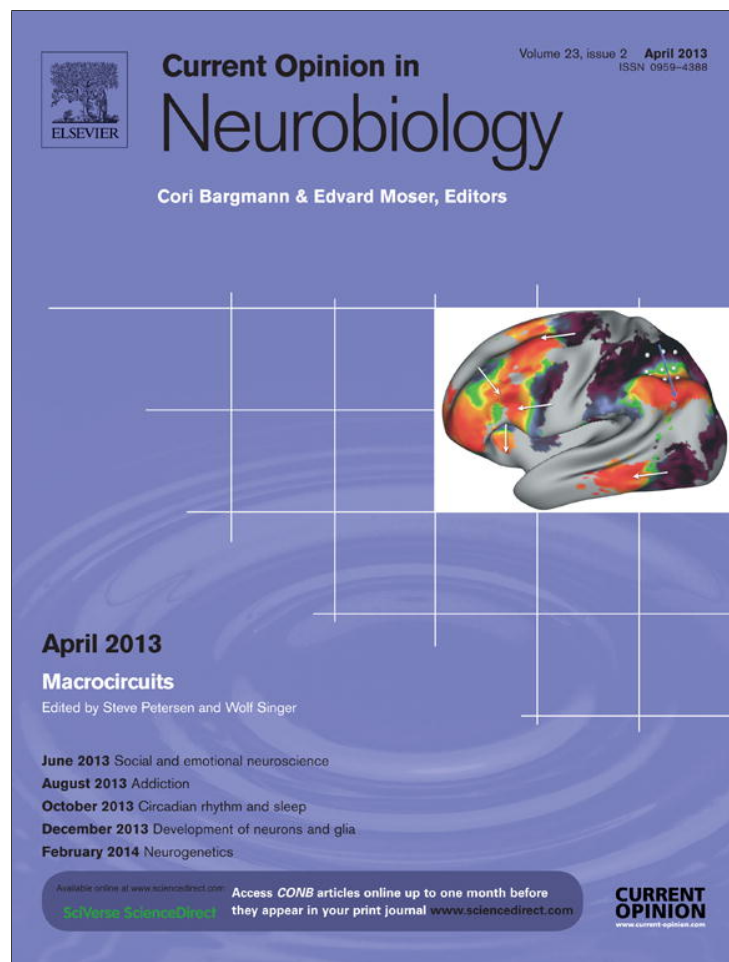


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Consciousness supporting networks

Athena Demertzi, Andrea Soddu and Steven Laureys

Functional neuroimaging shows that patients with disorders of consciousness exhibit disrupted system-level functional connectivity. Unresponsive/"vegetative state" patients preserve wakefulness networks of brainstem and basal forebrain but the cerebral networks accounting for external perceptual awareness and internal self-related mentation are disrupted. Specifically, the 'external awareness' network encompassing lateral fronto-temporo-parietal cortices bilaterally, and the 'internal awareness' network including midline anterior cingulate/mesiofrontal and posterior cingulate/precuneal cortices, are functionally disconnected. By contrast, patients in minimally conscious state 'minus', who show non-reflex behaviors, are characterized by right-lateralized recovery of the external awareness network. Similarly, patients who evolve to minimally conscious state 'plus' and respond to commands recover the dominant left-lateralized language network. Now, the use of active experimental paradigms targeting at detecting motor-independent signs of awareness or even establishing communication with these patients, challenge these two clinical boundaries. Such advances are naturally accompanied by legitimate neuroscientific and ethical queries demanding our attention on the medical implementations of this new knowledge.

