

Visual Cognition in Disorders of Consciousness: from VI to Top-Down Attention

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Abstract: What is it like to be at the lower boundaries of consciousness? Disorders of consciousness such as coma, the vegetative state, and the minimally conscious state are among the most mysterious and least understood conditions of the human brain. Particularly complicated is the assessment of residual cognitive functioning and awareness for diagnostic, rehabilitative, legal, and ethical purposes. In this article, we present a novel functional magnetic resonance imaging exploration of visual cognition in a patient with a severe disorder of consciousness. This battery of tests, first developed in healthy volunteers, assesses increasingly complex transformations of visual information along a known caudal to rostral gradient from occipital to temporal cortex. In the first five levels, the battery assesses (passive) processing of light, color, motion, coherent shapes, and object categories (i.e., faces, houses). At the final level, the battery assesses the ability to voluntarily deploy visual attention in order to focus on one of two competing stimuli. In the patient, this approach revealed appropriate brain activations, undistinguishable from those seen in healthy and aware volunteers. In addition, the ability of the patient to focus one of two competing stimuli, and switch between them on command, also suggests that he retained the ability to access, to some degree, his own visual representations. *Hum Brain Mapp* 00:000–000, 2012. © 2012 Wiley Periodicals, Inc.

Key words: traumatic brain injury; minimally conscious state; consciousness; cognition; fMRI; vision

INTRODUCTION

In recent years, much progress has been achieved in characterizing some of the most mysterious and least understood

conditions of the human brain such as coma, the vegetative state (VS) [Giacino et al., 2002; Jennett and Plum, 1972; The Multi-Society Task Force on PVS, 1994a,b], and the minimally conscious state (MCS) [Giacino et al., 2002]. These condition, often collectively referred to as disorders of consciousness (DOC), typically occur after catastrophic (traumatic or non-traumatic) brain injury, and affect the two cardinal elements of consciousness: wakefulness and awareness [Laureys, 2005]. Patients in an acute state of coma, for example, appear to be neither awake nor aware of themselves or their environment [Posner et al., 2007]. MCS patients, on the other hand, appear to be awake, and can demonstrate some level of awareness [Giacino et al., 2002]. In between these two conditions, VS patients exhibit a perplexing dissociation in which they appear to wake up and fall asleep periodically (inasmuch as they open and close their eyes) but show no recognizable sign of awareness [Monti et al., 2010a].

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From a diagnostic point of view, the main challenge relies in determining the level of residual cognition and awareness present. With respect to the latter issue, however, in the absence of an objective measure to quantify its presence, the boundary between awareness and nonawareness remains elusive, making it difficult to correctly distinguish VS from MCS patients. This is confirmed by a 40% estimated misdiagnosis rate by which (aware) MCS patients are mistakenly judged to be VS [Andrews et al., 1996; Childs et al., 1993; Gill-Thwaites and Munday, 2004; Schnakers et al., 2009]. Recent studies have shown that it is possible to employ noninvasive neuroimaging techniques, such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI), to covertly assess the presence of residual cognitive processing [Bekinschtein et al., 2009; Coleman et al., 2007; Faugeras et al., 2011; Monti et al., 2009a; Qin et al., 2008; Schnakers et al., 2008] as well as consciousness [Bekinschtein et al., 2011; Monti et al., 2010b; Owen et al., 2006]. Despite these advances, however, little is known about the degree of mental life possible in these patients [Bernat, 2002; Ropper, 2010], an issue that is paramount for guiding medical and rehabilitative decision-making, and for informing the legal and ethical discussions concerning life at the lower boundaries of consciousness [Andrews et al., 1996; Bernat, 2002; Elliott and Walker, 2005; Fins et al., 2008].

In this report we focus on the extent to which a severely injured brain can represent visual information, as a first exploration into what representation of the surrounding world is possible in a condition of impaired consciousness. Crucially, this assessment relies entirely on “brain behavior” rather than on motoric behavior [Monti and Owen, 2010], in consideration of the fact that motor output is often severely constrained in this patient group. Indeed, it has been shown recently that, in a subset of patients who fail to demonstrate motor response to commands, significant subthreshold muscle activity [Bekinschtein et al., 2008] and significant contralateral premotor cortex activation [Bekinschtein et al., 2011] can still be detected.

