

# **Brain function in brain death, coma, vegetative state, minimally conscious state and locked-in syndrome**

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Running title: Brain function in severe brain damage  
Word count abstract : 155 words  
Word count text (excluding references): 4865 words  
N° of references: 115

## **Abstract**

We review the nosological criteria and functional neuroanatomical basis for brain death, coma, vegetative state, minimally conscious state and the locked-in state. Functional neuroimaging is providing new insights into cerebral activity in patients with severe brain damage. Measurements of cerebral metabolism and brain activations in response to sensory stimuli using positron emission tomography (PET), functional magnetic resonance imaging (fMRI) and electrophysiological methods have significant potential to provide unique windows on to the presence, degree and location of any residual brain function. However, use of these techniques in severely brain-damaged persons is methodologically complex and requires careful quantitative analysis and interpretation. In addition, ethical frameworks to guide research in these patient populations must be further developed. At present, nosological distinctions confirmed by clinical examinations remain the standard for accurate diagnosis and prognosis. Neuroimaging techniques, while extremely promising, remain important tools for clinical research that should ultimately extend our understanding of the underlying mechanisms of these disorders.

## **Introduction**

An accurate and reliable evaluation of the level and content of consciousness in severely brain-damaged patients is of paramount importance for their appropriate management. Progress in intensive care efforts has increased the number of patients who survive severe acute brain damage. Although the majority of these patients recover from coma within the first days after the insult, some permanently lose all brainstem function (brain death), while others evolve to a state of ‘wakeful unawareness’ (vegetative state; VS). Those who recover, typically progress through different stages before fully or partially recovering consciousness (minimally conscious state; MCS) (figure 1). Clinical practice shows that recognizing unambiguous signs of conscious perception of the environment and of the self in such patients can be very challenging. This difficulty is reflected in the frequent misdiagnoses of VS, MCS and locked-in syndrome (LIS).<sup>1-7</sup> Bedside evaluation of residual brain function in severely brain-damaged patients is difficult because motor responses may be very limited or inconsistent. In addition, consciousness is not an all-or-none phenomenon<sup>8</sup> and its clinical assessment relies on inferences made from observed responses to external stimuli at the time of the examination.<sup>7</sup> In the present review, we will first define consciousness as it can be assessed at the patient’s bedside. We then review the major clinical entities of altered states of consciousness following severe brain damage. Finally, we will discuss recent functional neuroimaging findings in these conditions with a special emphasis on VS patients.

## **Consciousness, awareness and arousal**

Consciousness is a multifaceted concept that can be divided into two major components: the level of consciousness (i.e., arousal, wakefulness or vigilance) and the content of consciousness (i.e., awareness of the environment and of the self) (figure 2).<sup>9,10</sup> Arousal is supported by several brainstem neuronal populations that directly project to both thalamic and

cortical neurons.<sup>11</sup> Therefore depression of either brainstem or both cerebral hemispheres may cause reduced wakefulness. Brainstem reflexes are a key to the assessment of the functional integrity of the brainstem. However, profound impairment of brainstem reflexes can sometimes coexist with intact function of the reticular activating system if the tegmentum of the rostral pons and mesencephalon are preserved. Awareness is thought to be dependent upon the functional integrity of the cerebral cortex and its reciprocal subcortical connections; each of its many aspects resides to some extent in anatomically defined regions of the brain.<sup>12,13</sup> Unfortunately, for the time being, consciousness cannot be measured objectively by any machine. Its estimation requires the interpretation of several clinical signs. Many scoring systems have been developed for the quantification and standardization of the assessment of consciousness (for review see<sup>14</sup>).

## **Clinical definitions**

### **Brain death**

The concept of brain death as defining the death of the individual is largely accepted. Most countries have published recommendations for the diagnosis of brain death but the diagnostic criteria differ from country to country.<sup>15</sup> Some rely on the death of the brainstem only,<sup>16</sup> others require death of the whole brain including the brain stem.<sup>17</sup> However, the clinical assessments for brain death are very uniform and based on the loss of all brainstem reflexes and the demonstration of continuing apnoea in a persistently comatose patient.<sup>18</sup>

### **Coma**

Coma is characterized by the absence of arousal and thus also of consciousness. It is a state of unarousable unresponsiveness in which the patient lies with the eyes closed and has no awareness of self and surroundings. The patient lacks the spontaneous periods of wakefulness

and eye-opening induced by stimulation that can be observed in the VS.<sup>9</sup> To be clearly distinguished from syncope, concussion, or other states of transient unconsciousness, coma must persist for at least one hour. In general, comatose patients who survive begin to awaken and recover gradually within 2 to 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.

### **Vegetative state**

Patients in a VS are awake but are unaware of self or of the environment.<sup>19,20</sup> Jennett and Plum cited the Oxford English Dictionary to clarify their choice of the term "vegetative": to vegetate is to "live merely a physical life devoid of intellectual activity or social intercourse" and vegetative describes "an organic body capable of growth and development but devoid of sensation and thought". "*Persistent VS*" has been arbitrarily defined as a vegetative state still present one month after acute traumatic or non-traumatic brain damage but does not imply irreversibility.<sup>21</sup> "*Permanent VS*" denotes irreversibility. The Multi-Society Task Force on PVS concluded that three months following a non-traumatic brain damage and 12 months after traumatic injury, the condition of VS patients may be regarded as 'permanent'. These guidelines are best applied to patients who have suffered diffuse traumatic brain injuries and post anoxic events; other non-traumatic aetiologies may be less well predicted (see for example<sup>22,23</sup>) and require further considerations of aetiology and mechanism in evaluating prognosis. Even after these long and arbitrary delays, some exceptional patients may show some limited recovery. Particularly patients suffering non-traumatic coma without cardiac arrest who survive in VS for more than three months. The diagnosis of VS should be questioned when there is any degree of sustained visual pursuit, consistent and reproducible visual fixation, or response to threatening gestures,<sup>21</sup> but these responses are observed in some

patients who remain in VS for years. It is essential to establish the formal absence of any sign of conscious perception or deliberate action before making the diagnosis.

