HHS Public Access

Author manuscript

Semin Neurol. Author manuscript; available in PMC 2018 December 05.

Published in final edited form as:

Semin Neurol. 2017 October ; 37(5): 485–502. doi:10.1055/s-0037-1607310.

Functional Networks in Disorders of Consciousness

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Abstract

Severe brain injury may cause disruption of neural networks that sustain arousal and awareness, the two essential components of consciousness. Despite the potentially devastating immediate and long-term consequences, disorders of consciousness (DoC) are poorly understood in terms of their underlying neurobiology, the relationship between pathophysiology and recovery, and the predictors of treatment efficacy. Recent advances in neuroimaging techniques now enable the study of network connectivity, providing great potential to improve the clinical care of patients with DoC. Initial discoveries in this field were made using positron emission tomography (PET). More recently, functional magnetic resonance (fMRI) techniques have added to our understanding of functional network dynamics in this population. Both methods have shown that whether at rest or performing a goal-oriented task, functional networks essential for processing intrinsic thoughts and extrinsic stimuli are disrupted in patients with DoC compared with healthy subjects. Atypical connectivity has been well established in the default mode network as well as in other cortical and subcortical networks that may be required for consciousness. Moreover, the degree of altered connectivity may be related to the severity of impaired consciousness, and recovery of consciousness has been shown to be associated with restoration of connectivity. In this review, we discuss PET and fMRI studies of functional and effective connectivity in patients with DoC, and suggest how this field can move towards clinical application of functional network mapping in the future.

Keywords

Brain Injury; Coma; Consciousness; Network; Connectivity; fMRI; PET; Neuroimaging

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Introduction

Advances in neuroimaging over the past two decades have yielded novel insights into human consciousness and disorders of consciousness (DoC) in patients with severe brain injuries. DoCs are caused by disruption of neural networks that sustain arousal and awareness, the two essential components of consciousness. However, until recently, the mechanisms underlying impaired arousal and awareness in patients with DoC have been elusive, in large part due to a lack of advanced neuroimaging methods necessary to understand human neural network connectivity. Although clinically available tools (e.g., bedside behavioral examination, computed tomography, conventional magnetic resonance imaging [MRI], etc.) provide some information about lesions associated with DoC, advanced techniques are required to fully understand functional brain-behavior relationships in this population.

The first evidence in humans linking brain network disconnections to DoC was provided by positron emission tomography (PET) data. A series of studies comparing patients with no behavioral signs of conscious awareness to healthy subjects demonstrated differences in connectivity between the posterior cingulate cortex and frontal regions, association cortices and frontal regions[1], and the thalamus, frontal and cingulate cortices[2] (Figure 1). In addition, patients who demonstrated inconsistent but reliable evidence of conscious awareness had stronger connectivity (i.e., correlated activity) between the auditory, temporal and prefrontal association cortices when compared to unconscious patients[3]. These studies published between 1999 and 2004 formed the foundation upon which much of the current literature is based.

Shortly after these PET studies revealed aberrant connectivity in patients with DoC, a series of PET and functional MRI (fMRI) studies began to more completely characterize the functional properties of networks in the conscious human brain, leading to further discoveries in DoC. Specifically, investigators identified a constellation of regions in the cerebral cortex that is most active at rest[4] and that deactivates when healthy subjects perform goal-directed tasks.[5,6] The activity in these regions was also correlated during resting wakefulness, mind-wandering, and introspection, suggesting that they form a functionally connected network[7] now known as the Default Mode Network (DMN)[8]. The terms “internal” and “intrinsic” awareness network have also been used to describe regions that are functionally connected during the resting wakeful state.[9,10]

Since the publication of landmark PET and fMRI studies describing the functional connectivity properties of the DMN in the conscious human brain, a growing number of studies have consistently identified disruption of DMN functional connectivity in patients with acute and chronic DoC.[11–15] Moreover, resting-state fMRI (rsfMRI) studies have shown that DMN functional connectivity appears to normalize as patients recover conscious awareness.[12,13] Collectively, these studies suggest that DMN connectivity may be important for conscious awareness.

As fMRI evolved into a common technique for studying human brain function, it became clear that DoCs are characterized by abnormal connectivity across functional networks outside the DMN, including those involved in processing sensory stimuli and performing

higher-order cognitive tasks (i.e. extrinsic networks such as auditory, visual, sensorimotor, salience, and executive control networks).[16–19] In contrast to the internal awareness network of the DMN, which is anchored by core midline structures (i.e., anterior medial prefrontal and posterior cingulate cortices), external awareness relies on a distributed lateral fronto-temporo-parietal network of association cortices.[4,20] During task performance, the extrinsic network is activated, while at rest it is deactivated and negatively correlated with the intrinsic awareness network.[20,4]

Below, we review PET and fMRI studies of functional network connectivity in humans and how these complimentary techniques[21] are used to reveal network disconnections in patients with DoC. We begin by describing standard approaches for behavioral assessment of patients with DoC, as functional network mapping studies are invariably interpreted within the context of the behavioral diagnosis. Next, the methodological aspects of PET and fMRI are addressed, followed by a conceptual overview of functional and effective connectivity. We then discuss PET and fMRI studies of connectivity relevant to DoC. Of note, there is evidence of an underlying structural architecture that may provide a neuroanatomic basis for the impaired connectivity seen on fMRI in DoC.[22–26] A review of structural connectivity in DoC is provided elsewhere.[27] fMRI studies of DoC that rely on non-connectivity-based metrics, such as those showing that some patients who appear unconscious at the bedside retain capacity to perform tasks in the MRI scanner,[28,29] are not discussed as several comprehensive reviews on this topic have already been published.[30–33] Thus, we focus on investigations of functional and effective connectivity, as better knowledge of the network disruptions underlying impairments in conscious awareness may support the development of more precise assessments, more accurate prognostic markers, and better treatments for patients with DoC.

Behavioral Assessment of Consciousness

Following a severe brain injury, some patients emerge from coma into a vegetative state (VS, also known as unresponsive wakefulness syndrome [UWS][34]) or a minimally conscious state (MCS).[35] Patients diagnosed with VS/UWS have recovered spontaneous eye opening and what appear to be sleep-wake cycles,[36] although the electrophysiologic signals underlying these circadian rhythms are abnormal.[37–39] In MCS, there is inconsistent but clear evidence of purposeful behaviors (e.g., visual pursuit, localization to noxious stimulation, and simple command following).[35] MCS can be further subdivided into MCS “minus” (MCS-) and MCS “plus” (MCS+), which are distinguished by the presence of behaviors that suggest preservation of language function. Evidence of MCS+ may include reproducible command-following, object recognition, or intelligible verbalization.[40,41] Emergence from MCS (eMCS) is indicated by functional use of common objects or reliable communication.[35] Characterized by preserved cognitive function but complete or near-complete paralysis, locked-in syndrome (LIS) is often considered as a control condition in studies of VS/UWS and MCS because, despite significant impairments in overt expression, conscious awareness remains intact.[42,43]

Diagnostic assessment of patients with DoC is challenging because it relies on behavioral observation that may be biased by patient-related factors (e.g., fluctuating arousal, motor

deficits, language deficits, pain, sensory impairments, sedating medications,[44,45] etc.) or examiner error (e.g., over/under interpretation of observations[46]). Consequently, the approximate rate of misdiagnosing a patient who is conscious (MCS) as being unconscious (VS/UWS) on standard clinical examination is 40%.[47–49] This alarming misdiagnosis rate may lead to premature withdrawal of treatment, limitations in access to rehabilitation services, and misjudgment of a patient's ability to advocate for his or her own needs[50].

To reduce diagnostic error, improve the accuracy of prognostication, and enable monitoring of recovery and response to therapies, a number of standardized behavioral scales have been developed. The Coma Recovery Scale-Revised (CRS-R) is a 23-item hierarchical measure that assesses visual, auditory, motor, oromotor, and verbal function as well as communication and arousal in patients with DoC.[51] Out of 13 reviewed behavioral scales in 2010, it was the one scale recommended with only minor reservations by the American Congress of Rehabilitation Medicine for both clinical and research applications,[52] and it has been validated in multiple languages.[53–55] Importantly, the CRS-R was used as the "gold-standard" behavioral assessment tool that revealed evidence of consciousness (i.e. MCS) in the approximately 40% of patients who were misdiagnosed as VS/UWS in the aforementioned study.[49]

Yet, even standardized behavioral scales such as the CRS-R are susceptible to biases and missed signs of awareness. This limitation has been illustrated over the past decade in a series of stimulus-based fMRI studies showing that some patients with DoC who do not demonstrate command-following at the bedside do so covertly in the scanner[28,29] and that fMRI responses may herald further behavioral recovery.[28,56,57] Moreover, several PET and fMRI connectivity studies, which are the focus of this review, have revealed preservation or recovery of functional networks in patients who lack behavioral evidence of consciousness. These observations, coupled with methodological advances, have led to rapid progress in the field of research focused on studying the mechanisms underlying DoC.

Positron Emission Tomography (PET): Principles and Methods

PET is a neuroimaging technique that allows for quantification of metabolic processes in the brain. A radioactive tracer (i.e. molecule to which a radioactive atom has been attached and can be tracked) is administered intravenously to the patient. As it decays, it emits a positron, which has the opposite charge of an electron. The positron travels for some distance, losing energy and decelerating until it can interact with an electron. This interaction produces gamma rays that are emitted at 180° from one another and can be detected by the scanner. The sum of these reactions indicates the regions of the brain that emit the most radioactivity and which have thus metabolized a maximum number of radioactive atoms.