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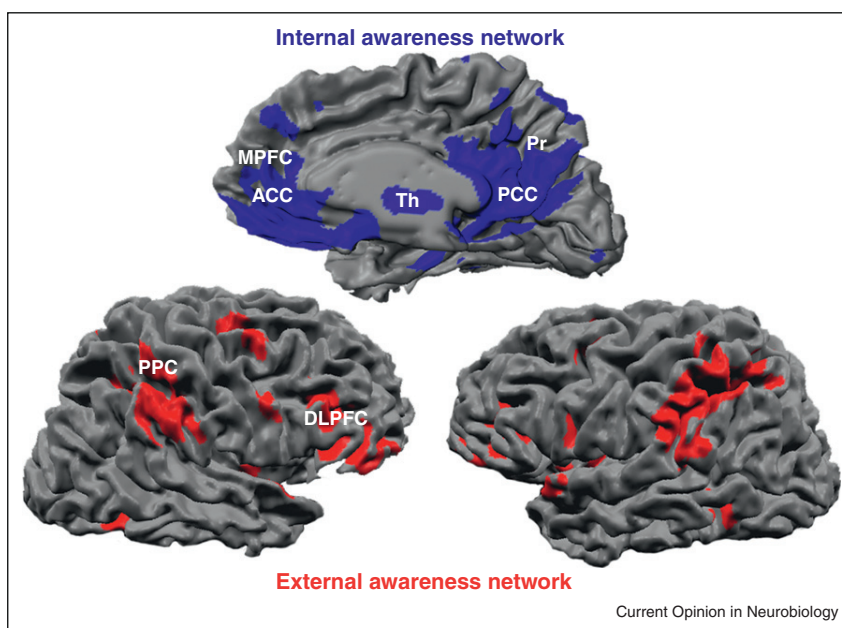
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What is 'minimally conscious'?

At present there is no generally accepted definition of consciousness [1]. As clinicians, we will reduce the complexity of this term and define consciousness operationally, separating two main components: wakefulness and awareness [2]. Wakefulness has been shown to critically depend upon the functional integrity of subcortical arousal systems over 50 years ago [(e.g., see 3)]. The level of wakefulness can be estimated by simple behavioral criteria based on eye opening ranging from absent, over stimulus-induced to spontaneous sustained eye opening.

For instance, every night when falling asleep, we experience a decrease of the level of wakefulness up to the point we lose awareness of our environment. Awareness is more difficult to define and more challenging to assess behaviorally [4]. We have recently proposed to reduce the phenomenological complexity of awareness into two further components: *external* awareness, namely everything we perceive through our senses (what we see, hear, feel, smell and taste), and *internal* awareness or stimulus-independent thoughts. Interestingly, the switch between the external and internal milieu was found not only to characterize overt behavioral reports but also had a cerebral correlate [5]. In particular, it was shown that behavioral reports of internal awareness were linked to the activity of midline anterior cingulate/mesiofrontal areas as well as posterior cingulate/precuneal cortices. Conversely, subjective ratings for external awareness seem to correlate with the activity of lateral fronto-parieto-temporal regions (Figure 1). These findings highlight that the anticorrelated pattern between the internal and external awareness system is of functional relevance to conscious cognition. Indeed, in an altered conscious state like hypnosis, where subjects report awareness alterations but remain fully responsive, hypnosis-related reductions in functional connectivity were shown in the external awareness system parallel to subjective ratings of increased sense of dissociation from the environment and reduced intensity of external thoughts [6]. Similar reductions in external awareness systems have been also shown for non-responsive conditions, such as deep sleep and anesthesia [(for a review see 7)]. Taken together these studies indicate that the two awareness networks mediate (at least partially) conscious ongoing mentation under the functions of a wide 'global neuronal workspace' [1,8]. An increasing list of evidence favors this hypothesis. Studies in healthy volunteers on perception in the visual, somatosensory and auditory domains confirm that the subtraction between perceived and unperceived stimuli identifies the lateral frontoparietal associative cortices [8].

Over the past fifteen years we have increased our understanding of the neural correlates of awareness [9]. The study of patients with disorders of consciousness provides unique opportunities to determine the sufficient and possibly the necessary conditions for conscious cognition to happen. Patients in coma are unconscious because, by definition, they cannot be awakened even when intensely stimulated. Patients will not remain in coma for months or years in contrast to what is sometimes reported in the media [10]. In a number of cases, patients will show such a massive brain damage that all brainstem function will be irreversibly lost and evolve to brain death [11]. Those