### **Minimally conscious state**

The criteria for MCS were recently proposed by the Aspen group to subcategorise patients above VS but unable to communicate consistently. To be considered as minimally conscious, patients have to show limited but clearly discernible evidence of consciousness of self or environment, on a reproducible or sustained basis, by at least one of the following behaviours: (1) following simple commands, (2) gestural or verbal yes/no response (regardless of accuracy), (3) intelligible verbalization, (4) purposeful behaviour (including movements or affective behaviour that occur in contingent relation to relevant environment stimuli and are not due to reflexive activity). The emergence of MCS is defined by the ability to use functional interactive communication or functional use of objects.<sup>24</sup> Further improvement is more likely than in VS patients.<sup>25</sup> However, some remain permanently in MCS. “*Akinetic mutism*” is a rare condition that has been described as a subcategory of the minimally conscious syndrome,<sup>26</sup> while other authors suggest that the term should be avoided.<sup>27</sup>

### **Locked-in syndrome**

The term "locked-in" syndrome was introduced by Plum and Posner in 1966 to reflect the quadriplegia and anarthria brought about by the disruption of corticospinal and corticobulbar pathways, respectively.<sup>9</sup> It is defined by (i) the presence of sustained eye opening (bilateral ptosis should be ruled out as a complicating factor); (ii) preserved awareness of the environment; (iii) aphonia or hypophonia; (iv) quadriplegia or quadriparesis; (v) a primary mode of communication that uses vertical or lateral eye movement or blinking of the upper eyelid to signal yes/no responses.<sup>26</sup>

## **Functional neuroanatomy**

### **Brain death**

Brain death results from irreversible loss of brainstem function.<sup>28</sup> Functional imaging using cerebral perfusion tracers and single photon emission computed tomography<sup>29-34</sup> or cerebral metabolism tracers and PET<sup>35</sup> typically show an “hollow skull phenomenon” in brain death patients, confirming the absence of neuronal function in the whole brain (figure 3).

### **Coma**

Coma can result from diffuse bihemispheric cortical or white matter damage secondary to neuronal or axonal injury, or from focal brainstem lesions that affect the pontomesencephalic tegmentum and/or paramedian thalami bilaterally. On average, grey matter metabolism is 50-70% of normal values in comatose patients of traumatic or hypoxic origin.<sup>36-39</sup> However, in patients with traumatic diffuse axonal injury both hyperglycolysis and metabolic depression have been reported.<sup>40-43</sup> In patients who recover from a postanoxic coma, cerebral metabolic rates for glucose are 75% of normal values.<sup>44</sup> Cerebral metabolism has been shown to correlate poorly with the level of consciousness, as measured by the Glasgow Coma Scale, in mild to severely head-injured patients studied within the first month following head trauma.<sup>45</sup> More recently however, using newer generation PET scanning, a correlation was observed between the level of consciousness and regional cerebral metabolism when patients were studied within 5 days of trauma.<sup>38</sup> Lower metabolism was reported in the thalamus, brainstem and cerebellar cortex of comatose compared to non-comatose brain trauma survivors. The mechanisms underlying these changes in cerebral metabolism are not yet fully understood. At present, there is no established correlation between cerebral metabolic rates of glucose or oxygen as measured by PET and patient outcome.

A global depression of cerebral metabolism is not unique to coma. When different anaesthetics are titrated to the point of unresponsiveness, the resulting reduction in brain metabolism is similar as that observed in comatose patients.<sup>46-48</sup> The lowest values of brain metabolism have been reported during propofol anesthesia (28% of normal values).<sup>46</sup> Another example of transient metabolic depression can be observed during deep sleep (stage III and IV).<sup>49,50</sup> In this daily physiological condition cortical cerebral metabolism can drop to nearly 40% of normal values (figure 4).

## **Vegetative state**

### ***Resting brain function***

In the VS the brainstem is relatively spared whereas the grey and/or white matter of both cerebral hemispheres are widely and severely damaged. Overall cortical metabolism of vegetative patients is 40-50% of normal values.<sup>37,44,51-60</sup> Some studies however, have found normal cerebral metabolism<sup>57</sup> or blood flow<sup>61</sup> in patients in a VS. In “*permanent*” VS (i.e., 12 months after a trauma or 3 months following a non-traumatic brain damage), brain metabolism values drop to 30-40% of normal values.<sup>37</sup> This progressive loss of metabolic functioning over time is the result of progressive Wallerian and transsynaptic neuronal degeneration. Characteristic of VS patients is a relative sparing of metabolism in the brainstem (encompassing the pedunculo-pontine reticular formation, the hypothalamus and the basal forebrain).<sup>62</sup> The functional preservation of these structures allows for the preserved arousal and autonomic functions in these patients. The other hallmark of the vegetative state is a systematic impairment of metabolism in the polymodal associative cortices (bilateral prefrontal regions, Broca’s area, parieto-temporal and posterior parietal areas and precuneus).<sup>58</sup> These regions are known to be important in various functions that are necessary for consciousness, such as attention, memory and language.<sup>63</sup> It is still controversial whether



the observed metabolic impairment in this large cortical network reflects an irreversible structural neuronal loss,<sup>64</sup> or functional and potentially reversible damage. However, in the rare cases where VS patients recover awareness of self and environment, PET shows a functional recovery of metabolism in these same cortical regions.<sup>59</sup> Moreover, the resumption of long-range functional connectivity between these associative cortices and between some of these and the intralaminar thalamic nuclei parallels the restoration of their functional integrity.<sup>65</sup> The cellular mechanisms which underlie this functional normalization remain putative: axonal sprouting, neurite outgrowth, cell division (known to occur predominantly in associative cortices in normal primates)<sup>66</sup> have been proposed candidate processes.<sup>67</sup> The challenge is now to identify the conditions in which, and the mechanisms by which, some vegetative patients may recover consciousness.

