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BRAIN FUNCTION IN THE VEGETATIVE STATE

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1. INTRODUCTION

The vegetative state (VS) is a devastating medical condition characterized by preserved wakefulness contrasting with absent voluntary interaction with the environment (Figure 1). It can be diagnosed soon after a brain injury and can be partially or totally reversible, or it may progress to a persistent VS or death. It is important to distinguish between VS, persistent VS and permanent VS. Persistent VS is arbitrarily coined as a VS present one month after acute traumatic or non-traumatic brain injury or lasting at least one month in patients with degenerative or metabolic disorders or developmental malformations,[1] but does not imply irreversibility. Permanent VS implies the prediction that the patient will not recover. It was introduced by the American Multi-Society Task Force on PVS [1] in 1994 to denote irreversibility after three months following a non-traumatic brain injury and twelve months after traumatic injury. However, even after these long and arbitrary delays, some patients may exceptionally recover. Hence, the American Congress of Rehabilitation Medicine advocates abandoning the term "permanent" in favor of simply specifying the length of time patients have spent in VS.[2] The question which most concerns relatives and doctors caring for patients with vegetative state is whether a recovery is possible. The Task Force analyzed the prognosis of these patients and identified three factors that clearly influenced the chances of recovery: age, etiology, and time already spent in VS. The outcome is better after

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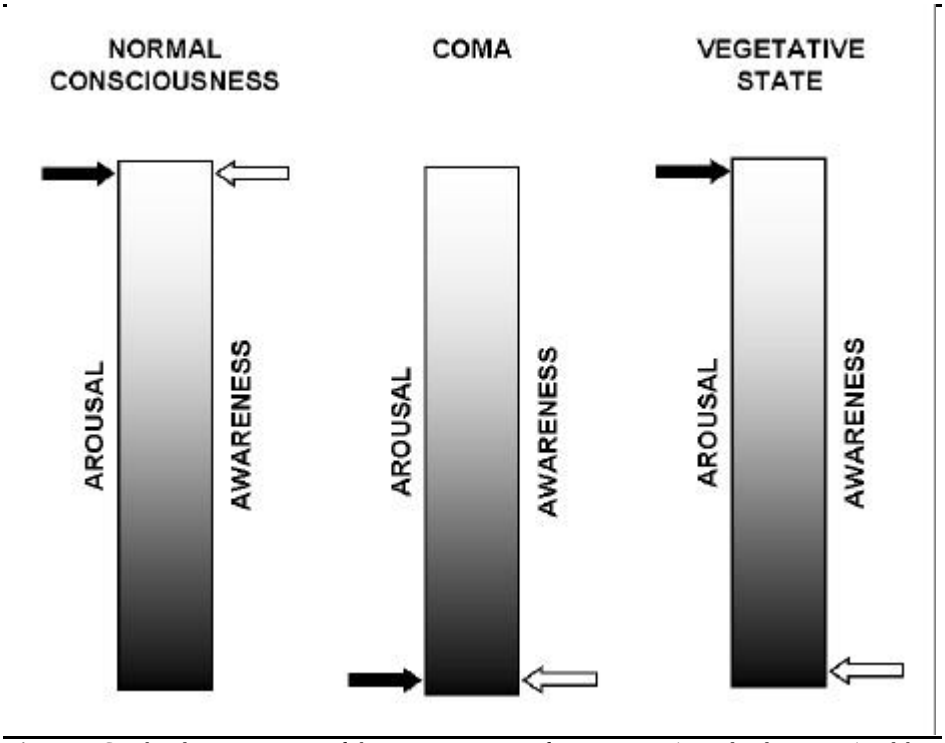

Figure 1. Graphical representation of the two components of consciousness (arousal and awareness) and their alterations in coma and the vegetative state.

traumatic than non-traumatic brain injury, better in children, and worse as time passes. Clinical, electroencephalographic (EEG), evoked potentials (EP), or structural imaging data do not permit an accurate prognostication in VS.[1]

The interest of functional imaging in VS is twofold. First, VS patients represent a 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 to identify the neural correlate of consciousness. Indeed, these patients represent genuine cases of abolition of consciousness but, contrary to coma patients, with preserved arousal. Consciousness is thought to represent an emergent property of cortical and subcortical neural networks and their reciprocal projections. Its multifaceted aspects can be seen as expressions of various specialized areas of the cortex that are responsible for processing external and internal stimuli, short- and long-term storage, language comprehension and production, information integration and problem solving, and attention.[3]

