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CHAPTER 17

Executive functions in the absence of behavior: functional imaging of the minimally conscious state

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Abstract: One of the major challenges in the clinical evaluation of brain injury survivors is to comprehensively assess the level of preserved cognitive function in order to inform diagnostic decisions and suggest appropriate rehabilitation strategies. However, the limited (if any) capacity for producing behavior in some of these patients often limits the extent to which cognitive functions can be explored via standard bedside methods. We present a novel neuroimaging paradigm that allows the assessment of residual executive functions without requiring the patient to produce any behavioral output. In particular, we target processes such as active maintenance of information through time and willful adoption of ''mind-sets'' that have been proposed to require conscious awareness. Employing an fMRI block design paradigm, healthy volunteers were presented with a series of neutral (i.e., not emotionally salient) words, and alternatively instructed to listen to all the words, or to count the number of times a given target is repeated. Importantly, the perceptual stimulation in the passive listening and the counting tasks was carefully matched. Contrasted with passive listening, the counting task revealed a fronto-parietal network previously associated with target detection and working memory. Remarkably, when tested on this same procedure, a minimally conscious patient presented a highly similar pattern of activation. Furthermore, the activity in these regions appeared highly synchronous to the onset and offset of the counting blocks. Considering the close matching of sensory stimulation across the two tasks, these findings strongly suggest that the patient could willfully adopt differential ''mind-sets'' as a function of condition, and could actively maintain information across time. Neither cognitive function was apparent when the patient was (behaviorally) tested at the bedside. This paradigm thus exemplifies the potential for fMRI to explore high-level cognitive functions, and awareness, in the absence of any behavioral response.

Keywords: functional magnetic resonance imaging; consciousness; disorders of consciousness; vegetative state; minimally conscious state; executive functions; target detection; working memory

One of the most ubiquitous and least understood concepts in the study of the human brain is ''consciousness'' (Laureys et al., 2007). In the absence of an agreed definition or measure (Seth et al., 2008), the only means we currently have to ascertain whether someone is conscious is if they

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directly tell us so. Assessing another individual's state of consciousness then essentially relies on them revealing, either via direct report or via some voluntary behavior, that they are both awake and aware. Generally, people experience little difficulty in recognizing a state of conscious wakefulness from states such as general anesthesia, deep sleep, or coma. Indeed, in the latter three cases, permanently closed eyes indicate low levels of arousal, and, more importantly, the absence of any goal-directed behavior seems to imply the lack of awareness (of the self and the environment). Conversely, a state of conscious wakefulness is recognizable by high levels of arousal, and especially by the presence of purposeful (i.e., non-reflexive) behavior, which requires — and thereby reveals the presence of — conscious awareness (see Laureys, 2005).

Recent advances in intensive care have greatly increased the number of patients that survive severe brain injury. Some patients thus go on to make a full recovery. Other brain injury survivors, however, regain high levels of arousal, but fail to demonstrate any sign of awareness, only exhibiting reflexive behavior. These patients are said to be in a vegetative state (VS; Jennett, 2002; Jennett and Plum, 1972). While this latter state can be permanent, some patients do regain a (fluctuating) level of awareness, thus progressing to a minimally conscious state (MCS; Giacino et al., 2002) either permanently or on the way to durable recovery of consciousness. A central challenge in the care of patients with disorders of consciousness is the assessment of their residual cognitive abilities. In particular, detection of any evidence of voluntary behavior that may signal a state of awareness is fundamental to disentangling VS from MCS. However, brain injury often constrains the ability to produce motoric output, restricting the possibility that a patient might demonstrate purposeful behavior, and thereby awareness. Consequently, use of motor behavior to assess residual cognition and awareness might, under such circumstances, underestimate residual brain function and misidentify conscious patients as unconscious (Monti et al., 2009; Owen and Coleman, 2008). Indeed, according to recent estimates, the misdiagnosis rate by which MCS patients are "mistaken" for VS is around 40% (Andrews et al., 1996; Childs et al., 1993). In the face of the important medical (Elliott and Walker, 2005), legal, and ethical ramifications (Fins et al., 2008) of such mistakes, correct diagnosis is essential. Many factors are known to have an impact on diagnostic error, including sensory impairments of the patient (e.g., blindness), and variable knowledge and expertise in administering clinical tests (see Andrews et al., 1996; Majerus et al., 2005). It appears increasingly clear, however, that use of motor behavior as an index of conscious awareness and residual cognition is also an important source of diagnostic error. In fact, this approach exposes a central conundrum in our understanding of consciousness. Our ability to detect whether someone is conscious depends crucially on his or her capacity for communicating that fact. Therefore, if someone were to be entirely aware but unable to produce any behavioral sign to indicate so, logically, there would be no way to determine that they were actually conscious (Monti et al., 2009; Owen and Coleman, 2008). Indeed, one recent study employing non-invasive neuroimaging has reported the case of a patient who, despite appearing vegetative by internationally agreed criteria and standard procedures, was, in fact, consciously aware (Owen et al., 2006).