### ***Brain activation studies***

The first H<sub>2</sub><sup>15</sup>O-PET study in a VS patient used an auditory paradigm. Compared to non-word sounds, the authors observed an activation in anterior cingulate and temporal cortices when a post-traumatic vegetative patient was auditorily presented a story told by his mother.<sup>68</sup> They interpreted this finding as possibly reflecting the processing of the emotional attributes of speech or sound. Another widely discussed PET study dealt with activity during visually presented photographs of familiar faces compared to that during meaningless pictures in an upper boundary vegetative or lower boundary minimally conscious post-encephalitis patient who subsequently recovered. Although there was no evidence of behavioural responsiveness except occasional visual tracking of family members, the visual association areas encompassing the fusiform face area showed significant activation.<sup>22</sup> In cohort studies of patients unequivocally meeting the clinical diagnosis of the VS, simple noxious somatosensory<sup>69</sup> and auditory<sup>60,70</sup> stimuli have shown systematic activation of primary

sensory cortices and lack of activation in higher order associative cortices from which they were functionally disconnected. High intensity noxious electrical stimulation activated midbrain, contralateral thalamus and primary somatosensory cortex in each and every one of the 15 vegetative patients studied, even in the absence of detectable cortical evoked potentials.<sup>69</sup> However, secondary somatosensory, insular, posterior parietal and anterior cingulate cortices, which were activated in all control subjects, failed to show significant activation in a single vegetative patient (figure 5). Moreover, in the VS patients, the activated primary somatosensory cortex was shown to exist as an island, functionally disconnected from higher-order associative cortices of the pain-matrix. Similarly, although simple auditory click stimuli activated bilateral primary auditory cortices in vegetative patients, hierarchically higher-order multimodal association cortices were not activated. Moreover, a cascade of functional disconnections were observed along the auditory cortical pathways, from primary auditory areas to multimodal and limbic areas,<sup>70</sup> suggesting that the observed residual cortical processing in the VS does not lead to integrative processes which are thought to be necessary for awareness.

### ***Vegetative patients with atypical behavioural fragments***

Stereotyped responses to external stimuli, such as grimacing, crying or occasional vocalization are frequently observed on examination of VS patients. These behaviours are assumed to arise primarily from brainstem circuits and limbic cortical regions that are preserved in VS. Rarely, however, patients meeting the diagnostic criteria for the VS exhibit behavioural features that *prima facie* appear to contravene the diagnosis. A series of studies of chronic vegetative patients examined with multimodal imaging techniques identified three such patients with unusual behavioural fragments. Preserved areas of high resting brain metabolism (measured with fluorine-18-labelled deoxyglucose PET) and uncompletely

preserved gamma-band responses (measured with magnetoencephalography) were fitted to structural data from an MRI as well as the behaviours of the patients.<sup>57</sup> Among those studied was a patient in VS for 20 years who infrequently expressed single words (typically epithets) unrelated to any environmental stimulation.<sup>71</sup> MRI images demonstrated severe subcortical damage. Resting FDG-PET measurements of the patient's brain revealed a global cerebral metabolic rate of <50% of normal across most brain regions with small regions in the left hemisphere expressing higher levels of metabolism. MEG responses to bilateral auditory stimulation were confined to the left hemisphere and localized to primary auditory areas (figure 6). Taken together, the imaging and neurophysiological data appeared to identify isolated sparing of left sided thalamo-cortical-basal ganglia loops that normally support language function in Heschl's gyrus, Broca's area and Wernicke's area. Similar observations in two other chronic VS patients provide novel evidence that isolated cerebral networks may remain active in rare cases of VS. Importantly, the preservation of these isolated behaviours does not herald further recovery in patients in chronic VS who have been repeatedly examined and carefully studied with imaging tools. Reliable observations of such unusual features should prompt further investigation in individual cases.

### **Minimally conscious state**

Because criteria for the MCS have only recently been introduced, there are very few functional imaging studies of patients in this condition. Preliminary data show that overall cerebral metabolism is decreased to values slightly higher but comparable to those observed in the VS. The medial parietal cortex (precuneus) and adjacent posterior cingulate cortex seem to be brain regions that differentiate minimally conscious from vegetative patients.<sup>72</sup> Interestingly, these areas are among the most active brain regions in conscious waking<sup>49,73,74</sup> and are among the least active regions in altered states of consciousness such as halothane-<sup>48</sup>

or propofol-<sup>75,76</sup> induced general anaesthesia, sleep,<sup>49,77</sup> hypnotic state,<sup>78,79</sup> dementia<sup>80,81</sup> and Wernicke-Korsakoff's or post-anoxic amnesia.<sup>82</sup> It has been suggested that this richly connected<sup>83</sup> multimodal posteromedial associative area is part of the neural network subserving human awareness (figure 7).<sup>63,74,84</sup>

Simple auditory stimulation has been shown to induce a more widespread activation in minimally conscious than in vegetative patients.<sup>60</sup> In the former, activation encompassed not only primary but also auditory associative areas, suggesting a more elaborate level of processing. Moreover, cortico-cortical functional connectivity was more efficient in the MCS, compared to the VS, between auditory cortex and a large network of temporal and prefrontal cortices. Such findings encourage ongoing developments of neuromodulatory and cognitive revalidation therapeutic strategies in MCS patients.<sup>85</sup>

In a recent study of response to natural language stimuli (e.g. meaningful sentences read at normal conversational speed by a real human voice), fMRI activation patterns of MCS patients exhibiting command following were examined during presentation of forward and backward narratives read in a familiar voice and containing personally meaningful content.<sup>86</sup> In the two patients studied, components of the cortical language networks showed selective activation compared to baseline conditions. Presentation of the narratives time-reversed (played backward) that shared most of the physical properties of the sounds, activated the same networks as forward narratives in the normal controls subject, but failed to activate the networks in the MCS patients. These findings correlate with low resting metabolic activity and suggest that a residual capacity to activate large integrative networks may remain in some MCS patients. Preservation of large-scale networks in MCS patients may underlie rare instances of late recoveries of verbal fluency in such patients (also see<sup>87</sup>).