2. GLOBAL IMPAIRMENT IN CEREBRAL METABOLISM

Positron Emission Tomography (PET) has shown a substantial reduction in global brain metabolism in patients in VS (Figure 2). In VS of various etiologies and durations, studies from our own[4-10] and other centers[11-15] have shown that cerebral metabolic rates for glucose (CMRGlu) are approximately 40 percent of normal values, whereas in patients in coma of hypoxic and traumatic origin, values are approximately 50 percent of normal.[16, 17] Compared to cerebral glucose metabolism, cerebral blood flow seems to show a larger interpatient variability in VS.[13] In long-standing post-hypoxic vegetative state, CMRGlu values decrease even further,[11,14] probably due to progressive Wallerian and transsynaptic degeneration. 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. When different anesthetics are titrated to the point of unresponsiveness, the resulting reduction in CMRGlu is nearly as low as that observed in VS patients.[18-20] During propofol anesthesia, brain metabolism sometimes decreases to 30 percent of normal values. Another example of transient metabolic depression has been observed by our own

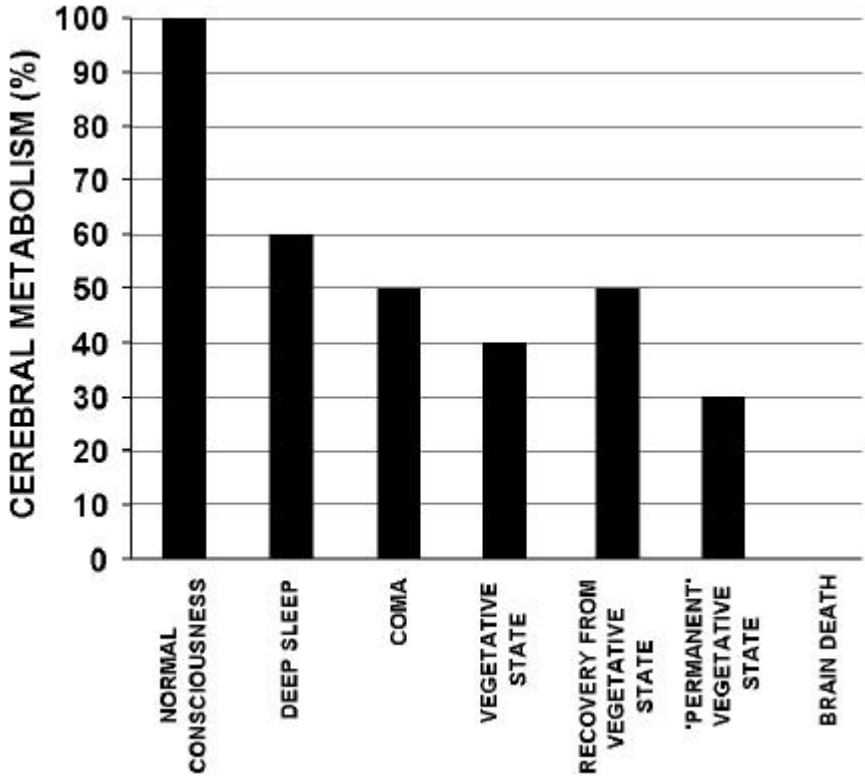

Figure 2. Cerebral metabolism in the different clinical entities (for references see text).

and other centers during slow-wave sleep.[21,22] In this daily physiological condition CMRGlu decreases to 60 percent of waking values (Figure 2).

More interestingly, we had the opportunity to scan a patient during VS and after recovery of consciousness.[10] To our surprise, global gray matter CMRGlu did not show a substantial increase after recovery. In this case, 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. Statistical Parametric Mapping (SPM)[23] analysis identified the most important decreases in metabolism, seen during VS but not after recovery, in the bilateral parietal associative cortices at the convexity and at the midline (precuneus and posterior cingulate).[10] To our knowledge there is only one other case published where PET scanning was performed during VS and after recovery of consciousness.[12] Again, global gray matter CMRGlu did not show a substantial increase after recovery (5.0 mg/100g.min versus 5.2 mg/100g.min). Although no SPM analysis was performed, region of interest (ROI) analysis showed the largest regional increase in parieto-occipital cortices. These data point to a critical role for the posterior associative cortices in the emergence of conscious experience.

