The neural correlate of (un)awareness: lessons from the vegetative state

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Abstract
The vegetative state is characterized by wakefulness without awareness. Awareness is difficult to assess in non-communicative patients. Functional neuroimaging shows that some parts of the cortex are still functioning in “vegetative” patients. External - for example painful - stimulation in these patients still activates “primary” sensory cortices but these are functionally disconnected from “higher order” associative areas needed for awareness. Such studies are disentangling the neural correlates of the vegetative from the minimally conscious state and have major clinical consequences.
Vegetative patients look “awake” but fail to show any behavioral sign of awareness. For family members – and inexperienced physicians and policy makers – it is difficult to accept that patients’ reflexive movements do not reflect consciousness. This reveals their (understandable) lack of clarity about the nature of consciousness, and especially its dual nature, which involves both dimensions of wakefulness and awareness.

Recent neuroimaging studies are revealing how wakefulness and awareness can come apart in the vegetative state, illuminating the relationships between awareness and: (i) *global* brain function; (ii) *regional* brain function; (iii) changes in *functional connectivity*; and (iv) primary versus associative *cortical activation* in response to external stimulation -highlighting possible perception of pain.

**Consciousness, awareness and wakefulness**

Consciousness is a multifaceted concept that has two major components: awareness of environment and of self (i.e., content of consciousness) and wakefulness (i.e., level of consciousness) (figure 1). You need to be awake in order to be aware (REM-sleep being a notorious exception). The contrastive approach as first proposed by Baars [1] (comparing brain activation in circumstances that do or do not give rise to consciousness in either of its two main senses of awareness and wakefulness) is now widely applied in functional neuroimaging. Very few groups, however, have studied situations where wakefulness and awareness are dissociated. The most tragic example is the vegetative state. Here, patients ‘awaken’ from their coma but show no ‘voluntary’ interaction with their environment.

**FIG-1**

Vegetative patients have their eyes wide open but are considered – by definition – unaware. They may grimace cry or smile (albeit never contingent upon specific external stimuli) and move their eyes, head and limbs in meaningless ‘automatic’ manner. The vegetative state, often, but not always, is chronic. Given proper medical care (meaning artificial hydration and nutrition) patients might survive for many years.

How certain can physicians be that these patients are completely unaware and insensate? “Might a grimace in response to pain not indicate a glimmer of awareness?” [2]. It is known that when the diagnosis is made with insufficient care, up to one in three “vegetative” patients actually are conscious – at least minimally conscious [2]. Clinical misdiagnosis is partly explained by the inherent difficulties in detecting signs of awareness in
patients with fluctuating arousal and perceptual, attentional and motor deficits. Functional neuroimaging studies are now measuring neural activity at rest and during external, for example “painful”, stimulation in these patients. In addition to its clinical and ethical importance, studying the vegetative state offers a still largely underestimated means to the study of human consciousness. In contrast to other unconscious states such as general anesthesia and deep sleep, where impairment in arousal cannot be disentangled from impairment in awareness, we are here offered a unique lesional approach enabling us to identify the neural correlates of (un)awareness.

**Awareness and global brain function**

Is awareness lost when overall cortical activity falls below a certain threshold? PET studies modulating arousal – and hence awareness – by means of anesthetic drugs have shown a drop in global brain metabolism to around half of normal values [3]. Similar global decreases in metabolic activity are observed in deep sleep [4], while in REM-sleep metabolism returns to normal waking values.

What happens in the vegetative state, that is in “wakefulness without awareness”? Here also, global metabolic activity decreases to about 50% of normal levels [5,6]. However, in some patients who subsequently recovered, global metabolic rates for glucose metabolism did not show substantial changes [7]. Moreover, some awake healthy volunteers have global brain metabolism values comparable to those observed in some patients in a vegetative state (Laureys et al., unpublished). Inversely, some well documented vegetative patients have shown close to normal global cortical metabolism [5] (figure 2).