## **Locked-in syndrome**

Classically, structural brain imaging (MRI) may show isolated lesions (bilateral infarction, haemorrhage, or tumor) of the ventral portion of the basis pontis or midbrain. According to some authors, electroencephalography (EEG) and evoked potentials do not reliably distinguish the LIS from the VS.<sup>88</sup> PET scanning has shown significantly higher metabolic levels in the brains of patients in a LIS compared to patients in the VS.<sup>51</sup> Moreover, preliminary voxel-based statistical analyses show that no supra-tentorial cortical areas show a significantly lower metabolism in LIS patients when compared to healthy controls.<sup>89</sup> These findings emphasize the need to quickly both make the diagnosis and recognize the terrifying situation of patients with intact awareness of self and environment in acutely locked-in immobile bodies. Health-care workers should adapt their bedside-behaviour and consider pharmacological anxiolytic therapy, taking into account the intense emotional state acute LIS patients go through. With appropriate medical care, life expectancy may be several decades and even if the chances of motor recovery are very limited, computer-based communication methods have drastically improved the quality of life of chronic LIS patients.<sup>5,90</sup>

## **Methodological issues**

The acquisition, analysis and interpretation of neuroimaging data in severe brain damage is methodologically extremely complex.<sup>91-93</sup> In quantitative PET studies, the absolute value of cerebral metabolic rates depends on many assumptions for which a consensus has not been established in cases of cerebral pathology. For example, the estimation of the cerebral metabolic rate of glucose using FDG-PET requires a correction factor, known as the lumped constant. It is generally accepted that this lumped constant is stable in normal brains. However, in traumatic brain injury, a significant global *decrease* in lumped constant has recently been reported<sup>94</sup> and in severe cerebral ischaemia, regional lumped constant values are

known to *increase* significantly as a result of glucose transport limitation.<sup>95</sup> Second, cerebral glucose use as measured by FDG may not always be as tightly coupled with oxygen use in patients because altered metabolic states, including anaerobic glycolysis, may occur acutely after brain damage.<sup>42,96,97</sup> Third, because PET provides measurements per unit volume of brain tissue, they may be affected by the inclusion of metabolically inactive spaces such as cerebrospinal fluid or by brain atrophy which may artificially lower the calculated cerebral metabolism.<sup>98-102</sup>

While metabolic studies are useful, they can only identify functionality at the most general level; that is, mapping cortical and subcortical regions that are *potentially* recruitable, rather than relating neural activity within such regions to specific cognitive processes. So called ‘activation studies’ using H<sub>2</sub><sup>15</sup>O-PET, fMRI or MEG together with established sensory paradigms may provide a viable method for assessing cognitive processing or potentially recruitable populations of neurons in severely brain-damaged patients. However, like metabolic studies, these investigations are methodologically complex and the results are often equivocal. For example, in brain-damaged patients, the coupling between neuronal activity and local haemodynamics, essential for all H<sub>2</sub><sup>15</sup>O-PET and fMRI activation measurements, is likely to be different from healthy controls,<sup>103-106</sup> making interpretation of such data sets extremely difficult. Notwithstanding this basic methodological concern, the choice of the experimental paradigm is also critical. For example, abnormal brain stem auditory evoked responses may make the use of auditory stimuli inappropriate and alternative stimuli (i.e. visual) should be considered. The paradigm should also be sufficiently complex to exercise the cognitive processes of interest, preferably beyond those that are simply involved in stimulus perception, yet not so complex that they might easily overload residual cognitive capacities in a tired or inattentive patient. In addition, it is essential that the experimental paradigm chosen produces well documented, anatomically specific, robust and reproducible

activation patterns in healthy volunteers in order to facilitate interpretation of imaging data in patients. In VS, MCS and LIS, episodes of low arousal and sleep are also frequently observed and close patient monitoring (preferably by means of simultaneous electroencephalographic recording) during activation scans is essential to avoid such periods. Spontaneous movements during the scan itself may also compromise the interpretation of functional neuroimaging data, particularly scans acquired using fMRI.<sup>107</sup> Data processing of functional neuroimaging data may also present challenging problems in patients with acute brain damage. For example, the presence of gross hydrocephalus or focal pathology may complicate co-registration of functional data (e.g. acquired with PET or fMRI) to anatomical data (e.g. acquired using structural MRI), and the normalisation of images to a healthy reference brain.<sup>108</sup> Under these circumstances statistical assessment of activation patterns is complex and interpretation of activation foci in terms of standard stereotaxic coordinates may be impossible. Finally, as for all PET studies in humans, issues of radiation burden must be considered in these patients and may preclude longitudinal or follow-up studies

PET methodology is employed, issues of radiation burden must also be considered and may preclude longitudinal or follow-up studies in many patients.

In summary, while metabolic and molecular<sup>109</sup> studies using PET and activation studies using PET, fMRI or MEG afford exciting new opportunities in the assessment of severely brain-damaged patients, all of these techniques are methodologically extremely complex and are subject to multiple difficulties of analysis and interpretation. Such concerns necessitate that, for the foreseeable future, functional imaging will compliment, rather than replace, standardized repeated clinical evaluation by experienced and appropriately qualified personnel.

## **Ethical issues**

Severely brain-damaged, non-communicative patients raise several ethical concerns.<sup>110-113</sup> Foremost is the concern that diagnostic and prognostic accuracy is assured, as treatment decisions typically include the possibility of withdrawal of life-support.<sup>20,114</sup> At present, although the imaging technologies reviewed above hold great promise to improve both diagnostic and prognostic accuracy, the gold standard remains the careful and repeated neurological exam by a trained examiner. It is an overarching responsibility for investigators in the field to obtain accurate clinical assessments prior to imaging of patients in these conditions. Moreover, it is essential that all relevant clinical details are made available at least in published appendices so that comparisons between studies are possible

Ethical concerns are often raised concerning the participation of severely brain-damaged patients in neuroimaging activation studies (especially to assess pain perception), studies that require invasive procedures (e.g., intra-arterial or jugular lines required for quantification of PET data or modelling), or the use of neuromuscular paralytics. By definition, unconscious or minimally conscious patients cannot give informed consent to participate in clinical research and written approval must typically be obtained from family or legal representatives depending on governmental and hospital guidelines in each country. Nonetheless, it is not without precedent for studies in these patient populations to be refused for grants, ethics committee approval or data publication based on a view that no research study is ethical in patients who cannot provide consent. We side with a proposed ethical framework that emphasizes balancing access to research and medical advances alongside protections for vulnerable patient populations.<sup>115</sup> Severe brain damage represents an immense social and economic problem that warrants further research. Unconscious, minimally conscious, and locked-in patients are very vulnerable and deserve special procedural protections. However, it is important to stress that they are also vulnerable to being denied



potentially life-saving therapy if clinical research that can only be done on such patients cannot be performed adequately.

