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Brain function in the vegetative state

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Abstract

Positron emission tomography (PET) techniques represent a useful tool to better understand the residual brain function in vegetative state patients. It has been shown that overall cerebral metabolic rates for glucose are massively reduced in this condition. However, the recovery of consciousness from vegetative state is not always associated with substantial changes in global metabolism. This finding 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 used voxel-based Statistical Parametric Mapping (SPM) approaches to characterize the functional neuroanatomy of the vegetative state. The most dysfunctional brain regions were bilateral frontal and parieto-temporal associative cortices. Despite the metabolic impairment, external stimulation still induced a significant neuronal activation (i.e., change in blood flow) in vegetative patients as shown by both auditory click stimuli and noxious somatosensory stimuli. However, this activation was limited to primary cortices and dissociated from higher-order associative cortices, thought to be necessary for conscious perception. Finally, we demonstrated 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.

Key words : Vegetative state ; consciousness ; functional neuroimaging ; positron emission tomography ; brain metabolism, cerebral blood flow ; functional connectivity ; brain plasticity.

Introduction

Progress of medicine in general and intensive care in particular 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, vegetative state) or will permanently lose all brain functions (i.e., brain death). Clinical practice shows how puzzling 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 locked-in syndrome, coma, minimally conscious state and vegetative state (Childs *et al*., 1993 ; Andrews *et al*., 1996). 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 (Wade and Johnston, 1999). 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 (Bernat, 1992).

In 1972, Jennet and Plum defined the vegetative state as a clinical condition of "wakefulness without awareness". They cited the Oxford English Dictionary to clarify their choice of the term "vegetative" as : "to vegetate is to live a merely 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". Table 1 summarizes the criteria for the diagnosis of vegetative state (The Multi-Society Task Force on PVS, 1994). It is important to distinguish between persistent and permanent vegetative state. A vegetative state is said *persistent* when it persists after an arbitrary period of one month after acute traumatic or

Table 1

Criteria of vegetative state

- 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 brainstem autonomic functions to permit survival with medical and nursing care.
- Bowel and bladder incontinence.
- Variably preserved cranial-nerve and spinal reflexes.

From the Multi-Society Task Force on PVS (1994).

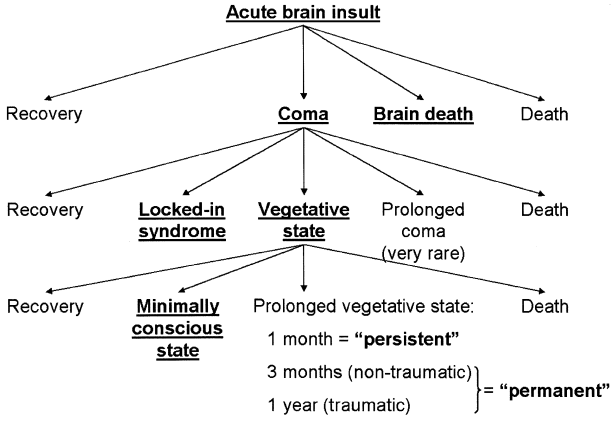

FIG. 1. — Flow chart of the different clinical conditions that follow a severe brain lesion.

non-traumatic brain injury (The Multi-Society Task Force on PVS, 1994) but this does not imply irreversibility. A vegetative state is said *permanent* when one predicts that the patient will not recover. This distinction was introduced by the American Multi-Society Task Force on PVS in 1994 to denote irreversibility after three months following a non-traumatic brain injury and twelve months after traumatic injury (Fig. 1). However, even after these long and arbitrary delays, some patients may exceptionally recover. Hence, the *American Congress of Rehabilitation Medicine* advocated to abandon the term "permanent" in favor of simply defining the duration of the vegetative state (American Congress of Rehabilitation Medicine, 1995).

