedation and physiological sleep. *Acta Anaesthesiol Scand*. 2008;52(2):289-294. doi:10.1111/j.1399-6576.2007.01537.x

93. Sattin D, Duran D, Visintini S, et al. Analyzing the Loss and the Recovery of Consciousness: Functional Connectivity Patterns and Changes in Heart Rate Variability During Propofol-Induced Anesthesia. *Front Syst Neurosci*. 2021;15(April):1-16. doi:10.3389/fnsys.2021.652080

94. Lewis LD, Piantoni G, Peterfreund RA, et al. A transient cortical state with sleep-like sensory responses precedes emergence from general anesthesia in humans. *Elife*. 2018;7:1-23. doi:10.7554/eLife.33250

95. Ordek G, Groth JD, Sahin M. Differential effects of ketamine/xylazine anesthesia on the cerebral and cerebellar cortical activities in the rat. *J Neurophysiol*. 2013;109(5):1435-1443. doi:10.1152/jn.00455.2012

96. Pal D, Silverstein BH, Lee H, Mashour GA. Neural Correlates of Wakefulness, Sleep, and General Anesthesia: An Experimental Study in Rat. *Anesthesiology*. 2016;125(5):929-942. doi:10.1097/ALN.0000000000001342

97. Boly M, Moran R, Murphy M, et al. Connectivity changes underlying spectral EEG changes during propofol-induced loss of consciousness. *J Neurosci*. 2012;32(20):7082-7090. doi:10.1523/JNEUROSCI.3769-11.2012

98. Hentschke H, Raz A, Krause BM, Murphy CA, Banks MI. Disruption of cortical network activity by the general anaesthetic isoflurane. *Br J Anaesth*. 2017;119(4):685-696. doi:10.1093/bja/aex199

99. Ming Q, Liou JY, Yang F, et al. Isoflurane-Induced Burst Suppression Is a Thalamus-Modulated, Focal-Onset Rhythm With Persistent Local Asynchrony and Variable Propagation Patterns in Rats. *Front Syst Neurosci*. 2021;14(January):1-11. doi:10.3389/fnsys.2020.599781

100. Guldenmund P, Demertzi A, Boveroux P, et al. Thalamus, Brainstem and Salience Network Connectivity Changes During Propofol-Induced Sedation and Unconsciousness. *Brain Connect*. 2013;3(3):273-285. doi:10.1089/brain.2012.0117

101. Paasonen J, Stenroos P, Salo RA, Kiviniemi V, Gröhn O. Functional connectivity under six anesthesia protocols and the awake condition in rat brain. *Neuroimage*. 2018;172(January):9-20. doi:10.1016/j.neuroimage.2018.01.014

102. Giacino JT. Disorders of consciousness: Differential diagnosis and neuropathologic features. *Semin Neurol*. 1997;17(2):105-111. doi:10.1055/s-2008-1040919

103. Leung LS, Luo T, Ma J, Herrick I. Brain areas that influence general anesthesia. *Prog Neurobiol*. 2014;122:24-44. doi:10.1016/j.pneurobio.2014.08.001

104. Boveroux P, Vanhaudenhuyse A, Bruno M-A, et al. Breakdown of within- and between-network resting state functional magnetic resonance imaging connectivity during propofol-induced loss of consciousness. *Anesthesiology*. 2010;113(5):1038-1053. doi:10.1097/ALN.0b013e3181f697f5

105. Guldenmund P, Vanhaudenhuyse A, Sanders RD, et al. Brain functional connectivity differentiates dexmedetomidine from propofol and natural sleep. *Br J Anaesth*. 2017;119(4):674-684. doi:10.1093/bja/aex257

106. Greicius MD, Kiviniemi V, Tervonen O, et al. Persistent default-mode network connectivity during light sedation. *Hum Brain Mapp*. 2008;29(7):839-847. doi:10.1002/hbm.20537

107. Del Pozo SM, Laufs H, Bonhomme V, Laureys S, Balenzuela P, Tagliazucchi E. Unconsciousness

reconfigures modular brain network dynamics. *Chaos An Interdiscip J Nonlinear Sci*. 2021;31(9):93117.

