Coma

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Two Dimensions of Consciousness: Arousal and Awareness

Consciousness is a multifaceted concept that has two dimensions: arousal, or wakefulness (i.e., level of consciousness), and awareness (i.e., content of consciousness). One needs to be awake in order to be aware (rapid eye movement (REM) sleep and lucid dreaming being notorious exceptions). Figure 1 shows that in normal physiological states (green), level and content are positively correlated (with the exception of the oneiric activity during REM sleep). Patients in pathological or pharmacological coma (i.e., general anesthesia) are unconscious because they cannot be awakened (pink). The vegetative state (VS; blue) is a unique dissociated state of consciousness (i.e., patients are seemingly awake but lack any behavioral evidence of 'voluntary' or 'willed' behavior). There is, of course, an irreducible philosophical limitation in knowing for certain whether any other being possesses a conscious life. Awareness is a subjective first-person experience, and its clinical evaluation is limited to evaluating patients' motor responsiveness. In addition to its clinical and ethical importance, studying these disorders offers a still largely underestimated means of studying human consciousness. In contrast to unconscious states such as general anesthesia and deep sleep (in which impairment in arousal cannot be disentangled from impairment in awareness), VS is characterized by a unique dissociation of arousal and awareness, offering a lesional approach to identifying the neural correlates of awareness. A major challenge is to unequivocally disentangle patients residing in the clinical 'gray zone' between the vegetative and the minimally conscious state (MCS). The locked-in syndrome (LIS) is a rare but horrifying situation in which patients awaken from their coma fully aware but remain mute and immobile; it is called a 'pseudodisorder of consciousness' because patients superficially look unconscious but in reality are fully aware only unable to show it due to severe paralysis.

Arousal is supported by several brain stem neuronal populations (i.e., the reticular activating system) that directly or via nonspecific thalamic nuclei project to cortical neurons. Hence, focal damage of the brain stem or diffuse damage of the cerebral hemispheres may cause reduced arousal. The evaluation of eye-opening and brain stem reflexes is a key to the clinical assessment of the functional integrity of the arousal systems. Awareness depends on the functional integrity of the cerebral cortex and its reciprocal subcortical connections (each of its aspects partly residing in spatially defined brain areas), but its underlying neural code remains to be elucidated. Therefore there is, at present, no validated objective 'consciousness meter.' The estimation of the multiple dimensions of consciousness requires the interpretation of several clinical signs, mainly based on the observation of 'voluntary' interaction with the examiner or the environment. Brain death, coma, VS, MCS, and LIS (see Figure 2) are all solely defined by clinical criteria. Many scoring systems have been developed for a standardized assessment of consciousness in severely brain-damaged patients.

Nosology of Disorders of Consciousness

Brain Death

Brain death means human death determined by neurological criteria. The current definition of death is the permanent cessation of the critical functions of the organism as a whole (i.e., neuroendocrine and homeostatic regulation, circulation, respiration, and consciousness). Most countries, including the US, require death of the whole brain including the brain stem, but some (e.g., UK and India) rely on the death of the brain stem only, arguing that the brain stem is at once the through-station for nearly all hemispheric input and output, the center generating arousal (an essential condition for conscious awareness), and the center of respiration. Clinical assessments for brain death, however, are uniform and are based on the loss of all brain stem reflexes and the demonstration of continuing cessation of respiration (by performing a standardized apnea test) in a persistently comatose patient (Table 1). There should be an evident cause of coma, and confounding factors such as hypothermia, drugs, and electrolyte and endocrine disturbances should be ruled out.

Brain death is classically caused by a massive brain lesion (e.g., trauma, intracranial hemorrhage, anoxia) which increases intracranial pressure to values superior to mean arterial blood pressure and hence causes intracranial circulation to cease and damages the brain stem due to herniation. Using the brain stem formulation of death, however, unusual but existing cases of catastrophic brain stem lesion (often of hemorrhagic origin) sparing the thalami and cerebral cortex can be declared brain death in the absence of clinical brain stem function, despite intact intracranial circulation. Hence a patient with a primary brain