In PET brain imaging, the most commonly used tracers are fludeoxyglucose (^{18}F-FDG) and ^{15}O-radiolabelled water ($H_2{}^{15}O$). Metabolism of these tracers provides an indirect measure of neural synaptic activity, based on the assumption that areas of high radioactivity (i.e. presence of the tracer) are associated with consumption of glucose or oxygen, respectively. ^{18}F-FDG is mainly used to study the brain at rest due to its half-life of approximately 110 minutes. In contrast, $H_2{}^{15}O$ has a two-minute half-life that makes it more appropriate to

study stimulus-based changes (but also means that it needs to be pumped directly from a cyclotron in the scan room). Typically, PET allows localization of changes in brain activity with a spatial resolution of approximately 5 to 10 mm^3, which represents the activity of several thousand cells. The temporal resolution is relatively low as it takes one to several minutes to obtain a single PET image.

Functional Magnetic Resonance Imaging (fMRI): Principles and Methods

MRI operates on the principle that hydrogen atoms in the brain are susceptible to excitation in a magnetic field and, upon relaxation, release varying amounts of energy that are converted into images of brain tissue. fMRI relies on detecting small changes in the MRI signal that are associated with neuronal activity. Specifically, when neurons depolarize, a hemodynamic response is triggered, increasing the amount of oxygenated blood relative to deoxygenated blood. Deoxygenated blood is paramagnetic, distorting the MR signal of the hydrogen atoms in surrounding tissue. Oxygenated blood is diamagnetic, thus when the ratio of oxygenated to deoxygenated blood increases there is a net increase in the MR signal that leads to a blood-oxygen-level dependent (BOLD) contrast in a region of increased neuronal activity.[58,59] When the brain is in a state of resting wakefulness (i.e. there is no external stimulus causing increased neuronal firing) regions of correlated low-frequency (<0.1Hz) *spontaneous* fluctuations in the BOLD signal time series can be detected.[60]

Notably, the hemodynamic response, which occurs over several seconds, is orders of magnitude slower than neuronal depolarization. Therefore, as with PET, fMRI can only serve as a proxy for brain activity that relies on the coupling of neuronal firing with cerebral blood flow. On the other hand, fMRI has relatively high spatial resolution (approximately 3mm) offering advantages over other advanced techniques of assessing brain activation such as PET, electroencephalography and magnetoencephalography.

Functional versus Effective Connectivity in PET and fMRI

Connectivity, or the way in which neurons transmit information between brain regions, can be measured or inferred using a variety of techniques. *In vivo* studies in humans rely largely on inferential measures of brain connectivity such as directional water diffusion for structural connectivity (not reviewed here), correlations in signal fluctuation derived from blood flow or metabolism for functional connectivity, and causational relationships between regions for effective connectivity. PET and fMRI are the most widely utilized measures for assessing functional and effective connectivity in DoC, although EEG[61–67] and MEG[68] have also been used.

Functional and effective connectivity provide different but complementary information regarding the relationship between brain regions. Functional connectivity is typically inferred on the basis of correlations in the ^{18}F-FDG metabolism or BOLD-derived time series of two or more brain regions. Functional connectivity results are statistical dependencies, and it is impossible to determine whether any one region modulates or drives activity in the others. Conversely, effective connectivity assesses the influence of one region over another by measuring the causal interaction between regions (i.e., context-specific

changes). This distinction between statistical inference and causal interaction is critical in understanding the range of conclusions allowable by specific study designs and results. In general, resting-state studies rely almost exclusively on functional connectivity, while effective connectivity can be assessed using stimulus-based fMRI/PET, concurrent transcranial magnetic brain stimulation, or modeling approaches.[69] One common method of modeling is psychophysiological interactions (PPI), where the interaction between a physiological factor (e.g., BOLD responses or metabolism) and psychological factor (e.g., cognitive task) is tested using a linear regression model. Within-subject or group differences are calculated by regressing the activity in any brain region on the activity of the seed region.[70]

Stimulus-based versus Resting-state Paradigms

Traditionally, investigators have used PET and fMRI to understand brain activity and connectivity during states of resting wakefulness, passive processing of stimuli, or goal-directed cognitive tasks. In resting-state conditions, subjects are instructed to lay awake in the scanner with eyes open or closed and to rest without thinking of anything specific, or to allow the mind to wander. During this period of wakefulness, connectivity in anatomically separated regions is evident in several “intrinsic” or “task-negative” resting-state networks. Perhaps the most thoroughly studied intrinsic network is the DMN, which primarily includes the posterior cingulate/retrosplenial cortex, precuneus, medial prefrontal cortex, inferior parietal lobule, and hippocampal formation, and is implicated in self-referential processing and internal awareness.[71,72] One key feature of the DMN is that it is deactivated during goal-directed behaviors.[73] The DMN has been fractionated into sub-networks of regions that appear to be connected during different types of internal processing (e.g., envisioning future events versus generating and maintaining a complex scene), but include a common core hub of structures.[74] Other intrinsic networks apparent during rest may support parallel cognitive functions. For example, the executive control network that is functionally connected at rest supports executively-mediated behaviors during task performance.[75] Several other cortical networks implicated in intrinsic awareness have also been identified[76] (Figure 2). For a comprehensive review of resting-state networks, see Rosazza et al (2011).[77] Advantages and limitations of rsfMRI are discussed in detail elsewhere.[78,79]

In contrast to resting-state paradigms, stimulus-based paradigms require subjects to either lay in the scanner during presentation of passive stimuli (e.g., auditory, visual, tactile) or to perform a cognitively demanding task that may involve working memory, processing speed, visual perception, or a host of other active mental manipulations. Each condition probes a unique set of subcortical and cortical (primary, secondary and association) nodes and networks. Networks that are apparent during stimulus-based fMRI have been called “extrinsic” or “task-positive” networks.[9] During resting wakefulness, extrinsic networks remain functionally connected and are negatively correlated with the DMN.[4,20]

A variety of analytic methods are available for probing networks and quantifying network connectivity. Both PET and fMRI analyses include the use of data reduction techniques, such as assessing correlations between a “seed” region/voxel and either *a priori* target regions of interest or the whole brain.[60] Independent component analysis is another data

reduction method that does not rely on *a priori* hypotheses.[80,81] Another consideration in analyzing and interpreting connectivity findings is determining the spatial localization of functional networks. Anatomic localization can be accomplished using visual inspection of the imaging results by experts in functional neuroradiology, or objectively labeling regions using standardized functional[76] and structural[82,83] atlas templates. To quantify connectivity characteristics, graph theoretical analysis can be applied.[84,85] Recent studies have also employed automated data-driven approaches to classify individual patients into diagnostic groups,[86] a technique that, if shown to be reliable, may have significant clinical applications in the future.

Cortico-cortical Connectivity in DoC

Cortico-cortical connectivity in DoC was originally studied using ^{18}F-FDG-PET during rest. Laureys et al. (1999)[1] were the first to report impaired regional cerebral glucose metabolism in the prefrontal, premotor, and parietotemporal association areas, as well as the posterior cingulate cortex/precuneus, in a small cohort of VS/UWS patients. In addition, there was evidence of impaired effective cortical connectivity between the prefrontal, premotor and posterior cingulate cortices as compared with healthy subjects.

Aberrant DMN connectivity is perhaps the most robust and widely reproduced finding in the field of DoC to date (see Table 1 for PET and Table 2 for fMRI findings). One ^{18}F-FDG-PET study reported a progressive recovery of metabolic activity within DMN nodes in patients with diagnoses ranging from VS/UWS, MCS, eMCS to LIS.[87] There was also a correlation between behavioral responsiveness (i.e. CRS-R scores) and metabolic activity in the intrinsic network. Another study investigated changes in regional metabolism using median glucose metabolic rates within a set of predetermined regions (i.e. frontoparietal network, precuneus, thalamus and brainstem).[88] VS/UWS and MCS could be distinguished based on metabolic preservation within the frontoparietal network and the precuneus in MCS patients.

These PET results are supported by fMRI studies showing that DMN connectivity correlates with a patient's level of conscious awareness, such that network connectivity increases across the spectrum of consciousness from coma to VS/UWS, MCS, eMCS and LIS.[13,16,89,90] Moreover, DMN functional connectivity distinguishes patients in MCS from those in VS/UWS with greater than 80% accuracy.[16,91] Boly et al[92] reported preserved but reduced cortico-cortical connectivity within the DMN in a patient diagnosed with VS/UWS studied 2.5 years following a cardiopulmonary arrest. The DMN has also been implicated in recovery from DoC. In a study of comatose patients with hypoxic-ischemic injury, DMN functional connectivity was found to be intact in patients who later regained consciousness but disrupted in all patients who did not regain consciousness.[93] Other studies have supported this finding by showing that DMN connectivity predicted recovery of consciousness in VS/UWS patients at 3 months post-injury.[14,17] Moreover, functional connectivity between the posterior cingulate cortex and medial prefrontal cortex – two core midline nodes of the DMN – was significantly different between comatose patients who went on to recover full consciousness and those who evolved to MCS or VS/UWS three

months after injury.[15] Figure 3 illustrates partially preserved DMN connectivity in a comatose patient.

Taken together, these findings indicate that preservation or recovery of DMN connectivity may be necessary to sustain conscious awareness. However, DMN connectivity is not sufficient to fully support consciousness because spontaneous low-frequency BOLD fluctuations at rest are found in both conscious and unconscious states.[92–96] Therefore, consciousness likely requires other intrinsic and extrinsic networks that are involved in sustaining self-awareness and purposeful interactions with the environment.