108. Barttfeld P, Uhrig L, Sitt JD, Sigman M, Jarraya B. Signature of consciousness in the dynamics of resting-state brain activity. *Proc Natl Acad Sci U S A*. 2015;112(3):887-892. doi:10.1073/pnas.1515029112

109. Grandjean J, Schroeter A, Batata I, Rudin M. Optimization of anesthesia protocol for resting-state fMRI in mice based on differential effects of anesthetics on functional connectivity patterns. *Neuroimage*. 2014;102(P2):838-847. doi:10.1016/j.neuroimage.2014.08.043

110. Brown EN, Lydic R, Schiff ND. General Anesthesia, Sleep, and Coma. *N Engl J Med*. 2010;363(27):2638-2650. doi:10.1056/nejmra0808281

111. Li D, Mashour GA. Cortical dynamics during psychedelic and anesthetized states induced by ketamine. *Neuroimage*. 2019;196:32-40. doi:10.1016/j.neuroimage.2019.03.076

112. Sanders RD, Gaskell A, Raz A, et al. Incidence of Connected Consciousness after Tracheal Intubation. *Anesthesiology*. 2017;126(2):214-222. doi:10.1097/aln.0000000000001479

113. Lennertz R, Pryor KO, Raz A, et al. Connected consciousness after tracheal intubation in young adults: an international multicentre cohort study. *Br J Anaesth*. 2023;130(2):e217-e224. doi:10.1016/j.bja.2022.04.010

114. Montupil J, Cardone P, Staquet C, et al. The nature of consciousness in anaesthesia. *Br J Anaesth Open*.:1-15.

115. Edlow BL, Sanz LRD, Polizzotto L, et al. Therapies to Restore Consciousness in Patients with Severe Brain Injuries: A Gap Analysis and Future Directions. *Neurocrit Care*. 2021;35:68-85. doi:10.1007/s12028-021-01227-y

116. Briand MM, Gosseries O, Staumont B, Laureys S, Thibaut A. Transcutaneous Auricular Vagal Nerve Stimulation and Disorders of Consciousness: A Hypothesis for Mechanisms of Action. *Front Neurol*. 2020;11(August). doi:10.3389/fneur.2020.00933

117. Kang Y, Jamison K, Jaywant A, et al. Longitudinal alterations in gamma-aminobutyric acid (GABAA) receptor availability over ~ 1 year following traumatic brain injury. *Brain Commun*. 2022;4(4):1-13. doi:10.1093/braincomms/fcac159

118. Gosseries O, Martial C. The Use of Psychedelics in the Treatment of Disorders of Consciousness: An interview of Olivia Gosseries. *ALIUS Bull*. Published online 2020:50-66. doi:https://doi.org/10.34700/gv0w-y052

119. Giacino JT, Whyte J, Bagiella E, et al. Placebo-Controlled Trial of Amantadine for Severe Traumatic Brain Injury. *N Engl J Med*. 2012;366(9):819-826. doi:10.1097/01.sa.0000433227.82776.07

120. Kim YW, Shin JC, An YS. Effects of methylphenidate on cerebral glucose metabolism in patients with impaired consciousness after acquired brain injury. *Clin Neuropharmacol*. 2009;32(6):335-339. doi:10.1097/WNF.0b013e3181b40678

121. Fridman EA, Krimchansky BZ, Bonetto M, et al. Continuous subcutaneous apomorphine for severe disorders of consciousness after traumatic brain injury. *Brain Inj*. 2010;24(4):636-641. doi:10.3109/02699051003610433

122. Meythaler JM, Brunner RC, Johnson A, Novack TA. Amantadine to improve neurorecovery in traumatic brain injury-associated diffuse axonal injury: a pilot double-blind randomized trial. *J Head Trauma Rehabil*. 2002;17(4):300-313.

123. Ghalaenovi H, Fattahi A, Koohpayehzadeh J, et al. The effects of amantadine on traumatic brain injury outcome: a double-blind, randomized, controlled, clinical trial. *Brain Inj*. 2018;32(8):1050-1055. doi:10.1080/02699052.2018.1476733

124. Whyte J, Rajan R, Rosenbaum A, et al. Zolpidem and restoration of consciousness. *Am J Phys Med Rehabil*. 2014;93(2):101-113. doi:10.1097/PHM.0000000000000069

125. Chatelle C, Thibaut A, Gosseries O, et al. Changes in cerebral metabolism in patients with a minimally conscious state responding to zolpidem. *Front Hum Neurosci*. 2014;8(DEC):1-8. doi:10.3389/fnhum.2014.00917

126. Szymkowicz E, Alnagger N. Seyfzadehdarabad F. Cardone P, Whyte J, O. G. Pharmacological treatments. In: Schnakers C, Laureys S, eds. *Coma and Disorders of Consciousness*. Springer; 2023.