In what follows, we present a novel neuroimaging approach aimed at exploring how deep the hiatus between cognition and behavior can run in patients with disorders of consciousness. Employing functional magnetic resonance imaging (fMRI), we develop a test of executive function that, without requiring any behavioral expression on the part of the patient, can reveal the integrity of high-level cognitive processes that are thought to be crucial to consciousness (Dehaene and Naccache, 2001). In particular, the procedure is designed to assess the residual ability to maintain information through time, and willfully allocate attention toward a stimulus. We first describe the results from a "proof of concept" study in a set of healthy participants, and then employ the same paradigm in a minimally conscious patient who could successfully complete the task.

Methods and materials

Participants

Twenty healthy volunteers (12 female) with no history of neurological disorder and one MCS patient participated in the experiment. Healthy volunteers signed informed consent prior to the experimental session. For the patient, assent was obtained from the next of kin. This study was approved by the Cambridge Local Research Ethics Committee.

Patient history

The patient was first hospitalized on October 28, 2007 after suffering a cardio-respiratory arrest, and was resuscitated in ITU (defibrillated/intubated and ventilated). A computed tomography scan (CT) on admission revealed no evidence of intracranial hemorrhage. However, it did reveal widespread loss of grey-white matter differentiation, consistent with an anoxic brain injury. The ventricles, basal cisterns, and other cerebrospinal fluid spaces were preserved and there was no evidence of severe swelling.

Patient behavioral assessment

The patient was behaviorally assessed multiple times throughout his stay at the Addenbrooke's Hospital (Cambridge, UK). When tested with the JFK Coma Recovery Scale (CRS; Giacino et al., 2004), the patient demonstrated a portfolio of behaviors consistent with the MCS, achieving a score of 13. In particular, command following and nonfunctional communication could be observed, behaviors that confirm the MCS diagnosis.

Task

Participants (i.e., healthy volunteers and the patient) were required to perform two tasks in alternating fashion. In both tasks, they were aurally presented with a sequence of 26 words, at 1 Hz. In the "passive listening" baseline task, participants were instructed to listen to the words that were presented. In the "target detection" task (or "counting" task, interchangeably), they were instructed to count the number of times they heard a given target word (different for every block). Two aural cues were used to distinguish baseline from counting blocks. Both cues started with a 250 ms tone followed by the words "Listen All" to signal a passive listening block, and the words "Count *[target word]*" to signal a target detection block (and to reveal the target word). Each cue lasted 4 s. Full instructions were delivered prior to the functional session.

Stimuli

A total of 120 monosyllabic words, recorded in a female voice, were available for each session. Out of these, 50 were randomly selected, uniquely for every participant, and randomly distributed in groups of 5 to each of 10 blocks (5 baseline, 5 target detection). Within each block, words that were randomly assigned to each be repeated 7, 6, 5, or 4 times (with 2 words being repeated 4 times), generating a total of 26 words per block. The 26 words were then randomly distributed across each block, under the sole constrain that no word appeared twice in a row. For the five counting blocks, the target was twice assigned to be the 7- and the 6-repetition word, and once the 5-repetition word. Which block featured the 7-, 6-, or 5-repetition targets was randomly varied for each participant. In this design, baseline and target detection blocks are thus perfectly matched in terms of perceptual stimulation, including repetition frequencies, while prompting (via the cue) for differing mental sets.

Experimental design

Volunteers and patients underwent one structural and one functional scan (as part of a longer fMRI experiment). In the functional session, participants performed five target detection blocks and five passive listening blocks, in an ABAB alternating fashion, always starting with passive listening (see Fig. 1). Each block started with a 4 s aural cue indicating the nature of the block (and a target word, for the counting blocks), followed by the 26 words.

