

# Chapter 3

## Linking Complex Alterations in Functional Network Connectivity to Disorders of Consciousness

Julia S. Crone and Martin M. Monti

**Abstract** In the last decade, research has focused on finding neural correlates of consciousness for diagnosis and prognosis after severe brain injury using neuroimaging studies. Because patients with disorders of consciousness are not or only limitedly capable of following instructions, studies investigating resting-state connectivity have been a focus of interest. This chapter gives an overview of the research on functional network connectivity in disorders of consciousness and common methods used to investigate these alterations such as independent component analysis, seed-based approaches, graph theory, and spectral dynamic causal modeling. Research demonstrates that properties of resting-state networks may provide further evidence for diagnosis and prognosis but also show limitations in interpretability. In addition, the existence of so-called hot zones of neuronal correlates of consciousness is discussed. In the second half of this chapter, we outline the caveats of resting-state functional imaging in severe brain injury. Motion, artifacts, normalization procedures, and interpretability pose serious obstacles when analyzing resting-state connectivity particularly in the injured brain. Nevertheless, resting-state connectivity analyses are a powerful tool to investigate patients with disorders of consciousness.

---

J.S. Crone, Ph.D. (✉)

Department of Psychology, University of California Los Angeles,  
Los Angeles, CA 90095, USA

e-mail: [j.crone@neurocognition.org](mailto:j.crone@neurocognition.org)

M.M. Monti, Ph.D.

Department of Psychology, University of California Los Angeles,  
Los Angeles, CA 90095, USA

Department of Neurosurgery, David Geffen School of Medicine at UCLA, Brain Injury  
Research Center (BIRC), Los Angeles, CA 90095, USA

© Springer International Publishing AG 2018

C. Schnakers, S. Laureys (eds.), *Coma and Disorders of Consciousness*,

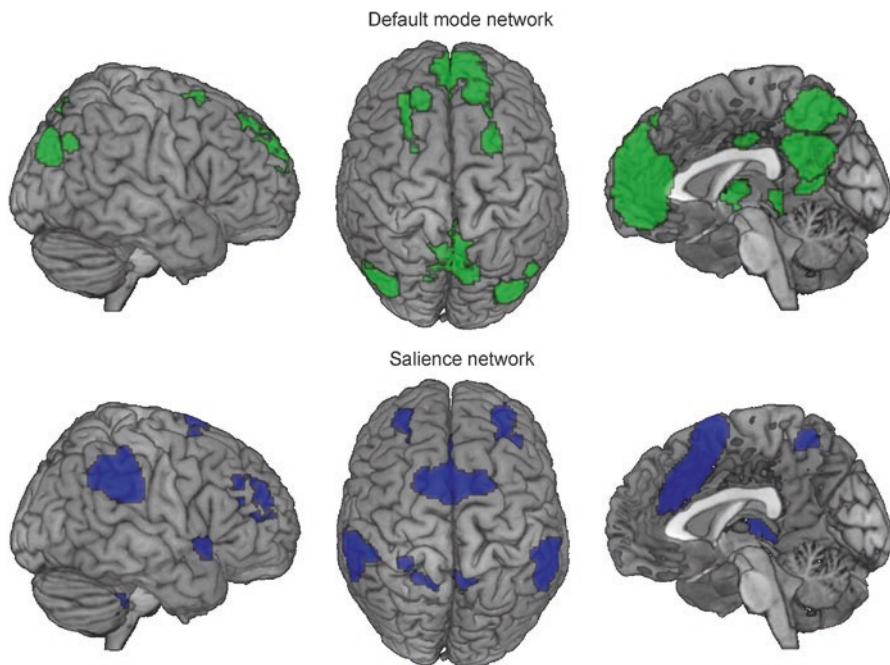
DOI 10.1007/978-3-319-55964-3\_3

Disorders of consciousness can be caused by severe brain injury and affect profoundly the structural and functional integrity of the brain's core architecture. Understanding the complexity of this architecture is the main challenge when linking brain function to cognitive deficits such as impaired consciousness. Neuroimaging in these patients has become a state-of-the-art tool to gain deeper insight into the functional and structural changes underlying their deficits and, more in general, the neuronal correlates of consciousness. The early investigations using neuroimaging in patients with disorders of consciousness revealed major alterations in brain connectivity [1–3]. The focus of these early studies was to find additional and more reliable diagnostic measures bearing in mind a lack of accuracy in the standard clinical assessment of their cognitive abilities [4] (see Chap. 1). To accomplish this goal, functional and structural characteristics of the brain are compared between different levels of impairment (ranging from coma, vegetative state, to the minimally conscious state) to uncover associations between the underlying degree of cognitive deficits and alterations in brain functioning.