Patients in a vegetative state usually show reflex or spontaneous eye opening and breathing. At times they seem to be awake with their eyes open, sometimes showing spontaneous roving eye movements and occasionally moving trunk or limbs in meaningless ways. At other times they may keep their eyes shut and appear to be asleep. They may be aroused by painful or prominent stimuli opening their eyes if they are closed, increasing their respiratory rate, heart rate and blood pressure and occasionally grimacing or moving. Pupillary, corneal, oculocephalic and gag reflexes are often preserved. Vegetative patients can make a range of spontaneous movements including chewing, teeth-grinding and swallowing. More distressingly, they can even show rage, cry, grunt, moan, scream or smile reactions spontaneously or to non-verbal sounds. Their head and eyes sometimes, inconsistently, turn fleetingly towards new sounds or sights. These abilities are also seen in another group of patients showing preserved wakefulness without awareness – namely, infants with anencephaly – and are considered to be of subcortical origin (The Medical Task Force on Anencephaly, 1990). The diagnosis of vegetative state should be questioned when there is any degree of sustained visual pursuit, consistent and reproducible visual fixation, or response to threatening gestures. When patients undergo a transition from the vegetative state to a state of awareness, one of the first and most readily observed clinical signs of this transition is the appearance of sustained visual pursuit. The crucial element to ascertain is the formal absence of any sign of conscious perception or deliberate action. Any evidence of communication, including a consistent response to command, or any purposeful movement rules out the diagnosis. This evidence can easily be missed, especially in patients whose senses and motor capacities are severely impaired and in whom a blink of an eye (e.g., locked-in syndrome) or the subtle movement of a finger (e.g. minimally conscious state) may provide the only evidence of awareness. Careful and prolonged observation is indispensable as fluctuating arousal or motivation can prevent the assessment of minimal yet present awareness in these patients.

Apallic state or syndrome is an archaic term for a condition that is now considered equivalent to vegetative state. The term neocortical death has been used differently by various authors. Some refer to it as a vegetative state with absence or substantial slowing of electrocortical activity on electroencephalography (EEG), in addition to the characteristics of vegetative state. Others equate neocortical death with the ostensible death of all neurons of the cerebral cortex. It is not clear whether this term denotes a clinical syndrome or its electrical, pathologic, or anatomical features (The Multi-Society Task Force on PVS, 1994). The American Neurological Association has suggested abandoning the terms apallic state or syndrome, neocortical death, coma vigile, alpha coma and permanent unconsciousness (ANA Committee on Ethical Affairs, 1993).

Three factors clearly influence the chances of recovery from vegetative state : age, etiology, and time already spent in a vegetative state. The outcome is better after traumatic than non-traumatic

Table 2

Whole-brain averaged global metabolism levels in vegetative state, anaesthesia and deep sleep (% decrease from normal)

Reference	Condition	Decrease in metabolism (mean ± SD and range)	Number of subjects
	Vegetative state (aetiology, duration)		
Levy *et al*. (1987)	Hypoxic/Traumatic, 3 weeks-68 months	60% (53-67%)[a]	7
De Volder *et al*. (1990)	Hypoxic, 5.5 weeks-16 weeks	53% (43-65%)[b]	7
Tommasino *et al*. (1995)	Hypoxic/Traumatic,		
	< 3 months (hypoxic) < 12 months (traumatic)	48%	6
	> 3 months (hypoxic) > 12 months (traumatic)	65%	4
Rudolf *et al*. (1999b)	Hypoxic		
	< 3 months	17%[a,c]	11
	> 3 months	33%[a,c]	13
Our data	Hypoxic / Toxic / Traumatic, 0.5 weeks-18 weeks	56 ± 15% (37-72%)[b]	30
	Non-REM Sleep		
Buchsbaum *et al*. (1989)	(stages II and III)	32%	12
Maquet *et al*. (1990a)	(stages III and IV)	44 ± 14%	4
	General anaesthesia (agent titrated to the point of unresponsiveness)		
Alkire *et al*. (1999)	Halothane	40 ± 9% (28-53%)	5
Alkire *et al*. (1997)	Isoflurane	46 ± 11% (29-55%)	5
Alkire *et al*. (1995)	Propofol	55% (35-72%)	6

[a]cortical metabolism ; [b]gray matter metabolism ; [c]no arterial blood sampling.

brain injury, better in children, and worse as time passes (The Multi-Society Task Force on PVS, 1994). Clinical, EEG, evoked potentials (EP), or structural imaging data do not permit to reliably predict the prognosis of individual vegetative patients (Jennett, 2002).

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.

Resting brain metabolism

Changes in global cerebral metabolism

Positron emission tomography (PET) has shown a substantial reduction in global brain metabolism in vegetative patients (Table 2). Studies from our group and others have shown a 50 to 60% decrease in brain metabolism in vegetative state of different etiology and duration. 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 comatose patients a 45% decrease in cerebral metabolism has been observed (Tommasino, 1994 ; Laureys *et al*., 2001a). De Volder and co-workers have shown that patients regaining consciousness after post-anoxic coma show cerebral metabolic rates for glucose (CMRGlu) that remain 25% below normal (De Volder *et al*., 1990). Compared to cerebral glucose metabolism, cerebral blood flow seems to have a larger inter-patient variability in the vegetative state (Levy *et al*., 1987). CMRGlu is lower in persistent vegetative state than in acute vegetative state (Tommasino *et al*., 1995). Progressive Wallerian and transsynaptic degeneration could be responsible for this progressive loss of metabolic functioning over time. At present, there is no established correlation between CMRGlu depression and patient outcome.