## **Conclusion**

Comatose, vegetative, minimally conscious or locked-in patients present unique problems for diagnosis, prognosis, treatment and everyday management. At the patient's bedside, the evaluation of possible cognitive function in these patients is difficult because voluntary movements may be very small, inconsistent and easily exhausted. Functional neuroimaging will never replace the clinical assessment of patients with altered states of consciousness. Nevertheless, it can objectively describe (using population norms) the regional distribution of cerebral activity at rest and under various conditions of stimulation. The quantification of brain activity differentiates patients who sometimes only differ by a brief and small movement of a finger. In our opinion, the future use of PET, MEG/EEG and especially fMRI will substantially increase our understanding of severely brain-damaged patients.

## **Search strategy and selection criteria**

References for this review were identified by searches of Pubmed up to April 2004 with the terms “brain death”, “coma”, “vegetative state”, “minimally conscious state” or “locked-in syndrome” combined with the term “positron emission tomography”, “magnetoencephalography” or “functional magnetic resonance imaging”, limited to English language and adult age. Articles referred to in these articles were also included. References were selected on the basis of relevance and accessibility. Abstracts and reports from meetings were included only when they related directly to previously published work. We excluded certain studies in which clinical details provided were insufficient to guarantee accuracy of diagnoses.

## **Authors’ contributions**

SL made the general plan of the review, did the literature search, contributed to all sections and made figures 1-5 and 7.

AMO reviewed the general plan of the review and the sections on methodology and functional neuroanatomy and made comments and amendments throughout during the final revision of the manuscript.

NDS reviewed the general plan of the review and contributed to the literature cited, abstract, introduction and all subsections and made figure 6.

## **Conflict of interest**

None declared

## **Acknowledgements**

SL is Research Associate at the Fonds National de la Recherche Scientifique (FNRS) and is supported by FNRS grants 3.4517.04 and by grants from the Fondation Médicale Reine Elisabeth, the Centre Hospitalier Universitaire Sart Tilman, the University of Liège, and the Mind Science Foundation. NDS is supported by NS02172, NS43451, and the Charles A. Dana Foundation.

## Figure legends

Figure 1. Flow chart of the different conditions that follow a cerebral insult. Classically vegetative state follows a coma; after 1 month the term "persistent vegetative state" is used; after 3 months (non-traumatic insult) or 1 year (traumatic insult) some authors use the term "permanent vegetative state" which implies no chance of recovery.

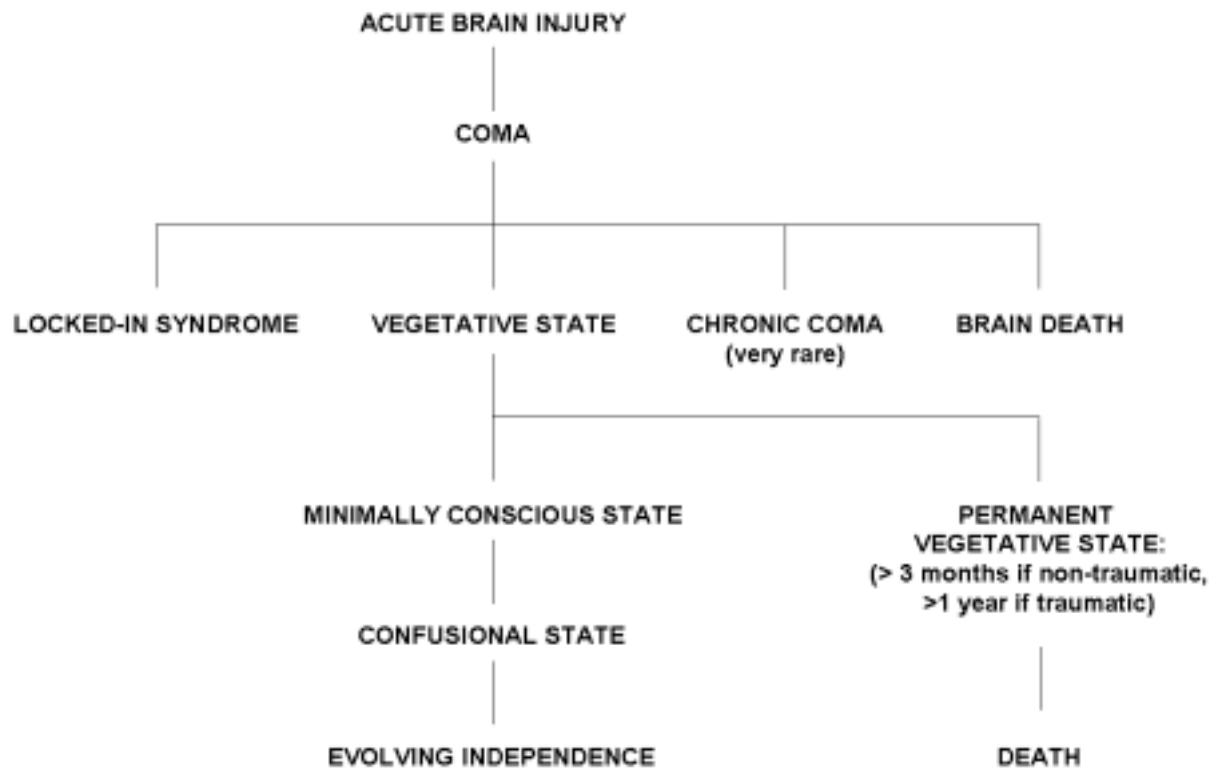


Figure 2. Graphical representation of the two components of consciousness (arousal and awareness) and their alterations in coma, the vegetative state, the minimally conscious state and in the locked-in syndrome.