Hence, the relationship between global levels of brain function and the presence or absence of awareness is not absolute. It seems that some areas in the brain are more important than others for its emergence. Can these “awareness-regions” be identified?

**FIG-2**

**“Awareness-regions” in the brain?**

Voxel-based statistical analyses have aimed to identify regions showing metabolic dysfunction when the vegetative state was contrasted to the conscious resting state in healthy controls. These studies have identified a dysfunction not in one brain region but in a wide frontoparietal network encompassing the polymodal associative cortices: bilateral lateral frontal regions, parieto-temporal and posterior parietal areas, mesiofrontal, posterior cingulate
and precuneal cortices ([6]; figure 3), known to be the most active ‘by default’ in resting non-stimulated conditions [8] (BOX).

Current analyzing techniques now also permit to assess awareness-related changes in functional integration - that is measuring differences in functional cerebral connectivity between vegetative patients and healthy controls.

BOX-1

**Vegetative state as a disconnection syndrome**
Awareness seems not exclusively related to the activity in the frontoparietal network but, as importantly, to the functional connectivity within this network and with the thalami. Indeed, long-range cortico-cortical (between latero-frontal and midline-posterior areas) and cortico-thalamo-cortical (between non-specific thalamic nuclei and midline-posterior cortices) ‘functional disconnections’ have been identified the vegetative state [6,9]. Moreover, recovery is paralleled by a functional restoration of the frontoparietal network [7] and part of its cortico-thalamo-cortical connections [9]. In addition to measuring resting brain function and connectivity, recent neuroimaging studies have identified which brain areas still “activate” during external *stimulation* in vegetative patients.

**Do patients in a vegetative state feel or hear anything?**
The most relevant question regards possible residual pain perception in “vegetative” patients. Studies using noxious high intensity electrical stimulation (experienced as painful in controls) showed robust activation in brainstem, thalamus and primary somatosensory cortex in each of fifteen well-documented vegetative state patients [10]. Importantly, hierarchically higher-order areas of the pain matrix (that is, secondary somatosensory, insular, posterior parietal and anterior cingulate cortices) failed to activate. Moreover, the activated primary somatosensory cortex was isolated and dissociated from the frontoparietal network, thought to be required for conscious perception.

Similarly, auditory stimulation in unambiguously vegetative patients activated primary auditory cortices but not higher-order multi-modal areas from which they were disconnected [11,12]. 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 [13]) that neural activity in primary cortices is necessary but not sufficient for awareness.
So, vegetative patients still show cerebral activation but this seems limited to subcortical and “low-level” primary cortical areas, unconnected to the fronto-parietal network necessary for awareness. Can functional neuroimaging disentangle the vegetative from the minimally conscious state?

**Vegetative is not minimally conscious**

It remains very challenging to behaviorally differentiate vegetative from minimally conscious patients because both are, by definition, non-communicative. Functional imaging can here be of utmost value in objectively differentiating activation patterns measured during external stimulation characteristic of either clinical entity [12]. Schiff et al. was the first to use fMRI in two minimally conscious patients and showed language-related auditory stimulation using personalized narratives [14]. In the same line, PET [15] and fMRI [16] reports have used complex auditory stimuli demonstrating large-scale network activation in the minimally conscious state, normally not observed in vegetative patients.

In conclusion, the increasing use of functional neuroimaging will improve our clinical characterization of vegetative and minimally conscious survivors of severe brain damage, not only to redefine their diagnosis, but also to differentiate patients in terms of treatment (including administration of analgesics and access to neuro-rehabilitation programs), outcome and end-of-life decisions.
Questions for future research

Given the absence of a thorough understanding of the neural correlates of consciousness, functional neuroimaging results should be used with appropriate caution as proof or disproof of awareness in severely brain-damaged patients. There is, at present, no validated objective “consciousness meter”. As pointed out by Owen et al. [17], a more powerful approach to identify ‘volition without action’ in patients who are unable to communicate their experiences, might be to scan patients when asked to perform a mental imagery task, rather than to use the above described passive external stimulation paradigms. Reproducible and anatomically specific activation in individual patients during tasks that unequivocally require ‘willed action’ or intentionality for their completion could be argued to unambiguously reflect awareness. Of course, negative findings in the same circumstances could not (and should not) be used as evidence for lack of awareness.