A global depression of cerebral metabolism is not unique to vegetative state or coma (see Table 2). In slow wave sleep overall brain metabolism decreases 44% below normal waking values (Buchsbaum *et al*., 1989 ; 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 CMRGlu is comparable to that observed in vegetative patients (Alkire *et al*., 1995 ; 1997 ; 1999).

Changes in regional cerebral metabolism

Using ROI (region of interest) analysis, previous PET studies have showed overall reduction in cortical metabolism (Levy *et al*., 1987 ; De Volder *et al*., 1990 ; Tommasino *et al*., 1995 ; Rudolf *et al*., 1999) with most profound reductions in the parieto-occipital and mesiofrontal cortices (De Volder *et al*., 1990). By means of a voxel-based Statistical Parametric Mapping analysis (SPM ; Friston, 1997), we have been able to identify a common

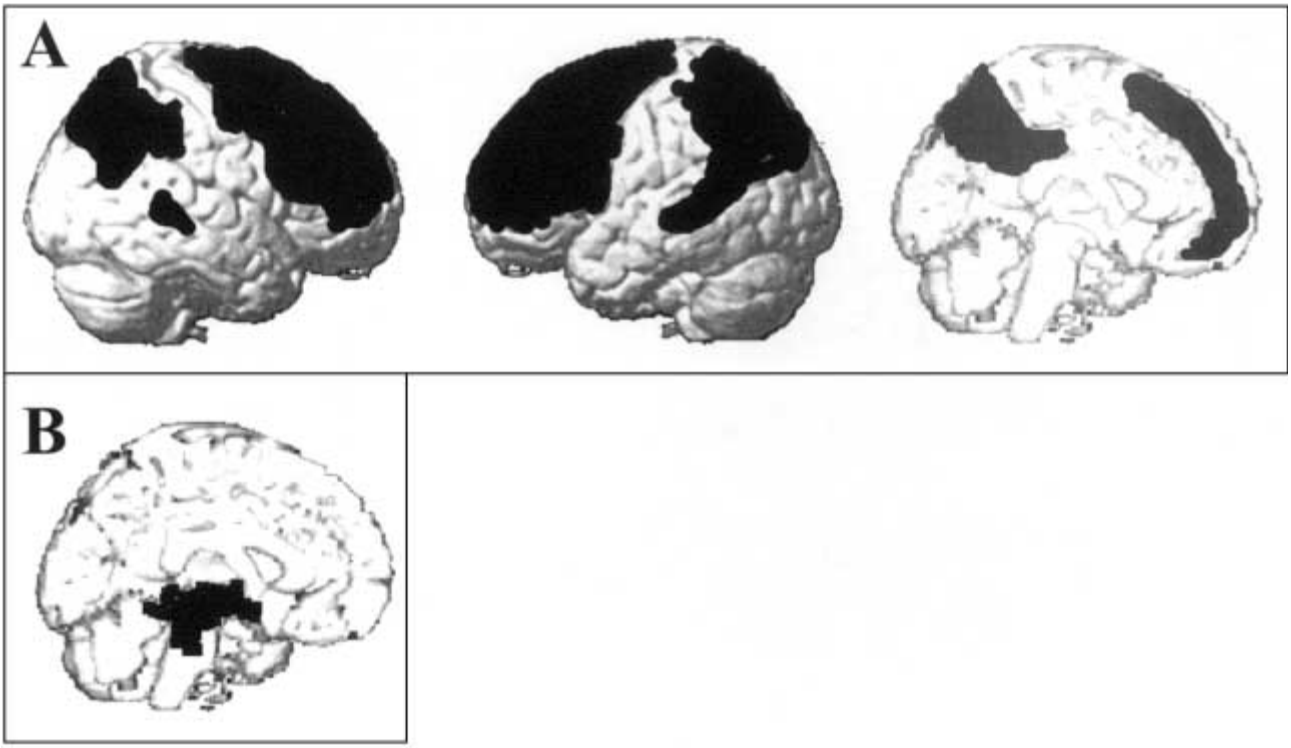

FIG. 2. — The common pattern of altered cerebral metabolism characterizing vegetative state patients : A schematic representation of areas where metabolism is (A) relatively most impaired and (B) relatively spared. From Laureys *et al*. (2000d).