Accordingly, correlation between CRS-R scores and metabolic activity in extrinsic networks has been shown with ^{18}F-FDG-PET.[87] fMRI studies also indicate that in DoC, extrinsic networks evident at rest are disrupted such that there is decreased interhemispheric connectivity in the pre- and post-central gyrus and intra-parietal sulcus,[97] between the medial frontal regions and medial parietal regions, as well as the left and right temporal parietal junction and right frontal gyrus.[84] Similarly, decreased connectivity in the salience and executive network, but increased connectivity in the inferior temporal gyrus, medial temporal lobe, and basal ganglia have been reported in DoC.[14] He et al. (2014)[98] also found increased connectivity in persons with DoC in the extrinsic network (insula, lingual gyrus, paracentral and supplementary motor area). Finally, in VS/UWS and MCS, there is increased connectivity at rest in networks implicated in emotional processing.[99] In addition to the DMN, connectivity within the fronto-parietal, salience, auditory, sensorimotor, and visual networks discriminated VS/UWS from MCS patients with an accuracy greater than 80%, with the auditory network demonstrating the highest classification accuracy (i.e. 96%).[16] These findings in non-DMN resting-state networks suggest that impaired connectivity in DoC is not restricted to a single network, but involves multiple networks distributed across the brain.

Stimulus-based studies can also provide information about cortico-cortical connectivity by correlating activity or metabolism across brain regions, and using modeling approaches or PPI. Several $H_2{}^{15}$O-PET studies have used stimulus-evoked activations to derive regions of interest that are subsequently employed as seeds in connectivity analyses. Using auditory and nociceptive stimulation, limited brain responses were observed in a majority of VS/UWS patients, whereas MCS patients showed responses similar to healthy subjects.[100–102] Indeed, activation studies performed on a VS/UWS group using auditory stimulation (i.e. tones) showed preserved functioning in the primary auditory cortex but not association areas (such as the temporoparietal junction).[103] Similarly, Laureys et al. reported that noxious stimulation (i.e. electrical stimulation of the median nerve) activated midbrain, contralateral thalamus, and primary somatosensory cortex in those patients without activating higher-order brain areas involved in perception processing.[104] In both studies, primary (i.e. non-association) cortical activity seemed to be functionally disconnected from higher-order association cortical activity. This observation was supported by another study reporting widespread activity in the insula, primary and secondary somatosensory cortices and posterior cingulate cortex but impaired functional connectivity in cortico–thalamo–cortical pathways,[105] suggesting that cortical processes in VS/UWS are primary, isolated and disconnected phenomena. On the other hand, in MCS patients, auditory stimuli with or

without emotional valence lead to more widespread activation involving association cortices.[3,102,106] This preserved connectivity between primary and association cortices suggests the existence of integrated and distributed neural processing in states of consciousness but not unconsciousness.

Stimulus-based fMRI studies have likewise shown disrupted connectivity in networks implicated in extrinsic and intrinsic processing. Disrupted DMN connectivity evident during a self-referential task in DoC patients compared to healthy subjects and in VS/UWS versus MCS patients[107] coincides with the disrupted connectivity reported at rest. Atypical limbic network connectivity has been reported during presentation of emotionally salient stimuli (e.g., pain cries) in VS/UWS patients compared with MCS patients and healthy subjects.[99,108,109]

Taken together, findings from both PET and fMRI, in resting-state and stimulus-based studies, suggest marked anomalies in cortical connectivity affecting multiple networks in DoC. Furthermore, cortical connectivity has been shown to be a potential diagnostic marker of conscious awareness[16,88,91] as well as an indicator of recovery of conscious awareness.[15,88,93] The results of these studies provide evidence for the role of cortical connectivity in sustaining consciousness, but also indicate that other factors, such as connectivity between cortical and subcortical regions, may contribute to the underlying neurobiology of DoC.

Subcortico-cortical Connectivity in DoC

The literature on subcortical connectivity and subcortico-cortical connectivity in DoC is not as extensive as that reviewed in the cortico-cortical connectivity section above. Nevertheless, there is clear evidence that connectivity within and between subcortical and cortical regions is disrupted in DoC. Particular attention has been given to connections between the thalamus, striatum, and cerebral cortex.

In 2000, Laureys et al[103] published a case study of a 28-year-old patient who sustained a global brain injury as the result of a cardiopulmonary arrest and remained in a VS/UWS for two months before recovering consciousness. $H_2{}^{15}O$ PET was performed at rest and following auditory and somatosensory stimulation two weeks after onset of the VS/UWS and four months after recovery of consciousness and partial functional independence (Figure 1). The baseline PET PPI analysis revealed altered functional connectivity between the intralaminar thalamic nuclei and prefrontal and anterior cingulate cortices. Follow-up PET suggested a restoration of thalamocortical connectivity similar to that observed in healthy subjects, suggesting that intralaminar nuclei and thalamocortical connectivity could be critical for recovery of consciousness. In another study, cortico-thalamic BOLD functional connectivity between the posterior cingulate/precuneus and the medial thalamus was absent in VS/UWS and brain death[92] but preserved to some degree in MCS.[29] In an effective connectivity analysis employing PPI, greater connectivity between the anterior thalamus and the prefrontal cortex was observed in patients who responded to an auditory detection task than those who did not.[110]

Interestingly, compared with healthy subjects, TBI patients diagnosed with DoC exhibited *increased* amplitude of low-frequency fluctuation in the putamen, hippocampus, and amygdala but *decreased* amplitude of low-frequency fluctuation in the thalamus and cerebral cortex.[111] The amplitude of low frequency fluctuations is measured by calculating the power within the frequency range between 0.01 and 0.1 Hz, providing an index of oscillation strength that serves as a proxy for the integrity of a network.[112] The 'mesocircuit hypothesis' proposed by Schiff in 2010[113] may explain this result, as it postulates that the frontocortico-striatopallidal-thalamocortical loop, which involves an inhibitory effect of striatum on the thalamus via the globus pallidus and an excitatory effect of the thalamus on cortex, is especially vulnerable to brain injury. In this hypothesis, disconnection of the cortex from the striatum leads to increased inhibition of the globus pallidus and downregulation of the thalamus, resulting in abnormal function within the cerebral cortex. A recent study in healthy subjects receiving propofol-induced anesthesia supports this mesocircuit hypothesis. Using effective connectivity and dynamic causal modeling, a decrease and subsequent increase in connectivity from globus pallidus to cortex was demonstrated as healthy subjects transitioned out of and back into consciousness.[114] Another anesthesia study showed a reduction in functional connectivity between the putamen and 12 cortical and subcortical regions, including the thalamus, but a relative preservation of thalamo-cortical connectivity during the transition to unconsciousness.[115] Further studies of striatal connectivity are needed to confirm the mesocircuit hypothesis and replicate the findings from anesthesia studies in patients with DoC.

Global Connectivity

The large number of networks that are affected by severe brain injury and the variety of conditions under which network disconnections are reported provides evidence for a global disconnection hypothesis. In fact, several studies have indicated that global connectivity during rest[84,109,116] as well as during presentation of emotional stimuli[108] is reduced in DoC. Moreover, in addition to impaired isolated networks, there appears to be a disruption in the balance or toggling between intrinsic and extrinsic awareness networks.[89,92,98,116,117] These findings suggest that a global disturbance of brain function may underlie aberrant individual network connectivity in patients with DoC. This global disconnection hypothesis is supported by the clinical observation that behaviors emanating from different networks (i.e. visual, motor and auditory) generally emerge together, rather than in isolation, as a patient recovers consciousness. In addition, experimental and theoretical approaches in healthy subjects support a global model of awareness.[118,119] Thus, the global disconnection hypothesis in DoC suggests that 1) no single network is sufficient for consciousness; 2) disruption of multiple networks simultaneously leads to unconsciousness; and 3) recovery requires simultaneous reintegration of multiple networks.

Discussion

Functional networks throughout the brain are disrupted in patients with DoC. Although most research has focused on the DMN, aberrant connectivity is evident when probing extrinsic cortical networks as well as subcortical networks, using resting-state and stimulus-based PET and fMRI. Moreover, measures of the interaction between networks and of global

connectivity show marked differences between patients with DoC and healthy subjects. Connectivity disruptions are generally more significant in patients who have greater impairment in conscious awareness, may distinguish patients with varying levels of consciousness, and may have prognostic value.

There is an ongoing debate about the underlying causes of impairments in conscious awareness. While many studies highlight the importance of individual networks in DoC, a growing body of literature in patients and healthy subjects suggests that awareness is associated with global connectivity (i.e., the integration of multiple networks simultaneously). In addition, given the central role of the thalamus and striatum in modulating and gating cortical activity, it is possible that preserved connectivity in these regions is key to maintaining conscious awareness and driving cortico-cortical connectivity. Nevertheless, most studies have not probed these subcortical regions, and future studies are needed to elucidate the role of subcortical connectivity in DoC.

Currently, functional network mapping in patients with DoC remains in the research domain, as the field is just beginning to understand the breadth and depth of disconnection underlying impaired consciousness. Furthermore, best practices for reducing physiological noise and motion artifacts are still being developed for functional network mapping techniques such as rsfMRI.[120] Nevertheless, recent studies have demonstrated that functional connectivity measures have high accuracy, sensitivity, and specificity for detection of conscious awareness at the single-subject level[16]. It remains to be seen whether functional connectivity techniques can identify conscious patients who appear unconscious at the bedside. If this is the case, the diagnostic utility of these methods will have a direct positive impact on a field that currently lacks reliable, reproducible, objective markers of conscious awareness.