Capitalizing on a relatively rich understanding of the neurocognitive systems underlying visual processing [Tootell et al., 1998], we developed an fMRI battery of tests probing increasingly complex stages of information processing along a known caudal to rostral occipitotemporal gradient. As illustrated in Figure 1, the battery assesses processing of visual information at multiple levels, from basic response to light, to response to visual properties such as color, motion, and coherent outlines/objects, as well as response to specific categories of objects (i.e., faces, houses). In addition, at the top level of the battery, we tested whether patients could access their visual representations, by assessing their ability to deploy top-down attention in order to resolve an ambiguous stimulus comprised of two conflicting stimuli in response to verbal cues (cf. Fig. 1).

We first developed the paradigm in a group of healthy volunteers and then tested its efficacy in a patient with a severe disorder of consciousness.

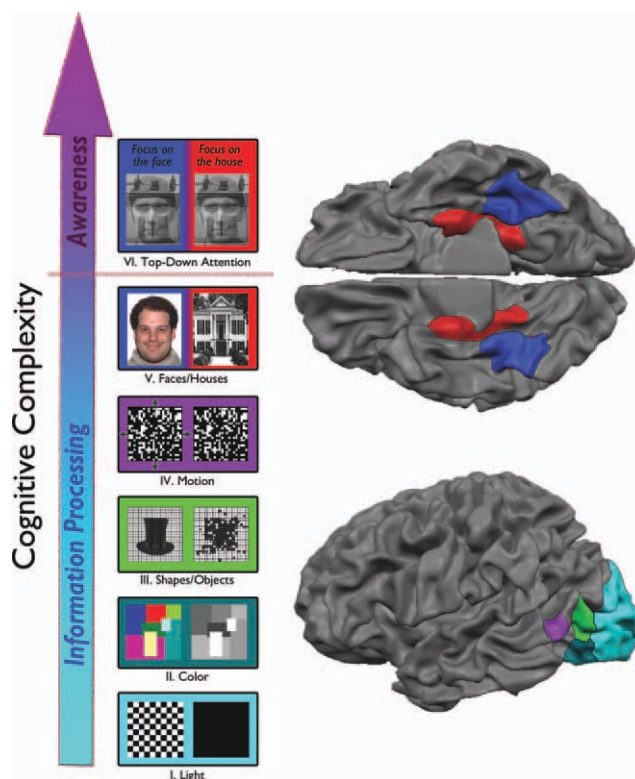


Figure 1.

Illustration of the levels of visual cognition probed by the battery of tests, and the approximate regions of the brain expected to be activated by each level. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

MATERIALS AND METHODS

Healthy Participants

Twenty-one volunteers (13 females) with no history of neurological disorder participated in the study. All participants signed informed consent before the experimental session and participated for monetary compensation.

Patient History and Description

One patient with a DOC was tested on the same battery of tasks. The patient was hospitalized following a traumatic brain injury in May 2006. Initial computed tomography scans revealed left parietal subdural and extradural hematoma, in addition to right subdural hematoma. Further scans also revealed evidence of diffuse hemorrhage. Overall, the neurological examination suggested the possibility of diffuse axonal injury. Over the next 2 years, assessment in specialized centers revealed inconsistent but reproducible evidence of awareness of the self and environment. When admitted for fMRI testing, 18 months postinjury, the patient scored 11 (out of a maximum of 23) on the JFK Coma Recovery Scale [Giacino et al., 2004],

consistent with an MCS diagnosis (CRS-R subscores: auditory: 2—localization to sound; visual: 3—pursuit eye movement; motor: 2—flexion withdrawal; oromotor/verbal: 2—vocalization/oral movement; communication: 0—none; arousal: 2—eye opening without stimulation). Overall, the presence of consciousness was revealed by the ability of the patient to visually track. However, in none of the behavioral assessments was it possible to observe any sign of command following.

The presence of a basic response to visual stimulation was assessed with visual evoked potentials elicited using a flash lamp at 3 Hz. Bilateral visual cortex responses were apparent, displaying latencies within an acceptable range (wave N1, left hemisphere O1 = 86.7 ms, midline Oz = 85.2 ms, right hemisphere O2 = 86.7 ms), and therefore confirming preserved neural axes along the retina to thalamus to primary visual cortex pathway.

The patient underwent the visual hierarchy paradigm described here as part of a wider set of fMRI tests which also included a test of mental imagery which is specifically designed to reveal evidence of command following in patients of this sort [Boly et al., 2007; Monti et al., 2010b; Owen et al., 2006].