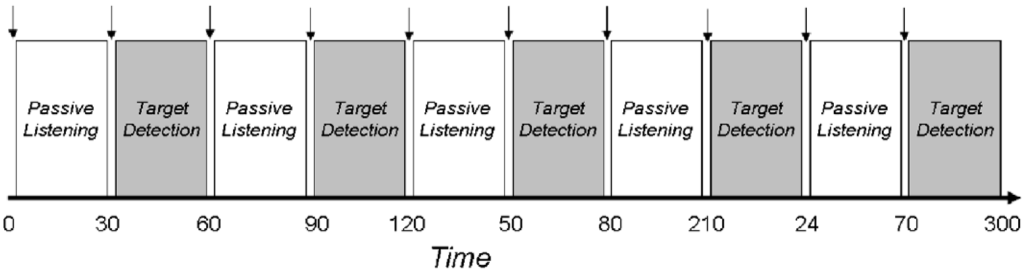

Fig. 1. Experimental design. Arrows depict cue delivery, while shaded and unshaded blocks represent stimulus delivery periods in the target detection and passive listening blocks, respectively.

fMRI data acquisition

Healthy volunteer data were acquired on a Siemens 3T Tim Trio at the MRC Cognition and Brain Sciences Unit, Cambridge (UK), while the patient data were acquired at the Wolfson Brain Imaging Centre at Addenbrooke's Hospital, Cambridge (UK). At both sites, T1 sensitive images were acquired with an MP-RAGE sequence at 1 mm isovoxel resolution. T2* sensitive images were acquired using the Siemens echo planar sequence for real-time scanning (32 descending slices, 3 mm^2 in-plane resolution, TR = 2 s, TE = 30 ms, FA = 78°).

fMRI data analysis

Analysis methods were performed using FSL 5.91 (FMRIB's Software Library, http://www.fmrib.ox.ac.uk/fsl; Smith et al., 2004). Prior to functional analyses, each individual Echo Planar Imaging (EPI) time series was motion corrected to the middle time point using a six-parameter, rigid-body method (as implemented in MCFLIRT; Jenkinson et al., 2002). Data were smoothed with a Gaussian kernel of 8 mm FWHM, and signal from extraneous non-brain tissue was removed using Brain Extraction Tool (BET; Smith, 2002). The 4D data was normalized to the grand-mean intensity by a single multiplicative factor and high-pass filtered (Gaussian-weighted least-squares straight line fitting, with sigma = 30.0 s). Finally, functional data was co-registered to structural images using a seven-parameter optimization method (Jenkinson and Smith, 2001).

Statistical analyses were performed using a general linear model approach, as implemented in FEAT (fMRI Expert Analysis Tool; Woolrich et al., 2001), including pre-whitening correction for autocorrelation. The model included one regressor of interest, representing the working memory blocks (and thus, implicitly, the baseline blocks), and seven regressors of noninterest. The latter included the cue period (for both working memory and baseline blocks) and six motion parameters. For each dataset (i.e., healthy volunteers and patient), we compared blood oxygenation level dependent (BOLD) signal observed in the target detection blocks to that observed in the baseline blocks. Z (Gaussianised T) statistic images were thresholded using clusters determined by $Z > 2.7$ and a (corrected) cluster significance threshold of $p = 0.001$ (Worsley et al., 1992).

For healthy volunteers, group average statistics were also computed. Prior to multi-subject analyses, each individual dataset was co-registered to the MNI152 standard template brain using a 12-parameter optimization method (Jenkinson and Smith, 2001). Group mean statistics for each contrast were generated with a mixed-effects model resulting from the use of within-session variance (i.e., fixed effects) at the single subject level and between-session variance (i.e., random effects) at the group level (Friston et al., 2005). Statistical parametric maps were computed in FLAME (Beckmann et al., 2003; Woolrich et al., 2004) and thresholded at $p < 0.05$ full-brain voxel-wise corrected.

Results

Healthy volunteers

Averaging across all healthy volunteers, the target detection versus passive listening contrast revealed activations spanning frontal, temporal, and parietal cortex, along with regions of the cerebellum (see Table 1 and Fig. 2). Frontal cortex was activated bilaterally in the sub-lobar sections of the inferior frontal gyrus (BA 47), and in the middle frontal gyrus (BA 10). Activation was also observed in the right superior frontal (BA 10) and cingulate gyri (BA 32), left precentral gyrus (BA 6), along with the medial frontal gyrus (in BA 6 and 32). Activation in posterior parietal cortex was focused in the left supramarginal gyrus (BA 40) and the right inferior parietal lobule (BA 40). Temporal cortex was activated in the right inferior gyrus (BA 20). Finally, activations were also detected bilaterally in various subregions of the posterior cerebellum, including the pyramis, uvula, inferior semilunar lobule, and vermis. This pattern of activation replicates previous studies of target detection in healthy volunteers (see Naghavi and Nyberg, 2005). Furthermore, this same general pattern is also robustly observed at the single subject level (cf. Fig. 4).