In the past 10 years, functional connectivity during resting state has become a particularly promising perspective for research in severe brain injury and impaired consciousness. Resting-state imaging has the great advantage of not involving task-related sensory input or behavioral output, which can be impaired by the specific nature of the brain injury and potentially mask the presence of (minimal) consciousness. Since the focus of interest lies on alterations in the basic brain functioning of patients with disorders of consciousness, rather than on specific deficits in higher-level cognitive domains, there is also no need to trigger these cognitive processes with specific tasks. Another reason for studying the resting state in patients is that without controlling the cognitive processes during task performance (which is impossible in unresponsive patients), task-specific stimuli may generate similar brain states independent of the patient's level of consciousness [5]. During resting state, fluctuations are observed in the blood oxygen level-dependent (BOLD) signal while performing functional magnetic resonance imaging (fMRI). These fluctuations show an organized pattern of functionality throughout the brain and are associated with cognitive functioning [6].

## **Alterations of Brain Networks in Disorders of Consciousness**

At rest, fluctuations in the BOLD signal of different brain regions are synchronized forming distinct networks throughout the brain [7, 8]. The most paradigmatic resting-state network, the so-called default mode network, connects the medial frontal cortex, medial posterior cortex, and temporoparietal regions [9] (see Fig. 3.1). A key characteristic of the default mode network is its activation during rest and deactivation during performance of various attention-demanding cognitive tasks [10–12]. It has been speculated that the BOLD fluctuations establishing the default mode network are related to conscious cognition [13], mind wandering [14], or internal reflection [9, 15] and that its deactivation reflects interruptions of



**Fig. 3.1** Examples of resting-state networks as defined here [22]. *Top (green)*: default mode network. *Bottom (blue)*: saliency network

introspective processing enabling attention-demanding actions [12, 16]. Supporting the latter speculations, this network is active rather than depressed during tasks involved in internal-directed cognition such as autobiographical memory, imagery spatial navigation, and theory of mind as demonstrated by a meta-analysis [17]. Single components of the default mode network are affected in different ways depending on the properties of the task such as emotional or self-referring features. But as a whole, the default mode network seems to play an enhanced role in attention focusing [18]. Nevertheless, the exchange of information within the default mode network is never turned off completely but rather adjusted at a fine-grained level as studies in sleep [19], in light sedation [20], as well as in deeply anesthetized monkeys [21] demonstrate.

In addition, the default mode network has been shown to be anticorrelated with other resting-state networks such as the dorsal attention network [10]. However, when studying local cell recordings in the cat brain across time, these anticorrelations are only present about 20% of the time, while 80% of the time, the two networks seem to cooperate depending on the state of mind [18].

The most common methods to study the default mode network are independent component analysis [23] and seed-based approaches [8]. While the independent component analysis is data-driven, the seed-based correlation analysis depends on spatial assumptions and regions of interest. Independent component analysis

attempts to separate a multivariate signal in (spatial) independent sources resulting in several independent connectivity maps of the brain. For the seed-based approach, connectivity depends on the time series of a selected seed region and its correlation with the time series of all other voxels. It is also possible to explore properties of resting-state networks using structural information such as probabilistic tractography, a diffusion tensor imaging method used to identify anatomical connections based on the molecular diffusion process in tissues in three-dimensional space.

The involvement of the default mode network in self- and attention-related tasks and its prominent occurrence has led researchers to investigate its alterations in disorders of consciousness. Studies demonstrate reduced functional connectivity within the default mode network in patients [24–29] and functional [30, 31] as well as structural [32] correlation with the level of behavioral responsiveness as measured by the Coma Recovery Scale-Revised [33] (see Chap. 1 for further detail on behavioral assessment). In addition, an intact default mode network was observed in comatose patients who eventually recovered consciousness but not in patients who did not awake from coma. This finding indicates that connectivity of the default mode network may have prognostic value for comatose patients [34]. A similar finding in patients in the vegetative state proposes that patients who do not emerge show reduced connectivity between regions within the default mode network compared to patients who regain consciousness [35]. Another link to the level of impairment has been found when investigating deactivation of the default mode network in response to language [36]. Only those patients who showed preserved responses to language in higher-cortical areas were able to interrupt ongoing mental processes to focus attention, that is, demonstrate a local decrease in BOLD activity.

The default mode network may be the most paradigmatic resting-state network, but it is not the only to be altered in disorders of consciousness. Differences in connectivity strength between patient groups have been shown also in the salience network [35] (see Fig. 3.1). When discriminating the impairment of various resting-state networks such as the default mode, frontoparietal, salience, auditory, visual, and sensorimotor in patients using a machine learning approach [37], functional connectivity in all networks showed a correlation with the level of behavioral responsiveness and a high discriminative capacity for separating patients according to their severity of impairment. As of a note, this finding could not be confirmed in a study investigating the specificity and sensitivity of the mere presence of various resting-state networks [29] which may be due to the fact that the default mode network was the only network identified in all subjects.