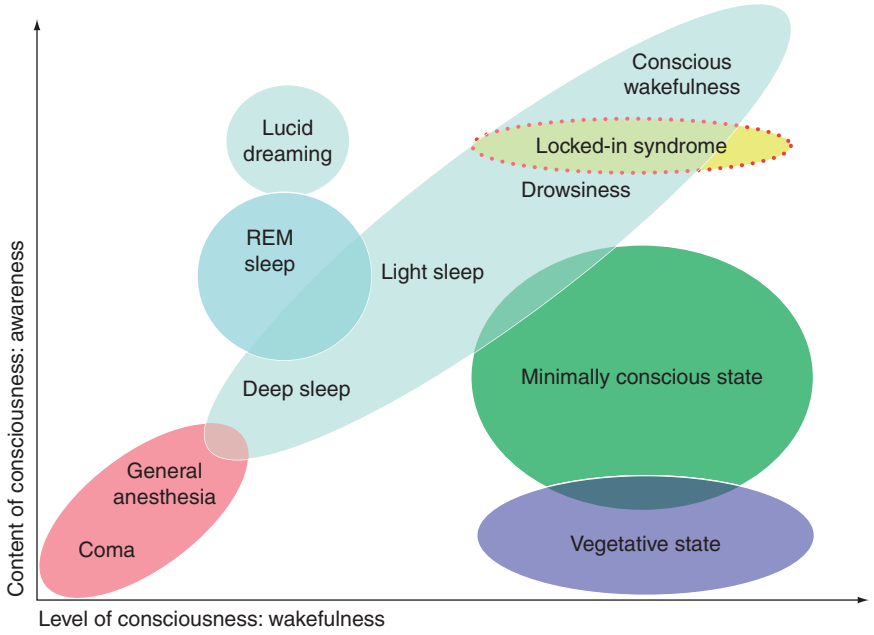

Figure 1 Oversimplified illustration of the two major dimensions of consciousness: the level of consciousness (i.e., arousal or wakefulness) and the content of consciousness (i.e., awareness or experience). Adapted from Laureys S (2005) The neural correlate of (un)awareness: Lessons from the vegetative state. *Trends in Cognitive Sciences* 9: 556–559.

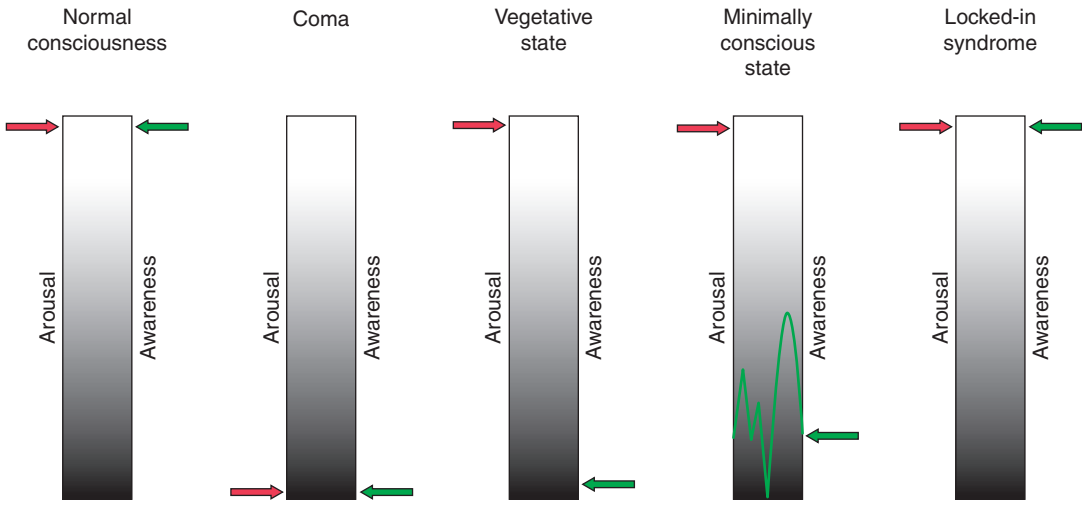

Figure 2 Graphical representation of the two dimensions of consciousness: arousal (red arrow) and awareness (green arrow) and their alterations in coma, the vegetative state, the minimally conscious state, and the locked-in syndrome. Adapted from Laureys S, Owen AM, and Schiff ND (2004) Brain function in coma, vegetative state, and related disorders. *Lancet Neurology* 3: 537–546.

stem lesion (who did not develop raised intracranial pressure) might theoretically be declared dead by the UK doctrine but not by the US doctrine.

Coma

Coma is a state of unarousable unresponsiveness characterized by the deficiency of the arousal systems (clinically assessed as the absence of stimulation-induced eye opening after having ruled out bilateral ptosis) and thus also by absence of awareness. The comatose patient lacks the sleep–wake cycles that can be observed in the VS. To be clearly distinguished from syncope, concussion, or other states of transient unconsciousness, coma must persist for at least 1 h. In general, comatose patients who survive begin to awaken and recover gradually within 2–4 weeks. This recovery may go no further than VS or MCS, or these may be stages (brief or prolonged) on the way to more complete recovery of consciousness. There are two main causes of coma: (1) bihemispheric

diffuse cortical or white matter damage secondary to neuronal or axonal injury and (2) brain stem lesions bilaterally affecting the subcortical reticular arousing systems (i.e., pontomesencephalic tegmentum and/or paramedian thalami).

VS

VS was defined in 1972 by Bryan Jennett and Fred Plum to describe those patients who 'awaken' from their coma (meaning they open their eyes spontaneously or on stimulation) but remain unaware of self or environment (meaning they show only reflex motor responses; Table 2). According to the *Oxford English Dictionary*, the term 'vegetative' describes "an organic body capable of growth and development but devoid of sensation and thought." It is very important to stress the difference between persistent and permanent VS, which are, unfortunately, too often abbreviated identically as PVS, causing unnecessary confusion. 'Persistent VS' has been arbitrarily defined as a VS still present 1 month after the acute brain damage, but the term does not imply irreversibility. In 1994, the US Multi-Society Task Force on PVS concluded that 3 months following nontraumatic brain damage and 12 months after traumatic injury, the condition of VS patients may be regarded as 'permanent.' Only in cases of 'permanent VS' do the ethical and legal issues surrounding withdrawal of treatment arise. It is essential that experienced examiners employing adapted standardized clinical assessment scales repeatedly establish the behavioral absence of any sign of conscious perception or deliberate action before making the diagnosis of VS.

