

## **RESIDUAL CEREBRAL FUNCTIONING IN THE VEGETATIVE STATE**

S Laureys<sup>1,2,6</sup>, ME Faymonville<sup>3</sup>, X De Tiège<sup>6</sup>, J Berré<sup>7</sup>, S Elincx<sup>6</sup>, S Antoine<sup>5</sup>, N Ligot<sup>6</sup>, M Boly<sup>1,2</sup>, C Schnakers<sup>1</sup>, B Sadzot<sup>2</sup>, I Hansen<sup>2</sup>, P Damas<sup>3</sup>, N Mavrouidakis<sup>8</sup>, JL Vincent<sup>7</sup>, M Lamy<sup>3</sup>, G Moonen<sup>2</sup>, A Luxen<sup>1</sup>, S Goldman<sup>6</sup> and P Maquet<sup>1,2</sup>

Cyclotron Research Center<sup>1</sup>, Department of Neurology<sup>2</sup>, Anesthesiology and Intensive Care Medicine<sup>3</sup> and Internal Medicine<sup>4</sup>, CHU Sart Tilman, University of Liège, Liège; Department of Neurology<sup>5</sup>, AZ-VUB, Brussels; PET/Biomedical Cyclotron Unit<sup>6</sup> and Department of Intensive Care<sup>7</sup> and Neurology<sup>8</sup>, ULB Erasme, Brussels, Belgium

**LIFE-SUSTAINING TREATMENTS AND VEGETATIVE STATE: Scientific advances and ethical dilemmas  
17-18-19-20 March, 2004 Rome, Italy**

### **Summary**

Cerebral metabolism is massively reduced in the vegetative state. However, recovery of consciousness from vegetative state is not always associated with substantial changes in global metabolism. This led us to hypothesize that some vegetative patients are unconscious not just because of a global loss of neuronal function, but rather due to an altered activity in some critical brain regions and to the abolished functional connections between them. We could show that the most dysfunctional brain regions in vegetative patients are bilateral frontal and parieto-temporal associative cortices. Yet, despite the metabolic impairment, external stimulation still induces a significant neuronal activation in vegetative patients as shown by both auditory and noxious stimuli. However, this activation is limited to primary cortices and dissociated from higher-order associative cortices, thought to be necessary for conscious perception. Finally, we could show that vegetative patients have impaired functional connections between distant cortical areas and between the thalami and the cortex and, more importantly, that recovery of consciousness is paralleled by a restoration of this cortico-thalamo-cortical interaction.

### **Introduction**

Technical progress of intensive care medicine has increased the number of patients who survive severe acute brain injury. Some of these patients recover from their coma within the first days after the insult, others will take more time and go through different stages before fully or partially recovering awareness (e.g., minimally conscious state) or will permanently lose all brain functions (i.e., brain death). Clinical practice shows how difficult it is to recognize unambiguous signs of conscious perception of the environment and of the self in

these patients. This difficulty is reflected by frequent misdiagnoses of the vegetative state (Andrews et al., 1996; Childs et al., 1993). Objective assessment of residual brain function is difficult in patients with severe brain injury because their motor responses may be limited or inconsistent (Laureys et al., 2002b). In addition, consciousness is not an all-or-none phenomenon but should rather be conceptualized as a continuum between different states. There is also a theoretical limitation to the certainty of our clinical diagnosis, since we can only infer the presence or absence of conscious experience in another person. The interest of functional imaging in the vegetative state is twofold. First, vegetative patients represent an important clinical problem, in terms of diagnosis, prognosis, treatment and everyday management. Second, it offers a lesional approach to the study of human consciousness and adds to the international research effort on identifying the neural correlate of consciousness. Indeed, these patients represent genuine cases of abolition of consciousness but, contrary to comatose patients, with preserved arousal.