127. Velema WA, Szymanski W, Feringa BL. Photopharmacology: Beyond proof of principle. *J Am Chem Soc*. 2014;136(6):2178-2191. doi:10.1021/ja413063e

128. Hüll K, Morstein J, Trauner D. In Vivo Photopharmacology. *Chem Rev*. 2018;118(21):10710-10747. doi:10.1021/acs.chemrev.8b00037

129. Fenno L, Yizhar O, Deisseroth K. The development and application of optogenetics. *Annu Rev Neurosci*. 2011;34:389-412. doi:10.1146/annurev-neuro-061010-113817

130. Pinto L, Goard MJ, Estandian D, et al. Fast modulation of visual perception by basal forebrain cholinergic neurons. *Nat Neurosci*. 2013;16(12):1857-1863. doi:10.1038/nn.3552

131. Liu J, Lee HJ, Weitz AJ, et al. Frequency-selective control of cortical and subcortical networks by central thalamus. *Elife*. 2015;4(Cl):1-27. doi:10.7554/elife.09215

132. Broichhagen J, Frank JA, Trauner D. A Roadmap to Success in Photopharmacology. *Acc Chem Res*. 2015;48(7):1947-1960. doi:10.1021/acs.accounts.5b00129

133. Stein M, Middendorp SJ, Carta V, et al. Azo-propofols: Photochromic potentiators of GABAA receptors. *Angew Chemie - Int Ed*. 2012;51(42):10500-10504. doi:10.1002/anie.201205475

134. Yue L, Pawlowski M, Dellal SS, et al. Robust photoregulation of GABA A receptors by allosteric modulation with a propofol analogue. *Nat Commun*. 2012;3(May):1012-1095. doi:10.1038/ncomms2094

135. Schoenberger M, Damijonaitis A, Zhang Z, Nagel D, Trauner D. Development of a new photochromic ion channel blocker via azologization of fomocaine. *ACS Chem Neurosci*. 2014;5(7):514-518. doi:10.1021/cn500070w

136. Rustler K, Maleeva G, Gomila AMJ, Gorostiza P, Bregestovski P, König B. Optical Control of GABAA Receptors with a Fulgimide-Based Potentiator. *Chem - A Eur J*. 2020;26(56):12722-12727. doi:10.1002/chem.202000710

137. Gomila AMJ, Rustler K, Maleeva G, et al. Photocontrol of Endogenous Glycine Receptors In Vivo. *Cell Chem Biol*. 2020;27(11):1425-1433.e7. doi:10.1016/j.chembiol.2020.08.005

138. Sansalone L, Bratsch-Prince J, Tang S, Captain B, Mott DD, Raymo FM. Photopotentiation of the GABAA receptor with caged diazepam. *Proc Natl Acad Sci U S A*. 2019;116(42):21176-21184. doi:10.1073/pnas.1902383116

139. Leippe P, Winter N, Sumser MP, Trauner D. Optical Control of a Delayed Rectifier and a Two-Pore Potassium Channel with a Photoswitchable Bupivacaine. *ACS Chem Neurosci*. 2018;9(12):2886-2891. doi:10.1021/acschemneuro.8b00279

140. Borghese CM, Wang HYL, McHardy SF, et al. Modulation of α1β3γ2 GABAA receptors expressed in X. laevis oocytes using a propofol photoswitch tethered to the transmembrane helix. *Proc Natl Acad Sci U S A*. 2021;118(8):1-8. doi:10.1073/pnas.2008178118

141. Prischich D, Gomila AMJ, Milla-Navarro S, et al. Adrenergic Modulation With Photochromic Ligands. *Angew Chemie - Int Ed*. 2021;60(7):3625-3631. doi:10.1002/anie.202010553

142. Barbero-Castillo A, Riefolo F, Matera C, et al. Control of Brain State Transitions with a Photoswitchable Muscarinic Agonist. *Adv Sci*. 2021;8(14):1-11. doi:10.1002/advs.202005027

143. Riefolo F, Matera C, Garrido-Charles A, et al. Optical Control of Cardiac Function with a Photoswitchable Muscarinic Agonist. *J Am Chem Soc*. 2019;141(18):7628-7636. doi:10.1021/jacs.9b03505

144. Riefolo F, Sortino R, Matera C, et al. Rational Design of Photochromic Analogues of Tricyclic Drugs. *J Med Chem*. 2021;64(13):9259-9270. doi:10.1021/acs.jmedchem.1c00504

145. Castagna R, Maleeva G, Pirovano D, Matera C, Gorostiza P. Donor-Acceptor Stenhouse Adduct Displaying Reversible Photoswitching in Water and Neuronal Activity. *J Am Chem Soc*. 2022;144(34):15595-15602. doi:10.1021/jacs.2c04920

146. Izquierdo-Serra M, Gascón-Moya M, Hirtz JJ, et al. Two-photon neuronal and astrocytic stimulation with azobenzene-based photoswitches. *J Am Chem Soc*. 2014;136(24):8693-8701. doi:10.1021/ja5026326

147. Miron J-P, Jodoin VD, Lespérance P, Blumberger DM. Repetitive transcranial magnetic stimulation for major depressive disorder: basic principles and future directions. *Ther Adv Psychopharmacol*. 2021;11:1-14. doi:10.1177/20451253211042696