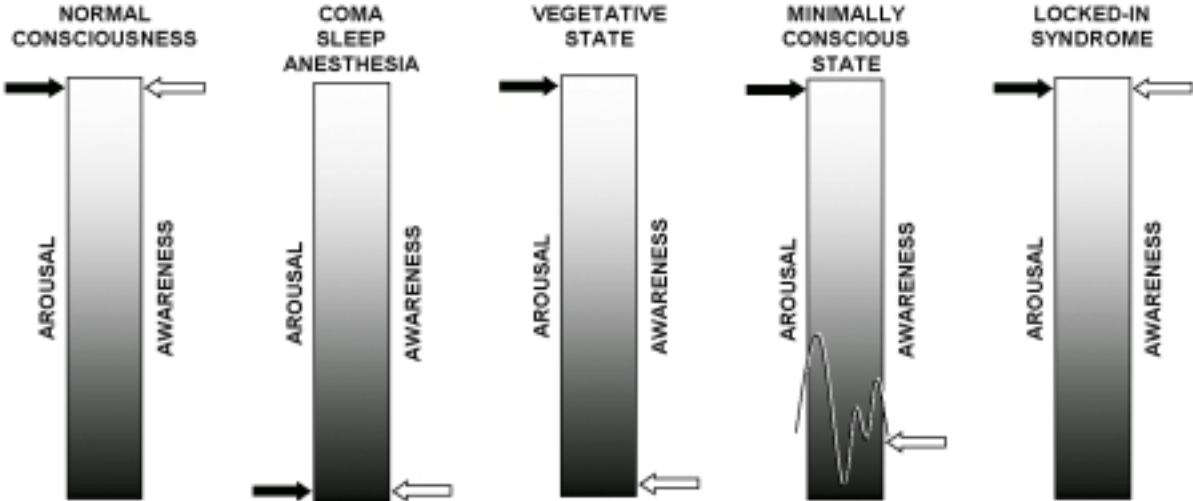


Figure 3. Cerebral metabolism in brain death measured by <sup>18</sup>F-fluorodeoxyglucose-PET: a clear-cut picture of “empty skull” tantamount to a “functional decapitation”.

[Sequence of images: sagittal (left); transverse (middle); and coronal (right)]

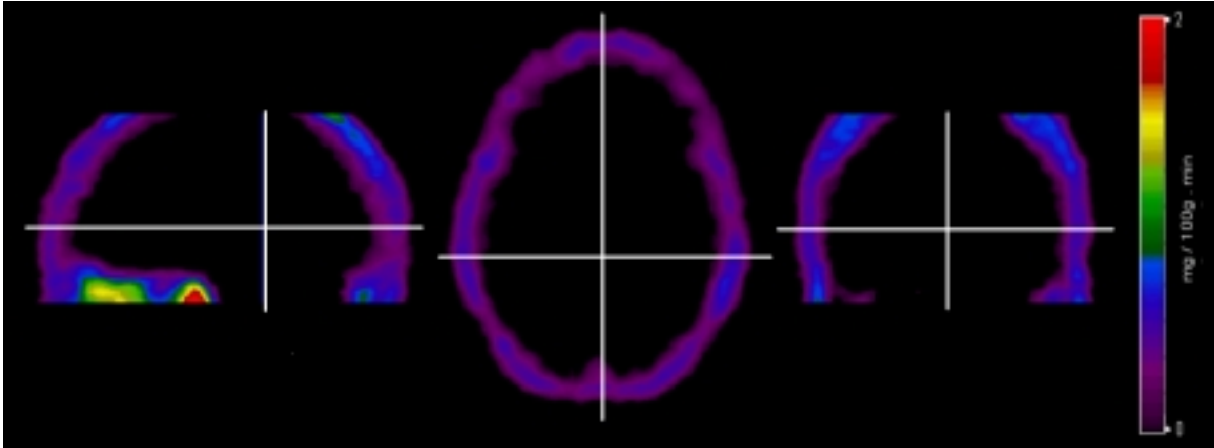


Figure 4. Cerebral metabolism in the different diagnostic groups (for references see text).