At present, much more data and methodological validation is urgently awaited before functional neuroimaging studies can be proposed to the medical community as a tool to disentangle the clinical gray-zone that separates vegetative states from states of minimal consciousness.
BOX 1 : Other examples of dissociation between awareness and arousal

In some other diseases patients also are seemingly ‘wakeful’ and may show automatic albeit non-purposeful behavior:

Seizures
Absence seizures present as brief episodes (5-10s) of staring and unresponsiveness, often accompanied by eye-blinking and lip-smacking. fMRI studies have shown widespread deactivations in frontoparietal associative cortices during these absences [18]. Temporal lobe seizures also may impair consciousness (they are than classified ‘complex partial’ whereas if they terminate without impaired consciousness are called ‘simple partial’). Loss of responsiveness in complex partial seizures usually persists for up to several minutes and patients may show oral and manual automatisms (e.g., picking, fumbling, cycling). Contrasting ictal with interictal conditions again revealed “marked bilateral deactivation in frontal and parietal association cortex. In contrast, temporal lobe seizures in which consciousness was spared were not accompanied by these widespread changes” [19].

Sleep-walking
Somnambulism (a parasomnia occurring during deep sleep) is another example of transient non-responsive ness with partially preserved arousal and semi-purposeful behavior such as ambulation. In one patient, the only one studied so far, “large areas of frontal and parietal association cortices remained deactivated during sleepwalking” [20] (BOX figure).

INSERT BOX FIGURE

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Oversimplified illustration of consciousness’ two major components: the level of consciousness (i.e., wakefulness or arousal) and the content of consciousness (i.e., awareness or experience). 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 (that is, general anesthesia) are unconscious because they cannot be awakened (red). Dissociated states of consciousness (blue) like the vegetative state (i.e., patients being seemingly awake but lacking any behavioral evidence of ‘voluntary’ or ‘willed’ behavior) or much more short lasting equivalents such as absence and complex partial seizures and sleepwalking offer a unique opportunity to study the neural correlates of awareness.
PET images illustrating that overall cerebral metabolic rates for glucose are about twice as high in the “conscious waking state” (A) (Laureys et al., unpublished) as compared to altered states of wakefulness such as general anesthesia (B; taken from [3]) and deep sleep (C; adapted from [4]). In the vegetative state (i.e., wakeful unawareness), however, overall global cortical metabolism sometimes may have close to normal values (patient 5 taken from [5] in a vegetative state following herniation and bilateral paramedian mesodiencephalic injury (red arrow; D). Vegetative patients who recover may show no substantial increases in global metabolic function as illustrated in a patient scanned in a vegetative state following CO intoxication (E) where recovery of awareness (F) was paralleled solely by restoration of activity in frontoparietal areas (white arrows; adapted from [7]).
BOX Figure
The common hallmark of the vegetative state seems to be the 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 to cortico-cortical [6] or cortico-thalamo-cortical disconnections [9] (schematized by blue arrows). Recent functional imaging studies in similar, albeit much more transient, dissociations between wakefulness and awareness resulting in ‘automatic’ unwilled action have shown decreased blood flow in this frontoparietal network when patients suffer from complex partial seizures (in green; fMRI data taken from [19]), absence seizures (in blue; single photon computed emission tomography data - SPECT; the most adapted imaging tool to study these unpredictable seizures - taken from [18]) and sleepwalking (in yellow; SPECT data taken from [20]).
References