From the standpoint of prognostication, several studies have demonstrated that preserved connectivity may predict recovery,[14,16,17] while disrupted connectivity may indicate poor outcome.[93] Prognostic studies are particularly challenging due to the inherent bias associated with self-fulfilling prophecies (i.e. withdrawal of life-sustaining care due to a poor prognosis) and because sample sizes tend to be small, possibly due to low follow-up rates. Rigorous evaluation of the prognostic utility of network mapping techniques will require large, prospective studies, perhaps on the multi-center level.

Data on the use of functional connectivity for assessing or predicting treatment efficacy are lacking. In one study, patients in MCS who responded (i.e. demonstrated more behaviors following treatment) to a trial of transcranial direct current stimulation (tDCS) showed a pre-treatment increase in left intra-network connectivity for regions coactivated with the left dorsolateral prefrontal cortex (DLPFC) and with the left inferior frontal gyrus. Non-responders showed a pre-treatment increase in connectivity between left DLPFC and midline cortical structures, including the anterior cingulate cortex and precuneus. The investigators suggested that connectivity within regions of the extrinsic control network may predict treatment responsiveness, an observation that, if validated, could allow for patient-specific, network-based approaches to therapy.[121] Future studies will need to replicate this finding and extend it to other clinically available treatments.

Limitations

A variety of unique challenges are inherent to applying advanced neuroimaging techniques to individuals diagnosed with DoC. First, this patient population is prone to medical instability, making it difficult to safely acquire functional imaging data. Second, many patients with DoC experience fluctuating arousal and restlessness, both of which may lead to uninterpretable (e.g., due to head motion[122]) and/or confounded results. Although some studies suggest that PET is more resilient to head motion than fMRI[30,90] both techniques are dependent on patients lying motionless, which can be difficult to achieve when patients are emerging from unconsciousness into consciousness. Complex motion-correction algorithms have been developed to address this issue in fMRI[123], but more work is needed to fully understand the effects of motion on resting-state imaging. Sedation is typically not a viable solution for connectivity studies as it may disturb the neural networks of interest.[115,124,125] This is less of a problem when ^{18}FDG-PET is being used, as the sedation would be administered during acquisition in the scanner, which is performed after absorption of the tracer by the brain tissue (20-30 minutes post-injection). Third, brain injury, and especially TBI, is highly heterogeneous in terms of lesion type, location, and trajectory of recovery. Therefore, reporting single-subject data is required and generalizing findings beyond those reported in individual studies should be done with caution.

One limitation specific to PET is that it necessitates intravenous injection of a radioactive tracer, although the exposure to harmful radiation is minimal. Recent studies suggest that PET and fMRI provide complimentary information, such that rsfMRI may be used to estimate metabolic maps produced by PET,[21,123] circumventing the need for invasive PET procedures. Similarly, PET can be used to measure functional network connectivity in patients for whom fMRI is contraindicated.

Both the metabolic consumption measured by PET and the BOLD signal measured by fMRI rely on physiological properties that are associated with neuronal depolarization but do not provide a direct measure of neuronal activity. Acute brain injuries can disturb the blood-brain barrier and alter the normal coupling between neuronal depolarization, metabolism, blood flow, and oxygenation. Confounding factors such as the behavioral state of the patient, hardware noise, and other potential influences on cerebral blood flow and metabolism must also be considered when interpreting findings.

Finally, there is no standardized method for collecting, analyzing, and interpreting PET or fMRI data. Paradigm design and subject instructions (e.g., eyes opened versus closed during rsfMRI,) as well as imaging parameters, DoC etiology, pathology, and chronicity vary widely across studies. In addition, although the field has started to move away from subjective readings of activation maps, standardized quantitative methods for interpreting findings have not been universally accepted. This is especially problematic when structural abnormalities prevent spatial normalization of patients' brains into standard atlas space. These factors make it difficult to compare findings across studies, generalize results, and move research discoveries into the clinical domain. Despite these limitations, multimodal neuroimaging techniques have been successfully used to study neural network connectivity

in patients with DoC and will continue to contribute to our understanding of DoC as methods become more advanced.

Future Directions

Despite the important insights that PET and fMRI studies have generated since 1999 about the brain networks that contribute to human consciousness, it remains to be determined which networks are necessary or sufficient for maintaining, preserving and recovering consciousness. In addition, the complexity and heterogeneity of study designs and analyses preclude integration of the knowledge about these networks with clinical decision-making.

Prior to translation into clinical practice, investigators will need to focus on larger sample sizes of DoC patients with similar etiologies and chronicity. There may be marked differences in traumatic versus non-traumatic DoC that are present acutely and/or chronically. Multi-site collaborations will likely be needed to achieve this goal. In addition, future studies that aim to demonstrate the clinical utility of functional network mapping will need to place more emphasis on single-subject analyses to address the sensitivity, specificity, and accuracy of decreased connectivity in DoC. Findings from the studies reviewed here will also need to be replicated and automated tools developed to enable rapid, robust and reproducible interpretation of data at the point of care for clinical decision-making. The wide variety of research-centric processing and analytic tools will need to be standardized and the results presented in easily interpretable formats to facilitate implementation of these methods in the clinical setting.[126]

Finally, most PET and fMRI studies investigating the neural mechanisms underlying DoC have focused on understanding which brain regions and connections support the preservation or recovery of conscious awareness rather than those contributing to maintaining arousal. There are two major methodological factors that currently limit knowledge about the subcortical networks mediating arousal. First, many nuclei responsible for sustaining arousal are located in the brainstem,[127] which is difficult to image due to susceptibility artifacts related to its position within the skull and due to pulsatile motion artifact related to blood vessels within the fourth ventricle. Second, these nuclei are so small that the small voxels needed to visualize them yield a low signal-to-noise ratio[128]. To gain a full understanding of how subcortical arousal networks are disrupted in DoC, future studies will need to develop new methods to investigate brainstem connectivity[129–131] (Figure 4).

Aberrant network connectivity seems to be a hallmark feature of DoC that may explain the underlying neurobiology of impaired consciousness. More work is required to understand how cortical and subcortical networks interact to integrate arousal and awareness and which networks are necessary and sufficient to maintain or recover consciousness. Given the rapid rate of advancement in this field, it is reasonable to project that clinical applications of these techniques to diagnosis, prognosis, and treatment will be available in the near future.

Acknowledgments

We thank Zachary D. Threlkeld, M.D., for assistance with processing the resting-state functional MRI data shown in Figures 3 and 4. This work was supported by the National Institutes of Health (K23NS094538), the American

Academy of Neurology/American Brain Foundation, the James S. McDonnell Foundation and the Biaggi Foundation.

Abbreviations

CRS-R	Coma Recovery Scale-Revised
DLPFC	dorsolateral prefrontal cortex
DMN	default mode network
DoC	Disorders of Consciousness
DTI	diffusion tensor imaging
eMCS	emerged from minimally conscious state
fMRI	functional magnetic resonance imaging
IPL	inferior parietal lobule
LIS	locked-in syndrome
MCS	minimally conscious state
MPFC	medial prefrontal cortex
nTBI	non-traumatic brain injury
PET	positron emission tomography
Pr	Precuneus
rsfMRI	resting-state functional magnetic resonance imaging
RSC	Retrosplenial Cortex
Th	thalamus
TBI	traumatic brain injury
tDCS	transcranial direct current stimulation
VTA	ventral tegmental area
VS/UWS	vegetative state

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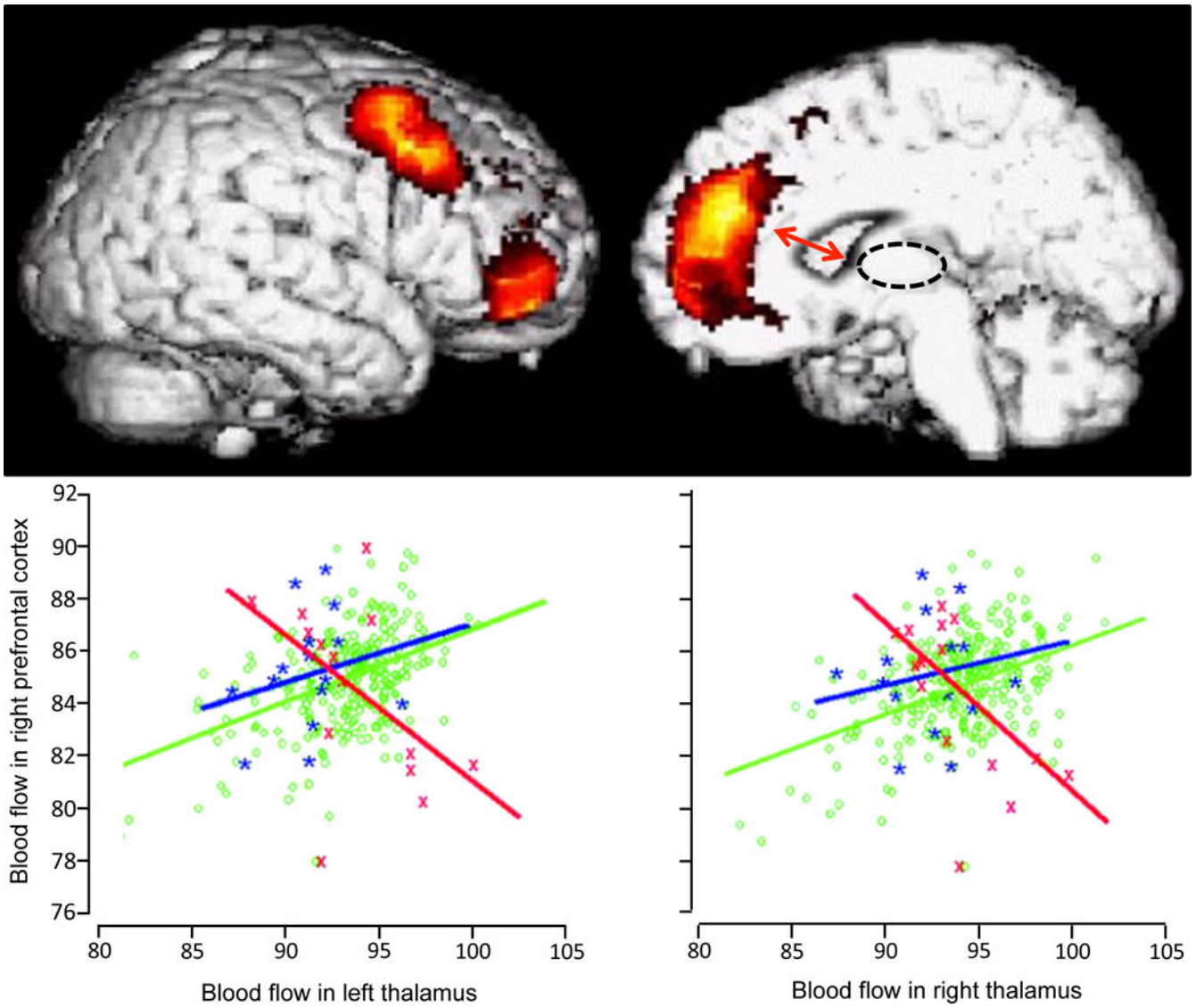