148. Cain JA, Spivak NM, Coetzee JP, et al. Ultrasonic Deep Brain Neuromodulation in Acute Disorders of Consciousness: A Proof-of-Concept. *Brain Sci*. 2022;12(4):1-15. doi:10.3390/brainsci12040428

149. Liu P, Gao J, Pan S, et al. Effects of High-Frequency Repetitive Transcranial Magnetic Stimulation on Cerebral Hemodynamics in Patients with Disorders of Consciousness: A Sham-Controlled Study. *Eur Neurol*. 2016;76(1-2):1-7. doi:10.1159/000447325

150. Cincotta M, Giovannelli F, Chiaramonti R, et al. No effects of 20 Hz-rTMS of the primary motor cortex in vegetative state: A randomised, sham-controlled study. *Cortex*. 2015;71:368-376. doi:10.1016/j.cortex.2015.07.027

151. He F, Wu M, Meng F, et al. Effects of 20Hz repetitive transcranial magnetic stimulation on disorders of consciousness: A resting-state electroencephalography study. *Neural Plast*. 2018;2018. doi:10.1155/2018/5036184

152. Liu X, Meng F, Gao J, et al. Behavioral and resting state functional connectivity effects of high

frequency rtms on disorders of consciousness: A sham-controlled study. *Front Neurol*. 2018;9(NOV):1-8. doi:10.3389/fneur.2018.00982

153. Fan J, Zhong Y, Wang H, Aierken N, He R. Repetitive transcranial magnetic stimulation improves consciousness in some patients with disorders of consciousness. *Clin Rehabil*. 2022;36(7):916-925.

154. He RH, Wang HJ, Zhou Z, Fan JZ, Zhang SQ, Zhong YH. The influence of high-frequency repetitive transcranial magnetic stimulation on endogenous estrogen in patients with disorders of consciousness. *Brain Stimul*. 2021;14(3):461-466. doi:10.1016/j.brs.2021.02.014

155. Chen J-M, Chen Q-F, Wang Z-Y, et al. Influence of High-Frequency Repetitive Transcranial Magnetic Stimulation on Neurobehavioral and Electrophysiology in Patients with Disorders of Consciousness. *Neural Plast*. 2022;2022.

156. Legostaeva L, Poydasheva A, Iazeva E, et al. Stimulation of the angular gyrus improves the level of consciousness. *Brain Sci*. 2019;9(5):103.

157. Xu C, Wu W, Zheng X, et al. Repetitive transcranial magnetic stimulation over the posterior parietal cortex improves functional recovery in nonresponsive patients: A crossover, randomized, double-blind, sham-controlled study. *Front Neurol*. 2023;14:1059789.

158. Weis S, Hausmann M, Stoffers B, Vohn R, Kellermann T, Sturm W. Estradiol modulates functional brain organization during the menstrual cycle: An analysis of interhemispheric inhibition. *J Neurosci*. 2008;28(50):13401-13410. doi:10.1523/JNEUROSCI.4392-08.2008

159. Henry R, Deckert M, Velmathi G, Schmidt B. Review of neuromodulation techniques and technological limitations. *IETE Tech Rev (Institution Electron Telecommun Eng India)*. 2016;33(4):368-377. doi:10.1080/02564602.2015.1106926

160. Poreisz C, Boros K, Antal A, Paulus W. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Res Bull*. 2007;72(4-6):208-214. doi:10.1016/j.brainresbull.2007.01.004

161. Pelletier SJ, Cicchetti F. Cellular and Molecular Mechanisms of Action of Transcranial Direct Current Stimulation : Evidence from In Vitro and In Vivo Models. *Int J Neuropsychopharmacol*. Published online 2015:1-13. doi:10.1093/ijnp/pyu047

162. de Souza Nicolau E, Farias de Alvarenga KA, Tenza-Ferrer H, et al. Transcranial direct current stimulation (tDCS) in mice. *J Vis Exp*. 2018;2018(139):5-11. doi:10.3791/58517

163. Acheson A, Conover JC, Fandl JP, et al. A BDNF autocrine loop in adult sensory neurons prevents cell death. *Nature*. 1995;374:450-453. doi:10.1038/374450a0

164. Middeldorp J, Hol EM. GFAP in health and disease. *Prog Neurobiol*. 2011;93(3):421-443. doi:10.1016/j.pneurobio.2011.01.005

165. Thibaut A, Bruno M-A, Ledoux D, Demertzi A, Laureys S. TDCS in patients with disorders of consciousness: Sham-controlled randomized double-blind study. *Neurology*. 2014;82(13):1112-1118. doi:10.1212/WNL.0000000000000260