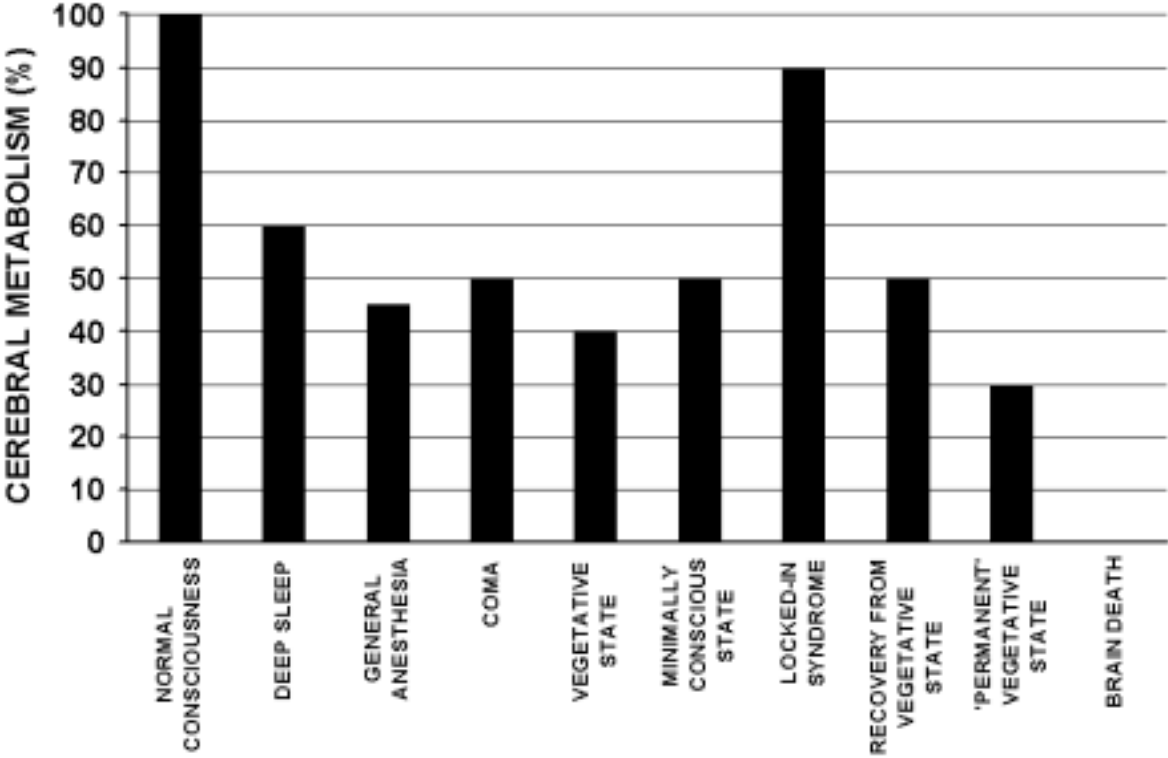


Figure 5. Pain perception in VS. (Upper) Brain regions, shown in red, that activated during noxious stimulation in controls [subtraction stimulation-rest] (Lower) Brain regions that activated during stimulation in VS patients, shown in red [subtraction stimulation-rest] and regions that activated less in patients than in controls [interaction (stimulation versus rest) x (patient versus control)], shown in blue. Projected on transverse sections of a normalized brain MRI template in controls and on the mean MRI of the patients (distances are relative to the bicommissural plane). Reproduced from Laureys et al<sup>69</sup> with permission from Elsevier.

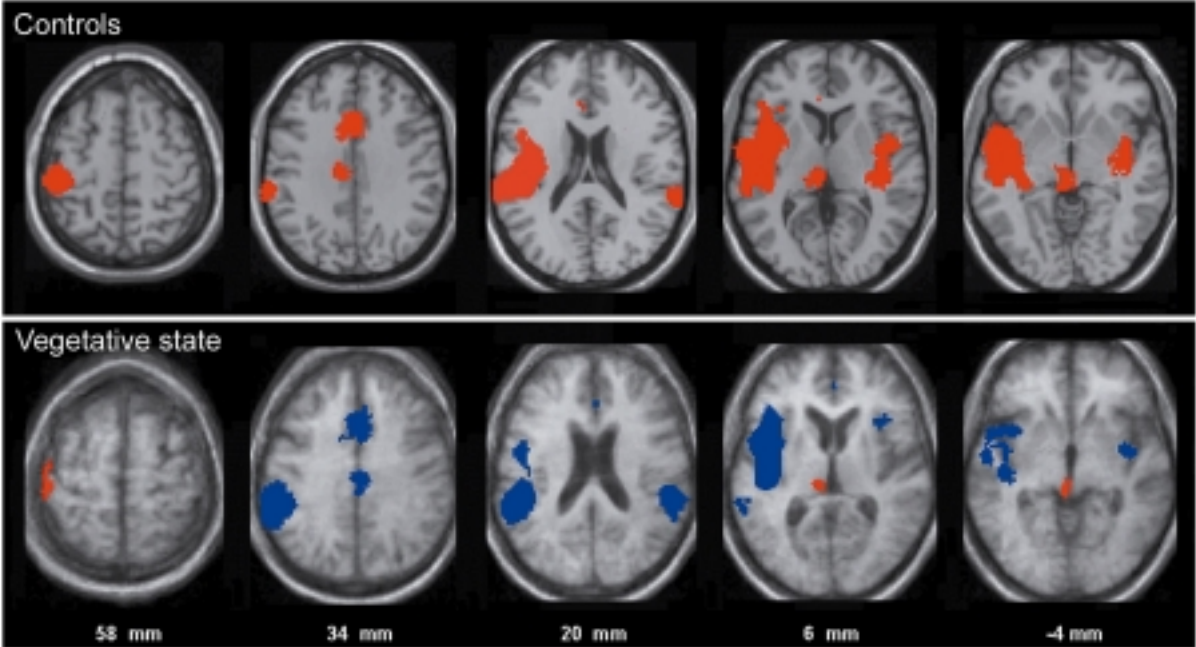




Figure 6. A. Preservation of regional cerebral metabolic activity in a chronic VS patient. FDG-PET data for VS patient with occasional expression of isolated words is displayed co-registered with structural MRI (from <sup>57</sup>) overlaid with locations of calculated MEG equivalent current dipoles identifying source of signal.<sup>71</sup> PET voxels are normalized by region and expressed on a colour scale ranging from 55 to 100% of normal. B. MEG dipole locations. Cross-hair and red dot corresponds to dipole location of maximal response at a latency of 50 milliseconds, other dipole fits at latencies of 21 (blue dot) and 35 msec (green dot) are also displayed (see 2D). C. MEG waveforms for right hemisphere gamma-band (20-50Hz filtered) mid-latency evoked activity in response to bilateral auditory stimulation. D. MEG waveforms for left hemisphere gamma-band (20-50Hz filtered) mid-latency evoked activity in response to bilateral auditory stimulation. Limited preservation of left sided auditory mid-latency evoked response supports the inference of a preserved isolated cerebral network within the left hemisphere (see text).

