Below is the unedited draft of the article that has been accepted for publication
(© Functional Neurology, 2014, V. 29, No 3, P. 201-205.)

Long-Lasting Coma

[1]Sergio Bagnato,* [1]Cristina Boccagni, [1]Antonino Sant'Angelo, [2]Alexander A. Fingelkurts, [2]Andrew A. Fingelkurts, [3]Cesare Gagliardo, and [1]Giuseppe Galardi.

[1] Unit of Neurophysiology and Unit for Severe Acquired Brain Injury, Rehabilitation Department, Fondazione Istituto San Raffaele G. Giglio, Cefalù (PA), Italy.
[2] BM-Science – Brain and Mind Technologies Research Centre, Espoo, Finland.
[3]Department of Medical and Forensic Biopathology and Biotechnologies, Section of Radiological Sciences, University of Palermo, Italy

Abstract

In this report, we describe a patient who has remained in a comatose state for more than one year after a traumatic and hypoxic brain injury. This state, which we refer to as long-lasting coma (LLC), may represent a disorder of consciousness with significantly different features from conventional coma, vegetative state, or brain death. On the basis of clinical, neurophysiological, and neuroimaging data, we hypothesize that a multi-level involvement of the ascending reticular activating system (ARAS) is required in LLC. This description may be useful for identification of other patients suffering from this severe disorder of consciousness and suggests important ethical implications.

Key words: ascending reticular activating system (ARAS); coma diagnosis; coma pathophysiology; coma prognosis; disorders of consciousness; vegetative state.

Introduction

Coma is usually a transient state that occurs as a result of a severe brain injury (Young, 2009). Generally, patients in a coma either progress to a full recovery of consciousness or die. A third and much less common mode of progression is the transition into unresponsive wakefulness syndrome (UWS, formerly known as vegetative state), a condition in which patients appear to be awake, but exhibit no signs of awareness of themselves or of their environment (Royal College of Physicians, 2003; Laureys et al., 2010). In accordance with these outcomes, persistence of a true comatose state four weeks after cerebral damage is considered to be very rare (Monti et al., 2010). Furthermore, in the past, the term "chronic coma" was used for patients who were more accurately classified as having UWS (Guérit, 1994). As a consequence, in the literature, no clinical, neurophysiological, or neuroimaging descriptions of patients in

a long-lasting coma (LLC) have been reported. In this report, we describe the case of a patient who persisted in a comatose state 14 months after the initial brain injury. We hope that this report will encourage a discussion about both the pathophysiological and ethical issues associated with this very rare clinical condition.

Case description and neurophysiological and neuroimaging data

A 46-year-old man with a history of epilepsy had an automobile accident that resulted in brain and thoracic trauma with cardio-respiratory arrest. He received advanced life support, recovered cardiopulmonary functions approximately 30 minutes after initiation of resuscitation, and subsequently was admitted to the intensive care unit (ICU) in a comatose state [Glasgow Coma Scale (GCS) 3]. A computed tomography scan showed a right brain parietal contusion, multiple facial and rib fractures, bilateral scapula fractures, and a fracture of the fourth lumbar vertebra. A brain magnetic resonance imaging (MRI) scan performed eight days after the injury revealed evidence of massive hypoxic damage associated with signs of traumatic brain injury (Fig. 1).

