Neuroimaging activation studies in the vegetative state: predictors of recovery?

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ABSTRACT – The vegetative state (VS) is a devastating clinical condition characterised by wakefulness without awareness. Functional neuroimaging permits to objectively measure brain responsiveness to external stimuli in VS. The literature on functional magnetic resonance imaging and positron emission tomography studies in these patients has been reviewed. Results from 15 studies were classified in: absent cortical activation or 'typical' activation of 'low level' primary sensory cortices and 'atypical' activation spreading to 'higher level' associative cortices. This descriptive review on 48 published cases suggests that 'atypical' activation patterns seem to herald recovery from VS with a 93% specificity and 69% sensitivity. Passive stimulation paradigms, however, do not permit to make strong claims about the absence or presence of consciousness. Recently proposed mental imagery paradigms permit to identify signs of consciousness in non-communicative brain damaged patients. The clinical application of these functional neuroimaging techniques awaits validation from ongoing multi-centric cohort studies in these challenging patients with chronic disorders of consciousness.

KEY WORDS: brain injury, coma, functional magnetic resonance imaging, minimally conscious state, positron emission tomography, vegetative state

Patients in a vegetative state (VS) present sleep–wake cycles but show no sign of awareness of the environment or of self. An accurate and reliable judgment of VS patients' awareness is of paramount importance for their diagnosis and prognosis. In clinical practice, the evidence for the existence of VS patients' awareness comes from bedside behavioural assessment. However, theoretically, awareness is a multifaceted concept. It mainly refers to the subject's own subjective experience, which is not equal to its communicable behavioural expression. Furthermore, for disorders of consciousness like VS, motor dysfunction and arousal fluctuations render the bedside assessment of awareness challenging.[1] Misdiagnosis in VS has been shown to be as high as 37–43%.[2,3,4] Diagnosing the VS is more difficult than diagnosing brain death (ie irreversible coma with absent brainstem reflexes). For the latter, complimentary examinations exist to confirm the clinical diagnosis (eg the absence of electrical cerebral activity as shown by an electroencephalogram (EEG) or of cerebral blood flow as shown by echo Doppler, angiography or scanning techniques).[5] Such objective diagnostic markers are also needed to confirm the clinical diagnosis of VS.

Ongoing developments and validation in healthy subjects of brain mapping techniques, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) now permit the use of brain 'activation studies' in clinical settings. Detecting residual brain function in VS by use of functional neuroimaging may provide useful information to the diagnosis and prognosis of these challenging patients. Such studies also provide an opportunity to study the neural correlates of consciousness.

This article includes papers on cerebral activation in VS published in English (PubMed search performed in January 2008; search terms 'vegetative state' and 'positron emission tomography'/'functional magnetic resonance imaging'). The first report of a successful cerebral activation study to external stimuli in VS appeared in 1997.[6] In the past year, 14 other papers were published (Table 1). These studies provide information about the pathophysiology of VS and will be discussed in the present review. Finally, the paper will try to evaluate if results obtained by functional neuroimaging yield any prognostic significance.

Typical primary cortical activation in VS

In most of the reviewed literature, VS patients show cortical activation limited to 'lower level' primary cortical areas – here coined 'typical' activation pattern. Using $H_2{}^{15}O$ PET blood flow studies, Laureys *et al* studied pain processing in VS. A high intensity electrical stimulation, at intensities that elicited pain in controls, was employed to the median nerve at the wrist in 15 non-sedated patients with VS and in 15 healthy controls. Noxious somatosensory stimuli activated midbrain, contralateral thalamus, and primary somatosensory cortex in each and every patient with VS, even in the absence of detectable cortical evoked potentials. The activated primary

Table 1. Functional neuroimaging activation studies in patients in a vegetative state.