Signed assent from the patient's next of kin was acquired before investigation. This study was approved by the Cambridge (UK) Local Research Ethics Committee.

Task

In the first five levels of the battery, participants were given no task other than to look at the display. At the sixth (and last) level, a brief aural and visual cue was administered at the beginning of each block, instructing participants to focus on one of two superimposed stimuli.

Stimuli

In the first level, a flashing checkerboard (at 2 Hz) was presented, in alternation with a black screen in an ABAB fashion, for 16-s blocks, (see below). In the second level, chromatic Mondrian patterns, similar to those used in previous studies of color perception [McKeefry and Zeki, 1997], were alternated with achromatic versions of the same displays. In every 16-s block, four patterns were presented, for 4 s each. Object perception, in the third level, was probed using the very same stimuli employed in previous research of object processing [Kourtzi and Kanwisher, 2000] (and exemplified in Fig. 1). Specifically, figures of concrete objects and abstract (but coherent) shapes were compared with scrambled versions of the same figures. In both conditions, each cycle included four stimuli of each type (i.e., coherent, scrambled), presented in random order. Each figure was shown only once. In the fourth level, a random display of dots moving with 100% congruence in each of four directions (0° , 90° , 180° , 270°), was alternated with a similar, but motionless, random display. In both conditions the random display of dots was

refreshed every 4 s. In each 16-s block of moving dots all four directions of movement were presented, in random order. In the fifth level, sensitivity to different categories of visual objects was tested by comparing blocks of pictures of faces to blocks of figures of houses. As for the previous levels, each block included four figures, presented in random order. Each figure was presented only once. At the top level of the battery, all blocks included a display which comprised a superimposed face and a house, as described in detail in a previous study [Hampshire and Owen, 2006]. Blocks only differed in whether participants were instructed to focus on the faces (in half the blocks) or on the houses (in the remaining blocks). Each block included four different superimposed figures, each presented for 4 s. Each overlay figure was presented twice, once in the blocks in which participants had to focus on the face, and once in the blocks in which participants had to focus on the house.

Experimental Design

The first five levels employed the same experimental design. Each lasted a total of 320 s, and included twenty 16-s blocks (i.e., 10 blocks for each condition). The two categories of stimuli (e.g., light vs. dark, faces vs. houses) were presented in alternating blocks. Within each block, the ordering of stimuli was fully randomized. Where multiple stimuli were available for each category (i.e., from the second level upwards), each block included four stimuli, displayed for 4 s each. The sixth level was almost identical to the previous ones, except for a 2-s cue, at the beginning of each block, instructing participants whether to focus on the faces or the houses. The verbal cue "look at the houses/faces" was delivered, concurrently, visually, and aurally. This last run lasted a total of 360 s.

fMRI Data Acquisition

Volunteer data was collected at the MRC Cognition and Brain Sciences Unit, Cambridge (UK) on a 3T Tim Trio Siemens system. T1-weighted images were acquired with a three-dimensional MP-RAGE sequence (TR 2,300 ms, TE 2.47 ms, TI 900 ms, 150 slices, $1 \times 1 \times 1.2 \text{ mm}^2$ resolution). T2* sensitive images were acquired using an echo planar sequence (TR = 2,000 ms, TE = 30 ms, FA = 78° , 32 descending slices, $3 \times 3 \times 3.75 \text{ mm}^2$ resolution). Patient data was also acquired on a 3T Tim Trio Siemens system, with identical parameters, at the Wolfson Brain Imaging Centre at Addenbrooke's Hospital, in Cambridge (UK).

fMRI Data Analysis

Analysis methods were performed using FSL 5.9.1, part of FSL (FMRIB's Software Library; available at: www.fmrib.ox.ac.uk/fsl). Before functional analyses, each individual EPI time-series was motion corrected to the middle time point using a six-parameter, rigid-body