#### BRAIN METABOLISM IN RESTING CONDITIONS

Positron emission tomography (PET) has shown that global brain metabolism in vegetative patients is reduced to 40 to 50% of normal values. In patients with a locked-in syndrome, overall supratentorial cerebral metabolism has been shown to be preserved partially (Levy et al., 1987) or fully (Laureys et al., 2001b), whereas in cerebral metabolism in comatose patients is reduced to approximately 55% of normal values (Laureys et al., 2001a; Tommasino, 1994). Compared to cerebral glucose metabolism, cerebral blood flow seems to have a larger inter-patient variability in the vegetative state (Levy et al., 1987). Brain metabolism is lower in persistent vegetative state than in acute vegetative state (Tommasino et al., 1995). Progressive Wallerian and trans-synaptic degeneration could be responsible for this progressive loss of metabolic functioning over time. At present, there is no established correlation between brain metabolism depression and patient outcome.

A global depression of cerebral metabolism is not unique to vegetative state or coma. In slow wave sleep overall brain metabolism decreases to 60% of normal waking values (Maquet et al., 1997). Another example of transient metabolic depression is observed during general anesthesia. Indeed, when different anesthetics are titrated to the point of unresponsiveness, the resulting reduction in cerebral metabolism is comparable to that observed in vegetative patients (Alkire et al., 1999) (Fig. 1).

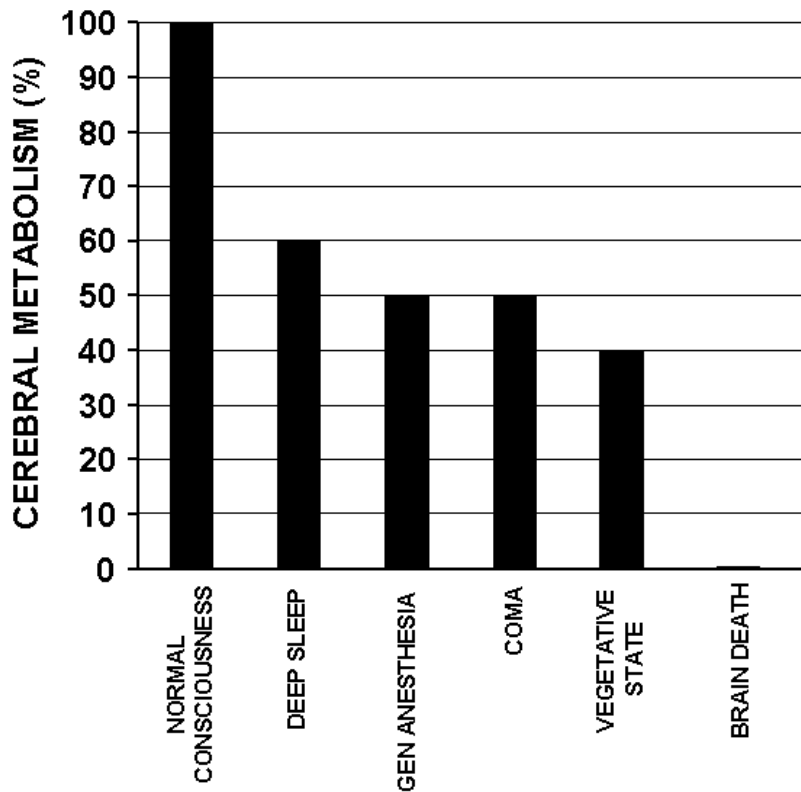


Fig 1. Cerebral metabolism in different unconscious states (for references see text).