Reference	Aetiology*[1]	PET/fMRI and interval*[2]	Findings		Outcome	Pattern
			Task	Activation area		
de Jong *et al* (1997)[6]	T (n=1)	**PET** 2 months	Mother told story vs non-word sounds	Anterior cingulate and temporal cortices	Remained VS	Atypical
Menon *et al* (1998);[16] Owen *et al* (2002)[11]	NT-Hypoxic (n=1)	**PET** 3 months	Moving coloured visual stimuli vs resting state	PVC	Good recovery*[3]	Typical
		PET 4 months	Familiar face vs control picture	Right fusiform gyrus		Atypical
Laureys *et al* (2002, 2000);[7,9] Boly *et al* (2004)[8]	T-DAI (n=3) NT (n=12)	**PET** 3 days–several months	Auditory click stimulation vs resting state	Bilateral PAC	11 remained VS, 4 recovered*[4] (T n=1, NT n=3)	Typical
			Noxious electrical stimulation vs resting state	Midbrain, contalateral thalamus and SI		
Moritz *et al* (2001)[12]	T (n=1)	**fMRI** 4 days	1 Hz blinking light vs resting state	Near PVC (L>R)	Good recovery (visual:L>R)	Atypical
			Listening to narrated text vs resting state	STG, left posterior temporal/angular gyrus, middle and inferior frontal gyrus		
			Bilateral palm scratch vs resting state	SI and right SMA		
Owen *et al* (2002)[11]	T (n=1)	**PET** 14 weeks	Noise vs resting state	Auditory region	Good recovery*[5]	Typical
			Spoken words vs SCN	Superior temporal plane bilaterally and posterior to auditory cortex		Atypical
	NT-Hypoxic (n=1)	**PET**	Noise vs resting state	No activation caused by head movement	Not mentioned	None
			Spoken words vs SCN			
Kassubek *et al* (2003)[23]	NT-Hypoxic (n=7)	**PET** 3 months–4 years	Painful stimulation vs resting state	SII, SI, contralateral cingulate cortex and ipsilateral posterior insula	Not mentioned	Atypical
Giocino *et al* (2006)[10]	T (n=2) NT (n=3)	**PET** 1–3 months	Pattern flashes vs darkness	Striate cortices	remained VS	Typical
Owen *et al* (2005b);[18] Coleman *et al* (2007)[13]	NT-Hypoxic (n=1)	**PET** 4 months	Hearing speech vs silence	Bilateral STG	Evolved to MCS*[6]	Atypical
			High vs low intelligibility	Left superior and middle TG		
		PET+fMRI 13 months	Hearing speech vs silence	Bilateral STG and middle TG		
			High vs low intelligibility	Left superior and middle TG		
			Hearing speech vs SCN	Bilateral STG and middle TG		
			Ambiguous sentences vs unambiguous sentences	Left posterior inferior temporal cortex		
Bekinschtein *et al* (2005)[17]	T (n=1)	**fMRI** 2 months	Words vs silence	Left transverse and superior temporal gyri and striate cortex	Good recovery*[7]	Atypical
Staffen *et al* (2006)[21]	NT-Hypoxic (n=1)	**fMRI** 10 months	SON vs another name	Bilateral MPFC left temporoparietal and superior frontal cortex	Remained VS	Atypical

continued

Table 1. Functional neuroimaging activation studies in patients in a vegetative state. – *continued*

Reference	Aetiology*[1]	PET/fMRI and interval*[2]	Findings		Outcome	Pattern
			Task	Activation area		
Owen *et al* (2006);[19] Coleman *et al* 2007)[13]	T (n=1)	**fMRI** 6 months	Hearing sentences vs SCN	Superior and middle temporal gyrus	Evolved to MCS*[8]	Atypical
			Ambiguous sentences vs unambiguous sentences	LIFG		
			Tennis imagery vs resting state	SMA		
			Imaging moving around a house vs resting state	PPA, PPC, PMC		
Di *et al* (2007)[15]	NT-Hypoxic (n=2) T (n=3)	**fMRI** 2 months–4 years	SON-FV vs resting state	PAC in temporal cortices	Remained VS	Typical
	T (n=2)	**fMRI** 4 months		PAC, associated auditory cortices in temporal cortex	Evolved to MCS*[9]	Atypical
Coleman *et al* (2007)[13]	NT (n=1)	**fMRI** 2 months	Hearing speech vs silence	Bilateral STG	Evolved to MCS*[6]	Atypical
			Meaningful speech vs SCN	Posterior portions of the temporal lobes		
			Ambiguous sentences vs unambiguous sentences	No activation		
	T (n=1) NT (n=3)	**fMRI** 9 months–9 years	Sound vs silence	No activation	Remained VS*[6]	None
			Meaningful speech vs SCN			
			Ambiguous sentences vs unambiguous sentences			