Figure 1

An oversimplified distinction of human awareness into awareness of the environment and of self-related mentation. Experimental works suggests that these two components have two distinct functionally alternating cerebral correlates. The external awareness network (areas in red) encompasses mainly lateral bilateral dorsolateral prefrontal cortices (DLPFC) and posterior parietal cortices (PPC). The internal awareness network (areas in blue) includes mainly midline posterior cingulate cortex (PCC)/precuneus (Pr) and anterior cingulate (ACC)/medial prefrontal cortices (MPFC). Apart from cortico-cortical connectivity, connectivity with subcortical structures, such as with the thalamus (Th) is considered to be essential to support wakefulness and ongoing conscious processing.

patients who will show a good recovery after coma classically will do so within the first days or weeks after the insult. A substantial fraction of coma patients will recover near-normal function of the subcortical 'wakefulness network' (located in the brainstem) while remaining without external signs of awareness. This condition of eyes-open wakefulness was coined 'persistent vegetative state' in the 1970s [12] and more recently it has been described in more neutral descriptive terms as 'unresponsive wakefulness syndrome' [13]. Vegetative/unresponsive (VS/UWS) patients classically breathe spontaneously and can make a wider range of movements than can be seen in coma. Depending on the partial or full recovery of subcortical wakefulness networks and brainstem function they can show spontaneous or stimulus-induced eye opening, blinking to visual threat; have auditory startle responses or orient the eyes or head to stimuli; show stereotyped posturing, normal flexion withdrawal to noxious stimulation or grasping; show gag, deglutition, oral reflexes or vocalizations. For clinicians dealing with acute or chronic disorders of consciousness, the main challenge is to disentangle these 'reflex' or automatic movements from any 'voluntary' or 'willed' behavior. The recovery of minimal, inconsistent but reproducible signs of awareness, in the absence of functional communication or object use, coins the diagnosis of minimally conscious state (MCS).

Depending on the complexity of these behaviors it was recently proposed that MCS patients be categorized as MCS– when only showing simple non-reflex movements, such as visual pursuit, orientation to pain or non-contingent behavior (e.g. smiling to the presence of a family member and not to others) and MCS+ when patients recover the ability to respond to simple commands (e.g. move your hand) [14,15].

It is important to stress that when aiming to say meaningful things about patients' consciousness, we are limited to make inferences based on patients' motor behavior [16]. Most of the time this works fine but, as we will see in some cases, consciousness can be present in the absence of consistent motor responsiveness.

Tracking the recovery of consciousness networks

With the advent of functional neuroimaging (functional MRI and PET) and electrophysiology (EEG and event related potentials) the study of residual brain function in patients with consciousness alterations has provided unique insights on the underlying brain mechanisms accounting for the presence of consciousness [17]. Based on this lesion paradigm, it is thought that consciousness does not require the whole brain's activity, but rather that

some areas are more critical than others to support consciousness. FDG-PET studies have demonstrated that when patients recover from coma to VS/UWS, they recover the wakefulness network (encompassing brainstem and basal forebrain) which explains the restoration of sustained spontaneous or stimulus-induced eye opening and of autonomic functions including spontaneous breathing [18]. However, recovery from VS/UWS does not coincide with near-normal metabolic activity in overall brain function. Voxel-based analyses between brain metabolic scans obtained in awake yet unaware VS/UWS patients compared to healthy controls (between-subject) or comparisons with recovery of awareness (within-subject) have highlighted the critical role of the widespread fronto-temporo-parietal associative cortical network [19]. Recently, FDG-PET data indicate that recovery of MCS-patients seems to be accompanied by a right-lateralized recovery of the external awareness network whereas the presence of command following, defining MCS+, classically parallels the recovery of the dominant left-lateralized language network [20]. Similar results have been observed in slow wave sleep and general anesthesia [(for review see 21)]. Interestingly, these findings were also confirmed in transient dissociative states of unresponsive wakefulness such as absence seizures, complex partial seizures or sleepwalking – all characterized by preserved automatic reflex motor behavior in the absence of response to commands and showing transient impaired activity in the fronto-temporo-parietal associative cortical network [2,22].