Another exciting approach to explore network properties of the brain is graph-theoretical techniques [38]. Graph theory is the study of mathematical structures used to model relations between objects and has been applied in all kinds of fields such as computer science, chemistry, physics, biology, economics, and sociology. In graph theory, complex networks are defined as a set of nodes connected by edges. Their constellation is described by network metrics. Clusters of functionally associated areas show a high density of local connections with few connections between

functionally segregated clusters [39, 40]. This small-world constellation ensures a high efficiency in information processing at a relatively low cost of wiring length [41]. These properties give rise to, for instance, the necessary balance to maintain a high level of cognition [42] between information segregation (as a capacity for specialized processing within densely interconnected brain regions) and integration (as a capacity to combine the specialized processing from segregated brain regions). Graph-theoretical approaches provide a perfect source to study the topological arrangement of functional communication and structural organization using metrics such as degree (number of edges of each node), clustering (degree to which the node's neighbors are also neighbors of each other), and efficiency (quantification of its robustness to failure).

Recent investigations applying graph-theoretical measures in disorders of consciousness demonstrate preserved small-world properties of the overall organization of the brain's network despite severe alterations [43–45]. For instance, comatose patients show critical impairment at the local level of network organization but no global alterations [43]. In contrast, when comparing minimal conscious state, vegetative state, and healthy controls, the balance between segregation and integration in both patient groups is globally affected as well. Another study compared the scale-free properties between propofol-induced loss of consciousness and the vegetative state [45]. Scale-free networks are characterized by high robustness to failure because of their highly heterogeneous degree distribution. The vast majority of nodes are connected to only a few other nodes with a tiny minority of actual hubs (nodes that are disproportional highly connected to other nodes). Therefore, the likelihood that randomly occurring failure affects a highly connected hub (and thus is fatal) is almost negligible. Interestingly, the deeply sedated brain demonstrates scale-free properties, while the vegetative state does not [45].

At a more local level, topological measures such as degree, efficiency, and clustering are reduced in patients in medial posterior regions [43, 44], while in frontal regions, findings depart depending on the study and patient population. In minimal conscious state and vegetative state, an increase in lateral frontal and a decrease in medial frontal regions have been detected [44]. In comatose patients, however, there was an increase in medial frontal regions [43]. In addition, the degree of segregation differs between vegetative state and minimal conscious state in medial parietal and is related to behavioral responsiveness in frontal regions.

Recently, a new method for resting-state fMRI data, spectral dynamic causal modeling [46], has been validated allowing to investigate alterations in the causal interaction of resting-state networks. Applying this approach to explore the effective connectivity within the default mode network revealed that the posterior cingulate cortex functions as the main driven hub in healthy subjects [47]. In patients with disorders of consciousness, disruption regarding self-inhibition and neuronal oscillations in the posterior cingulate cortex is a key aspect linking alterations in consciousness after severe brain injury to the intrinsic functional architecture of the default mode network [47].

## A Hot Zone of Neuronal Correlates of Consciousness?

In contrast to the recent findings reported above, there has been a long history of research on connectivity between the thalamus and the frontal cortex in disorders of consciousness. An initial study in one patient recovering consciousness after traumatic brain injury [48] (together with evidence from the animal model [49, 50] and from experimental manipulations testing conscious awareness of stimuli in healthy subjects [51–53]) highlights the role of thalamo-frontal connectivity in disorders of consciousness. The thalamus is highly reciprocal connected with cortical areas, especially with frontal regions. This theoretically makes the thalamus a perfect candidate for integrating information computed by cortical areas and therefore generating conscious awareness. However, the critical involvement of the thalamus for consciousness has not been confirmed. Recent evidence rather suggests a less prominent role of the thalamus in disorders of consciousness after traumatic brain injury. While the structural atrophy of the thalamus is related to motor function as well as communication, there is no relation with the level of arousal or overall conscious responsiveness in patients [54]. Studies investigating functional connectivity did not find significant correlations with the overall level of conscious responsiveness and thalamo-cortical connectivity in patients [3, 44]. This would be in line with evidence from studies investigating propofol- or sleep-induced loss of consciousness and demonstrating a rather secondary role of thalamo-cortical connectivity [55–59]. It is more likely that thalamo-cortical connectivity is crucial for effective cortical communication providing higher-order cognition and control of motor function [60].

Obviously, a much more consistent finding in patients with disorders of consciousness is alterations of the medial posterior regions. The posterior cingulate cortex with the adjacent precuneus is the most prominent part of the default mode network. The posterior cingulate cortex is not only sensitive to the state of arousal but serves as a complex control mechanism in respect to the breadth of attention (focused vs. broadly alert) and its direction (internally vs. externally) [61]. It is also part of the so-called rich club referring to brain regions with much higher interconnectivity throughout the brain than others which are suggested to play a critical role in overall brain communication by enabling highly efficient information integration [62]. The posterior cingulate cortex shows a complex pattern of interaction with different functional connectivity networks emphasizing a multifaceted role in global brain communication [63, 64]. This makes the posterior cingulate cortex as part of the default mode network to a major transit hub for exchange of information throughout the whole brain [65–68]. In disorders of consciousness, connectivity of medial posterior regions during resting state is found to be altered in all relevant studies often distinguishing between vegetative state and minimal conscious state patients [30, 44, 69, 70]. Based on these observations, Koch and coworkers plead for a temporo-parietal-occipital *hot zone* of neuronal correlates of consciousness [71]. Indeed, findings from fMRI studies make it tempting to speculate about the causal association between medial posterior regions and impaired consciousness

especially because specific hubs in the brain—if impaired—have fatal effects for the overall communication due to its structural organization as a scale-free network. However, precaution is required when drawing conclusion regarding the causal involvement of changes in the regional activity of the blood oxygen level-dependent (BOLD) signal in the severely damaged brain.