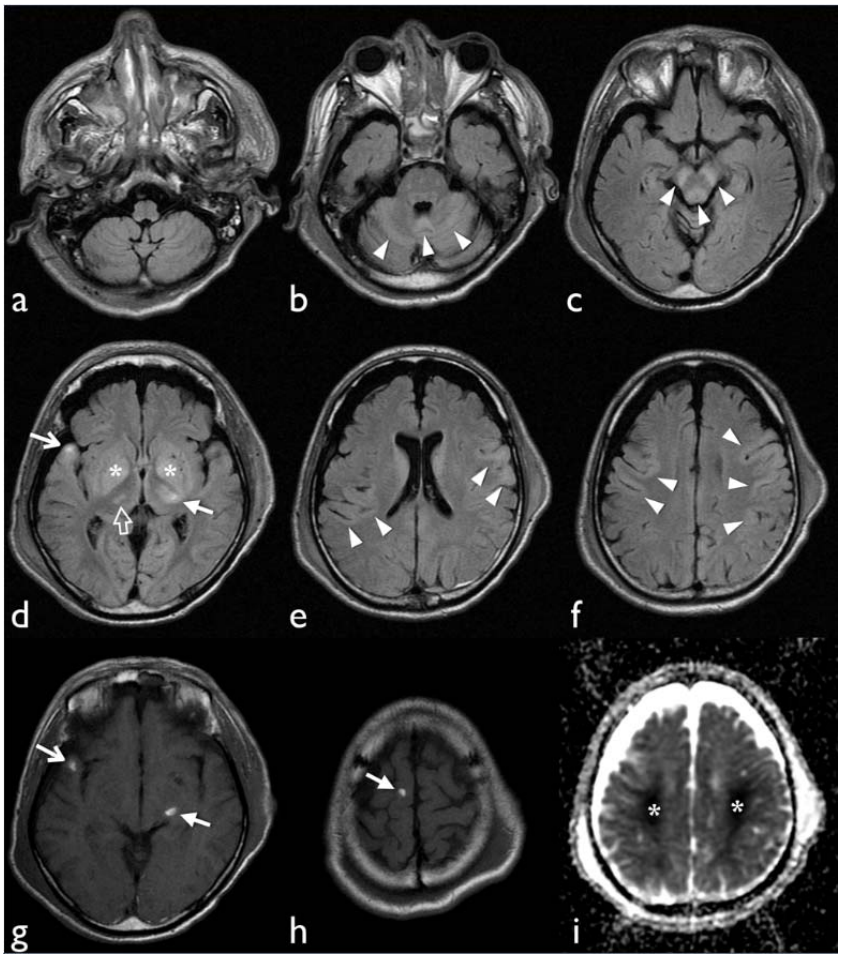

Figure 1. Brain MRI performed 8 days after the acute event. Axial T2-weighted fluid-attenuated inversion recovery (FLAIR-T2w) images of the medulla oblongata (a), pons (b), midbrain (c), basal ganglia (d), corona radiata (e), and centrum semiovale (f). Axial spin echo T1-weighted images of the diencephalon (g) and vertex (h). Axial apparent diffusion coefficient (ADC) map from a diffusion-

weighted imaging sequence acquired with b = 1000s/mm2 (i). Predominant cerebral hypoperfusion signs: bilateral hyperintense edematous white matter tracts and gyri with compressed sulci in FLAIR-T2w image (arrow head: b, c, e, f); hyperintense edematous globus pallidi in FLAIR-T2w image (asterisks: d) and deep white matter infarct within the watershed zone between anterior and middle cerebral artery territories showing restriction of diffusion in ADC maps (asterisks: i). The following signs of head trauma were evident: (1) a small hemorrhagic cerebral contusion involving the right superior temporal gyrus (arrow in d) with evidence of T1 shortening caused by extracellular methemoglobin (late subacute hemorrhage; arrow in g); (2) diffuse axonal injuries in the posterior arm of the left internal capsule (late subacute hemorrhagic lesions; full arrows in d and g) and at the vertex (h); (3) two small non-hemorrhagic shearing lesions in the right thalamus (empty arrow in d); (4) bilateral subdural fronto-temporal hygromas that were difficult to recognize in FLAIR-T2w images but clear in the ADC map; (5) edema of splanchnocranium' soft tissues with bleeding in the paranasal sinuses as an indirect sign of multiple fractures (a, b, c); and (6) extra-cranial subgaleal hematomas that were evident bilaterally (d, e, f, g, h, i).