MCS patient

The target detection minus passive listening contrast revealed, in the MCS patient, a pattern of activation similar to that observed in healthy volunteers (see Figs. 3 and 4). Extensive

Table 1. Group average healthy volunteer data for the target detection versus passive listening blocks

MNI coordinates			*Z*	Hem.	Region (Brodmann area)
x	*y*	*z*			
Frontal					
10	18	36	5.89	R	Cingulate gyrus (32)
−30	24	0	5.69	L	Inferior frontal gyrus (47)
−6	8	48	5.61	L	Medial frontal gyrus (32)
30	26	2	5.45	R	Inferior frontal gyrus (47)
−46	−2	52	5.32	L	Precentral gyrus (6)
−10	−2	64	5.16	L	Medial frontal gyrus (6)
36	48	26	4.98	R	Superior frontal gyrus (10)
−32	48	6	4.70	L	Middle frontal gyrus (10)
32	50	8	4.59	R	Middle frontal gyrus (10)
Temporal					
56	−24	−22	4.33	R	Inferior temporal gyrus (20)
52	−28	−20	4.32	R	Inferior temporal gyrus (20)
Parietal					
48	−42	42	5.43	R	Inferior parietal lobule (40)
−32	−48	36	4.75	L	Supramarginal gyrus (40)
66	−36	30	4.66	R	Inferior parietal lobule (40)
−44	−42	36	4.47	L	Supramarginal gyrus (40)
Cerebellum					
−6	−76	−40	4.61	L	Cerebellum (pyramis)
6	−80	−44	4.58	R	Cerebellum (uvula)
8	−76	−46	4.49	R	Cerebellum (inferior semilunar lobule)
−30	−74	−46	4.36	L	Cerebellum (inferior semilunar lobule)
−36	−68	−42	4.36	L	Cerebellum (pyramis)
−2	−76	−40	4.29	L	Cerebellum (pyramis of vermis)