## **Caveats of Resting-State Functional Imaging in Severe Brain Injury**

It is important to be mindful of the methodological and conceptual limitations that arise from functional connectivity studies investigating consciousness and severe brain injury when discussing the findings.

### ***Motion and Artifacts***

Acquiring, analyzing, and interpreting resting-state fMRI data in the severely damaged brain is more than challenging. Motion is the most problematic but also the most considered disadvantage when working with resting-state fMRI data in patients with disorders of consciousness. Patients in the vegetative state and especially in the minimally conscious state can exhibit high rates of spontaneous motion. To make things even more problematic, the correlation between motion and the level of recovery follows a u-shaped curve. Patients in the minimal state typically show more motion than patients in the vegetative state. In recovered patients, however, the trend is the opposite: with less motion, the better the recovery.

Motion artifacts in functional connectivity analyses are known to be highly problematic [72–76]. The effects are complex and may depend on the specific acquisition and analysis procedure chosen. Small head movements may produce spurious but organized effects on the BOLD signal which leads to false distance-dependent correlations. This problem is not trivial when the question of interest is correlated with the amount of motion, that is, when comparing high-motion groups with low-motion groups. Consequently, differences between vegetative state and minimal conscious state as well as between minimal conscious state and control groups may be completely due to differences in head motion. In addition, motion affects nearby voxels more than distant ones which has severe impact on the properties of networks such as long-distance vs. short-distance connectivity, efficiency, and clustering measures. This highly affects findings beyond the mere comparison of group differences. The awareness of these problematic issues has just arisen and denoising strategies are still evolving. Most of the functional connectivity studies which are reported in this chapter have not implemented sufficient approaches to control for motion artifacts.



A similar issue is the brain injuries themselves. Lesions can produce spurious artifacts which affect the variance of the BOLD signal in surrounding areas of interest. The severity of the lesions tends to correlate with the level of impaired consciousness and cognition, that is, vegetative state patients typically have a greater level of brain damage than minimal conscious state patients.

### ***Normalization and Selection of Region of Interest***

Less commonly discussed but definitely as delicate to deal with is the normalization procedure and selection of regions of interest in patients with severe traumatic brain injury. Commonly, the functional images acquired are automatically transferred into some sort of common referential space, such as the Montreal Neurological Institute (MNI) space, to conduct group comparisons. This is usually done for region of interest analyses such as graph-theoretical approaches or effective connectivity analyses and data-driven approaches at the group level such as independent component analysis likewise. To define a region of interest, the coordinates are identified in one common standard space and then applied to all subjects in the same space. This way it is ensured that the comparison of changes in the BOLD signal of a particular area in the brain is the same across subjects. For patients with severe brain lesions, however, there is no adequate solution for an automatic procedure of normalization into standard space [77–79]. The best but still not flawless method is cost function masking proposed by Brett et al. [80]. However, this process is not only very time consuming but, especially in brains with widespread and diffuse lesions, difficult to perform because it requires the manual tracing of the lesion borders.

In addition, the process of normalization as a purpose of defining common brain regions of interest does also not account for plasticity and adaptation of neighboring regions assimilating functions of lesioned parts.

An alternative approach in these patients is to process the data in single-subject space and define regions of interest functionally at the individual level if applicable. However, most of the studies performed in patients with disorders of consciousness used an automatic normalization procedure and coordinates in standard space to define regions of interest.

### ***Aspects of Interpretability When Using Functional Neuroimaging in Disorders of Consciousness***

Besides the specific methodological caveats of data preprocessing, the interpretability of findings is complicated for fMRI data in general but in disorders of consciousness particularly. The BOLD signal originates from changes in the deoxyhemoglobin concentration meaning it is sensitive to changes in cerebral blood flow, blood volume, and tissue oxygen consumption. Consequently, the measured BOLD response is dependent on the size and orientation of and the distance to the blood vessel. Intravascular



and extravascular water have also different influences on the BOLD signal, and these influences depend on the parameter settings during data acquisition. For simple connectivity analyses in which the time series of one region is compared to the time series of another, the challenge of modeling the BOLD response appropriately is not of such importance. However, when it comes to the interpretation of differences in connectivity between compared groups or the interpretation of an association with behavioral assessment, these factors are indeed significant.