After 41 days of hospitalization in the ICU, the patient was admitted to our Unit for Severe Acquired Brain Injuries (USABI), which specializes in rehabilitation of patients with post-acute disorders of consciousness. Over the following thirteen months of the patient's stay in USABI, he underwent daily neurological examinations performed by neurologists with expertise in evaluation of patients with disorders of consciousness (CB, AS). They documented the persistence of a comatose state without evidence of transition into UWS, according to the current diagnostic criteria (Royal College of Physicians, 2003). Neurological examination fourteen months after the initial brain injury showed the patient as GCS 4, with no brainstem reflexes, no respiratory trigger and a persistent need for respiratory support, and increased muscular tone and deep tendon reflexes. Brain death was ruled out by the ongoing presence of extensor posturing in the upper extremities after noxious stimulus presentation (Wijdicks et al., 2010). The patient's GCS score had been 3 until the third month after the brain injury, when it advanced to 4 (E1, V1, M2), and then no further changes occurred. The patient was also evaluated weekly with the Coma Recovery Scale Revised (CRS-R) instrument (Giacino et al., 2004), which is considered the better tool for the assessment of patients with disorders of consciousness (Seel et al., 2010). In the third month after the brain injury, the patient's CRS-R score was raised from 0 (where it had been since admission) to 1 when he exhibited abnormal posturing, changing his motor subscale score from 0 to 1. No further changes occurred thereafter. Monthly electroencephalographic (EEG) evaluations showed low amplitude (<20 μV) background activity, which was not reactive to opening of the eyes or to presentation of auditory or painful stimuli, and some epileptiform activity (Fig. 2). A 24-hour EEG recording was devoid of electrophysiological signs of sleep-wake cycles. An advanced quantitative EEG analysis based on operational architectonics (Fingelkurts et al., 2012a,b) will be reported in a separate article. The mismatch negativity evaluation, an event-related potential that is generated by the brain's automatic response to deviation of a physical stimulus from the preceding stimulus when repetitive auditory input is applied, revealed no responses either to frequent or deviant stimuli. Median nerve somatosensory evoked potentials (SEPs) showed no cortical or subcortical responses. Brainstem auditory evoked potentials (BEAPs) demonstrated a bilateral absence of all waves following the first one (i.e. II, III, IV, and V

waves). A blink reflex study confirmed brainstem involvement, showing a bilateral absence of R1 and R2 responses.