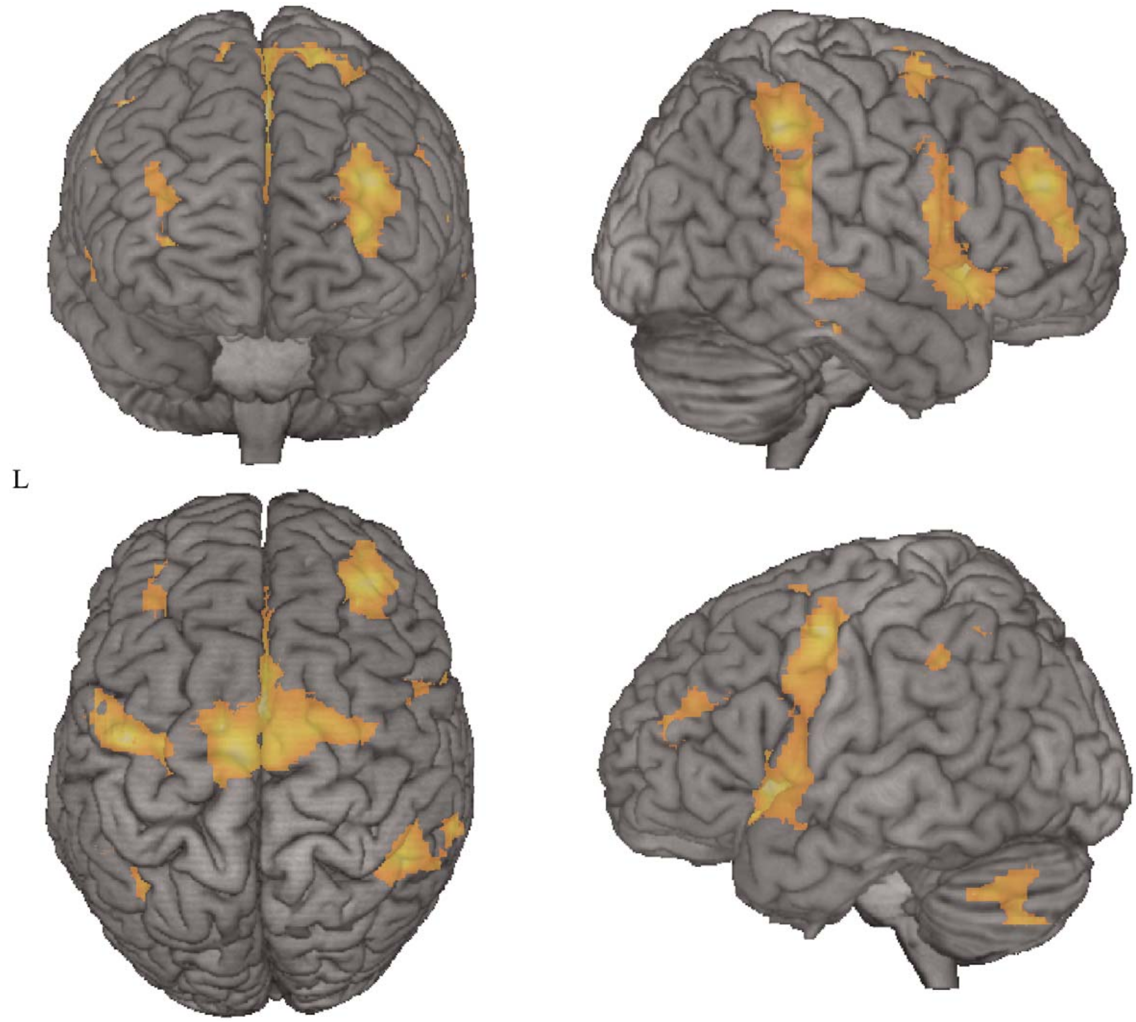

Fig. 2. Group data (healthy volunteers only). Group activation for the target detection versus passive listening contrast ($p < 0.05$ voxel-wise corrected).

activation was detected in frontal cortex, especially left lateralized, spanning the superior and middle frontal gyri, the sub-lobar section of the inferior frontal gyrus, and the post central gyrus. A large focus was localized in the medial wall of frontal cortex, spanning cingulate and medial frontal gyri. Extensive parietal activation was also detected in right supramarginal gyri (posterior section) and bilateral inferior parietal lobuli, extending dorsally into the superior parietal lobule (in the right hemisphere only). Temporal activation was revealed bilaterally in the planum temporale, medial temporal gyrus, and, although to a much lesser extent, in the inferior temporal gyri. Finally, subcortical activations were revealed in the cerebellum and posterior section of thalamus.

To compare the activations observed in the MCS patient with the normal variability seen in healthy volunteers, we report, in Fig. 4, all regions activated by at least three healthy participants (in blue–green–red) and those observed in the patient (in red–yellow, masked with the healthy volunteer group result). With the exception of the