This multifaceted interaction gets even more complicated when dealing with severe brain injury. In the healthy brain, neuronal activity typically evokes a concurrent increase in oxygen consumption, blood flow, and volume. Astrocytes and pericytes, non-neuronal brain cells, are highly involved in regulation of vasodilatory responses [81, 82] and thus a crucial element of the BOLD signal. Especially pericytes are significantly affected by impaired arterial blood supply such as in ischemia or traumatic brain injury. As a consequence, alteration of the BOLD signal in traumatic brain injury may rather mark the prolonged death of pericytes than impaired neuronal activity. However, the exact interaction between mechanisms caused by severe brain injury and its effects on the BOLD signal are unknown. This is exacerbated by the fact that alterations in structural connectivity are not directly related to functional connectivity. From simulations we know that changes in brain connectivity have widespread, complex effects on functional connectivity and are not restricted to local changes [42, 66, 83]. Straightforward interpretation of these alterations is illusive. For instance, increases in functional connectivity do not always go along with a strength in structural connectivity and cannot be entirely related, for example, to compensatory processes reflected by neural plasticity [83, 84].

Another complicating factor for interpretation we have to be aware of is that neuronal mechanisms identified with neuroimaging techniques do not necessarily reflect neuronal correlates of consciousness [85, 86]. Mechanisms identified and related to the level of consciousness in patients do not exclusively reveal its neuronal correlates but could rather be prerequisites for or consequences of conscious experience. In healthy subjects, an empirical distinction of these different brain processes is already a huge challenge that has not been resolved to a satisfactory extent so far. For patients with severe brain injury, however, this is even more challenging due to the earlier mentioned possible confounds.

It remains a challenge to specify the cause of changes in functional connectivity in the diseased brain and disentangle injury-specific influences on the BOLD signal from underlying structural and functional changes, or actual changes in cognitive function.

## Conclusion

Despite the general lack of awareness for conscientious interpretability of fMRI findings and the problematic aspects of data preprocessing, resting-state fMRI analyses in disorders of consciousness offer a unique insight into very specific alterations of the brain's network mechanisms that other methods cannot

provide. This approach enables the identification of impairments at the macro-scale level by shifting the spotlight on mechanisms of interaction that emerge exclusively at this broader scale. Previous research in disorders of consciousness has shown that functional connectivity is fundamentally reorganized and that affected hot zones such as medial parietal regions play a critical role for consciousness and cognition.

In combination with other methods and cautious interpretation, resting-state fMRI and functional connectivity analyses are a crucial part of investigating disorders of consciousness and enhance our knowledge of the brain mechanisms underlying impaired consciousness.

## References

1. Laureys S, Lemaire C, Maquet P, Phillips C, Franck G. Cerebral metabolism during vegetative state and after recovery to consciousness. *J Neurol Neurosurg Psychiatry*. 1999;67(1):121.
2. Laureys S, Goldman S, Phillips C, Van Bogaert P, Aerts J, Luxen A, et al. Impaired effective cortical connectivity in vegetative state: preliminary investigation using PET. *Neuroimage*. 1999;9(4):377–82.
3. Laureys S, Faymonville ME, Peigneux P, Damas P, Lambermont B, Del Fiore G, et al. Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. *Neuroimage*. 2002;17(2):732–41.
4. Owen AM, Menon DK, Johnsrude IS, Bor D, Scott SK, Manly T, et al. Detecting residual cognitive function in persistent vegetative state. *Neurocase*. 2002;8(5):394–403.
5. Crone JS, Höller Y, Bergmann J, Golaszewski S, Trinka E, Kronbichler M. Self-related processing and deactivation of cortical midline regions in disorders of consciousness. *Front Hum Neurosci*. 2013;7:504.
6. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med*. 1995;34(4):537–41.
7. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci*. 2007;8(9):700–11.
8. Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci U S A*. 2003;100(1):253–8.
9. Raichle ME, Snyder AZ. A default mode of brain function: a brief history of an evolving idea. *Neuroimage*. 2007;37(4):1083–90.
10. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van EDC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci U S A*. 2005;102(27):9673–8.
11. Shulman GL, Fiez JA, Corbetta M, Buckner RL, Miezin FM, Raichle ME, et al. Common blood flow changes across visual tasks: II. Decreases in cerebral cortex. *J Cogn Neurosci*. 1997;9(5):648–63.
12. Gusnard DA, Raichle ME. Searching for a baseline: functional imaging and the resting human brain. *Nat Rev Neurosci*. 2001;2(10):685–94.
13. Morcom AM, Fletcher PC. Does the brain have a baseline? Why we should be resisting a rest. *Neuroimage*. 2007;37(4):1073–82.
14. Andrews-Hanna JR, Reidler JS, Huang C, Buckner RL. Evidence for the default network's role in spontaneous cognition. *J Neurophysiol*. 2010;104(1):322–35.
15. Mason MF, Norton MI, Van Horn JD, Wegner DM, Grafton ST, Macrae CN. Wandering minds: the default network and stimulus-independent thought. *Science*. 2007;315(5810):393–5.