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 (Fig. 2A). This pattern is in agreement with postmortem findings where involvement of the association cortices is frequently encountered (Kinney and Samuels, 1994). These associative cortices are known to be involved in various consciousness-related functions such as attention (Posner, 1994), working memory (Courtney *et al*., 1998), episodic memory (Shallice *et al*., 1994), language (Mesulam, 1990) and conscious perception (Lumer *et al*., 1998),

Interestingly, the precuneus and adjacent posterior cingulate cortex are one of the most active cerebral regions (together with the anterior cingulate and mesiofrontal cortex) in conscious waking (Andreasen *et al*., 1995 ; Maquet *et al*., 1997 ; Gusnard and Raichle, 2001). Moreover, it is one of the least active regions in unconscious or minimally conscious states such as such as halothane anesthesia (Alkire *et al*., 1999), slow wave sleep (Maquet *et al*., 1997), rapid eye movement sleep (Maquet *et al*., 1996) and Wernicke-Korsakoff's or post-anoxic amnesia (Aupee *et al*., 2001). The precuneus is also the site of earliest reduction in glucose metabolism in Alzheimer's disease (Minoshima *et al*., 1997). These observations suggest that the precuneus and posterior cingulate cortex represent part of the critical neural network subserving conscious experience.

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 (Fig. 2B) (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. This finding is in line with the post-mortem neuropathological observations that these structures are relatively preserved in the vegetative state (Kinney and Samuels, 1994).

CHANGES IN CEREBRAL METABOLISM AFTER RECOVERY OF CONSCIOUSNESS

More interestingly, we have had the opportunity to scan a patient during vegetative state and after recovery of consciousness (Laureys *et al*., 1999b). Global gray matter CMRGlu 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. Using SPM (Friston, 1997), we identified the most important decreases in metabolism, seen during vegetative state but not after recovery, in the bilateral parietal associative cortices at the convexity and at the midline (precuneus and posterior cingulate cortex ; Laureys *et al*., 1999b). To our knowledge there is only one other case report of PET scanning during vegetative state and after

recovery of consciousness (De Volder *et al*., 1990). In this case also, global gray matter CMRGlu did not show a substantial increase after recovery (5.0 mg/100 g.min versus 5.2 mg/100 g.min). Although no SPM analysis was performed, ROI analysis showed the largest regional increase in parieto-occipital cortices. Again, these data point to a critical role for the posterior associative cortices in the emergence of consciousness.

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}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, cell division (known to occur predominantly in associative cortices in normal primates ; Gould *et al*., 1999) or even apoptosis. 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.

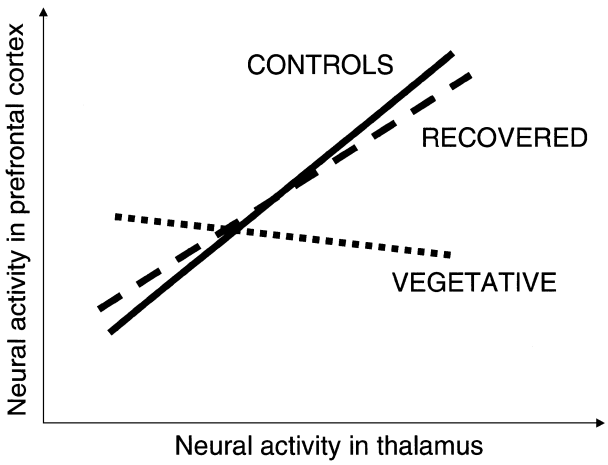

FIG. 3. — Schematic representation of a cerebral connectivity study in functional imaging. The graph shows the difference in modulation between the thalami and prefrontal cortices depending on the condition vegetative state, recovery of consciousness, and healthy control. Put simply, in controls an increase in activity in the thalami increases activity in the prefrontal cortices (full line), whereas in the vegetative state this functional relationship no longer exists (dotted line). Recovery of consciousness is paralleled by a return to near normal thalamo-cortical modulation (dashed line).