Figure 1.

$H_2{}^{15}O$-PET (Positron emission tomography) analysis of functional connectivity in disorders of consciousness (adapted from Laureys et al 2000[2]). The top row shows cortical regions (prefrontal and anterior cingulate cortices) where functional connectivity (indicated by red arrows) with intralaminar nuclei of both thalami (dashed circle) was different between a patient in VS/UWS and healthy subjects. These differences resolved when the patient recovered consciousness. The bottom row shows the metabolic relationship between both thalami and right prefrontal cortex in healthy subjects (green circles), compared with a patient in VS/UWS (red crosses) and after recovery (blue asterisks). This relationship appears to have normalized when the patient recovered from VS/UWS.

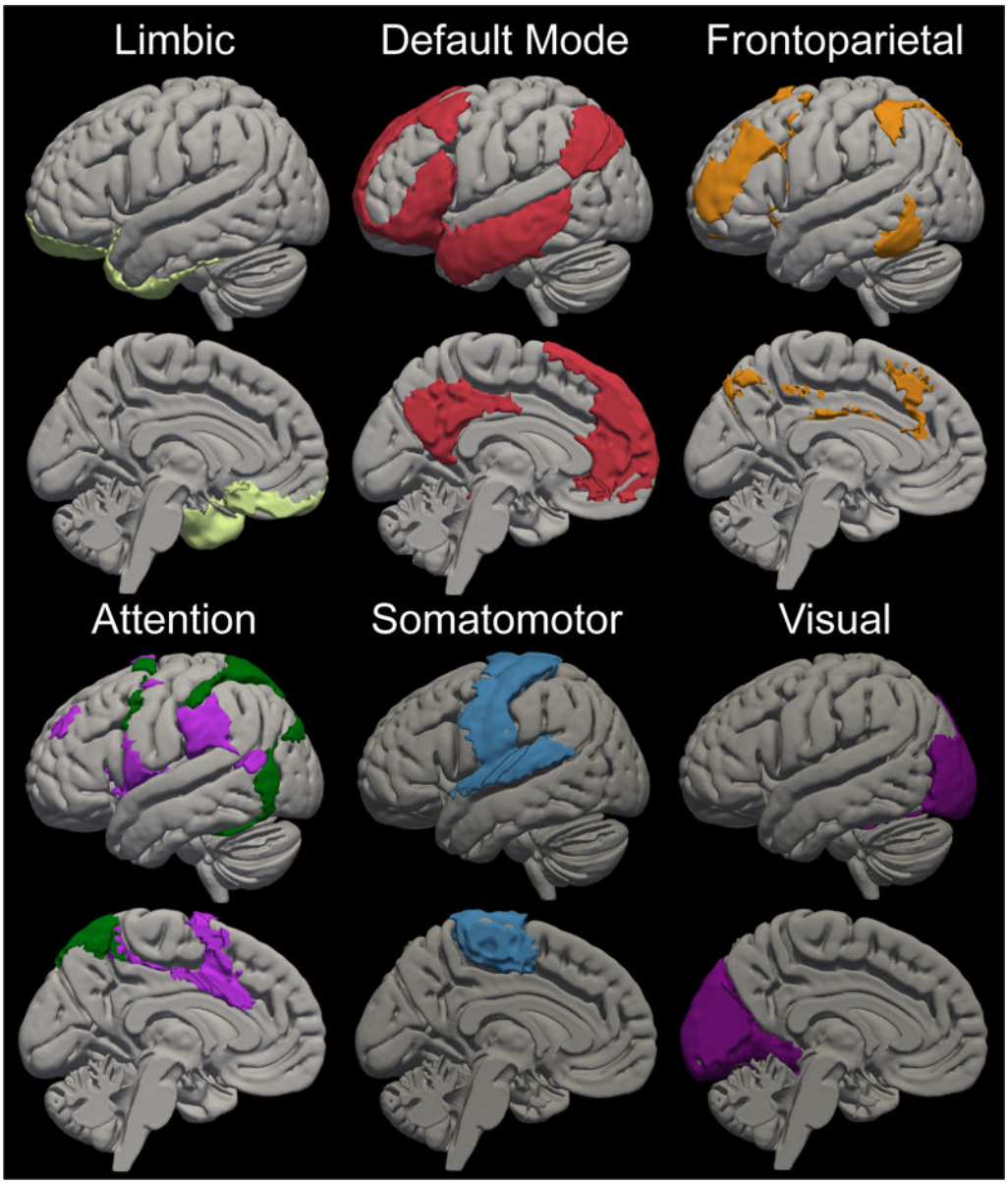

Figure 2.

Overview of cortical resting state networks whose disruption is implicated in the pathogenesis of DoC. All functional network nodes are from the Yeo 2011 Atlas[76] and rendered using FreeSurfer[134] FreeView visualization software. For the attention networks, the dorsal attention network is comprised of the green nodes and the ventral attention network is comprised of the violet nodes.

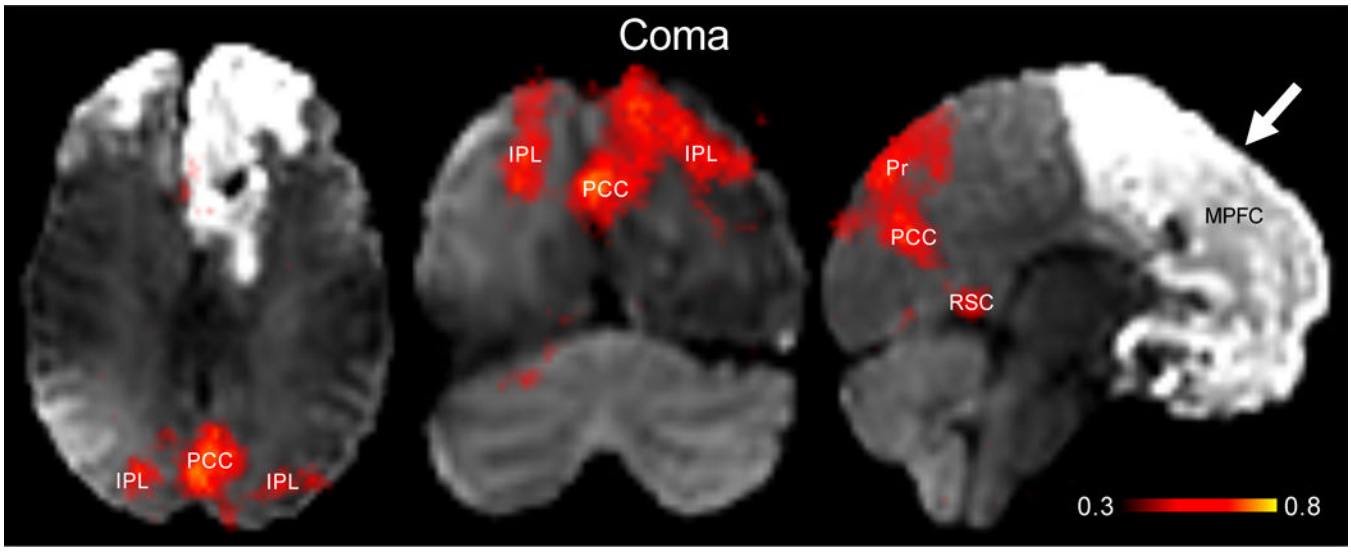

Figure 3.