16. Binder JR. Task-induced deactivation and the “resting” state. *Neuroimage*. 2012;62(2): 1086–91.
17. Spreng RN, Mar RA, Kim AS. The common neural basis of autobiographical memory, prospection, navigation, theory of mind, and the default mode: a quantitative meta-analysis. *J Cogn Neurosci*. 2009;21(3):489–510.
18. Popa D, Popescu AT, Paré D. Contrasting activity profile of two distributed cortical networks as a function of attentional demands. *J Neurosci*. 2009;29(4):1191–201.
19. Horowitz SG, Fukunaga M, de Zwart JA, van Gelderen P, Fulton SC, Balkin TJ, et al. Low frequency BOLD fluctuations during resting wakefulness and light sleep: a simultaneous EEG-fMRI study. *Hum Brain Mapp*. 2008;29(6):671–82.
20. Greicius MD, Kiviniemi V, Tervonen O, Vainionpää V, Alahuhta S, Reiss AL, et al. Persistent default-mode network connectivity during light sedation. *Hum Brain Mapp*. 2008;29(7): 839–47.
21. Vincent JL, Patel GH, Fox MD, Snyder AZ, Baker JT, Van Essen DC, et al. Intrinsic functional architecture in the anaesthetized monkey brain. *Nature*. 2007;447(7140):83–6.
22. Shirer WR, Ryali S, Rykhlevskaia E, Menon V, Greicius MD. Decoding subject-driven cognitive states with whole-brain connectivity patterns. *Cereb Cortex*. 2012;22(1):158–65.
23. Beckmann CF, DeLuca M, Devlin JT, Smith SM. Investigations into resting-state connectivity using independent component analysis. *Philos Trans R Soc Lond B Biol Sci*. 2005;360(1457): 1001–13.
24. Cauda F, Miconi BM, Sacco K, Duca S, D’Agata F, Geminiani G, et al. Disrupted intrinsic functional connectivity in the vegetative state. *J Neurol Neurosurg Psychiatry*. 2009;80(4): 429–31.
25. Boly M, Tshibanda L, Vanhauzenhuyse A, Noirhomme Q, Schnakers C, Ledoux D, et al. Functional connectivity in the default network during resting state is preserved in a vegetative but not in a brain dead patient. *Hum Brain Mapp*. 2009;30(8):2393–400.
26. Soddu A, Vanhauzenhuyse A, Bahri MA, Bruno MA, Boly M, Demertzi A, et al. Identifying the default-mode component in spatial IC analyses of patients with disorders of consciousness. *Hum Brain Mapp*. 2012;33(4):778–96.
27. Demertzi A, Gómez F, Crone JS, Vanhauzenhuyse A, Tshibanda L, Noirhomme Q, et al. Multiple fMRI system-level baseline connectivity is disrupted in patients with consciousness alterations. *Cortex*. 2014;52:35–46.
28. Hannawi Y, Lindquist MA, Caffo BS, Sair HI, Stevens RD. Resting brain activity in disorders of consciousness: a systematic review and meta-analysis. *Neurology*. 2015;84(12):1272–80.
29. Roquet D, Foucher JR, Froehlich P, Renard F, Pottecher J, Besancenot H, et al. Resting-state networks distinguish locked-in from vegetative state patients. *Neuroimage Clin*. 2016;12:16–22.
30. Vanhauzenhuyse A, Noirhomme Q, Tshibanda LJ, Bruno MA, Boveroux P, Schnakers C, et al. Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients. *Brain*. 2010;133(Pt 1):161–71.
31. Rosazza C, Andronache A, Sattin D, Bruzzone MG, Marotta G, Nigri A, et al. Multimodal study of default-mode network integrity in disorders of consciousness. *Ann Neurol*. 2016;79(5):841–853.
32. Fernández-Espejo D, Soddu A, Cruse D, Palacios EM, Junque C, Vanhauzenhuyse A, et al. A role for the default mode network in the bases of disorders of consciousness. *Ann Neurol*. 2012;72(3):335–43.
33. Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. *Arch Phys Med Rehabil*. 2004;85(12):2020–9.
34. Norton L, Hutchison RM, Young GB, Lee DH, Sharpe MD, Mirsattari SM. Disruptions of functional connectivity in the default mode network of comatose patients. *Neurology*. 2012;78(3):175–81.
35. Qin P, Wu X, Huang Z, Duncan NW, Tang W, Wolff A, et al. How are different neural networks related to consciousness? *Ann Neurol*. 2015;78(4):594–605.
36. Crone JS, Ladurner G, Holler Y, Golaszewski S, Trinka E, Kronbichler M. Deactivation of the default mode network as a marker of impaired consciousness: an fMRI study. *PLoS One*. 2011;6(10):e26373.