*[1]: NT = non-traumatic; T = traumatic; *[2]: Interval: the time spent in VS before scanning; *[3]: became responsive 2 months after the scan and further recovery 2 years later;*[4]: clinical status after 3 months; *[5]: developed a withdrawal to pain over several weeks and occasionally showed responses to commands; *[6]: at 6 months post fMRI; *[7]: progressed to MCS after 2 months and to partial independence after 18 months; *[8]: turned eyes to the right followed a moving mirror and fixated for more than five seconds; *[9]: clinical status after 3 months.
fMRI = functional magnetic resonance imaginging; MCS = minimally conscious state; PAC = primary auditory cortex; PET = positron emission tomography; PMC = primary motor cortex; PPA = parahippocampal gyrus; PPC = posterior parietal cortex; PVC = primary visual cortex; SI = primary somatosensory cortex; SII = secondary somatosensory cortex; SCN = signal-correlated noise; SMA = supplementary motor area; SON = subject's own name; SON-FV = subject's own name spoken by a familiar voice; STG = superior temporal cortex; VS = vegetative state.

somatosensory cortex was functionally disconnected from 'higher order' associative cortical areas, encompassing anterior cingulate, insular, prefrontal and posterior parietal cortices. In healthy controls, such stimuli activated primary and secondary somatosensory cortices, bilateral insular, posterior parietal and anterior cingulate cortices.[7]

The same group presented auditory click stimulation to 15 patients with VS and 18 controls. Compared to rest, auditory stimuli activated bilateral auditory cortices in all patients. Again, the activated primary auditory cortex was functionally disconnected from higher order areas encompassing posterior parietal, anterior cingulate and hippocampal areas. Whereas in control subjects, stimuli activated bilateral primary and contralateral auditory association cortices.[8,9] Laureys *et al* also passively presented simple visual stimuli (flashes) via goggles through closed eyelids to five VS patients with traumatic (n=2) and non-traumatic (n=3) brain damage.[10] Compared to darkness, flashes activated primary visual cortex in each patient. Owen *et al* used fMRI in two patients with VS. In patient one, a moving coloured grid (compared to darkness) elicited activation in primary visual cortex, while in another patient, noise stimulation (compared to resting state) activated primary auditory cortex.[11] Moritz *et al* studied a VS patient four days post-trauma and reported activation near primary visual cortex induced by flashing light (compared to darkness).[12] These studies support the view that simple somatosensory, auditory and visual stimuli typically activate primary cortices in patients with VS and fail to show robust activation in higher order associative cortices.

However, other studies suggest that presentation of more co plex stimuli elicit more widespread cortical activation in VS (ie induce atypical 'higher order' associative cortical activation).

Sometimes, VS patients fail to show any cerebral activation. This is illustrated in studies by Coleman *et al*[13] and Owen *et al*.[11] This phenomenon is fully understandable. On one hand, the fluctuation of arousal (ie patients might have been scanned during decreased levels of arousal) or the impairment caused by the brain damage in VS (ie patients show extensively damaged or disconnected cortex) may explain the absence of activation. On the other hand, due to uncontrolled head movements during scanning, false negative results in non-collaborative patients with VS are expected to occur more commonly than in collaborative healthy subjects. Finally, possible neuro-vascular coupling alterations in severely damaged brains might cause altered or absent activation as measured by haemodynamic techniques as PET or fMRI.[14]