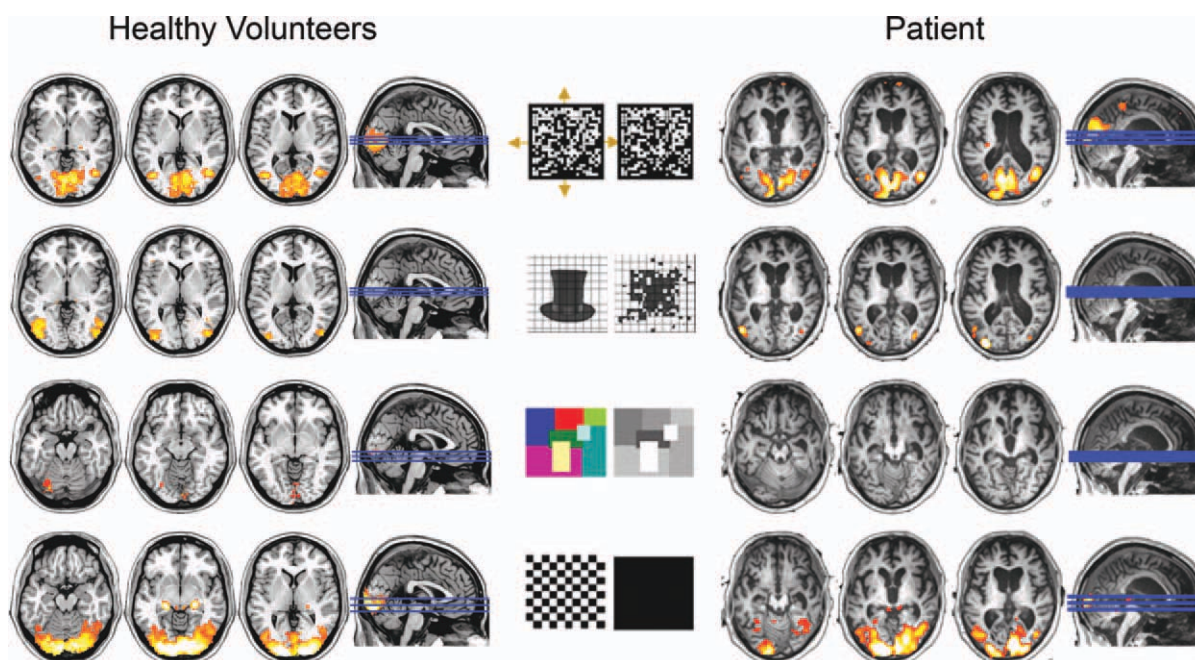


Figure 2.

Levels I–IV. Brain activation for healthy volunteers (left) and the patient (right). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

method (as implemented in MCFLIRT [Jenkinson et al., 2002]). Data were smoothed with a Gaussian kernel of 8 mm FWHM and signal from extraneous nonbrain tissue was removed using BET (Brain Extraction Tool [Smith, 2002]). The four-dimensional data were 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 were coregistered to structural images using a seven-parameter optimization method [Jenkinson et al., 2002]. Statistical analyses were performed using a general linear model approach, as implemented in FEAT (fMRI Expert Analysis Tool [Jenkinson and Smith, 2001]), including prewhitening correction for autocorrelation. Given the ABAB design, only the onset of the B task was modeled and included in the GLM regression, together with six regressors of noninterest (translation and rotation motion parameters). In the last run, an additional regressor of noninterest was added, modeling the cue delivery. In all runs, the blood oxygenation level dependant (BOLD) response to the stimuli of interest was compared with its baseline. In the last two runs, however, the reverse comparison was also performed, to isolate the neural response to perceiving and focusing on both faces and houses. Full brain single subject Z-statistic images were thresholded using clusters determined by $Z > 2.5$ and a (corrected) cluster significance threshold of $P = 0.001$ [Worsley et al., 1992].

In healthy volunteers, group average statistics were also computed. Before multisubject analyses, each individual data set was coregistered to the MNI152 standard template

brain using a 12-parameter optimization method [Jenkinson et al., 2002]. 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 [Henson, 2005]. Statistical parametric maps were computed in FLAME [Beckmann et al., 2003; Woolrich et al., 2004] and thresholded at $P < 0.05$ Bonferroni corrected. For the group of healthy volunteers and the patient alike, analysis of the last level of the hierarchy was restricted to the fusiform and parahippocampal gyri, as defined by structural masks derived from the Harvard-Oxford probabilistic atlas available in FSL.

RESULTS

When tested on the visual hierarchy, the patient exhibited a set of activations (Fig. 2 and Table I) that closely matched those observed in the healthy volunteers (Fig. 3 and Table II). These results not only demonstrate that all of the tested stages of visual processing were intact in the patient, but also confirm that he was able to willfully access visual representations and follow commands.