166. Wu M, Yu Y, Luo L, et al. Efficiency of repetitive transcranial direct current stimulation of the dorsolateral prefrontal cortex in disorders of consciousness: A randomized sham-controlled

study. *Neural Plast*. 2019;2019. doi:10.1155/2019/7089543

167. Thibaut A, Wannez S, Donneau AF, et al. Controlled clinical trial of repeated prefrontal tDCS in patients with chronic minimally conscious state. *Brain Inj*. 2017;31(4):466-474. doi:10.1080/02699052.2016.1274776

168. Martens G, Lejeune N, O'Brien AT, et al. Randomized controlled trial of home-based 4-week tDCS in chronic minimally conscious state. *Brain Stimul*. 2018;11(5):982-990. doi:10.1016/j.brs.2018.04.021

169. Estraneo A, Pascarella A, Moretta P, et al. Repeated transcranial direct current stimulation in prolonged disorders of consciousness: A double-blind cross-over study. *J Neurol Sci*. 2017;375:464-470. doi:10.1016/j.jns.2017.02.036

170. Huang W, Wannez S, Fregni F, et al. Repeated stimulation of the posterior parietal cortex in patients in minimally conscious state: A sham-controlled randomized clinical trial. *Brain Stimul*. 2017;10(3):718-720. doi:10.1016/j.brs.2017.02.001

171. Angelakis E, Liouta E, Andreadis N, et al. Transcranial direct current stimulation effects in disorders of consciousness. *Arch Phys Med Rehabil*. 2014;95(2):283-289. doi:10.1016/j.apmr.2013.09.002

172. Martens G, Fregni F, Carrière M, Barra A, Laureys S, Thibaut A. Single tDCS session of motor cortex in patients with disorders of consciousness: a pilot study. *Brain Inj*. 2019;33(13-14):1679-1683. doi:10.1080/02699052.2019.1667537

173. Vanhaudenhuyse A, Demertzi A, Schabus M, et al. Two distinct neuronal networks mediate the awareness of environment and of self. *J Cogn Neurosci*. 2011;23(3):570-578. doi:10.1162/jocn.2010.21488

174. Thibaut A, Di Perri C, Chatelle C, et al. Clinical response to tDCS depends on residual brain metabolism and grey matter integrity in patients with minimally conscious state. *Brain Stimul*. 2015;8(6):1116-1123. doi:10.1016/j.brs.2015.07.024

175. Bai Y, Xia X, Wang Y, et al. Fronto-parietal coherence response to tDCS modulation in patients with disorders of consciousness. *Int J Neurosci*. 2018;128(7):587-594. doi:10.1080/00207454.2017.1403440

176. Cavinato M, Genna C, Formaggio E, et al. Behavioural and electrophysiological effects of tDCS to prefrontal cortex in patients with disorders of consciousness. *Clin Neurophysiol*. 2019;130(2):231-238. doi:10.1016/j.clinph.2018.10.018

177. Zhang Y, Song W, Du J, Huo S, Shan G, Li R. Transcranial direct current stimulation in patients with prolonged disorders of consciousness: Combined behavioral and event-related potential evidence. *Front Neurol*. 2017;8(NOV). doi:10.3389/fneur.2017.00620

178. Carrière M, Mortaheb S, Raimondo F, et al. Neurophysiological correlates of a single session of prefrontal tdcs in patients with prolonged disorders of consciousness: A pilot double-blind randomized controlled study. *Brain Sci*. 2020;10(7):1-17. doi:10.3390/brainsci10070469

179. Hermann B, Raimondo F, Hirsch L, et al. Combined behavioral and electrophysiological evidence for a direct cortical effect of prefrontal tDCS on disorders of consciousness. *Sci Rep*. 2020;10(1):1-16. doi:10.1038/s41598-020-61180-2

180. Fan W, Fan Y, Liao Z, Yin Y. The effect of tDCS on patients with disorders of consciousness: a systematic review and meta-analysis. *Am J Phys Med \& Rehabil*. Published online 2023:10-1097.

181. Thibaut A, Fregni F, Estraneo A, et al. Sham-controlled randomized multicentre trial of transcranial direct current stimulation for prolonged disorders of consciousness. *Eur J Neurol*. 2023;(October 2022):3016-3031. doi:10.1111/ene.15974

182. Vitello MM, Briand MM, Ledoux D, et al. Transcutaneous vagal nerve stimulation to treat disorders of consciousness: Protocol for a double-blind randomized controlled trial. *Int J Clin Heal Psychol*. 2023;23(2). doi:10.1016/j.ijchp.2022.100360

183. Blumenfeld H. Neuroanatomical basis of consciousness. In: Laureys S, Gosseries O, Tononi G, eds. *The Neurology of Conciousness*. Second. Elsevier; 2016:3-29. doi:https://doi.org/10.1016/C2013-0-18738-7