It remains controversial whether the observed metabolic impairment in VS reflects functional and potentially reversible damage or irreversible structural neuronal loss. Rudolf and co-workers argue for the latter, using ^{11}C-flumazenil as a marker of neuronal integrity in evaluating acute anoxic VS patients.[24] We hypothesize that impairment in cortico-cortical and thalamo-cortical connectivity could explain part of the permanent, or in some fortunate cases transient, functional cortical impairment in VS.[25]

3. REGIONAL IMPAIRMENT IN CEREBRAL METABOLISM

3.1. Relatively Most Impaired Brain Areas

Using ROI analysis, previous PET studies have shown a reduction in overall cortical metabolism[11-14] with most profound reductions in the parieto-occipital and mesial frontal cortices.[12] By means of SPM analysis[23] we were able to identify the regional pattern of metabolic impairment common to our patients in VS.[9] The prefrontal, premotor and parietotemporal association cortices and the posterior cingulate/precuneus region showed the most severe functional impairment (Fig. 3B). This pattern is in agreement with postmortem findings where involvement of the association cortices is reported as a critical neuroanatomic substrate.[26] These associative cortices are known to be involved in various consciousness-related functions such as perception, attention, working memory, episodic memory, and language.

Interestingly, the medial parietal cortex (precuneus and posterior cingulate cortex) is one of the most active cerebral regions (together with the anterior cingulate and the prefrontal cortex) in conscious waking.[21,27,28] Moreover, it is systematically one of the least active regions in unconscious or minimally conscious states such as such as coma[17] (Fig. 3A), halothane anesthesia,[18] slow-wave sleep,[21] rapid eye movement sleep,[29] Wernicke-Korsakoff's and post-anoxic amnesia,[30] and hypnotic state.[31] This area is also the site of the earliest reductions in glucose metabolism in Alzheimer's disease.[32] These arguments suggest that the posterior parietal cortex might represent part of the neural network subserving conscious experience.

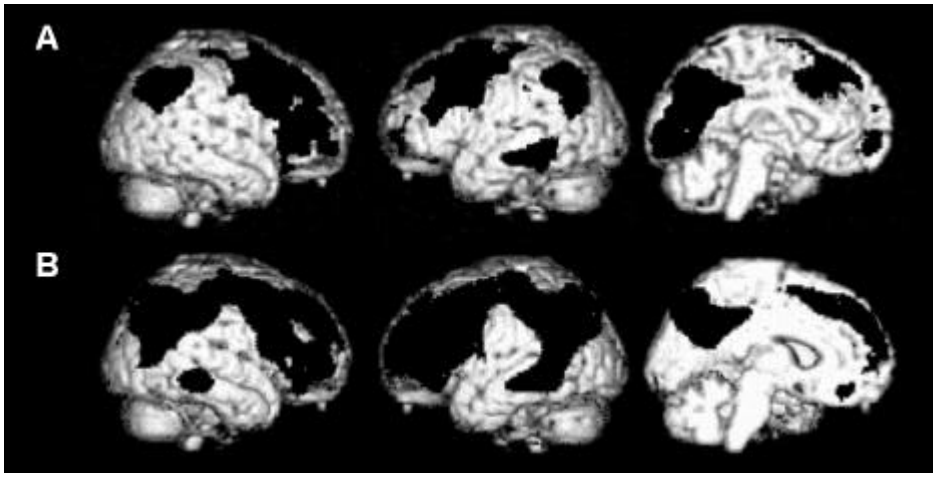

Figure 3. The common pattern of altered cerebral metabolism characterizing vegetative state patients. Using Statistical Parametric Mapping,[23] we identified areas where metabolism was relatively most impaired in comatose patients (A) and vegetative patients (B) compared to conscious controls (for methodological details see[9, 17]). A schematic representation of these areas is shown in black on a surface rendered normalized magnetic resonance image. Note that the functionally most impaired regions in both coma and the vegetative state are the associative cortices (frontal, parietotemporal and posterior cingulate/precuneus).

3.2. Relatively Spared Brain Areas

We observed another hallmark common to our patients in VS: the relative preservation of metabolism in the brainstem (encompassing the mesopontine reticular formation), basal forebrain, and posterior hypothalamus. This allows for the maintenance of vegetative functions in these patients: preserved sleep-wake cycles, autonomic and ventilatory control, and cranial nerve reflexes. This observation is in line with the post-mortem neuropathologic finding that these structures are relatively preserved in VS patients.[26]

4. FUNCTIONAL IMPAIRMENT IN CEREBRAL CONNECTIVITY

4.1. Cortico-Cortical Connectivity

Recently, functional imaging has offered an analytical tool to assess the functional connectivity between distant cerebral areas. Put simply, such a statistical analysis identifies brain regions that show condition-dependent differences in modulation with another (chosen) area. Using such a psychophysiological interaction analysis,[33] we were able to demonstrate that patients in vegetative state suffer from an altered cortico-cortical connectivity. Compared to control subjects, patients in VS showed an altered modulation between the left frontal cortices and the medial parietal cortex.[9] This impaired fronto-parietal connectivity in VS is in accordance with experiments in non-human primates

demonstrating that the functional integrity of the prefrontal cortex and its interactions with modality specific posterior brain regions is critical for working memory.