The study of coma and related states has shown that consciousness is not an emergent property of sensory cortical activation in isolation. Auditory stimulation with simple clicks in MCS patients activated widespread temporal auditory areas and most importantly lead to functional connectivity changes with the external awareness network [23]. Similar activation and connectivity changes were observed in normal conscious controls but not in VS/UWS patients where activation was limited to isolated low-level auditory cortices, functionally disconnected from the external awareness network [24]. By contrast, emotionally salient stimuli, such as baby cries and the patient's own name, led to much more widespread temporal activation also recruiting anterior and posterior midline cortices [25,26]. Similarly, in MCS patients, presentation of a story told by their mother led to more widespread activation [27]. Novel technological developments now permit to assess the directionality of this long-range cortico-cortical connectivity. Using dynamic causal modeling on auditory oddball evoked potential data obtained with high-density EEG, it was shown that only MCS patients (but not VS/UWS patients) showed feedback or top-down connections from higher-order frontal associative areas to hierarchically lower-level auditory regions [28]. A study combining transcranial magnetic stimulation with simultaneously recorded

EEG confirmed the importance of long-range connectivity from the posterior parietal associative cortex. Only MCS and not VS/UWS patients showed such long-range connectivity changes. This technique also permitted to longitudinally follow connectivity changes in patients who recovered (or failed to recover) from VS/UWS [29]. These early functional connectivity studies highlight the importance of connectivity measurements in the emergence of human conscious awareness. In particular, global yet specific cerebral functional identification of thalamo-cortical connectivity has led to the development of thalamic deep brain stimulation paradigms for the treatment of post-traumatic MCS patients [30].

Within 'global workspace', the posterior midline regions encompassing precuneus and adjacent posterior cingulate cortex seem to form a critical hub. Indeed, these areas are the most metabolically active cortical regions in normal conscious waking, are mostly impaired in patients in coma or VS/UWS whereas they are minimally active in MCS patients. Its critical role in consciousness was confirmed by a much mediatized case of 'miracle recovery from coma' named Terry Wallis [30]. Nineteen years after his traumatic brain injury this patient was still considered 'vegetative' and started to speak. When carefully examining the patient's medical files it became clear he was in a MCS already months after the trauma. Using MRI and diffusion tensor imaging in Mr. Wallis, Schiff and collaborators reported axonal regrowth, nearly two decades after the acute insult, in the aforementioned posterior midline structures [31]. This case not only illustrates the problem of misdiagnosing disorders of consciousness if merely based on behavioral unstandardized tools [32] but also the possibility of neural plasticity even many years after the acute insult [33]. More recent fMRI studies have confirmed these findings and demonstrated a consciousness-dependent non-linear breakdown in functional connectivity of the so-called default mode 'midline core' network when comparing normal consciousness to MCS, VS/UWS and comatose states [34].

Conclusions

Studying VS/UWS patients has shown that awareness seems an emergent property of collective critical cortico-thalamo-cortical network dynamics, involving the frontoparietal global workspace [35]. At the moment, it remains controversial whether consciousness should be considered as a binary all-or-none phenomenon or continuous [36]. Based on clinical experience and on recent evidence from careful studies in normal healthy volunteers [(e.g., 37)] we here consider consciousness on a continuous non-linear scale.

Despite the best clinical assessment, we are still limited to make inferences about consciousness based on motor responsiveness, possibly leading to an underestimation of conscious awareness. Recently, the so-called 'active'