184. Ilyas A, Pizarro D, Romeo AK, Riley KO, Pati S. The centromedian nucleus: Anatomy, physiology, and clinical implications. *J Clin Neurosci*. 2019;63:1-7. doi:10.1016/j.jocn.2019.01.050

185. Sadikot AF, Rymar V V. The primate centromedian-parafascicular complex: Anatomical organization with a note on neuromodulation. *Brain Res Bull*. 2009;78(2-3):122-130. doi:10.1016/j.brainresbull.2008.09.016

186. Clascá F. Thalamic Output Pathways. In: Halassa MM, ed. *The Thalamus*. MIT; 2022:45-70. doi:10.1017/9781108674287.004

187. Schiff ND. Central thalamic contributions to arousal regulation and neurological disorders of consciousness. *Ann N Y Acad Sci*. 2008;1129:105-118. doi:10.1196/annals.1417.029

188. Schiff ND, Plum F. The role of arousal and "gating" systems in the neurology of impaired consciousness. *J Clin Neurophysiol*. 2000;17(5):438-452. doi:10.1097/00004691-200009000-00002

189. Zhou J, Liu X, Song W, et al. Specific and nonspecific thalamocortical functional connectivity in normal and vegetative states. *Conscious Cogn*. 2011;20(2):257-268. doi:10.1016/j.concog.2010.08.003

190. Tasserie J, Uhrig L, Sitt JD, et al. Deep brain stimulation of the thalamus restores signatures of consciousness in a nonhuman primate model. *Sci Adv*. 2022;8(11):1-18. doi:10.1126/sciadv.abl5547

191. Cohadon F, Richer E. Deep cerebral stimulation in patients with post-traumatic vegetative state. *Neurochirurgie*. 1993;39(5):281-292.

192. Schiff ND, Giacino JT, Kalmar K, et al. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. *Nature*. 2007;448(7153):600-603. doi:10.1038/nature06041

193. Gummadavelli A, Motelow JE, Smith N, Zhan Q, Schiff ND, Blumenfeld H. Thalamic stimulation to improve level of consciousness after seizures: Evaluation of electrophysiology and behavior. *Epilepsia*. 2015;56(1):114-124. doi:10.1111/epi.12872

194. Yamamoto T, Kobayashi K, Kasai M, Oshima H, Fukaya C, Katayama Y. DBS therapy for the vegetative state and minimally conscious state. *Acta Neurochir Suppl*. 2005;(93):101-104. doi:10.1007/3-211-27577-0_17

195. Minamimoto T, Kimura M. Participation of the thalamic CM-Pf complex in attentional orienting. *J Neurophysiol*. 2002;87(6):3090-3101. doi:10.1152/jn.2002.87.6.3090

196. Morais P, Rubio-Garrido P, de Lima R, et al. The arousal-related "central thalamus" stimulation site simultaneously innervates multiple high-level frontal and parietal areas. *J Neurosci*. Published online 2023:In Press.

197. Schiff ND. Central thalamic deep brain stimulation to support anterior forebrain mesocircuit function in the severely injured brain. *J Neural Transm*. 2016;123(7):797-806. doi:10.1007/s00702-016-1547-0

198. Schiff ND. Central Lateral Thalamic Nucleus Stimulation Awakens Cortex via Modulation of Cross-Regional, Laminar-Specific Activity during General Anesthesia. *Neuron*. 2020;106(1):1-3. doi:10.1016/j.neuron.2020.02.016

199. Redinbaugh MJ, Afrasiabi M, Phillips JM, et al. *Thalamic Deep Brain Stimulation Paradigm to Reduce Consciousness: Cortico-Striatal Dynamics Implicated in Mechanisms of Consciousness*. Vol 18.; 2022. doi:10.1371/journal.pcbi.1010294

200. Yamamoto T, Katayama Y, Kobayashi K, Oshima H, Fukaya C, Tsubokawa T. Deep brain stimulation for the treatment of vegetative state. *Eur J Neurosci*. 2010;32(7):1145-1151. doi:10.1111/j.1460-9568.2010.07412.x

201. Edlow BL, Takahashi E, Wu O, et al. Neuroanatomic Connectivity of the Human Ascending Arousal System Critical to Consciousness and Its Disorders. *J Neuropathol Exp Neurol*. 2012;71(6):531-546. doi:10.1097/NEN.0b013e3182588293.Neuroanatomic

202. Fuller P, Sherman D, Pedersen NP, Saper CB, Lu J. Reassessment of the structural basis of the ascending arousal system. *J Comp Neurol*. 2011;519(5):933-956. doi:10.1002/cne.22559