4.2. Thalamo-Cortical Connectivity

Based on the putative role of high-frequency oscillatory thalamocortical circuitry underlying human consciousness in healthy volunteers,[34] our center has assessed the functional integrity of the thalamocortical connectivity in VS patients. Using the same analytical methodology[9] we identified brain areas that showed a different functional connectivity with both thalami in patients in VS compared to controls. We indeed observed an impaired functional relationship between the activity in the thalami and fronto-parietal associative cortices,[6] partially restoring normal function after recovery of consciousness.[25] The thalamus contains both specific thalamo-cortical relay nuclei and so-called nonspecific intralaminar nuclei. The former are the necessary relay for all sensory afferent stimuli (except some olfactory information). The latter have been implicated in the maintenance of thalamo-cortico-thalamic synchronous oscillations. Among these activities, 40 Hz oscillations seem to be deeply, although not exclusively, involved in conscious experience.[34,35] Thus, thalamic nuclei seem critical for the maintenance of human awareness.

5. CEREBRAL ACTIVATION AFTER EXTERNAL STIMULATION

In 1989, Momose and co-workers described a patient in VS whose CMRGlu increased after cervical spinal cord stimulation.[36] More recently, using magnetoencephalography[15,37,38] or $H_2{}^{15}O$-PET,[39,40] cerebral activation has been described during sensory stimulation in VS patients. De Jong and co-workers presented to a VS patient both a story told by his mother and non-word sound. They observed an activation [with one type of stimulus or both?] in anterior cingulate and temporal cortices which they interpreted as possibly reflecting the processing of emotional attributes of speech or sound.[39] Menon and co-workers presented to a VS patient photographs of familiar faces and meaningless pictures. The visual association areas showed significant activation when faces were compared to meaningless stimuli.[40] Our group has assessed the central processing of noxious somatosensory stimuli in the VS.[8] Changes in regional cerebral blood flow and event related potentials were measured during high intensity electrical stimulation of the median nerve in VS patients and compared to data obtained in healthy controls. Noxious stimulation activated midbrain, contralateral thalamus and primary somatosensory cortex in each and every VS patient, even in the absence of detectable cortical evoked potentials (Figure 4). However, a large network of hierarchically 'higher-order' multi-modal association areas failed to activate: the secondary somatosensory cortices, the insular regions, the posterior parietal and prefrontal areas and the anterior cingulate cortex (regions that are known to be involved in pain affect, attention and memory). Moreover, primary somatosensory cortex, the only cortical region that activated in vegetative patients, was no longer functionally connected (i.e., no longer communicated) with the rest of the brain (i.e., the 'higher order' brain regions thought to be necessary for conscious processing). Hence, somatosensory stimulation of VS patients, at intensities that elicited pain in controls, resulted in increased neuronal activity