37. Demertzi A, Antonopoulos G, Heine L, Voss HU, Crone JS, de Los Angeles C, et al. Intrinsic functional connectivity differentiates minimally conscious from unresponsive patients. *Brain*. 2015;138:2619–31.
38. Bondy JA, Murty USR. *Graph theory with applications*. London: Macmillan; 1976.
39. Achard S, Salvador R, Whitcher B, Suckling J, Bullmore E. A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. *J Neurosci*. 2006;26(1):63–72.
40. Salvador R, Suckling J, Coleman MR, Pickard JD, Menon D, Bullmore E. Neurophysiological architecture of functional magnetic resonance images of human brain. *Cereb Cortex*. 2005;15(9):1332–42.
41. Achard S, Bullmore E. Efficiency and cost of economical brain functional networks. *PLoS Comput Biol*. 2007;3(2):e17.
42. Honey CJ, Sporns O. Dynamical consequences of lesions in cortical networks. *Hum Brain Mapp*. 2008;29(7):802–9.
43. Achard S, Delon-Martin C, Vertes PE, Renard F, Schenck M, Schneider F, et al. Hubs of brain functional networks are radically reorganized in comatose patients. *Proc Natl Acad Sci U S A*. 2012;109:20608–13.
44. Crone JS, Soddu A, Holler Y, Vanhaudenhuyse A, Schurz M, Bergmann J, et al. Altered network properties of the fronto-parietal network and the thalamus in impaired consciousness. *Neuroimage Clin*. 2013;4:240–8.
45. Liu X, Ward BD, Binder JR, Li SJ, Hudetz AG. Scale-free functional connectivity of the brain is maintained in anesthetized healthy participants but not in patients with unresponsive wakefulness syndrome. *PLoS One*. 2014;9(3):e92182.
46. Friston KJ, Kahan J, Biswal B, Razi A. A DCM for resting state fMRI. *Neuroimage*. 2014;94:396–407.
47. Crone JS, Schurz M, Höller Y, Bergmann J, Monti M, Schmid E, et al. Impaired consciousness is linked to changes in effective connectivity of the posterior cingulate cortex within the default mode network. *Neuroimage*. 2015;110:101–9.
48. Laureys S, Faymonville ME, Luxen A, Lamy M, Franck G, Maquet P. Restoration of thalamo-cortical connectivity after recovery from persistent vegetative state. *Lancet*. 2000;355(9217):1790–1.
49. Baker R, Gent TC, Yang Q, Parker S, Vyssotski AL, Wisden W, et al. Altered activity in the central medial thalamus precedes changes in the neocortex during transitions into both sleep and propofol anesthesia. *J Neurosci*. 2014;34(40):13326–35.
50. Panagiotaropoulos TI, Kapoor V, Logothetis NK. Subjective visual perception: from local processing to emergent phenomena of brain activity. *Philos Trans R Soc Lond B Biol Sci*. 2014;369(1641):20130534.
51. Dehaene S, Changeux JP, Naccache L, Sackur J, Sergent C. Conscious, preconscious, and subliminal processing: a testable taxonomy. *Trends Cogn Sci*. 2006;10(5):204–11.
52. Dehaene S, Naccache L. Towards a cognitive neuroscience of consciousness: basic evidence and a workspace framework. *Cognition*. 2001;79(1–2):1–37.
53. Dehaene S, Naccache L, Cohen L, Bihan DL, Mangin JF, Poline JB, et al. Cerebral mechanisms of word masking and unconscious repetition priming. *Nat Neurosci*. 2001;4(7):752–8.
54. Lutkenhoff ES, Chiang J, Tshibanda L, Kamau E, Kirsch M, Pickard JD, et al. Thalamic and extrathalamic mechanisms of consciousness after severe brain injury. *Ann Neurol*. 2015;78:68–76.
55. Monti MM, Lutkenhoff ES, Rubinov M, Boveroux P, Vanhaudenhuyse A, Gosseries O, et al. Dynamic change of global and local information processing in propofol-induced loss and recovery of consciousness. *PLoS Comput Biol*. 2013;9(10):e1003271.
56. Boly M, Perlberg V, Marrelec G, Schabus M, Laureys S, Doyon J, et al. Hierarchical clustering of brain activity during human nonrapid eye movement sleep. *Proc Natl Acad Sci U S A*. 2012;109(15):5856–61.