functional neuroimaging or event-related potential paradigms have been developed to assess motor-independent responses to commands. The first of such 'active' mental imagery paradigms have been developed using fMRI. In a collaborative effort between Cambridge and Liège, healthy volunteers were asked to perform a series of tasks (e.g., imagine singing a song in your head or imagine your mother's face). The most robust and reproducible patterns of brain activation were obtained using motor imagery (i.e., imagine playing tennis) and spatial navigation (i.e., imagine walking around in your house), leading to the predicted activation of supplementary motor cortex and parahippocampal areas respectively [38]. Using this tool, both teams together with Cornell University, have identified a series of severely brain damaged patients who were clinically diagnosed as being VS/UWS or MCS- and who yet showed robust fMRI evidence of response to command, and consequently conscious awareness [39,40,41]. In one of these cases, functional communication could even be established by explaining to the patient to do the motor imagery task to communicate 'yes' and the spatial navigation task to communicate 'no'. This patient, a 22-year-old man who was sent to Liège for a one-week diagnostic assessment, is another example of clinical misdiagnosis. Indeed, this patient had the clinical diagnosis of VS/UWS while standardized behavioral assessments showed that he was actually in a MCS [40]. To a series of simple questions (e.g., is your father's name Alexander) the automated user-independent analysis of the acquired fMRI data classified the brain's responses as a 'yes' or 'no' answer. Correct answers were obtained and reported by the blinded examiners for five consecutive questions. Only for the last question no answer could be elicited merely caused by absent brain activation. As a consequence, this patient could be considered as being in a *functional locked-in syndrome*, given it was only functional neuroimaging that permitted to establish the yes–no communication to closed questions (in contrast to *classical locked-in syndrome* where an eye-coded yes–no communication can be established) [15].

Evidently, the study by Monti *et al.* [40] should be seen as a proof of concept rather than a practical communication tool. As soon as the patient was taken out of the MRI machine, no communication whatsoever was possible. Hence, portable and cheaper EEG-based equivalents [e.g., 42, 43, 44] have been developed for more routine clinical use [(for recent review see 45)]. Such *brain computer interfaces* (BCI) have already been used successfully in real clinical settings. It is important to stress that the absence of brain activation to commands cannot be taken as proof of absence of consciousness and frequently false negative results have been reported in MCS+ patients [e.g., 44]. Repeated fMRI and EEG BCI assessments would be needed to increase the confidence for true negative findings. In addition, we also need to tackle the problem of false positives, namely the fact that unconscious patients

may show artifact or noise-related activation [46]. Future studies should deal with these issues in large patient cohort and also assess test–retest variability of these novel technologies in this specific context.

In conclusion, our clinical boundaries are increasingly being challenged by neuroimaging or electrophysiology studies in patients with disorders of consciousness who show motor-independent signs of awareness or communication. Such advances are naturally accompanied by legitimate neuroscientific and ethical queries, such as on pain perception and management as well as end-of-life options [47–50]. In the future, efforts should be made towards *consciousness classification* metrics, where system-level functional neuroimaging and electrophysiology will provide an objective means to better characterize the underlying mechanisms accounting for conscious cognition and its recovery after severe acquired brain injury.

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References and recommended reading

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

- of special interest
 - of outstanding interest
1. Baars B, Ramsay TZ, Laureys S: **Brain, conscious experience and the observing self.** *Trends Neurosci* 2003, **12**:671–675.
 2. Laureys S: **The neural correlate of (un)awareness: lessons from the vegetative state.** *Trends Cogn Sci* 2005, **12**:556–559.
 3. Damasio A, Meyer K: **Consciousness: an overview of the phenomenon and of its possible neural basis.** In *The Neurology of Consciousness: Cognitive Neuroscience and Neuropathology*. Edited by Laureys S, Tononi G. Oxford:UK: Academic Press; 2009: 3–14.
 4. Majerus S, Gill-Thwaites H, Andrews K, Laureys S: **Behavioral evaluation of consciousness in severe brain damage.** *Prog Brain Res* 2005, **150**:397–413.
 5. Vanhaudenhuyse A, Demertzi A, Schabus M, Noirhomme Q, Bredart S, Boly M, Phillips C, Soddu A, Luxen A, Moonen G *et al.*: **Two distinct neuronal networks mediate the awareness of environment and of self.** *J Cogn Neurosci* 2011, **3**:570–578. This study utilizes behavioral and neuroimaging techniques and shows the cognitive-behavioral counterpart of the external and internal awareness networks of the so-called 'resting state' condition.
 6. Demertzi A, Soddu A, Faymonville ME, Bahri MA, Gosseries O, Vanhaudenhuyse A, Phillips C, Maquet P, Noirhomme Q, Luxen A *et al.*: **Hypnotic modulation of resting state fMRI default mode and extrinsic network connectivity.** *Prog Brain Res* 2011, **193**:309–322.
 7. Heine L, Soddu A, Gomez F, Vanhaudenhuyse A, Tshibanda L, Thonnard M, Charland-Verville V, Kirsch M, Laureys S, Demertzi A: **Resting state networks and consciousness. Alterations of multiple resting state network connectivity in physiological, pharmacological and pathological consciousness states.** *Frontiers in Psychology* 2012, **3**:1–12.