MCS

In 2002, the Aspen Neurobehavioral Conference Workgroup published the diagnostic criteria for MCS to subcategorize patients above VS but unable to functionally communicate their thoughts and feelings. On a reproducible or sustained basis, MCS patients show limited but clearly discernible evidence of awareness of self or environment (Table 3). The emergence of MCS is characterized by the recovery of interactive communication or functional use of objects. Further improvement is more likely than in VS patients. However, some patients may remain permanently in MCS. At present, no time intervals for 'permanent MCS' have been agreed on.

'Akinetic mutism' (a condition characterized by severe poverty of movement, speech, and thought without associated arousal disorder or descending

Table 1 Criteria for brain death (American Academy of Neurology guidelines)

- Demonstration of coma
- Evidence for the cause of coma
- Absence of confounding factors, including hypothermia, drugs, electrolyte, and endorcrine disturbances
- Absence of brain stem reflexes
- Absent motor responses
- Apnea
- A repeat evaluation in 6 h is advised, but the amount of time is considered arbitrary
- Confirmatory laboratory tests are required only when specific components of the clinical testing cannot be reliably evaluated

Table 2 Criteria for the vegetative state (US Multi-Society Task Force on Persistent Vegetative State guidelines)

- No evidence of awareness of self or environment and an inability to interact with others
- No evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli
- No evidence of language comprehension or expression
- Intermittent wakefulness manifested by the presence of sleep–wake cycles
- Sufficiently preserved hypothalamic and brain stem autonomic functions to permit survival with medical and nursing care
- Bowel and bladder incontinence
- Variably preserved cranial nerve and spinal reflexes

Table 3 Criteria for the minimally conscious state (Aspen Neurobehavioral Conference Workgroup)

Clearly discernible evidence of awareness of self or environment, on a reproducible or sustained basis, by at least one of the following behaviors:

- Purposeful behavior (including movements or affective behavior that occurs in contingent relation to relevant environment stimuli and are not due to reflexive activity), such as:
  - Pursuit eye movement or sustained fixation occurring in direct response to moving or salient stimuli
  - Smiling or crying in response to verbal or visual emotional (but not neutral) stimuli
  - Reaching for objects demonstrating a relationship between object location and direction of reach
  - Touching or holding objects in a manner that accommodates the size and shape of the object
  - Vocalizations or gestures occurring in direct response to the linguistic content of questions
- Following simple commands
- Gestural or verbal yes/no response (regardless of accuracy)
- Intelligible verbalization

Emergence from the minimally conscious state requires reliable and consistent demonstration of at least one of the following behaviors:

- Functional interactive communication: accurate yes/no responses to six of six basic situational orientation questions (including items as, "Are you sitting down?" and "Am I pointing to the ceiling?") on two consecutive evaluations
- Functional use of two different objects (such as bringing a comb to the head or a pencil to a sheet of paper) on two consecutive evaluations

motor tract impairment) is an outdated term that should be avoided and is now considered to be a subcategory of the minimally conscious syndrome.

LIS

The category of LIS (pseudocoma) was introduced by Fred Plum and Jerome Posner in 1966 to refer to the constellation of quadriplegia and anarthria brought about by the disruption of, respectively, the brain stem's corticospinal and corticobulbar pathways. The syndrome describes patients who are aroused and awake but selectively deefferented (i.e., have no means of producing speech or limb or face movements). Usually the anatomy of the responsible lesion in the brain stem is such that locked-in patients are left with the capacity to use vertical eye movements and blinking to communicate their awareness of internal and external stimuli. Acute vascular bilateral ventral pontine lesions are its most common cause. Patients with such lesions often remain comatose for some days or weeks, needing artificial respiration, and then gradually wake up, remaining paralyzed and voiceless, superficially resembling someone in a coma or a VS. Table 4 lists the clinical criteria of LIS. The syndrome is subdivided, on the basis of the extent of motor impairment, into (1) classical LIS (characterized by total immobility except for vertical eye movements or blinking); (2) incomplete LIS (permitting remnants of voluntary motion); and (3) total LIS (consisting of complete immobility including all eye movements, combined with preserved consciousness).

Clinimetric Evaluation, Diagnosis, and Prognosis

Consciousness Scales

In 1974, Graham Teasdale and Bryan Jennett published the Glasgow Coma Scale (GCS). This standardized bedside tool to quantify arousal and awareness now is the gold standard in coma research. The GCS has tree components assessing eye opening and verbal and motor responses. Some authors have disagreed that evaluation of spontaneous or stimulation-induced opening of the eyes is sufficiently indicative of brain stem arousal system activity and have proposed coma scales that include brain stem reflexes. However, only the GCS has known a widespread use because the others generally are more complex. A simpler system, the Glasgow-Liège Scale (GLS), combines the GCS with five brain stem reflexes (i.e., fronto-orbicular, oculocephalic, pupillary, and oculocardiac reflexes). The increasing use of intubation and mechanical ventilation has rendered the verbal component of the GCS unassessable in many coma patients. Recently, the Full Outline of Un-Responsiveness (FOUR; also the number of components tested: eye, motor, brain stem reflexes, and respiratory function) scale proposed a hand-position test (i.e., asking the patient to make a fist or a 'thumbs-up', or 'V-for-victory' sign) as an alternative to the verbal component of the GCS.

The GCS, GLS, and FOUR scales lack reliability in assessing chronic disorders of consciousness. For these patients, more-sensitive scales are the Coma Recovery Scale-Revised (CRS-R), the Sensory Modality Assessment and Rehabilitation Technique (SMART), and the Wessex Head Injury Matrix (WHIM). The CRS-R is a recent scale specifically developed to differentiate VS from MCS and explicitly incorporating current diagnostic criteria. The basic structure of the CRS-R is similar to the GCS, but its subscales are much more detailed, targeting more-subtle signs of recovery of awareness.