More specifically, as depicted in Figure 2, comparison of flashing checkerboards with a black screen revealed widespread occipital activations in striate and extrastriate cortices. Coherent shapes and objects, when contrasted to scrambled versions of the same figures, revealed robust bilateral activation in a region of occipital cortex consistent

TABLE I. DOC patient: Activation peaks for each contrast

	<i>x</i>	<i>y</i>	<i>z</i>	<i>Z</i>
<i>Checkerboards</i>				
Occipital pole	8	-90	6	19.90
Occipital pole	-12	-96	-8	15.00
Lateral occipital cortex	28	-92	2	11.90
Intracalcarine sulcus	18	-82	-2	9.98
Lateral occipital cortex	-26	-94	2	9.92
Thalamus	-8	-34	0	4.24
Thalamus	10	-30	0	3.41
<i>Colors</i>				
n/a				
<i>Shapes</i>				
Lateral occipital complex (inferior division)	-38	-90	18	9.78
Lateral occipital complex (superior division)	-28	-74	36	5.81
Lateral occipital complex (inferior division)	-52	-70	0	5.53
Lateral occipital complex (inferior division)	38	-80	6	3.94
Lateral occipital complex (superior division)	36	-84	14	3.73
<i>Motion</i>				
Intracalcarine cortex	-10	-78	8	10.30
Intracalcarine cortex	6	-84	2	8.10
Occipital pole	18	-90	36	8.67
Occipital pole	-16	-104	12	7.75
Lateral occipital cortex (V5)	46	-72	8	8.59
Lateral occipital cortex (V5)	-36	-74	10	5.60
<i>Faces</i>				
Lateral occipital cortex (superior division)	-52	-64	38	5.43
Lateral occipital cortex/fusiform gyrus	42	-78	-8	10.10
Lateral occipital cortex (inferior division)	52	-78	2	5.06
Fusiform gyrus	46	-54	-16	8.75
Lingual gyrus	-8	-82	-2	6.07
Fusiform gyrus	-48	-52	-18	3.58
<i>Houses</i>				
Intracalcarine cortex	8	-86	4	21.34
Parahippocampal gyrus	-24	-48	-8	12.25
Parahippocampal gyrus	22	-42	-10	20.30
Occipital pole	-22	-92	-10	11.10
<i>Faces overlay</i>				
Fusiform gyrus	48	-50	27	5.46
Lateral occipital complex	46	-70	-14	6.28
Fusiform gyrus	-42	-68	-16	4.00
<i>Houses overlay</i>				
Parahippocampal gyrus	24	-44	-12	5.23
Parahippocampal gyrus	-24	-48	-14	4.01

with the localization of the lateral occipital complex (LOC) [Kourtzi and Kanwisher, 2000]. Motion stimuli elicited bilateral activation at the junction between the middle temporal and occipital cortices, consistent with previous localization of the human motion selective area MT/V5

[Tootell et al., 1995], as well as large segments of medial occipital cortex. These results closely replicate what was observed in healthy volunteers.

Similarly, in both the patient and the controls, pictures of faces, as compared with pictures of houses, revealed strong bilateral activation in the face selective fusiform area (FFA) (see Fig. 3 and Table II) [Kanwisher et al., 1997; Puce et al., 1995]. The converse subtraction elicited strong bilateral activation in the parahippocampal place selective area (PPA) [Epstein and Kanwisher, 1998].

At the top level of the battery, a comparison of epochs in which the patient was instructed to focus on the faces, versus epochs in which he was instructed to focus on the houses, revealed significant activity in right FFA. The reverse comparison elicited strong bilateral activation in the PPA. The same results were observed in healthy volunteers. This result is noteworthy because the stimuli in the two conditions were absolutely identical (i.e., the very same images featured in both conditions), and therefore, the activation must reflect a purely top-down shift of attention. Furthermore, the time-course of the peak voxels in the PPA and FFA for both the patient and a sample subject (Fig. 3, respectively), closely match the onset and offset of each epoch, confirming that the subtraction results reflected a consistent, sustained, and alternating up- and down-modulation of the fusiform and parahippocampal regions.