203. Muindi F, Kenny JD, Taylor NE, et al. Electrical stimulation of the parabrachial nucleus induces reanimation from isoflurane general anesthesia. *Behav Brain Res*. 2016;306:20-25. doi:10.1016/j.bbr.2016.03.021

204. Pillay S, Vizuete J, Liu X, Juhasz G, Hudetz AG. Brainstem stimulation augments information integration in the cerebral cortex of desflurane-anesthetized rats. *Front Integr Neurosci*. 2014;8(FEB):1-13. doi:10.3389/fnint.2014.00008

205. Monti JM, Monti D. The involvement of dopamine in the modulation of sleep and waking. *Sleep Med Rev*. 2007;11(2):113-133. doi:10.1016/j.smrv.2006.08.003

206. Taylor NE, Van Dort CJ, Kenny JD, 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;113(45):12826-12831. doi:10.1073/pnas.1614340113

207. 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;121(2):311-319. doi:10.1097/ALN.0000000000000117

208. Deco G, Cruzat J, Cabral J, et al. Awakening: Predicting external stimulation to force transitions between different brain states. *Proc Natl Acad Sci U S A*. 2019;116(36):18088-18097. doi:10.1073/pnas.1905534116

209. Florian B, Gosseries O, Weinhouse G, Bonhomme V. Normal Sleep Compared to Altered Consciousness During Sedation. In: Weinhouse GL, Devlin JW, eds. *Sleep in Critical Illness: Physiology, Assessment, and Its Importance to ICU Care*. Springer; 2022:51-68. doi:10.1007/978-3-031-06447-0_4

210. Kaisti KK, Långsjö JW, Aalto S, et al. Effects of sevoflurane, propofol, and adjunct nitrous oxide on regional cerebral blood flow, oxygen consumption and blood volume in humans. *Anesthesiology*. 2003;99(3):603-613. doi:10.1097/00000542-200309000-00015

211. Panda R, López-González A, Gilson M, et al. Whole-brain analyses indicate the impairment of posterior integration and thalamo-frontotemporal broadcasting in disorders of consciousness. *Hum Brain Mapp*. 2023;(November 2022):4352-4371. doi:10.1002/hbm.26386

212. Gutzen R, Bonis G De, Luca C De, et al. Comparing apples to apples - Using a modular and adaptable analysis pipeline to compare slow cerebral rhythms across heterogeneous datasets. *arXiv*. Published online 2022:1-34.

213. Pinho AL, Amadon A, Ruest T, et al. Data descriptor: Individual brain charting, a high-resolution fMRI dataset for cognitive mapping. *Sci Data*. 2018;5:1-15. doi:10.1038/sdata.2018.105

214. Banville H, Chehab O, Hyvärinen A, Engemann DA, Gramfort A. Uncovering the structure of clinical EEG signals with self-supervised learning. *J Neural Eng*. 2021;18(4). doi:10.1088/1741-2552/abca18

215. Sanz LRD, Lejeune N, Blandiaux S, et al. Treating Disorders of Consciousness With Apomorphine: Protocol for a Double-Blind Randomized Controlled Trial Using Multimodal Assessments. *Front Neurol*. 2019;10(March):1-10. doi:10.3389/fneur.2019.00248

216. Giacino JT, Katz DI, Schiff ND, et al. Practice guideline update recommendations summary: Disorders of consciousness. *Neurology*. 2018;91(10):450-460. doi:10.1212/wnl.0000000000005926

217. Liston C, Chen AC, Zebley BD, et al. Default Mode Network Mechanisms of Transcranial Magnetic Stimulation in Depression. *Biol Psychiatry*. 2014;76(7):517-526. doi:10.1016/j.biopsych.2014.01.023.Default

218. Assadzadeh S, Annen J, Sanz LRD, et al. Method for Quantifying Arousal and Consciousness in Healthy States and Severe Brain Injury via EEG-Based Measures of Corticothalamic Physiology. *J Neurosci Methods*. 2023;109958:117686. doi:10.1016/j.jneumeth.2023.109958

219. Perl YS, Pallavicini C, Ipiña IP, et al. Perturbations in dynamical models of wholebrain activity dissociate between the level and stability of consciousness. *PLoS Comput Biol*. 2021;17(7):1-24. doi:10.1371/journal.pcbi.1009139

220. López-González A, Panda R, Ponce-Alvarez A, et al. Loss of consciousness reduces the stability of brain hubs and the heterogeneity of brain dynamics. *bioRxiv*. Published online 2020. doi:10.1101/2020.11.20.391482

221. Tagliazucchi E, Chialvo DR, Siniatchkin M, et al. Large-scale signatures of unconsciousness are consistent with a departure from critical dynamics. *J R Soc Interface*. 2016;13(114). doi:10.1098/rsif.2015.1027