Table 4 Criteria for the locked-in syndrome (American Congress of Rehabilitation Medicine)

- Sustained eye opening (bilateral ptosis should be ruled out as a complicating factor)
- Quadriplegia or quadriparesis
- Aphonia or hypophonia
- A primary mode of communication that uses vertical or lateral eye movement or blinking of the upper eyelid to signal yes/no responses
- Preserved awareness of the environment

Brain Death

Because many of the areas of the supratentorial brain (including the neocortex, thalami, and basal ganglia) cannot be tested for clinical functions accurately in a comatose patient, most of the bedside tests for brain death (such as cranial nerve reflexes and apnea testing) directly measure functions of only the brain stem. Since the first clinical definition of brain death nearly 50 years ago, no patient in apneic coma properly declared dead on the basis of neurological criteria has ever regained consciousness. Complementary neurophysiological tests such as electroencephalography (EEG), event-related potentials (ERPs), angiography, Doppler sonography, and scintigraphy reliably and objectively confirm the clinical diagnosis.

Coma

The management and prognosis of coma depend on many factors, such as etiology, the patient's general medical condition, age, clinical signs, and complementary examinations. After 3 days of observation,

absence of pupillary or corneal reflexes, stereotyped or absent motor response to noxious stimulation, isoelectrical or burst suppression pattern EEG, bilateral absent cortical responses on somatosensory evoked potentials, and (for anoxic coma) biochemical markers such as high levels of serum neuron-specific enolase are known to herald bad outcome. Visual and brain stem auditory evoked potentials are of limited prognostic use. Prognosis in traumatic coma survivors is better than in anoxic cases. Predicting outcome in toxic, metabolic, and infectious comatose states is challenging, and many unexpected cases of recovery have been reported.

VS

Whereas coma and brain death characteristically are acute conditions (lasting no more than days to weeks), the VS and MCS may become chronic entities. Vegetative patients, unlike brain dead or comatose patients, can move extensively, and studies have shown how difficult it is to differentiate 'automatic' from 'willed' movements in these patients. This results in an underestimation of behavioral signs of awareness and hence a misdiagnosis. It is known that when the diagnosis is made with insufficient care, up to one in three 'vegetative' patients actually are at least minimally conscious. Physicians also frequently tend to erroneously diagnose VS in older demented nursing home residents. Clinical testing for absence of awareness is much more problematic and slippery than testing for absence of arousal, brain stem reflexes, and apnea in irreversible coma. Given appropriate medical treatment, meaning artificial nutrition and hydration, VS patients may survive for many years.

Over the past decade, investigators have struggled to find an objective test that could reliably predict outcome for vegetative individuals. In contrast to coma and brain death, there are no validated diagnostic or prognostic markers for VS patients. The chances of recovery depend on the patient's age, etiology (worse for anoxic causes), and time spent in the VS. Recent data suggest that damage to the corpus callosum and brain stem indicate bad outcome in traumatic VS.

MCS

Because criteria for MCS have only recently been introduced, there are few clinical studies of patients in this condition. As stated above, it remains very challenging to behaviorally differentiate minimally conscious from vegetative patients because both are, by definition, noncommunicative. VS is one end of a spectrum of awareness, and the subtle differential diagnosis with MCS necessitates repeated evaluations by experienced examiners. As with VS, traumatic etiology has a better prognosis than does nontraumatic (anoxic) MCS. Preliminary data show that overall outcome for MCS is better than for VS.

LIS

In acute LIS, eye-coded communication may be difficult because of fluctuating arousal and limited control of voluntary eye movements. More than half the time, it is family members, not the physician, who first realize that the patient is aware. Distressingly, the diagnosis takes on average more than 2.5 months. In some cases it has taken 4–6 years before aware and sensitive patients, locked in an immobile body, have been recognized as being conscious. Some memoirs written by locked-in patients well illustrate the clinical challenge of recognizing the syndrome. Striking examples are *Look Up for Yes*, by Julia Tavalaro, and *Only the Eyes Say Yes*, by Phillippe Vigand.

While motor recovery remains very limited in LIS, life expectancy (with adequate medical care) may be several decades. Sensory evoked potentials are not reliable predictors of prognosis, but motor evoked potentials might evaluate the potential motor recovery. Eye-controlled computer-based communication technology now allows patients to control their environment, use a word processor coupled to a speech synthesizer, and access the Internet. Outsiders often assume that the quality of life with LIS is so poor that it is not worth living. Recent surveys, however, have revealed that chronic LIS patients self-report meaningful quality of life and that the demand for euthanasia is infrequent.