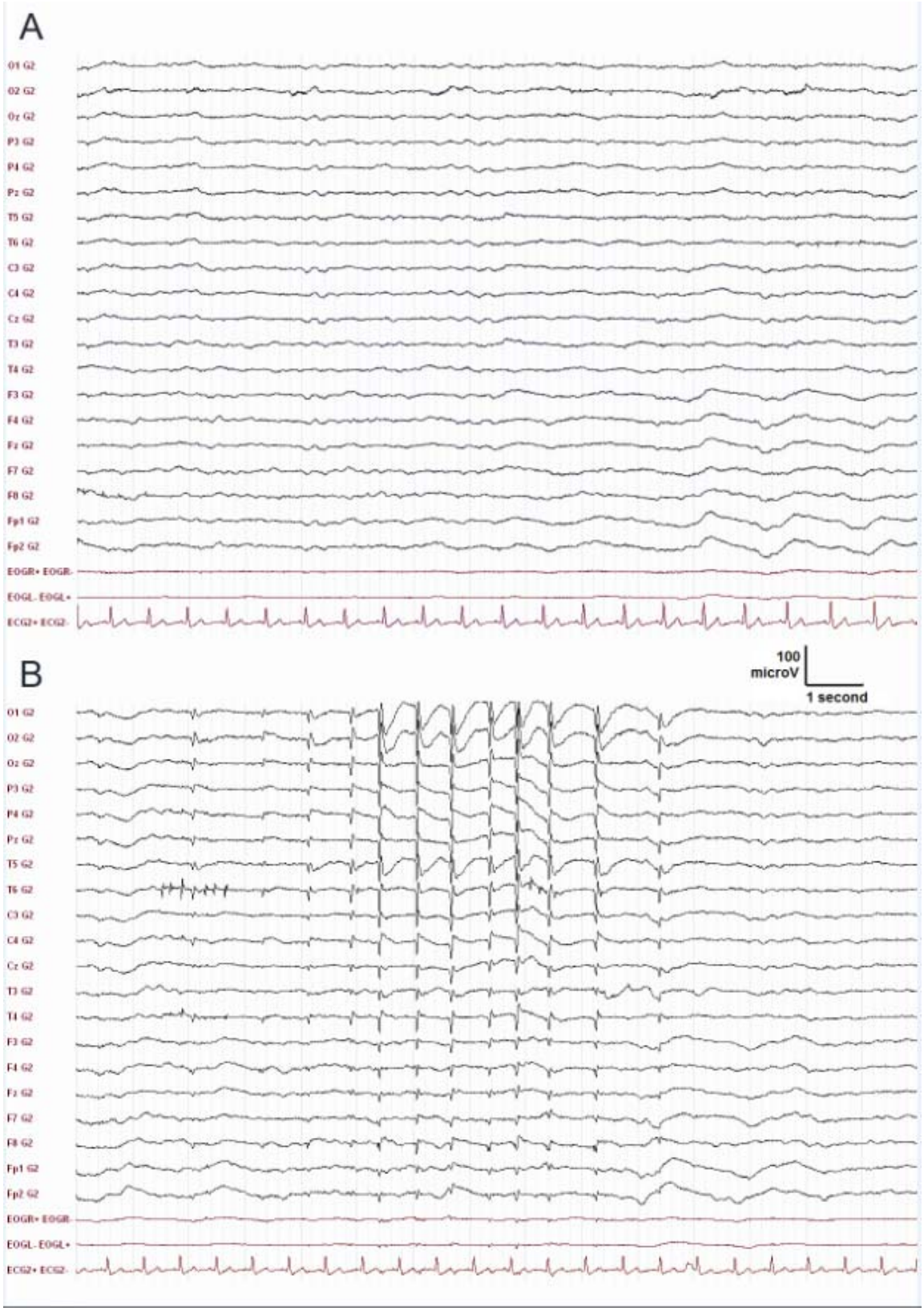

Figure 2. EEG results. A. EEG record revealing low amplitude (< 20 μV) background activity at 3-4 Hz (delta and theta bands). B. Epileptiform discharges with spikes and spike-waves associated with bilateral shoulder myoclonus. Intermittent epileptiform discharges and associated myoclonus were responsive to intravenous administration of benzodiazepines, without changes in the level of consciousness, suggesting

that the epileptiform activity was not affecting the patient's consciousness. At the time of the EEG recording, the patient was medicated with 2000 mg of levetiracetam per day. Both A and B are from an EEG recorded approximately nine months after the brain injury. Spontaneous electrical brain activity was recorded from 20 electrodes (O1, O2, Oz, P3, P4, Pz, T5, T6, C3, C4, Cz, T3, T4, F3, F4, Fz, F7, F8, Fp1, Fp2) placed in accordance with the International 10-20 System (band-pass, 0.5–70 Hz; sampling rate, 200 Hz). G2 is an arbitrary name for the common ear-linked reference. The impedance of the recording electrodes was monitored during data acquisition and was always below 5 kΩ. The last three channels (in red) show the horizontal and vertical electro-oculogram (EOGR and EORL, respectively) and the electrocardiogram (ECG). These channels have been added to reveal any ocular or electrocardiographic artifacts. Both pages in the figure encompass a recording period of 15 seconds.

Approximately four months after the brain injury, the patient underwent an 18F-fluorodeoxyglucose positron emission tomography study (FDG-PET) that revealed severe and widespread reduction in brain metabolism, with the exception of the anterior regions of the frontal lobes (Fig. 3).

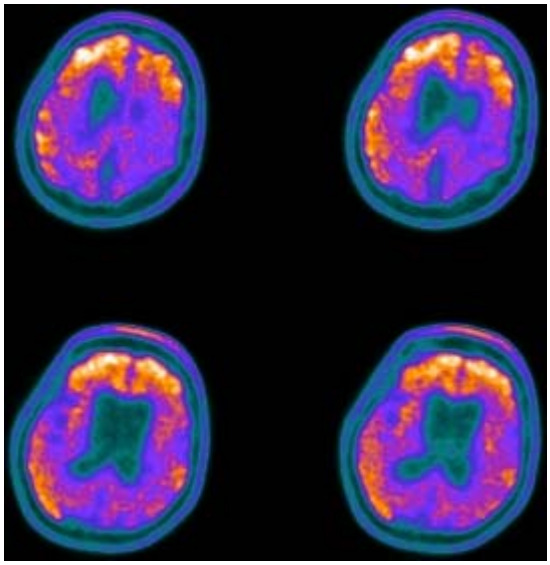

Figure 3. Brain glucose metabolism. Visual and statistical analysis of FDG-PET data revealed widespread and severe cerebral hypometabolism, with the exception of the anterior regions of both frontal lobes.

Written informed consent was obtained from the patient's legal guardian for all procedures, and the study was approved by the local ethical committee.

Discussion

Coma is traditionally defined as a condition of unarousable unconsciousness due to dysfunction of the brain's ascending reticular activating system (ARAS), which is responsible for arousal and maintenance of wakefulness (Young, 2009). The ARAS is composed of a complex and diffuse network of neurons projecting from multiple brainstem nuclei to the cortex, via thalamic and extrathalamic pathways. In

particular, ARAS brainstem nuclei project to the intralaminar nuclei in the thalamus, which in turn have diffuse activating efferents to the cerebral cortex (Edlow et al., 2012). Furthermore, ARAS nuclei project to the hypothalamus, integrating arousal with autonomic function and circadian rhythms (Morin, 2013), as well to the cholinergic neurons of the basal forebrain, contributing to cortical activation (Fuller et a., 2011).