Using voxel-based statistical methods, we could identify a common regional pattern of metabolic impairment in a set of vegetative state patients (Laureys et al., 1999a). The prefrontal, premotor and parietotemporal association cortices and the posterior cingulate/precuneus region showed the most severe functional impairment. These associative cortices are known to be involved in various consciousness-related functions such as attention, working memory, episodic memory, mental imagery, inner speech and conscious perception. Interestingly, this network is one of the most active in conscious waking and decreases its activity in unconscious or minimally conscious states such as such as coma, general anesthesia, and slow wave or rapid eye movement sleep (Baars et al., 2003) (Fig. 2). Another hallmark of the vegetative state is the relative preservation of metabolism in the brainstem (encompassing the mesopontine reticular formation), basal forebrain, and posterior hypothalamus (Laureys et al., 2000d). This allows for the maintenance of vegetative functions in these patients such as: sleep-wake cycles, autonomic and ventilatory control, and cranial nerve reflexes.

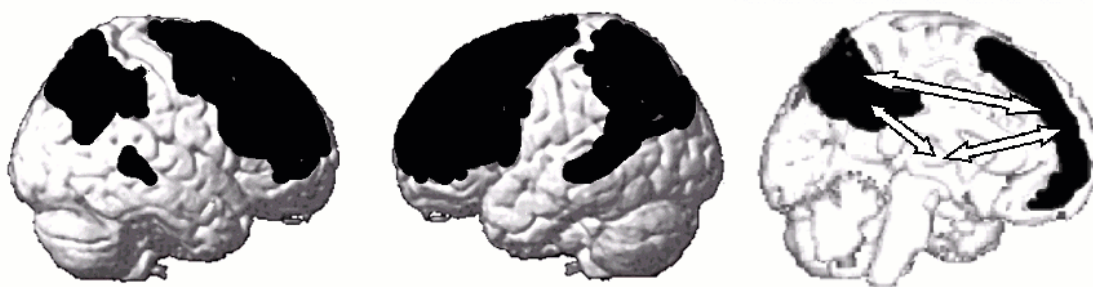


Fig 2. The functional impairment of a widespread fronto-parietal network of associative cortices (shown in black) characterizes vegetative state patients. The arrows represent the impaired cortico-cortical and cortico-thalamo-cortical connections.

More interestingly, we have had the opportunity to scan a patient during vegetative state and after recovery of consciousness (Laureys et al., 1999b). Global cortical metabolism did not show a substantial increase after recovery (4.5 mg/100g.min versus 4.7 mg/100g.min). In this patient, the recovery of consciousness seemed related to a modification of the regional distribution of brain function rather than to the global resumption of cerebral metabolism. The most important decreases in metabolism, seen during vegetative state but not after recovery, were bilateral parietal associative cortices at the convexity and at the midline (Laureys et al., 1999b).

It remains controversial whether the observed metabolic impairment in the vegetative state reflects functional and potentially reversible damage or irreversible structural neuronal loss. Rudolf and co-workers argued for the latter, using  $^{11}\text{C}$ -flumazenil as a marker of neuronal integrity in evaluating acute post-anoxic vegetative patients (Rudolf et al., 2000). We hypothesize that an impairment in cortico-cortical and thalamo-cortical modulation (i.e., functional connectivity) may at least in part explain the cerebral impairment in the vegetative state. The cellular mechanisms which underlie this functional normalization remain putative: axonal sprouting, neurite outgrowth or neurogenesis. In our opinion, the residual cerebral plasticity of some vegetative patients has been largely overlooked by the medical community and deserves further investigation (Laureys et al., 2000f). The challenge is now to identify the conditions in which, and the mechanisms by which, some vegetative patients may recover consciousness.

Finally, we could also demonstrate ‘functional disconnections’ between distal cortical areas (left prefrontal cortices and posterior cingulate cortex; Laureys, et al. 1999a) and between the thalami and the cortex (intralaminar nuclei and precuneus; (Laureys et al., 2000c) when patients in a vegetative state were compared to healthy controls. The altered cortico-thalamo-

cortical modulation in vegetative patients is in line with the role of high frequency oscillatory thalamocortical circuitry underlying human consciousness in healthy volunteers (Llinas et al., 1998). Finally, we could show that these altered cortico-thalamo-cortical loops restored near normal values after recovery of consciousness (Laureys et al., 2000e).