Atypical 'higher order' associative cortical activation in VS

Di *et al*[15] used fMRI to study cerebral activation to the subject's own name (SON) uttered by a familiar voice. As compared to rest, SON activated primary auditory cortices in five VS patients, none of whom recovered. In contrast, two VS patients showed 'higher level' associative activation and recovered three months after the fMRI study. Similarly, Menon and colleagues[16] described a 26-year-old VS patient with acute disseminated encephalomyelitis. PET scanning was done four months after onset and showed activation of right occipito-temporal associative cortices (encompassing the fusiform face area) when familiar faces were compared to scrambled pictures. Two months after scanning the patient recovered consciousness. In another study,[11] a VS patient studied 14 weeks after trauma showed bilateral superior temporal associative cortical activation when sentences were spoken (as compared to signal-correlated noise) and recovered consciousness some months later. In the fMRI study in an acute post-traumatic VS patient mentioned above,[12] listening to narrated text versus scanning noise activated associative temporal, parietal and prefrontal areas. Follow-up at three months showed good clinical recovery. Beckinschtein *et al* described a post-traumatic VS case who, after two months in a VS, progressed to MCS and then, over the next 18 months, partially regained independent living. During VS, an fMRI was performed involving passive listening blocks of words, white noise or silence. The word versus silence comparison revealed temporal-lobe activation probably extending outside Heschl's gyrus. The fMRI study performed after recovery showed more widespread activation encompassing the language networks.[17] Using a hierarchical auditory stimulation paradigm in fMRI, Coleman *et al*[13] reported seven VS patients, three of whom (one traumatic and two non-traumatic) showed temporal activation in the low-level auditory contrast (all sounds versus silence) and mid-level speech perception contrast (meaningful speech versus signal-correlated noise).[18,19] The remaining four patients showed no activation in response to sound compared with silence. The three patients with higher-level associative cortical activation emerged to MCS when re-assessed six months after fMRI scanning whereas the four remaining patients remained vegetative.

In summary, these neuroimaging data seem to show that atypical 'higher order' associative cortical activation in VS heralds recovery of some level of consciousness some months later. An often-asked question is whether the presence of such brain activation in patients in VS indicates a level of conscious awareness. A novel approach to this conundrum has been proposed by using fMRI during mental imagery tasks.[20]

fMRI shows signs of consciousness

Owen *et al*[19] have used an fMRI paradigm[20] where non-communicative patients are asked to perform mental imagery tasks at specific points during scanning. In one exceptional VS patient studied five months after a traumatic brain insult, activation was observed in the supplementary motor area after being asked to imagine playing tennis. When asked to perform a spatial navigation imagery task (ie imagine visiting all of the rooms of the house), activation was observed in premotor cortex, parahippocampal gyrus and posterior parietal cortex. Indistinguishable activation patterns were seen in healthy volunteers. Interestingly, when re-examined six months later the patient showed inconsistent visual tracking – the most frequently encountered clinical sign of recovery from VS.[19] In contrast to the passive neuroimaging paradigms discussed so far, this novel approach provides convincing evidence for the presence of consciousness in a patient clinically diagnosed as VS. Because the only difference between the conditions that elicited task-specific activation was in the instruction given at the beginning of each scanning session, the activation observed can only reflect the intentions of the patient, rather than some property of the stimuli. In this sense, the decision to 'imagine playing tennis' rather than simply 'rest' is an act of willed intention and, therefore, clear evidence for awareness and command-following in the absence of voluntary motor responsiveness.

Atypical activation without recovery

de Jong *et al*[6] performed a PET study two months post-trauma in a 16-year-old boy in VS. They detected activation in anterior cingulate, right middle temporal and right premotor areas when the patient was presented a story told by the patient's mother (as compared to non-word sounds). The authors proposed that this activation might reflect appropriate cortical processing of emotional attributes of sound or speech. However, treatment was withdrawn and the patient died three months after insult while clinically VS.