Resting-state functional MRI (rsfMRI) analysis of default mode network (DMN) connectivity in a comatose patient. DMN connectivity was identified using a seed in the left posterior cingulate cortex (PCC). The functional connectivity map is superimposed on the patient's diffusion-weighted images. The patient was a 55-year-old woman who was scanned six days after an aneurysmal subarachnoid hemorrhage, which resulted in intracranial hypertension and bilateral ischemic strokes involving the anterior cerebral artery territories (hyperintensities, arrow). Her Coma Recovery Scale-Revised score was 1 and Glasgow Coma Scale score was 5T (Eyes=1, Motor=3, Verbal=1T) at the time of the scan, indicating coma. She was sedated with a continuous infusion of propofol throughout the scan. Despite her comatose state and administration of propofol, DMN analysis revealed partial preservation of DMN functional connectivity, specifically between the bilateral PCC, precuneus (Pr), inferior parietal lobules (IPL) and retrosplenial cortex (RSC). Connectivity between the PCC and the medial prefrontal cortex (MPFC) was absent. Color maps represent the spatial distribution of positive correlation coefficients thresholded at ≥ 0.3. RsfMRI data were acquired on a 3 Tesla Siemens Skyra MRI scanner (Siemens Medical Solutions; Erlangen, Germany) using a 32-channel head coil. The rsfMRI sequence utilized 3 mm isotropic voxels with TR = 2.4 s and 150 total volumes. Functional connectivity data were processed using CONN[135] (http://www.nitrc.org/projects/conn).

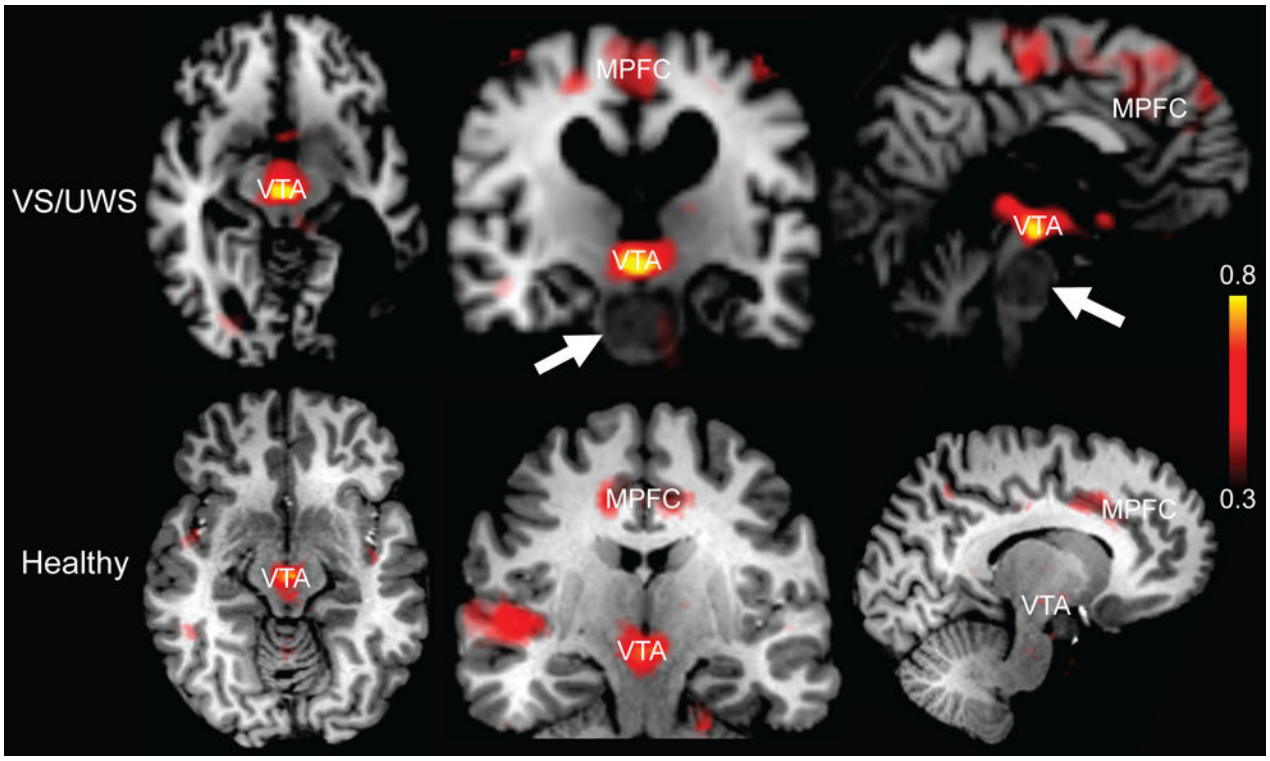

Figure 4.

Resting-state functional MRI (rsfMRI) analysis of brainstem-cortical connectivity in a patient whose behavioral diagnosis suggested a vegetative state/unresponsive wakefulness syndrome (VS/UWS; top row). The patient's connectivity data are compared to a healthy subject's connectivity results (bottom row). Connectivity was identified using a seed in the ventral tegmental area (VTA), which is a dopaminergic arousal nucleus known to activate the cerebral cortex. The patient was a 46-year-old man who was scanned seven days after an ischemic stroke involving the basilar artery territory, which resulted in infarction of the basis pontis (arrows) and multiple regions of the ponto-mesencephalic tegmentum. His initial exams were consistent with a locked-in syndrome, but at the time of the rsfMRI scan his Coma Recovery Scale-Revised score was 1 and Glasgow Coma Scale score was 4T (Eyes=2, Motor=1, Verbal=1T), indicating VS/UWS. He was sedated with a continuous infusion of low-dose propofol throughout the scan. Despite his behavioral diagnosis of VS/UWS and administration of propofol, connectivity appeared preserved between the VTA and the medial prefrontal cortex (MPFC). This observation was consistent with the neuroanatomic localization of the infarct, which spared the VTA. Color maps represent the spatial distribution of positive correlation coefficients thresholded at ≥ 0.3. RsfMRI acquisition parameters were the same as those reported in Figure 3. Functional connectivity data were processed using CONN[135] (http://www.nitrc.org/projects/conn) and the resulting connectivity maps were superimposed on each subject's T1-weighted MPRAGE dataset.

Table 1

PET network studies in patients diagnosed with disorders of consciousness

Authors (year)	*N* (Etiology)	Diagnosis	Time Post-Injury	Method; Networks	Main Findings
Annen et al (2016)[132]	25 (12 TBI, 11 nTBI, 1 mixed, 1 infection)	7 VS/UWS 12 MCS 6 eMCS	1 month - 8 years	^{18}F-FDG-PET/MRI; DMN	DoC patients showed a decreased glucose standardized uptake value compared with healthy subjects in all DMN regions (thalamus, precuneus/ posterior parietal cortex, inferior parietal, mesio-frontal cortex). EMCS showed a significantly stronger thalamo-cortical function–structure relationship compared with DoC using MRI.
Di Perri et al (2016)[89]	58 (29 TBI 22 nTBI, 7 mixed)	21 VS/UWS 24 MCS 13 eMCS	27 ± 44 months	^{18}F-FDG-PET/fMRI; DMN	Brain metabolism increased in regions showing positive correlations with the DMN and decreased in regions anticorrelated with the DMN (i.e. measured through seed-based fMRI analysis). In healthy subjects and those in eMCS, increased metabolism was associated with increased DMN connectivity, and decreased metabolism was associated with regions anticorrelated with the DMN. In VS/UWS and MCS, there was decreased positive DMN connectivity and pathological positive values in DMN anticorrelations (between-network hyper connectivity) accompanied by decreased metabolism. Both positive and negative fMRI–PET correlations could be used to distinguish VS/UWS or MCS from healthy subjects or eMCS.
Laureys et al. (1999)[1]	4 (1 TBI, 3 nTBI)	VS/UWS	15 days - 5 years	^{18}F-FDG-PET; cortico-cortical	Significant difference in effective connectivity between the left prefrontal and premotor cortex and the posterior cingulate cortex in DoC patients as compared to healthy subjects. Common pattern of significantly impaired regional cerebral glucose metabolism in all patients in the left and right middle and superior frontal gyri, the left inferior frontal gyrus, the left inferior parietal lobule, the left middle temporal gyrus, the right superior temporal gyrus, the posterior cingulate cortex/precuneus, and the left pre- and postcentral gyri.
Rosazza et al (2016)[90]	85 (26 TBI, 59 nTBI)	49 VS/UWS 30 MCS 6 eMCS	3 – 252 months	^{18}F-FDG-PET; DMN	Brain glucose metabolism observed within DMN areas yielded the best diagnostic accuracy (VS/UWS VS. MCS) as compared with fMRI, and showed the highest correlation coefficient with CRS-R scores.
Soddu et al (2012[12])	11 (5 TBI, 6 nTBI)	8 VS/UWS 1 MCS 2 LIS	<1 month –4 years	^{18}F-FDG-PET; DMN	VS/UWS patients showed fewer connections in the DMN areas, when compared with healthy subjects, contrary to LIS patients who showed near-normal connectivity. In MCS, unilateral right DMN connectivity was observed with rsfMRI, which correlated with PET measurements of metabolic activity, suggesting its neuronal origin.
Stender et al (2014)[133]	41 (15 TBI, 26 nTBI)	14 VS/UWS 21 MCS 6 eMCS	10 days – 9 years)	^{18}F-FDG-PET; frontoparietal network, precuneus, thalamus and brainstem	VS/UWS and MCS were distinguishable based on metabolic preservation within the frontoparietal network and the precuneus but not based on activity in the thalamus and brainstem.
Thibaut et al (2012)[87]	70 (23 TBI, 47 nTBI)	24 VS/UWS 28 MCS 10 eMCS 8 LIS	11 days - 270 months	^{18}F-FDG-PET; internal (DMN) and external network	VS/UWS patients showed metabolic dysfunction in both thalami and in a widespread cortical network encompassing the extrinsic network (i.e. bilateral posterior parietal and prefrontal areas) and the internal network (i.e. DMN), compared with healthy subjects. MCS patients showed metabolic dysfunction in both thalami and in the internal network. EMCS patients showed metabolic dysfunction in the posterior cingulate cortex and adjacent retrosplenial cortex. LIS patients showed metabolic dysfunction only in infratentorial regions (i.e. the cerebellum). CRS-R total scores positively correlated with a widespread cortical network encompassing