Residual Cerebral Function

Brain Death

The EEG in brain death shows absent electrocortical activity (i.e., isoelectric recording) with a sensitivity and specificity of around 90%. This makes the EEG the most validated and, because of its wide availability, preferred confirmatory test for brain death. Somatosensory evoked potentials typically indicate arrest of conduction at the cervicomedullary level, and brain stem auditory evoked potentials usually show only a delayed wave I (originating in the cochlear nerve). Cerebral angiography and transcranial Doppler sonography document with very high sensitivity and 100% specificity the absence of cerebral blood flow in brain death. Similarly, radionuclide cerebral imaging such as single-photon emission computed tomography (CT) and positron-emission tomography (PET) demonstrate the hollow-skull sign confirming

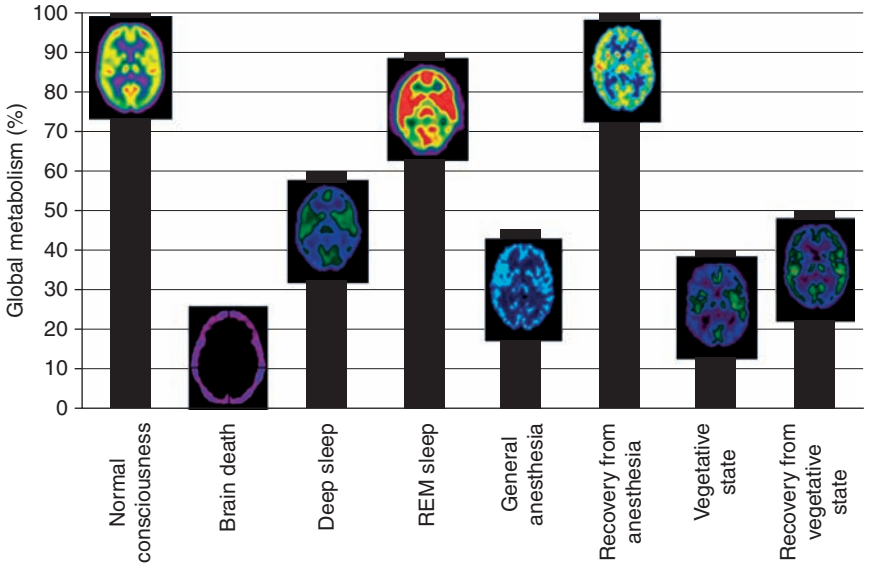

Figure 3 Cerebral metabolism in conscious wakefulness, in brain death (hollow skull sign confirming the absence of neuronal function in the whole brain in irreversible coma), physiological (slow wave sleep) and pharmacological (general anesthesia) modulation of arousal reflecting massive global decreases in cortical metabolism (in REM sleep, metabolic activity is paradoxically prominent); and in wakefulness without awareness (i.e., the vegetative state). Note that recovery from the vegetative state may occur without substantial increase in overall cortical metabolism, emphasizing that some areas in the brain are more important than others for the emergence of awareness. Images of halothane-induced loss of consciousness from Alkire M, Pomfrett CJ, Haier RJ, et al. (1999) Functional brain imaging during anesthesia in humans: Effects of halothane on global and regional cerebral glucose metabolism. *Anesthesiology* 90: 701–709.

the absence of neuronal function in the whole brain (Figure 3).

Anatomopathology in brain death patients receiving maximal artificial means of support will inevitably end up showing the so-called respirator brain, and after about a week, an autolyzed liquefied brain will pour from the opened skull.

Coma

The electrical activity of the brain as measured by the EEG tends to become nonreactive and slower as the depth of coma increases, regardless of the underlying cause. As stated above, the bilateral absence of cortical potentials (called N20 waves because they occur after about 20 ms) on somatosensory evoked potentials herald bad outcome. In cases in which cortical potentials are present, so-called endogenous ERPs might be useful. The presence of 'mismatch negativity,' that is, a negative component elicited after 100–200 ms by any change or 'mismatch' in a sequence of monotonous auditory stimuli (i.e., an 'oddball paradigm') indexes some persistent automatic information processing and is correlated with recovery of at least minimal consciousness.

Cortical metabolism in coma survivors is on average 50–70% of normal reference values. Cerebral metabolism correlates poorly with the level of consciousness, as measured by the GCS, in severely head-injured patients. A global depression of cerebral metabolism is not unique to coma. When anesthetic drugs are titrated to the point of unresponsiveness, the resulting reduction in brain metabolism is similar to that observed in pathological coma. Another example of transient metabolic depression can be observed during slow wave sleep. In this daily physiological condition, cortical cerebral metabolism can drop to nearly 40% of normal values, although in REM sleep, metabolism returns to normal waking values (Figure 3).

VS

In VS the EEG most often shows a diffuse slowing (i.e., generalized polymorphic delta or theta rhythm); only sporadically is it of very low voltage or isoelectric. Somatosensory evoked potentials may show preserved primary somatosensory cortical potentials, and brain stem auditory evoked potentials often show preserved brain stem potentials in vegetative patients. Endogenous evoked potentials measuring, for example, the brain's response to complex auditory stimuli such as the patient's own name (compared with other names) record a so-called P300 response (i.e., a positive wave elicited around 300 ms poststimulus when patients detect an unpredictable target in the regular train of stimuli). In brain-damaged patients, the use of emotionally meaningful stimuli such as the patient's own name increases the chances of obtaining

a P300 response. Recent data show that the P300 is not a reliable marker of awareness but rather indicates automatic processing, because it could be recorded in well-documented VS patients who never recovered (Figure 4).

In contrast to the functional decapitation observed in irreversible coma or brain death, vegetative patients show substantially reduced (40–50% of normal values) but not absent overall cortical metabolism. In some vegetative patients who subsequently recovered, global metabolic rates for glucose metabolism did not show substantial changes (Figure 3). Hence, the relationship between global levels of brain function and the presence or absence of awareness is not absolute. It rather seems that some areas in the brain are more important than others for its emergence.