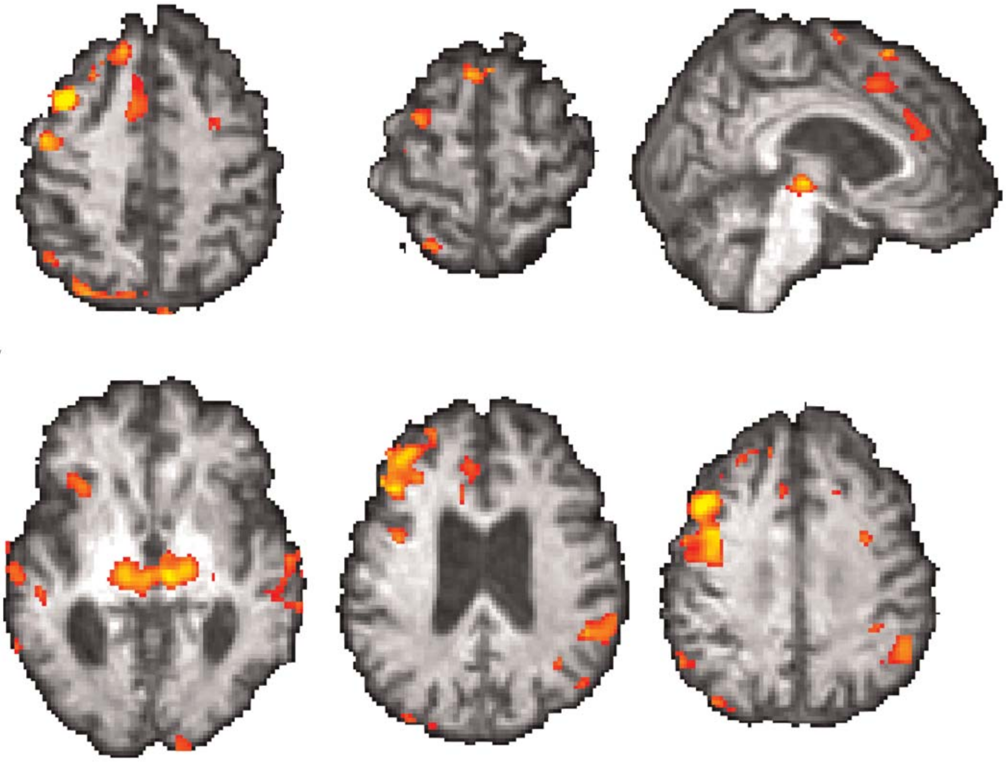

Fig. 3. Patient data. Brain results for the target detection versus passive listening contrast ($Z > 2.7$, $p = 0.001$ corrected).

left parietal cluster, the patient data falls well within what is seen in healthy volunteers performing the same task. Moreover, as exemplified by the time course of the medial frontal cluster (Fig. 4), the observed activations were protracted along the 30 s counting blocks. In addition, Fig. 5 shows that the activations were repetitively and consistently time locked to the counting task, peaking and falling in synchrony with its onset and offset. It is noteworthy, however, that passive listening and counting blocks were perfectly matched for perceptual stimulation.

Discussion

Compared to simple listening, the counting task elicited, in all healthy volunteers, a pattern of activation similar to that reported in previous studies of executive function, including target detection and working memory (see Naghavi and Nyberg, 2005). The very fact that the two (perceptually identical) tasks elicited different patterns of activation confirms that our paradigm does elicit the expected cognitive processes including maintenance of information through time and willful adoption of ''mind-sets'' (as well as language comprehension). When tested on the same task, the MCS patient exhibited an extremely similar set of activations. While it is not possible to infer which of these cognitive processes such activations reflect exactly (Henson, 2005), it is difficult to interpret these results without accepting that the patient retained several types of cognitive ability. In particular, the patient must have retained sufficient linguistic processing to comprehend the instructions, the ability to maintain information through time, and the ability to monitor incoming stimuli. The difference in activation across periods of identical stimulation also indicates that the patient could willfully adopt, on command, different ''mind-sets'' as a