Unfortunately, due to excessive movement (>3 cm), the color processing level of the battery could not be analyzed in the patient. In healthy volunteers, however, colored Mondrian patterns, as compared with the same displays shown in monochrome shades, resulted in activations in occipital cortex as well as ventral occipitotemporal cortex consistent with previous reports of color sensitive human V4 [McKeefry and Zeki, 1997] or V8 [Hadjikhani et al., 1998] and nearby regions [Beauchamp et al., 1999].

In the same scanning session, the patient also underwent a test of awareness in which participants are instructed to alternate epochs of mental imagery with epochs of rest [Boly et al., 2007; Monti et al., 2010b; Owen et al., 2006]. However, in contrast to the results obtained in the visual hierarchy, presented here, no activation could be detected in the expected neuroanatomical locations in the supplementary motor area (SMA) and PPA, during either the motor (i.e. “imagine playing tennis”) or the spatial imagery (i.e. “imagine walking around the rooms of your house”) tasks.

DISCUSSION

Detecting residual cognitive function and consciousness in patients surviving severe brain injury is extremely challenging but crucial for correct diagnosis, care taking strategies, and general quality of life [Andrews et al., 1996; Elliott and Walker, 2005]. We used fMRI to assess, in a systematic fashion, the integrity of visual processing in a