Anatomopathologic features in anoxic VS encompass multifocal laminar cortical necrosis, diffuse leucoencephalopathy, and bilateral thalamic necrosis; VS following blunt head injury classically shows diffuse white matter damage with neuronal loss in thalami and hippocampi. However, these postmortem studies have not permitted a detailed regional topography of cerebral damage characteristic of VS. Voxel-based statistical analyses of metabolic PET data have identified a metabolic dysfunction in a wide frontoparietal network encompassing the polymodal associative cortices: bilateral lateral frontal regions; parietotemporal and posterior parietal areas; and mesiofrontal, posterior cingulate, and precuneal cortices (Figure 5), known to be the most active 'by default' in resting nonstimulated conditions.

In some other conditions, patients also show merely reflex or automatic motor activity while behaviorally seeming 'awake.' In absence seizures (characterized by brief episodes of unresponsiveness and staring, frequently accompanied by purposeless eye blinking and smacking), functional magnetic resonance imaging (MRI) studies have shown decreases in blood oxygen level-dependent signals in a wide

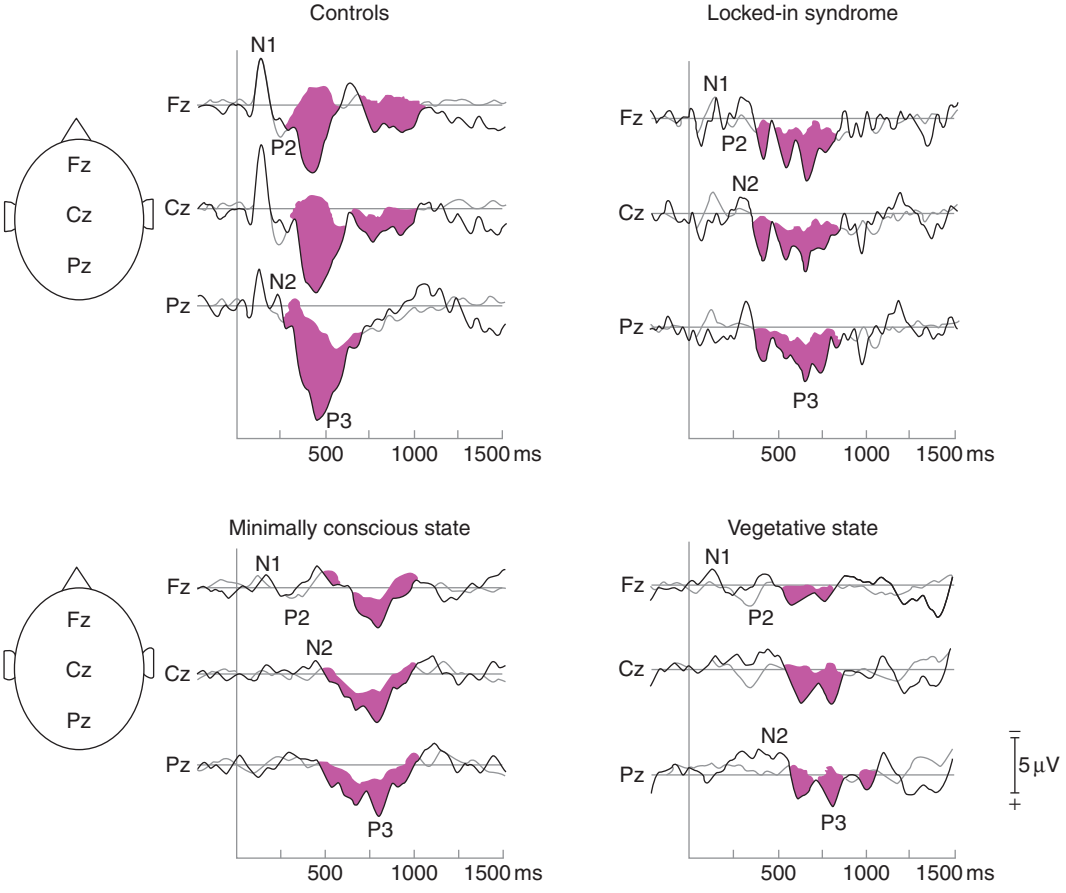

Figure 4 Endogenous event-related potentials to the patient's own name (thick traces) and to other first names (thin traces) in five healthy controls, four patients with locked-in syndrome, six minimally conscious state patients, and five vegetative state patients. Note that the differential P300 response (in pink) can also be observed in some well-documented VS patients (who never recovered) and hence is not a reliable indicator of awareness. Adapted from Perrin F, Schnakers C, Schabus M, et al. (2006) Brain response to one's own name in vegetative state, minimally conscious state, and locked-in syndrome. *Archives of Neurology* 63: 562–569.