## BRAIN ACTIVATION DURING STIMULATION

In 1989, Momose and co-workers described a vegetative patient who increased cerebral metabolism after cervical spinal cord stimulation (Momose et al., 1989). More recently, the H<sub>2</sub><sup>15</sup>O infusion technique has been used to study changes in regional cerebral blood flow during auditory (de Jong et al., 1997) and visual (Menon et al., 1998) stimulation. Compared to non-word sounds, de Jong and co-workers observed an activation in anterior cingulate and temporal cortices when their post-traumatic vegetative patient was presented a story told by his mother. They interpreted this finding as possibly reflecting the processing of emotional attributes of speech or sound (de Jong et al., 1997). Menon and co-workers presented photographs of familiar faces and meaningless pictures to a vegetative patient who subsequently recovered. The visual association areas showed significant activation when faces were compared to meaningless stimuli (Menon et al., 1998).

Our group was the first to study pain perception in persistent vegetative state patients (Laureys et al., 2002a). Using PET, we measured changes in regional cerebral blood flow during high intensity electrical stimulation of the median nerve at the wrist compared to rest in fifteen patients and in fifteen healthy controls. Evoked potentials were recorded simultaneously. Brain glucose metabolism was also quantified in each patient. The stimuli were experienced as highly unpleasant to painful in controls. In patients, overall cerebral metabolism was 40% of normal values. Nevertheless, noxious somatosensory stimulation activated midbrain, contralateral thalamus and primary somatosensory cortex in each and every vegetative patient, even in the absence of detectable cortical evoked potentials. Secondary somatosensory, bilateral insular, posterior parietal and anterior cingulate cortices did not show activation in any patient and the activated primary somatosensory cortex was functionally disconnected from higher-order associative cortices.

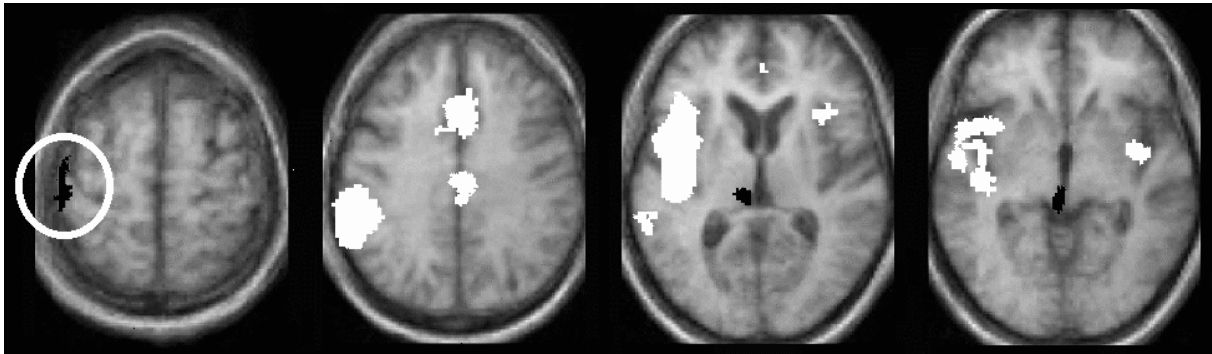


Fig 3. Brainstem, thalamus and primary somatosensory cortex (white circle) activate during noxious stimulation in persistent vegetative state patients (shown in black) but higher-order associative cortices do not (shown in white) (Adapted from Laureys et al., 2002a).