8. Dehaene S, Changeux JP: **Experimental and theoretical approaches to conscious processing**. *Neuron* 2011, **2**:200-227.
9. Laureys S, Schiff ND: **Coma and consciousness: paradigms (re)framed by neuroimaging**. *Neuroimage* 2012, **2**:478-491.
10. Racine E, Amaram R, Seidler M, Karczewska M, Illes J: **Media coverage of the persistent vegetative state and end-of-life decision-making**. *Neurology* 2008, **13**:1027-1032.
11. Laureys S: **Science and society: death, unconsciousness and the brain**. *Nat Rev Neurosci* 2005, **11**:899-909.
12. Jennett B, Plum F: **Persistent vegetative state after brain damage. A syndrome in search of a name**. *Lancet* 1972, **7753**:734-737.
13. Laureys S, Celesia GG, Cohadon F, Lavrijnsen J, Leon-Carrion J, Sannita WG, Szabon L, Schmutzhard E, von Wild KR, Zeman A *et al.*: **Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome**. *BMC Med* 2010, **8**:68.
14. Gosseries O, Bruno MA, Chatelle C, Vanhauzenhuyse A, Schnakers C, Soddu A, Laureys S: **Disorders of consciousness: what's in a name?** *NeuroRehabilitation* 2011, **1**:3-14.
15. Bruno MA, Vanhauzenhuyse A, Thibaut A, Moonen G, Laureys S: **From unresponsive wakefulness to minimally conscious PLUS and functional locked-in syndromes: recent advances in our understanding of disorders of consciousness**. *J Neurol* 2011, **7**:1373-1384.
16. Sanders RD, Tononi G, Laureys S, Sleigh JW: **Unresponsiveness not equal unconsciousness**. *Anesthesiology* 2012, **4**:946-959.
17. Laureys S, Boly M: **The changing spectrum of coma**. *Nat Clin Pract Neurol* 2008, **10**:544-546.
18. Laureys S, Owen AM, Schiff ND: **Brain function in coma, vegetative state, and related disorders**. *Lancet Neurol* 2004, **9**:537-546.
19. Thibaut A, Bruno MA, Chatelle C, Gosseries O, Vanhauzenhuyse A, Demertzi A, Schnakers C, Thonnard M, Charland-Verville V, Bernard C *et al.*: **Metabolic activity in external and internal awareness networks in severely brain-damaged patients**. *J Rehabil Med* 2012, **5**:487-494.
- Here, PET scan group-level analysis shows that in MCS+ patients who can follow simple commands, the left hemisphere, encompassing the language network, is more metabolically active compared to MCS- patients who do not have the ability of command-following or language comprehension. This study illustrates the difficulty to quantify awareness in the presence of aphasia in patients with disorders of consciousness.
20. Bruno MA, Majerus S, Boly M, Vanhauzenhuyse A, Schnakers C, Gosseries O, Boveroux P, Kirsch M, Demertzi A, Bernard C *et al.*: **Functional neuroanatomy underlying the clinical subcategorization of minimally conscious state patients**. *J Neurol* 2012, **6**:1087-1098.
21. Boveroux P, Bonhomme V, Boly M, Vanhauzenhuyse A, Maquet P, Laureys S: **Brain function in physiologically, pharmacologically, and pathologically altered states of consciousness**. *Int Anesthesiol Clin* 2008, **3**:131-146.
22. Blumenfeld H: **Impaired Consciousness in Epilepsy**. *Lancet Neurol* 2012, in press.
23. Boly M, Faymonville ME, Peigneux P, Lambermont B, Damas P, Del Fiore G, Degueldre C, Franck G, Luxen A, Lamy M *et al.*: **Auditory processing in severely brain injured patients: differences between the minimally conscious state and the persistent vegetative state**. *Arch Neurol* 2004, **2**:233-238.
24. Laureys S, Faymonville ME, Degueldre C, Fiore GD, Damas P, Lambermont B, Janssens N, Aerts J, Franck G, Luxen A *et al.*: **Auditory processing in the vegetative state**. *Brain* 2000, **8**:1589-1601.
25. Laureys S, Perrin F, Faymonville M-E, Schnakers C, Boly M, Bartsch V, Majerus S, Moonen G, Maquet P: **Cerebral processing in the minimally conscious state**. *Neurology* 2004, **5**:916-918.
26. Di HB, Yu SM, Weng XC, Laureys S, Yu D, Li JQ, Qin PM, Zhu YH, Zhang SZ, Chen YZ: **Cerebral response to patient's own name in the vegetative and minimally conscious states**. *Neurology* 2007, **12**:895-899.