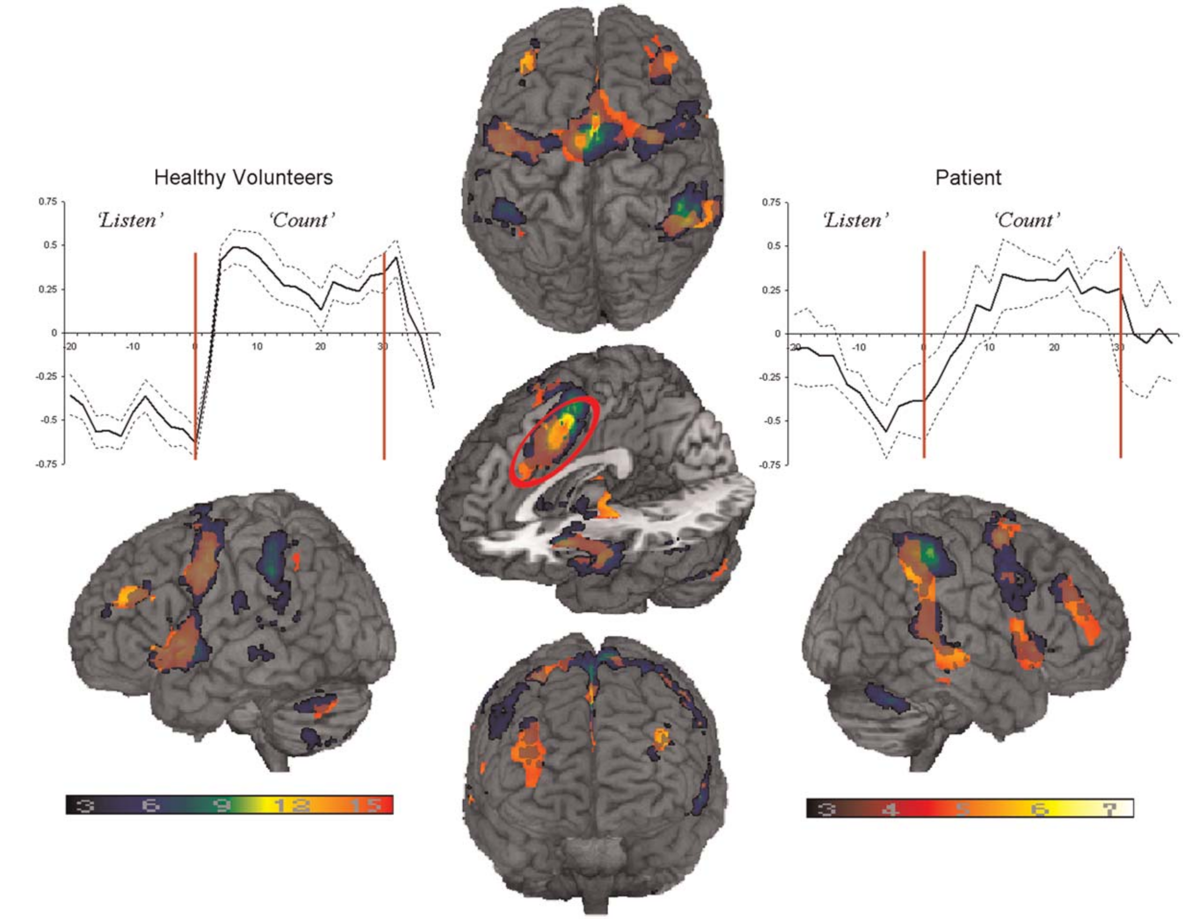

Fig. 4. Single subject and patient data. Overlay of the single subjects (dark shades; blue-green-red in the web version) and patient (light shades; orange-yellow in the web version) results for the target detection minus passive listening contrast. Graphs depict the average peristimulus activation profile of a representative ROI in medial cortex (highlighted in white; red in the web version) for the group of healthy volunteers and the patient (dashed lines indicate the standard error).

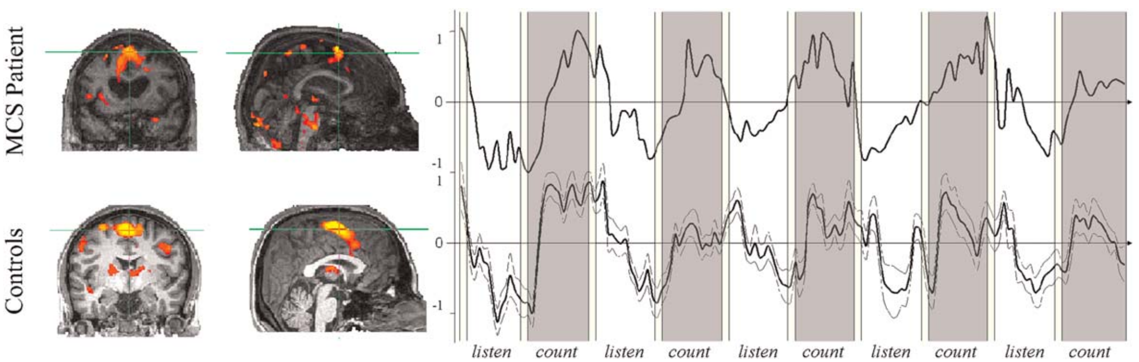

Fig. 5. ROI time course. Activation time course of the medial frontal cluster for the patient and healthy volunteers (dashed lines indicate the standard error).

function of condition. Furthermore, he must have been capable of voluntarily assigning, in a top-down fashion, saliency to words (i.e., the targets) that would otherwise be ''neutral'' and logically incapable of eliciting such activation automatically. Remarkably, none of these cognitive abilities was apparent when the patient was tested at the bedside. While behavioral signs of awareness were apparent, including some level of command following, the information provided by the fMRI assessment far exceeded what could be learned with the standard clinical tools.

Previous studies have used electroencephalography (EEG) and event-related potentials (ERPs) to investigate the ability of patients to detect and recognize targets among distracters (Di et al., 2007; Perrin et al., 2006; Qin et al., 2008). These studies, however, have used the patient's own name as the target word; that is, an intrinsically salient and over-learned stimulus. Under these circumstances, differential brain response to the target stimulus, compared to nontargets, is very informative in terms of residual linguistic processing, but is not a good indicator of whether such a response is voluntary or purely automatic. In one notable exception, however, the own name paradigm was adapted to include, as targets, both the patient's own name and other ''non-salient'' names (e.g., similarly frequent names that had no relation to the patient or his/her family; Schnakers et al., 2008). In that study, all the tested MCS patients exhibited a significant response when passively listening to their own name, as in the above mentioned studies. In addition, however, five out of fourteen patients showed greater activity for hearing their own name when instructed to count its occurrences as opposed to when they passively heard it. Remarkably, a similar effect was found, in a different subset of four patients, for neutral targets (i.e., not the patient's own name).