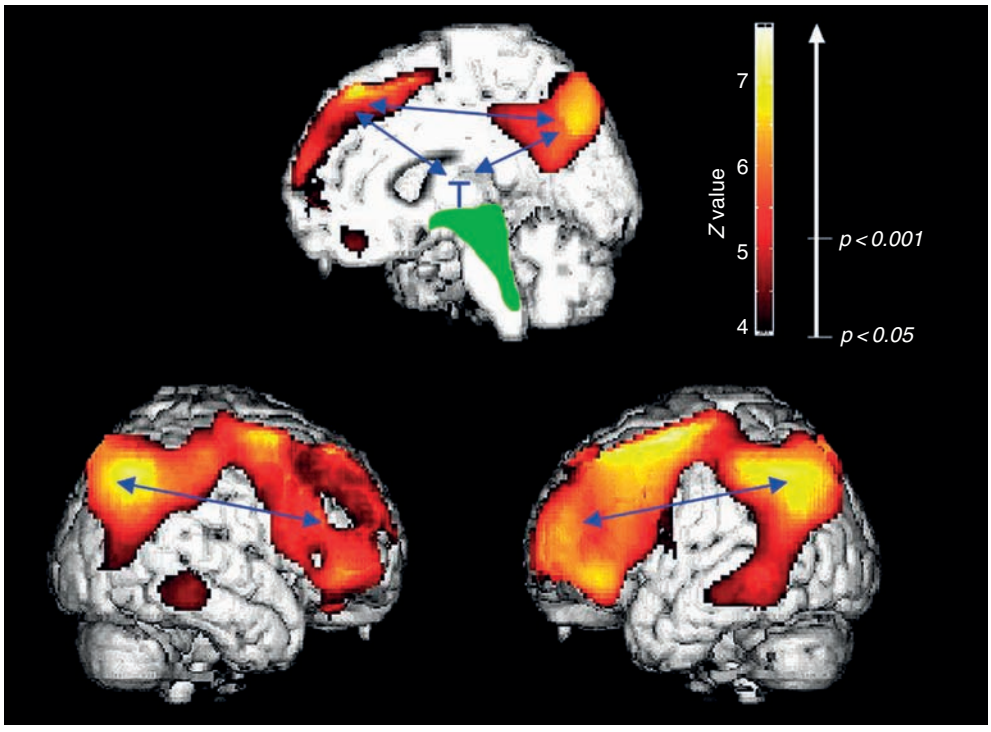

Figure 5 The common hallmark of the vegetative state is a metabolic dysfunctioning of a widespread cortical network encompassing medial and lateral prefrontal and parietal multimodal associative areas. This might be due to either direct cortical damage or corticocortical or thalamocortical disconnections (schematized by blue arrows). Also characteristic of the vegetative state is the relative sparing of metabolism in the brain stem (encompassing the pedunculopontine reticular formation, hypothalamus, and basal forebrain, represented in green), allowing for the patients' preserved arousal and autonomic functions. Adapted from Laureys S (2005) The neural correlate of (un)awareness: Lessons from the vegetative state. *Trends in Cognitive Sciences* 9: 556–559.

frontoparietal network, similar to that identified in VS patients. In some temporal lobe seizures that impair consciousness (coined 'complex partial') while preserving automatic activities such as picking, fumbling, or even cycling, single-photon emission CT has shown similar widespread deactivation in frontal and parietal association cortices. In contrast, temporal lobe epilepsy with sparing of consciousness (termed 'simple partial') is not accompanied by such frontoparietal dysfunction. Another example of transient nonresponsiveness with preserved automatic behavior such as ambulation can be observed in sleepwalkers. Again, deactivations in large areas of frontal and parietal association cortices were demonstrated by means of SPECT imaging during sleepwalking. Taken together, these observations point to the critical role of the frontoparietal associative cortices in the generation of conscious awareness.

However, awareness seems not exclusively related to the activity in this 'global workspace' cortical network but also, it is important to note, to the functional connectivity within this system and with the thalami. Long-range frontoparietal and thalamocortical (with nonspecific intralaminar thalamic nuclei) 'functional disconnections' have been identified in VS. Moreover, recovery is paralleled by a functional restoration of this frontoparietal network and part of its thalamocortical connections.

The most relevant question regards possible residual perception and cognition in vegetative patients. In well-documented VS patients, noxious high-intensity electrical stimulation (experienced as painful in controls) resulted in activation in brain stem, thalamus, and primary somatosensory cortex, but hierarchically higher-order areas of the pain matrix encompassing the anterior cingulate cortex failed to activate (Figure 6). It is important to note that the activated cortex was isolated and functionally disconnected from the frontoparietal network, considered critical for conscious perception. Similarly, auditory stimulation in VS was found to activate primary auditory cortices but not higher-order multimodal areas from which they were disconnected. The activation in primary cortices in awake but unaware patients confirms Crick and Koch's early hypothesis (based on visual perception and monkey histological connectivity) that neural activity in primary cortices is necessary but not sufficient for awareness.