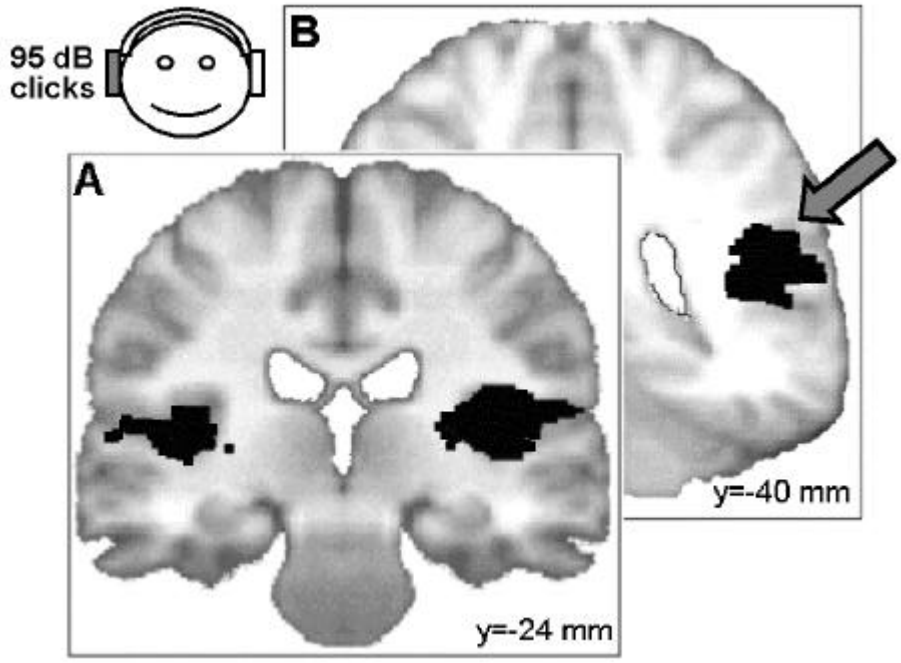

Figure 4. Areas of regional blood flow (rCBF) increase during auditory stimulation in VS patients projected on a coronal MRI section, 24 and 40 mm behind the anterior commisural line. The arrow points to the auditory association areas where rCBF showed significantly less activation in VS compared to controls. (Adapted from ref.[5])

in primary somatosensory cortex, even if resting brain metabolism was severely impaired. However, this activation of primary cortex seems to be isolated and dissociated from higher-order associative cortices.

Similarly, auditory stimulation activated bilateral primary auditory areas but, in contrast to controls, not the higher-order associative areas in the temporo-parietal junction (Figure 5). In VS patients, auditory association cortex was functionally disconnected from the posterior parietal association area, anterior cingulate cortex and hippocampus.[5] Thus, despite an altered resting metabolism, primary sensory cortices still activate during external stimulation, whereas hierarchically higher-order downstream multimodal association areas do not. In the absence of a generally accepted neural correlate of consciousness,[35] it is difficult to make definite judgments about conscious perception in VS patients. However, the cascade of functional disconnections along the sensory cortical pathways, from primary areas to multimodal and limbic areas, suggests that the observed activation of primary sensory cortex subsists as an island, dissociated from higher-order cortices that would be necessary to produce awareness.

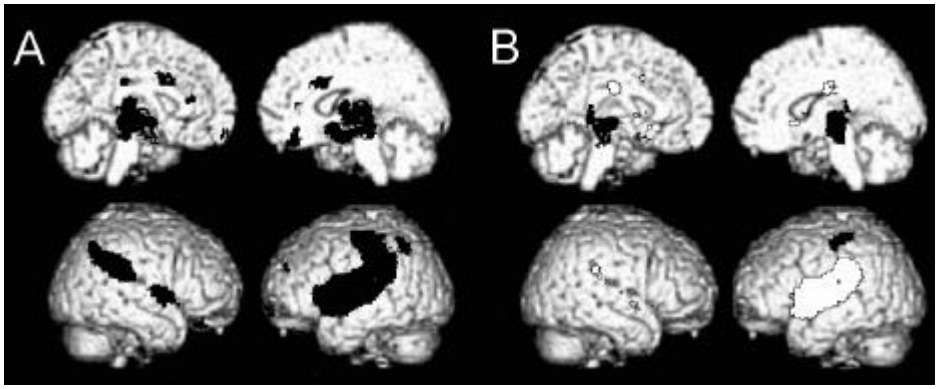

Figure 5. (A) Brain regions, shown in black, that activated during noxious stimulation in controls [subtraction stimulation-rest] projected on a 3-D spatially normalized brain MRI. (B) Brain regions that activated during stimulation in PVS patients, shown in black [subtraction stimulation-rest] and regions that activated less in patients than in controls [interaction (stimulation versus rest) x (patient versus control)], shown in white. (Adapted from ref.[8])

6. CONCLUSION

At present, the potential for recovery of awareness from the VS cannot be predicted reliably by any clinical or neurodiagnostic test. Functional imaging studies of residual brain function in VS provide an opportunity to understand the basic neural processes underlying human consciousness. Past studies from our own and other centers have used functional neuroimaging to study the residual brain function in such patients. These efforts identified a decrease in *global* metabolism of 40 percent. However, some patients who recovered from a VS, showed a modification of the *regional* distribution of brain function rather than a resumption of global metabolism. This leads to the hypothesis that some VS 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. We were able to identify the common neural correlate of VS. The most severely affected brain regions were localized in the frontal and parietal associative cortices. On the contrary, brainstem, posterior hypothalamus, and basal forebrain were the most spared brain regions. By means of a psychophysiological interaction analysis[33] we subsequently demonstrated that patients in VS indeed suffer from an altered thalamo-cortical and cortico-cortical connectivity. Using cerebral activation paradigms, ongoing international research efforts will more closely correlate functional imaging with behavioral assessment, electrophysiological findings, and eventually, outcome.

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