222. Hahn G, Zamora-López G, Uhrig L, et al. Signature of consciousness in brain-wide synchronization

patterns of monkey and human fMRI signals. *Neuroimage*. 2021;226(November 2020):117470. doi:10.1016/j.neuroimage.2020.117470

223. Phillips AJK, Robinson PA, Kedziora DJ, Abeysuriya RG. Mammalian sleep dynamics: How diverse features arise from a common physiological framework. *PLoS Comput Biol*. 2010;6(6):1-19. doi:10.1371/journal.pcbi.1000826

224. Kringelbach ML, Deco G. Brain States and Transitions: Insights from Computational Neuroscience. *Cell Rep*. 2020;32(10):108128. doi:10.1016/j.celrep.2020.108128

225. Joglekar MR, Mejias JF, Yang GR, Wang XJ. Inter-areal Balanced Amplification Enhances Signal Propagation in a Large-Scale Circuit Model of the Primate Cortex. *Neuron*. 2018;98(1):222-234.e8. doi:10.1016/j.neuron.2018.02.031

226. Van Vugt B, Dagnino B, Vartak D, et al. The threshold for conscious report: Signal loss and response bias in visual and frontal cortex. *Science (80-)*. 2018;360(6388):537-542. doi:10.1126/science.aar7186

227. Amunts K, Rowald A, Petkoski S, et al. *The Coming Decade of Digital Brain Research-A Vision for Neuroscience at the Intersection of Technology and Computing*.; 2022.

228. Ponce-Alvarez A, Uhrig L, Deco N, et al. Macroscopic quantities of collective brain activity during wakefulness and anesthesia. *Cereb Cortex*. 2022;32(2):298-311.

229. Cofré R, Herzog R, Mediano PAM, et al. Whole-brain models to explore altered states of consciousness from the bottom up. *Brain Sci*. 2020;10(9):1-29. doi:10.3390/brainsci10090626

230. Demertzi A, Sitt JD, Sarasso S, Pinxten W. Measuring states of pathological (un)consciousness: Research dimensions, clinical applications, and ethics. *Neurosci Conscious*. 2020;2017(1):1-13. doi:10.1093/nc/nix010

231. Martens G, Ibáñez-Soria D, Barra A, et al. A novel closed-loop EEG-tDCS approach to promote responsiveness of patients in minimally conscious state: A study protocol. *Behav Brain Res*. 2021;409(April). doi:10.1016/j.bbr.2021.113311

232. Piarulli A, Bergamasco M, Thibaut A, Cologan V, Gosseries O, Laureys S. EEG ultradian rhythmicity differences in disorders of consciousness during wakefulness. *J Neurol*. 2016;263(9):1746-1760. doi:10.1007/s00415-016-8196-y

233. Bodart O, Gosseries O, Wannez S, et al. Measures of metabolism and complexity in the brain of patients with disorders of consciousness. *NeuroImage Clin*. 2017;14:354-362. doi:10.1016/j.nicl.2017.02.002

234. Alnagger N, Cardone P, Martial C, Laureys S, Annen J, Gosseries O. The current and future contribution of neuroimaging to the understanding of disorders of consciousness. *Press Medicale*. 2023;52(2):104163. doi:10.1016/j.lpm.2022.104163

235. Hansen ML, Hyttel-Sørensen S, Jakobsen JC, et al. The clinical effects of cerebral near-infrared spectroscopy monitoring (NIRS) versus no monitoring: a protocol for a systematic review with meta-analysis and trial sequential analysis. *Syst Rev*. 2021;10(1):1-14. doi:10.1186/s13643-021-01660-2

236. Salehpour F, Mahmoudi J, Kamari F, Sadigh-Eteghad S, Rasta SH, Hamblin MR. Brain

Photobiomodulation Therapy: A Narrative Review. *Mol Neurobiol*. 2018;55(8):6601-6636. doi:10.1007/s12035-017-0852-4

237. Brunoni AR, Fregni F, Pagano RL. Translational research in transcranial direct current stimulation (tDCS): A systematic review of studies in animals. *Rev Neurosci*. 2011;22(4):471-481. doi:10.1515/RNS.2011.042

238. Kringelbach ML, Jenkinson N, Owen SLF, Aziz TZ. Translational principles of deep brain stimulation. *Nat Rev Neurosci*. 2007;8(8):623-635. doi:10.1038/nrn2196

239. Lefaucheur JP, Antal A, Ayache SS, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin Neurophysiol*. 2017;128(1):56-92. doi:10.1016/j.clinph.2016.10.087

240. Bronstein JM, Tagliati M, Alterman RL, et al. Deep brain stimulation for Parkinson disease an expert consensus and review of key issues. *Arch Neurol*. 2011;68(2):165-171. doi:10.1001/archneurol.2010.260