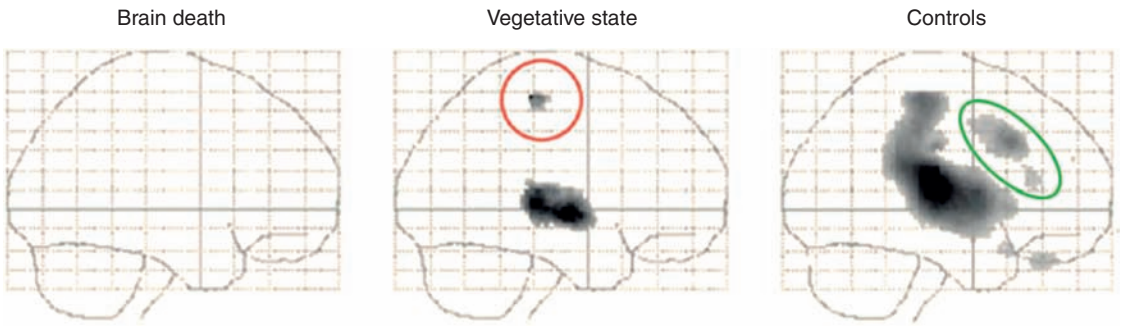

Figure 6 High-intensity somatosensory stimuli fail to induce any subcortical or cortical neural activation in irreversible coma with clinical absence of brain stem reflexes (i.e., brain death). In the vegetative state, subcortical (upper brain stem and thalami) and cortical (primary somatosensory cortex; red circle) activation can be observed. However, this preserved cortical activation is limited to the primary cortex and fails to reach higher-order associative cortices from which it is functionally disconnected. In healthy volunteers, reporting the stimuli as painful, stimulation resulted in a wide neural network activation (the so-called pain matrix) including the anterior cingulate cortex (green ellipse). Data from Laureys S, Faymonville ME, Peigneux P, et al. (2002) Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. *Neuroimage* 17: 732–741 and shown on 'glass brains.'

MCS

PET studies measuring cerebral metabolism at rest are unable to reliably differentiate vegetative from minimally conscious individuals. Functional imaging can here be of utmost value in objectively differentiating activation patterns measured during external stimulation characteristic of either clinical entity. Complex auditory stimuli with emotional valence, such as personalized narratives or the patient's own name, activate language-related cortical areas not observed during presentation of meaningless stimuli in MCS. Such context-dependent higher-order auditory processing in MCS patients (often is not assessable at the patient's bedside) indicate that content does matter when talking to MCS patients.

However, given the absence of a thorough understanding of the neural correlates of consciousness, functional neuroimaging results must be used with caution as proof or disproof of awareness in severely brain-damaged patients. Recently, Adrian Owen, from Cambridge, proposed a more powerful approach for identifying 'volition without action' in noncommunicative brain-damaged patients (rather than the use of passive external stimulation paradigms): scanning patients when they are asked to perform a mental imagery task. Reproducible and anatomically specific activation in individual patients during tasks that unequivocally require 'willed action' or intentionality for their completion unambiguously reflect awareness. Of course, negative findings in the same circumstances cannot be used as evidence for lack of awareness. In one exceptional VS patient, task-specific activation was observed, unequivocally demonstrating conscious awareness in the absence of reliable behavioral motor signs of voluntary interaction with the environment. It is interesting that the patient subsequently recovered. Other studies also showed that VS patients with atypical brain activation patterns on functional neuroimaging afterwards showed clinical signs of recovery of consciousness, albeit sometimes many months later.

Investigations using MRI diffusion tensor imaging, which gauges the integrity of the white matter, are increasing scientific understanding of the brain mechanisms underlying recovery from VS. A team led by Nicholas Schiff of Cornell University, for instance, recently used diffusion tensor imaging to show the regrowth of axons in the brain of Terry Wallis, an Arkansas man in posttraumatic MCS who started talking in 2003 after 19 years of silence.

LIS

Classically, the EEG is relatively normal (or minimally slow) and reactive to external stimuli in LIS, but unreactive alpha rhythms (i.e., 'alpha coma' patterns) may also be observed. Cognitive ERPs and brain–computer interfaces may document awareness and permit communication in the extremely challenging cases of complete LIS. Residual cognition in LIS has long remained *terra incognita*. Recently, standard neuropsychological testing batteries have been adapted and validated for eye response communication. In classical LIS caused by a brain stem lesion, these studies have shown preserved attention, memory, executive functioning, and phonological and lexicosemantic performance.

PET scanning has shown significantly higher metabolic levels in the brains of patients in LIS compared with patients in VS. Voxel-based comparisons with healthy controls showed that no supratentorial cortical area has a significantly impaired metabolism in classical LIS. Conversely, hyperactivity was observed in bilateral amygdala of acute, but not chronic, LIS patients. The amygdala is known to be involved in emotions, especially negative emotions such as fear and anxiety. The absence of metabolic signs of

reduced function in any area of the gray matter reemphasizes the fact that LIS patients suffer from a pure motor de-efferentation and recover an entirely intact intellectual capacity. The increased activity in the amygdala might relate to the terrifying situation of an intact awareness in a mute but sensitive being. Healthcare workers should be aware of this condition, adapt their bedside behavior, and consider pharmacological anxiolytic therapy.

Conclusion

Brain death, coma, VS, and MCS represent different pathological alterations of both dimensions of consciousness (involving arousal and awareness) or, for LIS, of the motor signs of consciousness. At the bedside, the evaluation of conscious perception and cognition in these conditions is difficult and sometimes erroneous. Electrophysiological and functional neuroimaging studies can objectively describe the regional distribution of cerebral activity at rest, under various conditions of passive stimulation, and during 'active' mental imagery tasks. These studies are increasing our understanding of the neural correlates of arousal and awareness and will improve the diagnosis, prognosis, and management of disorders of consciousness. But at present, much more data and methodological validation are awaited before functional neuroimaging studies can be proposed to the medical community as a tool for disentangling the clinical gray zone that separates conscious from unconscious survivors of acute brain damage.

See also: Awareness: Functional Imaging; Brain Trauma; Coma and Other Pathological Disorders of Consciousness; Consciousness: Theories and Models; Consciousness: Philosophy; Consciousness: Neural Basis of Conscious Experience; Reticular Activating System; Stroke: Injury Mechanisms; Vegetative State.

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