Authors (year)	*N* (Etiology)	Diagnosis	Time Post-Injury	Method; Networks	Main Findings
					both the external network (i.e. bilateral posterior parietal and prefrontal areas) and part of the internal/DMN network (i.e. the precuneus and adjacent posterior cingulate cortex).
Boly (2004)[3]	20 (5 TBI, 15 nTBI)	15 VS/UWS 5 MCS	20 - 124 days	$H_2{}^{15}O$-PET; cortico-cortical	Patients in MCS demonstrated stronger functional connectivity between the secondary auditory cortex and temporal and prefrontal association cortices as compared with patients in VS.
Kassubek et al (2003)[105]	7 nTBI	VS/UWS	3 months - 4 years	$H_2{}^{15}O$-PET and ^{18}F-FDG-PET; network involved in pain processing	Pain-induced activation was found in the posterior insula/secondary somatosensory cortex (SII), postcentral gyrus/primary somatosensory cortex (SI), and the cingulate cortex contralateral to the stimulus and in the posterior insula ipsilateral to the stimulus. At rest, severely impaired functional connectivity in cortico–thalamo–cortical (between thalamus and frontal cortex) pathways was reported (^{18}F-FDG-PET).
Laureys et al (2000)[2]	1 nTBI	VS/UWS	2 weeks and 3 months	$H_2{}^{15}O$-PET; cortico-cortical and thalamo-cortical	Altered connectivity between frontal and parietal associative cortices in VS/UWS; significant difference in modulation between both thalami and the right prefrontal and anterior cingulate cortices when the patient was in a VS/UWS; after recovery, thalamocortical modulation was no longer different from that of healthy subjects.

Review of DoC Connectivity studies using PET. Organized by type of PET study (FDG, $H_2{}^{15}O$) then alphabetically.

CRS-R Coma Recovery Scale-Revised, *DLPFC* dorsolateral prefrontal cortex, *DMN* default mode network, *DoC* Disorders of Consciousness, *DTI* diffusion tensor imaging, *eMCS* emerged from minimally conscious state, *fMRI* functional magnetic resonance imaging, *LIS* locked-in syndrome, *MCS* minimally conscious state, *nTBI* non-traumatic brain injury, *PET* positron emission tomography, *TBI* traumatic brain injury, *tDCS* transcranial direct current stimulation, *VS/UWS* vegetative state/unresponsive wakefulness syndrome

Table 2

fMRI network studies in patients diagnosed with disorders of consciousness

Authors (Year)	N (Etiology)	Diagnoses	Time Post- Injury	Method; Networks	Main Findings
Amico et al (2017)[116]	57 (28 TBI, 29 nTBI)	2 coma 17 VS/UWS 21 MCS 13 EMCS 4 LIS	> 27 days	rsfMRI; global connectivity, DMN, visual network, somato-motor network, dorsal attention network, ventral attention network, limbic system network, fronto-parietal network, subcortical network, cerebellar network	Global connectivity (including all networks) during rest is associated with CRS-R total score and arousal subscale score; visual-somato-motor connectivity is associated with time since onset, and functional communication; fronto-parietal-DMN connectivity is also associated with level of conscious awareness as well as with functional communication, in this network, there is anti-correlation between hemispheres in healthy subjects that diminishes as level of consciousness decreases.
Boly et al (2009)[92]	2 (nTBI)	1 VS/UWS 1 Brain dead	VS: 2.5 years Brain dead: acute	rsfMRI; DMN, cortico-thalamic, and cortical task-related network	Absent cortico-thalamic BOLD functional connectivity between posterior cingulate/precuneus and medial thalamus in VS/UWS and brain death; preserved but reduced cortico-cortical connectivity within the default network in VS/UWS but absent in brain death; preserved but reduced anticorrelations in VS/UWS and absent in brain death between posterior cingulate/precuneus and a task-positive cortical network (including lateral frontoparietal cortices, frontal eye field, inferior and medial temporal cortex, supplementary and pre-supplementary motor area, premotor cortex, insula, inferior frontal cortex)
Cauda et al (2009)[11]	3 (2 TBI, 1 mixed)	VS/UWS	20 months	rsfMRI; DMN	DMN disconnections with decreased connectivity in dorso-lateral prefrontal cortex and anterior cingulate cortex in the right>left hemisphere
Crone et al (2014)[84]	59 (10 TBI, 47 nTBI, 2 mixed)	34 VS/UWS 25 MCS	7days - 27 years	rsfMRI; Global connectivity, fronto-parietal networks, thalamo-cortical networks	Graph theory property of modularity (the degree to which clusters of nodes are densely connected) reduced in VS/UWS and MCS compared with healthy subjects; path length and global efficiency did not differ between groups. Of the 5995 potential pairs of nodes (55 nodes in each hemisphere correlated with every other node) functional connectivity significantly differed in 455 pairs between healthy subjects and MCS, 510 pairs between control subjects and VS/UWS, and 31 pairs between MCS and VS/UWS. Connectivity differences were predominantly in the fronto-parietal regions (between the medial frontal regions and medial parietal regions) and between the left and right thalamus, as well as the left and right temporal parietal junction and right frontal gyrus.
Cavaliere et al (2016)[121]	16 (10 TBI, 6 nTBI)	16 MCS	3 - 7 years	rsfMRI; DLPFC with other cortical regions	tDCS responders showed increased left intra-network connectivity between left DLPFC and left inferior frontal gyrus. Non-responder patients showed increased connectivity between left DLPFC and midline cortical structures, including anterior cingulate cortex and precuneus.
Demertzi et al (2014)[91]	53 (17 TBI, 34 nTBI, 2 mixed)	24 VS/UWS 24 MCS 5 Coma	5 days - 27 years	rsfRMI; DMN and extrinsic networks including executive control network, auditory network	More neuronal components were identified in healthy subjects compared with VS/UWS and coma but not compared with MCS; DMN, auditory and bilateral executive control networks were less identifiable in patients compared to healthy subjects; more patients in MCS showed components of neuronal activity in the left executive control network as compared to patients in VS/UWS;

Authors (Year)	N (Etiology)	Diagnoses	Time Post- Injury	Method; Networks	Main Findings
					DMN and the auditory network elicited high accuracy (85.3%) in differentiating patients from healthy subjects.
Demertzi et al (2015)[16]	73 (21 TBI, 47 nTBI, 5 mixed)	6 Coma 25 VS/UWS 41 MCS 1 eMCS	2 days - 27 years	rsfMRI; DMN, frontoparietal network, salience network, auditory network, sensorimotor network, visual network	DMN, frontoparietal, salience, auditory, sensorimotor and visual networks discriminated MCS from VS/UWS patients with >80% accuracy; auditory network (including right superior temporal transverse gyrus, bilateral precentral gyrus, anterior cingulate cortex and visual cortex) had highest classification accuracy
Di Perri et al (2013)[99]	18 (8 TBI, 10 nTBI)	11 VS/UWS 7 MCS	1 - 84 months	rsfMRI; DMN and limbic networks	Within-network hypoconnectivity observed for all DMN nodes in VS/UWS and MCS patients compared with healthy subjects; no significant hypoconnectivity between the thalamus and the DMN nodes in patients compared with healthy subjects; in VS/UWS, anterior cingulate and posterior cingulate cortex were hyperconnected to insula, orbitofrontal cortex, and occipital cortex regions; intraparietal cortex was hyperconnected to insula, orbitofrontal cortex, and occipital cortex regions; and hippocampus was hyperconnected to midbrain ventral tegmental area, insula, and cerebellum; in MCS, anterior cingulate and posterior cingulate cortex were hyperconnected to insula, orbitofrontal cortex, and temporal-occipital cortex, and intraparietal cortex was hyperconnected to temporal and occipital cortex; hippocampus was hyperconnected to the parietotemporal junction; in VS/UWS, ventral tegmental area was hyperconnected to hippocampus and temporal cortex.
Di Perri (2016)[89]	58 (29 TBI 22 nTBI, 7 mixed)	21 VS/UWS 24 MCS 13 eMCS	1 - 312 months	rsfMRI; DMN, extrinsic network	Identified consciousness-level-dependent increases in positive default mode network connectivity (VS/UWS<MVS<eMVS<healthy) in the anterior cingulate and mesioprefrontal cortex, posterior cingulate cortex and precuneus, temporo-parietal junctions, superior-middle frontal gyri, right temporal cortex, and cerebellum; each patient group was statistically different from the healthy group but patient groups did not differ from one another. Identified consciousness-level-dependent increases in negative default mode network connectivity in DLPFC, inferior parietal lobule, intraparietal sulcus, occipital-temporal cortices, the medial frontal gyrus and paracentral lobule, insula, and cuneus bilaterally; each patient group was statistically different from healthy subjects and differences were found between VS/UWS and eMCS, and between MCS and eMCS; there were no differences in between-network anticorrelations (i.e., between DMN and task-positive network) between VS/UWS and MCS, but VS/UWS+MCS patients had pathological between-network hyperconnectivity between the networks compared with healthy subjects; patients who had emerged from MCS showed partial recovery of anticorrelations between the two networks
He et al (2014)[98]	12 (4 TBI 8 nTBI)	9 VS/UWS 3 MCS	2 - 7 months	rsfMRI; internal and external networks	Decreased connectivity in patients in midline areas associated with internal awareness (i.e. medial prefrontal cortex, anterior cingulate cortex, posterior cingulate cortex, thalamus, orbitofrontal cortex, parahippocampus, caudate, cuneus, inferior parietal lobule, and precuneus); strengthened connectivity in external network (i.e. insula, lingual gyrus, paracentral and supplementary motor area).