CHANGES IN FUNCTIONAL CEREBRAL CONNECTIVITY

The functional role played by any component (e.g., neuronal population) of a connected system (e.g., the brain) is largely defined by its connections. It is only since recently that we have an analytical tool to assess the functional or effective connectivity between distant cerebral areas in functional imaging (Friston *et al*., 1997). Functional connectivity is defined as the temporal correlation of a neurophysiological index (i.e., rCMRGlu or rCBF) measured in different remote brain areas, whereas effective connectivity is defined as the influence one neural system exerts over another (Buchel and Friston, 1997). A psychophysiological interaction analysis explains the activity in one cortical area in terms of an interaction between the influence of another area and some experimental condition (i.e., being a vegetative patient or a conscious control). A psychophysiological interaction means that the contribution (i.e., regression slope) of one area to another changes significantly with the experimental context assessed with the general linear model as employed by statistical parametric mapping (Friston *et al*., 1997). The statistical analysis will identify brain regions that show condition-dependent differences in modulation with another (chosen) area (Fig. 3). It is important to stress that one cannot guarantee that these connections are direct (i.e., they may be mediated through other areas) and that the two regions can have a common input (a third area, which shows context-sensitive responses, may be providing input to the two areas implicated in the psychophysiological interaction).

Using such psychophysiological interaction analyses, we could 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 (Fig. 4). The observed impairment in fronto-parietal connectivity in the vegetative state is in accordance with experiments in non-human primates where the functional integrity of the prefrontal cortex and its interactions with modality specific posterior brain regions is considered critically dependant for working memory (Goldman-Rakic, 1988). The altered 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).

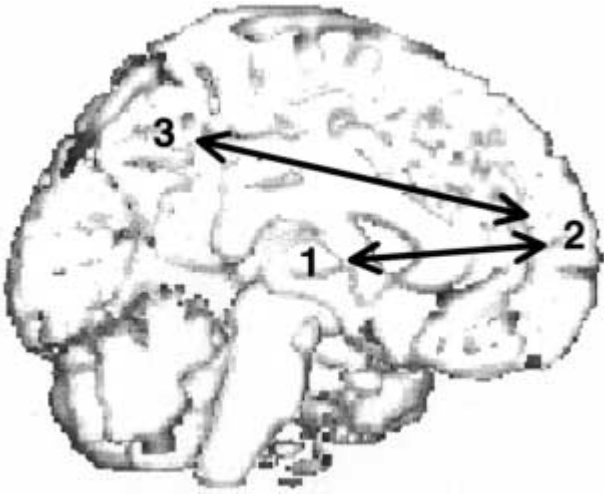

FIG. 4. — Simplified representation of the altered thalamo-cortical and cortico-cortical networks in the vegetative state. Compared to normal controls, vegetative patients suffer from an altered modulation between the thalami (1) and the prefrontal cortices (2) and between the latter and the medial parietal cortex (i.e., precuneus) and posterior cingulate cortex (3).

Cerebral activation during external stimulation

In 1989, Momose and co-workers described a vegetative patient who increased CMRGlu after cervical spinal cord stimulation (Momose *et al*., 1989). More recently, the $H_2{}^{15}O$ 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 non-sedated 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. Moreover, in patients in a persistent vegetative state, as compared to controls, the activated primary somatosensory cortex was functionally disconnected from higher-order associative cortices.

Similarly, auditory stimulation (95 dB clicks) 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). It is 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. Finally, apart from their clinical interest, these data complement to the current debate among neuroscientists concerning the relationship between neuronal activity in the nervous system (especially in primary cortex) and human consciousness (Crick and Koch, 1995 ; Tononi and Edelman, 1998).

Conclusion

The vegetative state is a devastating medical condition of wakefulness unaccompanied by any evidence of awareness. It represents a problem in terms of diagnosis, prognosis, treatment and everyday management. At the patient's bedside, the evaluation of possible cognitive function in severely brain-injured patients is difficult because voluntary movements may be very limited, inconsistent and easily exhausted. Functional neuroimaging cannot replace the clinical assessment of patients with altered states of consciousness. Nevertheless, it 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. Past studies from our own and other centers have used PET to study brain metabolism in such patients during wakeful periods. Those efforts identified a decrease in global metabolism of 50 to 60%. However, some patients who recovered from a vegetative state, improved their regional distribution of brain function rather than showing a resumption of global metabolism. This led us to postulate 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. Using voxel-based Statistical Parametric Mapping techniques we were able to identify the common neural correlate of vegetative patients. The most severely affected brain regions were localized in the frontal and parieto-temporal associative cortices. On the contrary, brainstem, posterior hypothalamus, and basal forebrain were the most spared brain regions. By means of functional connectivity analyses we further demonstrated that patients in a vegetative state suffer from thalamo-cortical and cortico-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, using cerebral activation paradigms, we have shown a preserved neural reactivity to auditory and noxious somatosensory stimuli (despite the well-known massive metabolic cortical depression). This cerebral activation, however, was limited to subcortical and primary cortical areas but seemed isolated and 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 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.

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