It has recently been proposed that disconnection of specific brainstem arousal nuclei from the thalamus and basal forebrain induces traumatic coma (Edlow et al., 2013). The possibility of emerging from traumatic coma has its anatomical underpinnings in the redundancy of the ascending arousal control system, which suggests an adaptive mechanism for the recovery of consciousness when some components, but not the entire system, are clinically disrupted. The pathophysiology of hypoxic coma is less characterized and most likely involves both damage of the ascending arousal control system at the subcortical level (i.e., the thalamus) and widespread cortical damage. Indeed, widespread cortical damage may result in inability to arouse cortical areas (Weiss et al., 2007). Based on these concepts, we can simplistically characterize the disruption of consciousness in coma as a process that, depending on the etiology, differentially affects some or all parts of a multilevel system, which includes the brainstem (ARAS), thalamus (activating cortex nuclei), and cerebral cortex as its main components.

A poor outcome from coma occurs when either (i) the entire multilevel system is involved in the context of an irreversible disruption of brain function (brain death), or (ii) ascending arousal control is recovered, but not awareness, which is primarily dependent on the cortical regions (transition into UWS). The patient in this report progressed in a third manner, persisting in a comatose state. All of the clinical, neurophysiological, and neuroimaging data indicated massive brain damage involving the brainstem and the subcortical and cortical regions of the ascending wakefulness control system. An important point to note is that the patient had a two-fold cause of brain injury, a traumatic brain injury followed by hypoxic damage. This unusual condition probably caused both a disconnection of ARAS brainstem nuclei from the thalamus and basal forebrain (typical of traumatic coma), and thalamic and cortical damage (typical of hypoxic coma). As a consequence, all of the major systems involved in wakefulness control were likely critically affected.

Clinical, neurophysiological, and neuroimaging data suggest that LLC may represent the most severe consciousness disorder, just above brain death. FDG-PET showed islands of preserved brain metabolism in the anterior regions of the frontal lobes. Although the overall brain metabolism was severely depressed, these findings are different from those of brain death, in which FDG-PET typically show the absence of neuronal function in the whole brain (Laureys et al., 2004). Thus, the term "long-lasting" should be preferred over "chronic" coma, as the latter suggests an irreversible condition that is still not supported by the current data. We propose that LLC be considered a new category of disorder of consciousness, with clinical and pathophysiological features that differ from coma, UWS, or brain death (Table I). This condition should be assumed when (i) a comatose state lasts more than 4 weeks (unlike coma), without any sign of recovery of reticular activating system functions (unlike UWS), and (ii) clinical,

neurophysiological and neuroimaging data demonstrate massive brain damage with both brainstem and cortical functions severely affected, but not completely abolished (unlike brain death). There is most likely bilateral involvement of the thalamus in LLC as well (Schiff, 2008). However, these concepts need to be confirmed by findings obtained from more cases.

Table I. The primary distinguishing features of disorders of consciousness.

Disorder of consciousness	Clinical behavior	Pathophysiology	Evolution
MCS	Minimal, but clear, evidence of self or environmental awareness.	Impairment of cortical functions to a level just above the minimum required to have awareness.	May last indefinitely or may evolve to a higher level of consciousness.
UWS	Dissociation between wakefulness (recovered) and awareness (lacking).	Impairment of cortical functions below the minimum required for awareness.	May last indefinitely or may evolve to a higher level of consciousness (MCS).
COMA	State of unarousable unconsciousness lasting less than four weeks.	Transitory impairment of the brain's ARAS.	May evolve to: 1) Full recovery of consciousness, 2) A disorder of consciousness (MCS, UWS or LLC), or 3) Brain death.
LLC	**State of unarousable unconsciousness lasting more than four weeks.**	**Long-lasting impairment of the brain's ARAS**	**Unknown.**
BRAIN DEATH	State of irreversible unarousable unconsciousness.	Irreversible loss of the entire brain's functions.	No evolution is possible. This state is equivalent to death.