Authors (Year)	N (Etiology)	Diagnoses	Time Post- Injury	Method; Networks	Main Findings
Norton et al (2012)[93]	14 (nTBI)	Coma	1 - 6 days	rsfMRI; DMN	Present and intact DMN was observed in controls and those patients who subsequently regained consciousness, but was disrupted in all patients who failed to regain consciousness.
Ovadia-Caro et al (2012)[97]	8 (1 TBI, 2 nTBI)	1 BD 2 Coma 2 VS/UWS 2 MCS 1 LIS	1 week – 4 years	rsfMRI; extrinsic network and other cortical regions	Decreased or absent inter-hemispheric functional connectivity (i.e. extrinsic network; seeds were in pre- and post-central gyrus and intra-parietal sulcus of the right hemisphere) in patients compared with non-brain injury subjects and LIS. Interhemispheric connectivity correlated with level of consciousness. One VS/UWS patient had connectivity in the normal range and was the only subject in the sample to recover consciousness approximately one month post-scan.
Qin et al (2015)[17]	133 (109 TBI; 133 nTBI)	56 VS/UWS 29 MCS 48 Brain injury but fully conscious	Mean range 68 - 149 days	rsfMRI; salience network, executive control network, and DMN	Salience network (supragenual anterior cingulate cortex as seed region, bilateral anterior insula, bilateral thalamus) connectivity is reduced in VS/UWS as compared to MCS and fully conscious brain injury patients; salience network connectivity correlates with behavioral signs of consciousness; DMN connectivity predicts recovery of consciousness. Executive control network (right dorsal lateral prefrontal cortex as seed region, left dorsal lateral prefrontal cortex, bilateral inferior parietal lobule, precuneus) connectivity and DMN (posterior cingulate cortex as seed region, bilateral lateral parietal cortex, right temporal pole, medial prefrontal cortex) connectivity reduced in VS/UWS compared to conscious brain injury patients but not between VS/UWS and MCS. DMN, but not salience and executive control network connectivity predicted recovery of consciousness in VS/UWS patients at three or more months post-injury
Rosazza et al (2016)[90]	119 (36 TBI 83 nTBI)	72 VS/UWS 36 MCS 11 Severe disability	2 - 252 months	rsfMRI; DMN	DMN functional connectivity strength differentiates MCS from VS/UWS patients and is correlated with the behavioral diagnosis, as measured with CRS-R.
Silva et al (2015)[15]	27 (14 TBI, 13 nTBI)	Coma	2 - 9 days	rsfMRI; DMN and extrinsic network	DMN connectivity (seed in posterior cingulate cortex) disrupted in comatose patients; decreased correlation over time between PCC and lateral parietal cortices (supramarginal gyrus) associated with external awareness. Connectivity with precuneus remained intact in comatose patients; functional connectivity strength between posterior cingulate cortex and medial prefrontal cortex significantly different between comatose patients who emerged from MCS and those who evolved to MCS or VS/UWS (i.e. unfavorable outcome) 3 months post-injury.
Soddu et al (2012)[12]	11 (5 TBI, 6 nTBI)	8 VS/UWS 1 MCS 2 LIS	1 month – 4 years	rsfMRI; DMN, external control network	Fewer DMN (precuneus/posterior cingulate, medial prefrontal cortex ventral, medial prefrontal cortex anterior, bilateral posterior parietal lobe, bilateral superior frontal gyrus, bilateral middle temporal gyrus anterior, bilateral parahippocampal/mesiotemporal, bilateral thalamus) connections in VS/UWS versus healthy subjects and LIS subjects; connectivity measures reflected a combined result of both the reduction in the positive correlation between the regions of the DMN and of the anticorrelation with the regions of the external control network (bilateral supramarginal gyrus,

Semin Neurol. Author manuscript; available in PMC 2018 December 05.

Authors (Year)	N (Etiology)	Diagnoses	Time Post- Injury	Method; Networks	Main Findings
					bilateral middle temporal gyrus posterior, supplementary motor area)
Vanhaudenhuyse et al (2010)[12]	14 (2 TBI, 12 nTBI)	5 Coma 4 VS/UWS 4 MCS 1 LIS	<1 month – 5 years	rsfMRI; DMN	A significant correlation between DMN connectivity strength in all areas and the level of consciousness was reported. The PCC/ precuneus was found to be the peak area of significance for the correlation between connectivity and consciousness. PCC/ precuneus connectivity could also differentiate MCS from unconscious patients. No brain area was found to be more present in DMN connectivity maps in unconscious compared with MCS patients
Wu et al (2015)[14]	99 (17 TBI, 82 nTBI)	14 Coma 18 VS/UWS 27 MCS 40 Preserved Consciousness	4 days - 22 months	rsfMRI; DMN, salience/executive control network, striatal network	Functional connectivity strength decreased in the DMN (posterior cingulate cortex, medial prefrontal cortex, and inferior parietal lobule) and salience/executive control network (middle cingulate cortex and anterior insula, and the intraparietal sulcus) and increased in the inferior temporal gyrus, medial temporal lobe, and basal ganglia with loss of consciousness; significant positive correlation between functional connectivity in DMN and CRS-R and negative correlation between medial temporal lobe/inferior temporal gyrus and CRS-R; functional connectivity strength in the DMN positively correlated with recovery outcome on the Glasgow Outcome Scale; connectivity in the medial temporal lobe/inferior temporal gyrus negatively correlated with the Glasgow Outcome Scale 3 months post imaging; functional connectivity strength patterns predicted whether patients in VS/UWS and coma would regain consciousness with accuracy of 81.25%, sensitivity of 88.89%, and specificity of 71.43%; most discriminative region was the posterior cingulate cortex/precuneus.
Yao et al (2015)[111]	11 TBI	GCS < 8	2 - 11 days	rsfMRI; thalamo-cortical and striatal-cortical	Increased amplitude of low-frequency fluctuation in the anterior cingulate, cortex, hippocampus, insula, amygdala and putamen, and reduced in the precuneus, thalamus, pre-central and post-central gyri in patients versus healthy subjects.
de Pasquale et al (2015)[109]	3 nTBI	2 VS/UWS 1 recovered from DoC	2 - 24 months	rsfMRI and stimulus-based fMRI; global connectivity	Average overall connectivity in VS/UWS was lower than in the non-DoC and healthy state; observed a 60% increase in the average connectivity value in the emotional stimulus versus resting condition.
Huang et al (2014)[107]	11 (4 TBI, 7 nTBI)	6 VS/UWS 5 MCS	36 - 301 days	rsfMRI and stimulus-based fMRI	During resting-state, reduced low-frequency fluctuation amplitudes were evident in perigenual anterior cingulate cortex, medial prefrontal cortex, and posterior cingulate cortex compared with healthy subjects. These regions overlapped with the self-referential stimulus-based fMRI task; functional connectivity was stronger in the MCS versus VS/UWS group
Crone et al (2011)[117]	25 (12 TBI, 13 nTBI)	17 VS/UWS 8 MCS	16 days - 8 years	stimulus-based fMRI; DMN	Deactivation in medial regions is reduced in MCS and absent in VS/UWS patients compared to healthy subjects when listening to sentences; behavioral scores assessing the level of consciousness correlate with deactivation in patients; on single-subject level, all healthy subjects but only 2 patients in MCS and 6 with VS/UWS showed deactivation.
Kotchoubey et al (2013)[108]	12 (1 TBI, 11 nTBI)	6 VS/UWS 6 MCS	1 - 50 months	stimulus-based fMRI; emotion networks	Activations in VS/UWS were reduced compared with those in MCS during presentation of emotionally salient sounds in anterior

Authors (Year)	N (Etiology)	Diagnoses	Time Post- Injury	Method; Networks	Main Findings
					cingulate cortex, insula, postcentral gyrus, cerebellum, inferior/ middle temporal gyri, and angular gyrus. These regions were used as seeds in global connectivity analysis. MCS showed similar global connectivity to healthy subjects while VS/UWS connectivity was limited to the vicinity of the seed regions (i.e., no long-range connectivity between seed regions and other cortical and subcortical brain areas was observed).
Monti et al (2015)[110]	28 (16 TBI, 11 nTBI, 1 unknown)	8 VS/UWS 16 MCS 4 eMCS	3 - 131 months	stimulus-based fMRI; thalamo-cortical	Psychophysiologic interaction analysis revealed that the main factor distinguishing patients who responded to the auditory detection task from those who did not was greater connectivity between the anterior portion of thalamus and prefrontal cortex.

Review of DoC Connectivity studies using fMRI. Organized by type of fMRI study (rsfMRI, stimulus-based) then alphabetically.

BD brain death, *CRS-R* Coma Recovery Scale-Revised, *DLPFC* dorsolateral prefrontal cortex, *DMN* default mode network, *DoC* Disorders of Consciousness, *DTI* diffusion tensor imaging, *eMCS* emerged from minimally conscious state, *fMRI* functional magnetic resonance imaging, *LIS* locked-in syndrome, *MCS* minimally conscious state, *nTBI* non-traumatic brain injury, *PET* positron emission tomography, *rsfMRI* resting-state functional magnetic resonance imaging, *TBI* traumatic brain injury, *tDCS* transcranial direct current stimulation, *VS/UWS* vegetative state/unresponsive wakefulness syndrome