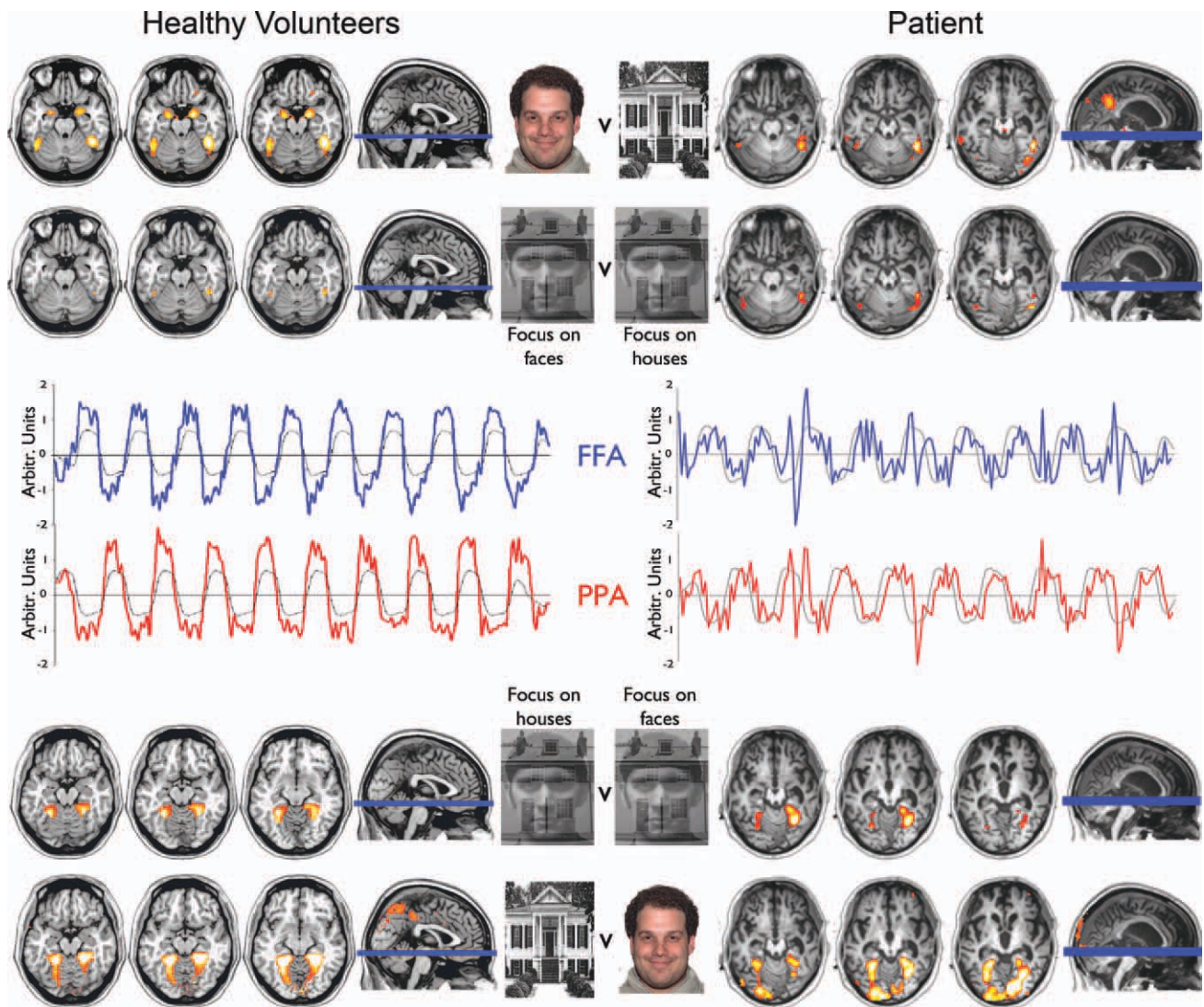


Figure 3.

Levels V–VI. Brain activation and illustrative voxel time-course for healthy volunteers (left) and the patient (right). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

patient with impaired consciousness. The results suggest that, despite the severe brain injury and the impairment of consciousness, several aspects of visual cognition were preserved, indicating that the patient may have relatively sophisticated (visually driven) representations of his environment, and that the visual modality is available for diagnostic and rehabilitative purposes. This result is particularly important in this clinical setting, since it is well known that visual impairment is one of the leading causes of misdiagnosis in this patient group. In a large retrospective study, for example, blindness and severe visual impairment accounted for 65% of patient misdiagnoses [Andrews et al., 1996]. Similarly, in other studies, aspects of visual cognition have been used to discriminate

between VS and MCS patients [Schnakers et al., 2006; Vanhaudenhuyse et al., 2008], and can signal recovery from VS [Giacino et al., 2002]. Furthermore, at the highest level, the results suggest that the patient could comprehend language, access the contents of (some) visual information, and follow commands—something that could not be established at the bedside despite repeated examinations.

It is important to stress, however, that the results presented here should be taken as a proof-of-concept, and do not allow any inference concerning the prevalence of this kind of “brain behavior” in the population in general. Indeed, at the time of this finding, only five other patients had participated in the task. Preliminary analyses suggest that response to passive stimulation is likely to be

TABLE II. Healthy volunteers: Activation peaks for each contrast

	x	y	z	Z
<i>Checkerboards</i>				
Occipital pole	18	-100	10	16.94
Occipital pole	-16	-100	2	16.94
Lingual gyrus	8	-90	-8	16.16
Lateral occipital cortex	-30	-90	-8	14.44
Lateral occipital cortex	30	-90	-2	13.92
Thalamus	22	-28	-4	14.92
Thalamus	-22	-28	-8	14.88
<i>Colors</i>				
Lingual gyrus	18	-78	-16	5.3
Occipital fusiform gyrus (V4)	24	-66	-16	5.19
Lingual gyrus	2	-90	-10	7.4
Occipital pole	-14	-104	6	7.47
Occipital pole	14	-98	10	4.96
<i>Shapes</i>				
Lateral occipital cortex (inferior division)	-44	-74	-8	9.37
Lateral occipital cortex (inferior division)	46	-78	-8	7.82
Lateral occipital cortex (inferior division)	48	-68	-12	7.87
<i>Motion</i>				
Lingual gyrus	12	-76	0	9.04
Lingual gyrus	-8	-76	2	8.07
Lateral occipital cortex/V5	46	-68	2	8.59
Lateral occipital cortex/V5	-42	-70	6	8.65
Occipital pole	10	-96	10	7.23
Occipital pole	-6	-100	2	6.5
<i>Faces</i>				
Amygdala	20	-6	-16	10.61
Amygdala	-20	-6	-18	8.64
Fusiform gyrus	44	-48	-20	11.29
Fusiform gyrus	-44	-54	-22	9.23
Lateral occipital cortex (inferior division)				
Frontal orbital cortex	24	30	-20	5.34
<i>Houses</i>				
Parahippocampal gyrus	24	-40	-14	11.84
Parahippocampal gyrus	-26	-44	-10	12.97
Lingual gyrus	14	-78	-4	6.51
<i>Faces overlay</i>				
Fusiform gyrus	44	-48	-20	4.8
Fusiform gyrus	-42	-48	-22	4.23
<i>Houses overlay</i>				
Parahippocampal gyrus	26	-46	-16	7.63
Parahippocampal gyrus	-28	-46	-12	8.22

observable across VS and MCS patients, in keeping with the very few existing case reports [Giacino et al., 2006, 2009; Menon et al., 1998]. In our sample, one MCS patient exhibited appropriate activity in all passive levels, while other three (one VS and two MCS) exhibited limited activation in response to checkerboards and motion stimuli. Finally, one VS patient exhibited no response to any of the tasks. Whether one in six is a realistic estimate of the prev-

alence of this kind of “active” brain behavior in patients with disorders of consciousness, and the degree by which behavioral and neuroimaging results might mismatch in this context, remains entirely to be assessed (data collection for a large-cohort report is currently ongoing).