Using auditory presentation of the SON, Staffen *et al*[21] performed an fMRI study in a patient in post-anoxic VS at 10 months. Compared to other names, SON activated bilateral medial prefrontal, left temporal-parietal and superior frontal cortices. The patient remained VS and died one year after scanning.

These studies indicate that atypical response patterns, encompassing 'higher level' associative cortical activation, can be observed in some VS patients who fail to subsequently recover. Such findings are in line with the study by Schiff *et al*[22] who found that VS patients with atypical behavioural fragments can show residual isolated brain processing in the absence of clinical recovery.

Finally, Kassubek *et al*[23] observed activation to noxious stimuli in contralateral primary and secondary somatosensory, anterior cingulate and ipsilateral posterior insular cortices in seven hypoxic VS patients studied three months to four years post-insult. This study is in contrast with Laureys *et al*'s results showing solely primary cortical activation during noxious stimulation.[7] Unfortunately, there is no information on patients' outcome in the former study.[23]

Does cerebral activation predict clinical recovery?

All in all, eight PET studies including 32 patients[6–11,16,18,23] and six fMRI studies including 17 patients[12,13,15,17–21] (one patient was studied by both PET and fMRI) have been reviewed (Table 1). Among these 48 patients (16 of whom were traumatic), 25 patients (52%; 8 traumatic) showed typical activation patterns, five patients (10%; 1 traumatic) showed no activation and 18 patients (38%; 7 traumatic) showed atypical activation patterns. In studies employing multiple stimuli (both simple and complex; eg meaningless noise and words), the results obtained from the most complex stimuli have been taken into account. Often, complex stimuli recruit higher level cortices.[11–13,18,19] In 40 patients, outcome data were published or were obtained by contacting the authors (Table 2).

In eight patients no outcome data were available (seven atypical activations[23] and one absence of activation[11]). Nine out of the 11 patients with atypical 'higher order' associative cortical activation patterns (82%; 6 traumatic) recovered consciousness. Twenty-one out of the 25 patients with typical primary cortical activation patterns (84%; 7 traumatic) and four patients without any cortical activation (100%; 1 traumatic) failed to recover. Hence, this analysis of functional neuroimaging data published on VS patients shows that a high level associative cortical activation (as compared to absent or low-level primary activation) seems to predict recovery of consciousness with a 93% specificity and 69% sensitivity (Table 2; chi-square testing $p<0.001$).

Table 2. Published functional magnetic resonance imaging and positron emission tomography activation studies stratified depending on activation patterns (absent or 'low level' primary cortical activation versus atypical 'higher order' associative cortical activation) and outcome (death or permanent vegetative state (VS) versus recovery from VS). Note that atypical 'higher order' activation more often is followed by recovery of consciousness.

Cerebral activation	No activation or primary cortical activation	Atypical 'higher order' cortical activation	Total
Bad outcome	25	2	27
Good outcome	4	9	13
Total	29	11	40

Conclusion

This review of the sparse and heterogeneous literature on VS suggests that functional imaging activation studies can provide valuable prognostic information. It is important to stress that much more studies are needed in order to provide more evidence. The included (uncontrolled and unblinded) studies all employed different patient assessments methods and different imaging methodology (ie different sensory modalities using different stimulation paradigms). Future efforts should focus on large multi-centric cohort studies with standardised behavioural and neuroimaging paradigms, previously validated in healthy controls. Complex auditory stimuli with emotional valence are particularly powerful for studying residual brain function in VS. Presentation of the patient's own name is of particular interest because it is a potent attention-grabbing auto-referential stimulus. Using such passive paradigms does not necessarily give absolute answers to the presence or absence of consciousness, but seem the most convenient to be validated as diagnostic and prognostic fMRI markers in cerebral activation studies. At present, the field of neuro-rehabilitation lacks evidence-based treatment for disorders of consciousness such as the VS. Functional neuroimaging could help to objectively measure the effect of pharmacological and non-pharmacological therapeutic interventions.[24] Finally, the medical community needs to define an ethical framework permitting to study brain function and plasticity in these non-communicative severely brain damaged patients unable to provide consent.[25]

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