Long-lasting coma may represent a disorder of consciousness with specific clinical and pathophysiological features. Details on clinical and pathophysiological features of other disorder of consciousness may be found in: Giacino et al., 2002; Young, 2009; Monti et al., 2010; Wijdicks et al., 2010; Bagnato et al., 2013. ARAS, ascending reticular activating system; LLC, long-lasting coma; MCS, minimally conscious state; UWS, unresponsive wakefulness syndrome.

The ethical implications surrounding LLC are remarkable. Considering its peculiar characteristics, specific ethical guidelines governing the care of patients suffering from LLC are mandatory. This necessity is even more pressing in the cases of patients who did not specify end-of-life decisions. In accordance with Italian laws, the patient described in this report received all essential care needed to support his life functions (i.e., mechanical respiration, artificial hydration and alimentation), to treat complications (i.e., infections), and to promote an improvement in consciousness state (i.e., specific rehabilitation).

In conclusion, in this report we have described a case of LLC, a new type of disorder of consciousness that is characterized by the persistence of a state similar to coma, resulting from a widespread disruption of the ascending arousal control system. We believe that this description may be useful for identifying other patients in LLC, in either intensive or post-intensive clinical settings. We also hope that this report will stimulate the scientific community to undertake studies aimed at identifying the prevalence of LLC,

to define standard diagnostic criteria, and to promote exhaustive debates about pathophysiological and ethical issues related to this condition.

***References*:**

Bagnato S, Boccagni C, Sant'Angelo A, et al (2013). Emerging from an unresponsive wakefulness syndrome: brain plasticity has to cross a threshold level. Neurosci Biobehav Rev 37: 2721-2736.

Edlow BL, Haynes RL, Takahashi E, et al (2013). Disconnection of the Ascending Arousal System in Traumatic Coma. J Neuropathol Exp Neurol 72: 505-523.

Edlow BL, Takahashi E, Wu O, Benner T, et al (2012). Neuroanatomic connectivity of the human ascending arousal system critical to consciousness and its disorders. J Neuropathol Exp Neurol 71: 531-546.

Fingelkurts AA, Fingelkurts AA, Bagnato S, et al (2012a). Toward operational architectonics of consciousness: basic evidence from patients with severe cerebral injuries. Cogn Process 13 :111-131.

Fingelkurts AA, Fingelkurts AA, Bagnato S, et al (2012b). DMN operational synchrony relates to self-consciousness: evidence from patients in vegetative and minimally conscious states. Open Neuroimag J 6: 55-68.

Fuller PM, Sherman D, Pedersen NP, et al (2011). Reassessment of the structural basis of the ascending arousal system. J Comp Neurol 519: 933-956.

Giacino JT, Ashwal S, Childs N, et al (2002). The minimally conscious state. Definition and diagnostic criteria. Neurology 58: 349-353.

Giacino JT, Kalmar K, Whyte J (2004). The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil 85: 2020-2029.

Guérit JM (1994). The interest of multimodality evoked potentials in the evaluation of chronic coma. Acta Neurol Belg 94: 174-182.

Laureys S, Celesia GG, Cohadon F, et al (2010). Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. BMC Medicine 8: 68.

Laureys S, Owen AM, Schiff ND (2004). Brain function in coma, vegetative state, and related disorders. Lancet Neurol 3 : 537-546.

Monti MM, Laureys S, Owen AM (2010). The vegetative state. BMJ 341: c3765.

Morin LP (2013). Neuroanatomy of the extended circadian rhythm system. Experimental Neurology 243: 4-20.

Royal College of Physicians (2003). The vegetative state: Guidance on diagnosis and management [Report of a Working Party]. Royal College of Physicians, London.

Schiff ND (2008). Central thalamic contributions to arousal regulation and neurological disorders of consciousness. Ann N Y Acad Sci 1129: 105-118.

Seel RT, Sherer M, Whyte J, et al (2010). Assessment scales for disorders of consciousness: evidence-based recommendations for clinical practice and research. Arch Phys Med Rehabil 91: 1795-1813.

Weiss N, Galanaud D, Carpentier A, et al (2007). Clinical review: Prognostic value of magnetic resonance imaging in acute brain injury and coma. Crit Care 11: 230.

Wijdicks EF, Varelas PN, Gronseth GS, et al (2010). Evidence-based guideline update: determining brain death in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 74: 1911-1918.

Young GB (2009). Coma. Ann N Y Acad Sci 1157: 32-47.