The study reported here takes this same idea one step further, making exclusive use of neutral words as targets and nontargets. In both approaches, differential activity across tasks for neutral words is difficult to explain without assuming a conscious decision on the part of the patient to actively maintain in working memory a target word and to monitor incoming stimuli. In addition, while Schnakers and colleagues focus on the detection of targets, our study focuses on the more general notion of executive functions, including willful adoption of ''mind-sets,'' maintenance of information in working memory, and monitoring of incoming stimuli. Crucially, our task addresses the process of ''holding in mind'' information through time, which is considered to require conscious awareness (Dehaene and Naccache, 2001). Furthermore, our fMRI approach is also able to reveal that this particular task elicits activation in regions that are thought to be a crucial component of the neural basis of consciousness (Baars, 2002; Baars et al., 2003; Dehaene et al., 2003; Rees et al., 2002).

Conclusions

Detecting consciousness in brain injury survivors is critical for appropriate diagnosis and patient management (Bernat, 2006). Objective assessment on the basis of observed and elicited behavior, however, can be extremely challenging in patients with little ability for behavioral output. Use of noninvasive neuroimaging techniques to detect residual cognitive abilities and awareness may thus be crucial to reducing diagnostic error (Owen and Coleman, 2008). While there is at present limited information on the prognostic value of ''activation'' paradigms, the increasing number of studies reporting the integrity of cognitive functions that are not detectable at the bedside (Coleman et al., 2007; Laureys et al., 2002; Owen et al., 2006; Schnakers et al., 2008) does warrant the use of such tools to supplement standard diagnostic assessments.

Experimental approaches such as the one we present here directly address processes that are thought to require consciousness (Dehaene and Naccache, 2001). First, successful completion of our target detection task requires durable and explicit maintenance of information through time including task instructions and the target word. Such processes, as pointed out by Dehaene and Naccache (2001), are not possible in the absence of awareness. For example, while much information processing can occur automatically (e.g., Dehaene et al., 1998), the neural response to nonconscious stimuli is typically short lived, and access to such information tends to decay very quickly (Dehaene et al., 2006). Beyond active maintenance of information, our paradigm also requires intentional behavior, which also implies consciousness (Dehaene and Naccache, 2001). In the absence of a conscious decision to keep in mind the target word and monitor incoming stimuli, the careful matching of perceptual stimulation in the two conditions should yield identical neural activity.

Overall, these findings further confirm the potential for neuroimaging to define both the extent and the precise nature of cognitive processing that is available to patients with disorders of consciousness, without the need for any behavioral (i.e., physical) response (Laureys et al., 2004; Owen and Coleman, 2008; Owen et al., 2007). Indeed, in the MCS case report here, fMRI provided novel information about the patient's working memory abilities that far exceeded expectations based on the standard behavioral assessment. It is important to keep in mind, however, that application of this technology to such patient groups requires careful consideration of many issues (see Giacino et al., 2006; Owen and Coleman, 2007). First, not all patients will benefit from undergoing neuroimaging testing. Where sufficient levels of behavior are preserved, simple motor responses may suffice to assess residual cognition and awareness. Second, neuroimaging tools often impose constraints on the ability of patients to enter their environment (e.g., compatibility with the magnetic field in MRI) and require a level of cooperation throughout the experimental session (e.g., limited motion) that may not always be possible. Third, differences in the coupling of hemodynamic response and neuronal firing (Gsell et al., 2000; Rossini et al., 2004), as well as the pathological anatomy and functional neuroanatomy in this patient group, may affect the interpretability of neuroimaging data.

Several studies have shown that brain responses to stimuli can be detected in the absence of conscious processing (e.g., Dehaene et al., 1998; Vuilleumier et al., 2002a, 2002b). Classifying brain activity as conscious thus requires careful neuroimaging methodology with different conditions being closely matched for perceptual stimulation, and only differing with respect to the required mind-set. Under such circumstances, differential activations across conditions cannot be explained in terms of automatic brain response and hence reveal conscious processing. Finally, it should also be noted that, as for behavioral testing, negative results in neuroimaging experiments cannot be taken as evidence of lack of awareness or cognition. Indeed, lack of brain response may simply result from the patient being asleep throughout the session, or unwilling to cooperate. Nonetheless, when careful methodology is employed, activation studies may be used in patients with disorders of consciousness as ''neural markers'' of residual cognitive abilities and awareness, thus providing information that may well exceed bedside assessments and valuably inform the diagnostic process.

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