Similarly, auditory stimulation activated bilateral primary, but not associative, auditory cortices in vegetative patients (Laureys et al., 2000b). Functional connectivity assessment revealed that the auditory association cortex was ‘disconnected’ from posterior parietal cortex, anterior cingulate cortex and hippocampus (Laureys et al., 2000a). Thus, despite an altered resting metabolism, primary cortices still seem to activate during external stimulation in vegetative patients whereas hierarchically higher-order multimodal association areas do not. The observed cortical activation is isolated and dissociated from higher-order associative cortices, suggesting that the observed residual cortical processing in the vegetative state is insufficient to lead to integrative processes thought to be necessary to attain the normal level of awareness (Schiff *et al.*, 2002). Minimally conscious patients, however, did show activation of the auditory cortices in a much more similar way than did controls (Boly et al., 2003).

It is very important to stress that these results should be interpreted at the ‘population-level’ and must be used with great caution regarding clinical or ethical decisions in individual persons in a vegetative state. Future studies, using more powerful techniques such as functional MRI, are needed to assess noxious and cognitive processing of individual patients studied over time.

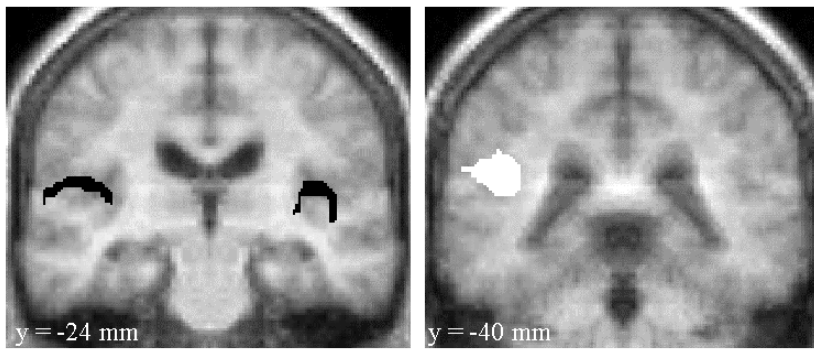


Fig 4. Bilateral primary auditory cortices (shown in black) activate during auditory stimulation in vegetative state patients but higher-order associative auditory cortices (shown in white) do not (Adapted from Laureys et al., 2000b).

## CONCLUSION

The vegetative state is a devastating medical condition of wakefulness unaccompanied by any evidence of awareness. At the patient's bedside, the evaluation of possible cognitive function in vegetative patients is difficult because voluntary movements may be very limited, inconsistent and easily exhausted. Functional neuroimaging can describe objectively how deviant from normal is the cerebral activity and its regional distribution, at rest and under various conditions of stimulation. In our opinion, the use of PET on growing scale and the future use of functional MRI will substantially increase our understanding of severely brain-injured patients. We have shown that certain vegetative patients remain unconscious not because of a widespread neuronal loss, but due to the impaired activity in some critical brain areas and to an altered functional relationship between them. The most severely affected brain regions in vegetative state patients are localized in the frontal and parieto-temporal associative cortices. By means of functional connectivity analyses we further demonstrated that patients in a vegetative state suffer from cortico-cortical and cortico-thalamo-cortical 'functional disconnections'. Moreover, in the rare patients who recovered consciousness, we observed a restoration of regional metabolic brain function and resumption of cortico-thalamo-cortical functional connectivity. Finally, we have quantified a preserved neural reactivity to noxious and auditory stimuli (despite the well-known massive metabolic cortical depression). This cerebral activation, however, is isolated and limited to subcortical and primary cortical areas it is disconnected from the higher-order cortices considered to be necessary for conscious perception. In the absence of a generally accepted neural correlate of human consciousness, it remains very difficult to interpret functional neuroimaging data from severely brain-injured patients as a proof or disproof of their 'unconsciousness'. We hope that further research

efforts will more closely correlate functional imaging with behavioral assessment, electrophysiological findings, and possibly outcome in these challenging neurological patients.

#### ACKNOWLEDGEMENTS

SL and PM are respectively Research Associate and Research Director at the Fonds National de la Recherche Scientifique de Belgique (FNRS). We thank the family of the patients and the patients who subsequently recovered for their collaboration to our research projects.

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