27. Bekinschtein TA, Leiguarda R, Armony J, Owen AM, Carpintero S, Niklison J, Olmos L, Sigman L, Manes FF: **Emotion processing in the minimally conscious state**. *J Neurol Neurosurg Psychiatry* 2004, **5**:788.
28. Boly M, Garrido MI, Gosseries O, Bruno MA, Boveroux P, Schnakers C, Massimini M, Litvak V, Laureys S, Friston K: **Preserved feedforward but impaired top-down processes in the vegetative state**. *Science* 2011, **6031**:858-862.
29. Rosanova M, Gosseries O, Casarotto S, Boly M, Casali AG, Bruno MA, ●● Mariotti M, Boveroux P, Tononi G, Laureys S *et al.*: **Recovery of cortical effective connectivity and recovery of consciousness in vegetative patients**. *Brain* 2012, **135**:1308-1320.
- This study uses transcranial magnetic stimulation (TMS) combined with high density EEG in patients with disorders of consciousness. It was shown that TMS pulses in VS/UWS patients elicit slow wave stereotypical EEG responses under the stimulated area. By contrast, MCS patients showed more complex EEG responses which were more widespread to large-distance and contralateral areas. Interestingly, longitudinal measurements in patients who gradually recovered consciousness revealed that such a clear-cut response change could occur at an early stage, before reliable communication could be established with the patient and before the spontaneous EEG showed significant modifications.
30. Schiff ND, Giacino JT, Kalmar K, Victor JD, Baker K, Gerber M, Fritz B, Eisenberg B, O'Connor J, Kobylarz EJ *et al.*: **Behavioural improvements with thalamic stimulation after severe traumatic brain injury**. *Nature* 2007, **7153**:600-603.
31. Voss HU, Ulug AM, Dyke JP, Watts R, Kobylarz EJ, McCandliss BD, Heier LA, Beattie BJ, Hamacher KA, Vallabhajosula S *et al.*: **Possible axonal regrowth in late recovery from the minimally conscious state**. *J Clin Invest* 2006, **7**:2005-2011.
32. Schnakers C, Vanhauzenhuyse A, Giacino JT, Ventura M, Boly M, Majerus S, Moonen G, Laureys S: **Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment**. *BMC Neurol* 2009:35.
33. Demertzi A, Schnakers C, Soddu A, Bruno M-A, Gosseries O, Vanhauzenhuyse A, Laureys S: **Neural plasticity lessons from disorders of consciousness**. *Front Psychol* 2011, **1**:1-7.
34. Vanhauzenhuyse A, Noirhomme Q, Tshibanda LJ, Bruno MA, Boveroux P, Schnakers C, Soddu A, Perlberg V, Ledoux D, Bricchant JF *et al.*: **Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients**. *Brain* 2010, **133(Pt 1)**:161-171.
35. Laureys S, Antoine S, Boly M, Elincx S, Faymonville ME, Berre J, Sadzot B, Ferring M, De Tieghe X, van Bogaert P *et al.*: **Brain function in the vegetative state**. *Acta Neurol Belg* 2002, **4**:177-185.
36. Seth AK, Dienes Z, Cleeremans A, Overgaard M, Pessoa L: **Measuring consciousness: relating behavioural and neurophysiological approaches**. *Trends Cogn Sci* 2008, **8**:314-321.
37. Sergent C, Dehaene S: **Is consciousness a gradual phenomenon? Evidence for an all-or-none bifurcation during the attentional blink**. *Psychol Sci* 2004, **11**:720-728.
38. Boly M, Coleman MR, Davis MH, Hampshire A, Bor D, Moonen G, Maquet PA, Pickard JD, Laureys S, Owen AM: **When thoughts become action: an fMRI paradigm to study volitional brain activity in non-communicative brain injured patients**. *Neuroimage* 2007, **3**:979-992.
39. Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard JD: **Detecting awareness in the vegetative state**. *Science* 2006, **5792**:1402.
40. Monti MM, Vanhauzenhuyse A, Coleman MR, Boly M, Pickard JD, ●● Tshibanda L, Owen AM, Laureys S: **Willful modulation of brain activity in disorders of consciousness**. *N Engl J Med* 2010, **7**:579-589.
- With this fMRI 'active paradigm', command following was probed in patients with disorders of consciousness by means of two validated mental imagery tasks. It was shown that of the 54 studied patients, 5 were able to willfully modulate their brain activity, two out of whom did not show any voluntary behavior at the bedside. One patient was further able to use this technique to answer 'yes' or 'no' to questions during functional MRI acquisitions.