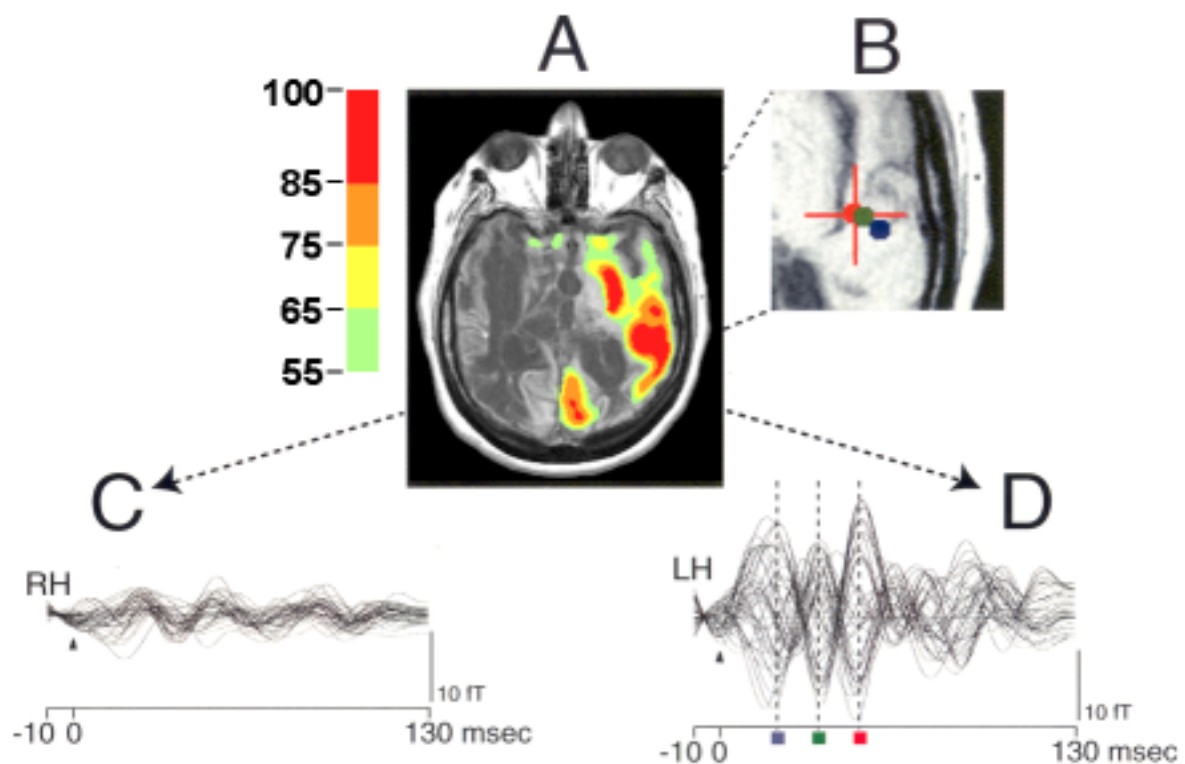
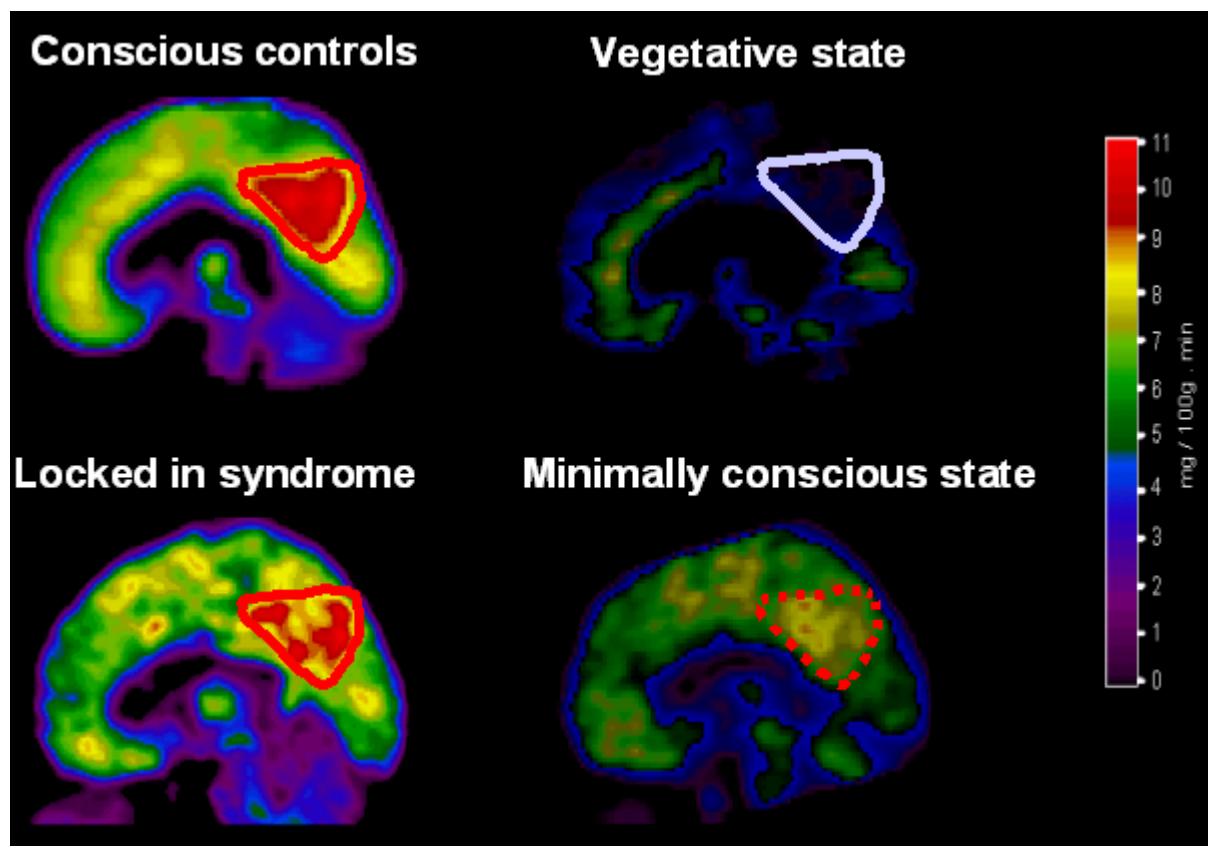


Figure 7. Illustration of resting cerebral metabolism obtained in control subjects and patients in a vegetative state, locked-in syndrome and minimally conscious state. Images are shown in a sagittal plane and represented according to the same colour-scale. Note that in normal conscious waking, the medial posterior cortex (encompassing the precuneus and adjacent posterior cingulate cortex, delineated by a red line) is the metabolically most active region of the brain; in waking vegetative patients, this same area (delineated by a blue line) is the metabolically least active region. In the locked-in syndrome, no supratentorial brain region shows significant decreases in metabolism. In the minimally conscious state, the precuneus and posterior cingulate cortex shows an intermediate metabolism, higher than in vegetative patients, but lower than in conscious controls. We hypothesize that this region represents part of the neural network subserving - human – consciousness .



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