57. Silva A, Cardoso-Cruz H, Silva F, Galhardo V, Antunes L. Comparison of anesthetic depth indexes based on thalamocortical local field potentials in rats. *Anesthesiology*. 2010;112(2):355–63.
58. Mhuircheartaigh RN, Rosenorn-Lanng D, Wise R, Jbabdi S, Rogers R, Tracey I. Cortical and subcortical connectivity changes during decreasing levels of consciousness in humans: a functional magnetic resonance imaging study using propofol. *J Neurosci*. 2010;30(27):9095–102.
59. Fuller PM, 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):933–56.
60. Schiff ND. Recovery of consciousness after brain injury: a mesocircuit hypothesis. *Trends Neurosci*. 2010;33(1):1–9.
61. Leech R, Sharp DJ. The role of the posterior cingulate cortex in cognition and disease. *Brain*. 2014;137(Pt 1):12–32.
62. van den Heuvel MP, Sporns O. Rich-club organization of the human connectome. *J Neurosci*. 2011;31(44):15775–86.
63. Leech R, Braga R, Sharp DJ. Echoes of the brain within the posterior cingulate cortex. *J Neurosci*. 2012;32(1):215–22.
64. Leech R, Kamourieh S, Beckmann CF, Sharp DJ. Fractionating the default mode network: distinct contributions of the ventral and dorsal posterior cingulate cortex to cognitive control. *J Neurosci*. 2011;31(9):3217–24.
65. Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Wedeen VJ, et al. Mapping the structural core of human cerebral cortex. *PLoS Biol*. 2008;6(7):e159.
66. Honey CJ, Sporns O, Cammoun L, Gigandet X, Thiran JP, Meuli R, et al. Predicting human resting-state functional connectivity from structural connectivity. *Proc Natl Acad Sci U S A*. 2009;106(6):2035–40.
67. Deshpande G, Santhanam P, Hu X. Instantaneous and causal connectivity in resting state brain networks derived from functional MRI data. *Neuroimage*. 2011;54(2):1043–52.
68. Yan C, He Y. Driving and driven architectures of directed small-world human brain functional networks. *PLoS One*. 2011;6(8):e23460.
69. Crone JS, Soddu A, Höller Y, Vanhaudenhuyse A, Schurz M, Bergmann J, et al. Altered network properties of the fronto-parietal network and the thalamus in impaired consciousness. *Neuroimage Clin*. 2014;4:240–8.
70. Fernández-Espejo D, Junque C, Cruse D, Bernabeu M, Roig-Rovira T, Fábregas N, et al. Combination of diffusion tensor and functional magnetic resonance imaging during recovery from the vegetative state. *BMC Neurol*. 2010;10:77.
71. Koch C, Massimini M, Boly M, Tononi G. Neural correlates of consciousness: progress and problems. *Nat Rev Neurosci*. 2016;17(5):307–21.
72. Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage*. 2012;59(3):2142–54.
73. Power JD, Cohen AL, Nelson SM, Wig GS, Barnes KA, Church JA, et al. Functional network organization of the human brain. *Neuron*. 2011;72(4):665–78.
74. Satterthwaite TD, Wolf DH, Loughead J, Ruparel K, Elliott MA, Hakonarson H, et al. Impact of in-scanner head motion on multiple measures of functional connectivity: relevance for studies of neurodevelopment in youth. *Neuroimage*. 2012;60(1):623–32.
75. Van Dijk KR, Sabuncu MR, Buckner RL. The influence of head motion on intrinsic functional connectivity MRI. *Neuroimage*. 2012;59(1):431–8.
76. Power JD, Schlaggar BL, Petersen SE. Recent progress and outstanding issues in motion correction in resting state fMRI. *Neuroimage*. 2015;105:536–51.
77. Andersen SM, Rapcsak SZ, Beeson PM. Cost function masking during normalization of brains with focal lesions: still a necessity? *Neuroimage*. 2010;53(1):78–84.
78. Ashburner J, Friston KJ. Unified segmentation. *Neuroimage*. 2005;26(3):839–51.

79. Crinion J, Ashburner J, Leff A, Brett M, Price C, Friston K. Spatial normalization of lesioned brains: performance evaluation and impact on fMRI analyses. *Neuroimage*. 2007;37(3):866–75.
80. Brett M, Leff AP, Rorden C, Ashburner J. Spatial normalization of brain images with focal lesions using cost function masking. *Neuroimage*. 2001;14(2):486–500.
81. MacVicar BA, Newman EA. Astrocyte regulation of blood flow in the brain. *Cold Spring Harb Perspect Biol*. 2015;7(5). pii: a020388.
82. Hall CN, Reynell C, Gesslein B, Hamilton NB, Mishra A, Sutherland BA, et al. Capillary pericytes regulate cerebral blood flow in health and disease. *Nature*. 2014;508(7494):55–60.
83. Alstott J, Breakspear M, Hagemann P, Cammoun L, Sporns O. Modeling the impact of lesions in the human brain. *PLoS Comput Biol*. 2009;5(6):e1000408.
84. Kim J, Horwitz B. How well does structural equation modeling reveal abnormal brain anatomical connections? An fMRI simulation study. *Neuroimage*. 2009;45(4):1190–8.
85. Aru J, Bachmann T, Singer W, Melloni L. Distilling the neural correlates of consciousness. *Neurosci Biobehav Rev*. 2012;36(2):737–46.
86. de Graaf TA, Hsieh PJ, Sack AT. The ‘correlates’ in neural correlates of consciousness. *Neurosci Biobehav Rev*. 2012;36(1):191–7.