244 **Macrocircuits**

41. Bardin JC, Fins JJ, Katz DI, Hersh J, Heier LA, Tabelow K, Dyke JP, Ballon DJ, Schiff ND, Voss HU: **Dissociations between behavioural and functional magnetic resonance imaging-based evaluations of cognitive function after brain injury.** *Brain* 2011, **134(Pt 3)**:769-782.
42. Cruse D, Chennu S, Chatelle C, Bekinschtein TA, Fernandez-Espejo D, Pickard JD, Laureys S, Owen AM: **Bedside detection of awareness in the vegetative state: a cohort study.** *Lancet* 2011, **9809**:2088-2094.
43. Lulé D, Noirhomme Q, Kleih SC, Chatelle C, Halder S, Demertzi A, Bruno M-A, Gosseries O, Vanhaudenhuyse A, Schnakers C, et al.: **Probing command following in patients with disorders of consciousness using a brain-computer interface.** *Clin Neurophysiol* 2012, in press.
44. Cruse D, Chennu S, Chatelle C, Fernandez-Espejo D, Bekinschtein TA, Pickard JD, Laureys S, Owen AM: **Relationship between etiology and covert cognition in the minimally conscious state.** *Neurology* 2012, **11**:816-822.
45. Chatelle C, Chennu S, Noirhomme Q, Cruse D, Owen AM, Laureys S: **Brain-computer interfacing in disorders of consciousness.** *Brain Inj* 2012, **26**:1510-1522.
46. Soddu A, Vanhaudenhuyse A, Demertzi A, Marie-Aurelie B, Tshibanda L, Di H, Melanie B, Papa M, Laureys S, Noirhomme Q: **Resting state activity in patients with disorders of consciousness.** *Funct Neurol* 2011, **1**:37-43.
47. Demertzi A, Ledoux D, Bruno M-A, Vanhaudenhuyse A, Gosseries O, Soddu A, Schnakers C, Moonen G, Laureys S: **Attitudes towards end-of-life issues in disorders of consciousness: a European survey.** *J Neurol* 2011, **6**:1058-1065.
48. Demertzi A, Racine E, Bruno MA, Ledoux D, Gosseries O, Vanhaudenhuyse A, Thonnard M, Soddu A, Moonen G, Laureys S: **Pain perception in disorders of consciousness: neuroscience, clinical care, and ethics in dialogue.** *Neuroethics* 2012:1-14.
49. Jox RJ, Bernat JL, Laureys S, Racine E: **Disorders of consciousness: responding to requests for novel diagnostic and therapeutic interventions.** *Lancet Neurol* 2012, **8**:732-738.
50. Kuehlmeier K, Borasio GD, Jox RJ: **How family caregivers' medical and moral assumptions influence decision making for patients in the vegetative state: a qualitative interview study.** *J Med Ethics* 2012, **38**:332-337.