Although this study presents an initial step toward understanding what the world might “look like” at the lower boundaries of consciousness, it is important to be clear about what inferences these data support. The results observed in the first five levels of the battery do not necessarily confirm that the patient was “seeing” the stimuli. Differential brain activation in response to different stimulation only confirms that the brain detected a difference between the two types of stimulation (with or without subjective perception). Indeed, it is well known that brain activation in response to visual input can occur in the absence of subjective perception [Dehaene et al., 2006]. However, in the last level of the battery, differential brain activation was observed in response to the same stimulation, presented under differing “mind-sets.” The results are difficult to interpret without assuming that there was a willful decision by the patient to focus, as instructed, on one of the two possible perceptions of the conflicting visual display. It is also important to highlight that, while it is well known that resolution of ambiguous or bistable visual displays can occur spontaneously [Tong et al., 1998], this would not be expected to occur at regular 16 s intervals, as observed here, matching not only the timing of the cue delivery, but also the content of the cue itself. Nevertheless, whether the “subjective” experience of the patient matches that typical of healthy individuals is impossible to determine—as much as it is not possible to compare the subjective experiences of any two healthy individuals. Could automatic processes, elicited to the verbal cue “look at the faces/houses” account for the observed results? This is unlikely for several reasons. First, the words “face” and “house” alone have been shown to produce no appreciable activation in fusiform and parahippocampal regions [Reinholz and Pollmann, 2005]. Second, semantic priming effects, which typically are observed in the form of decreased activation, occur in different regions than those reported here, including prefrontal, lateral temporal, and parietal cortices [Giesbrecht et al., 2004; Kircher et al., 2009]. Finally, priming effects peak within 3 to 4 s, and return to baseline within 8 s of the stimulus [Rissman et al., 2003], a temporal profile that does not match the protracted 16 s activity observed in our study.

It is interesting to note that while this patient could demonstrate top-down allocation of attention on command in response to the ambiguous stimuli presented, he was unable to show command following when a previously validated mental imagery paradigm was used [Boly et al., 2007; Owen et al., 2006]. It is possible that, at the time of the mental imagery task, the patient had transiently lost consciousness, fallen asleep, or decided not to comply with the instructions. On the other hand, it is also possible that the mental imagery task required some additional

cognitive process that was not available to the patient, thus preventing successful completion of the task, despite being aware. This possibility would be consistent with the highly variable etiology typical of this patient group, especially following traumatic brain injury, where the specific site of the trauma and consequent neural damage may produce different patterns of sensory deprivation, highlighting the necessity for a comprehensive and multimodality approach to patient testing [Coleman et al., 2009]. In this latter scenario, the visual hierarchy, and in particular the top-down attention task, provides an additional approach for assessing the presence of consciousness in this patient group.

Overall, one of the greatest difficulties in this patient group is the fact that, at the boundary between intermittent minimal awareness and complete lack of awareness, it is still unknown how much mental life is possible after catastrophic brain injury [Ropper, 2010]. This ambiguity often underlies much of the legal, economic, and ethical debate surrounding these patients. Functional neuroimaging may be uniquely suited to map residual cognitive function in this setting [Lamme, 2010], especially where behavioral output is limited or constrained [Monti et al., 2009b; Owen and Coleman, 2008]. Indeed, a growing number of studies have started to probe relatively sophisticated aspects of the mental life of these patients, including language comprehension [Coleman et al., 2007], the ability to maintain information through time [Monti et al., 2009a], self-awareness [Qin et al., 2010], willful adoption of mental states [Owen et al., 2006], and even the capacity for basic communication [Monti et al., 2010b]. As this evidence accumulates, the elements of mental life that may be maintained at the lower boundaries of consciousness become increasingly clear.

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REFERENCES

- Andrews K, Murphy L, Munday R, Littlewood C (1996): Misdiagnosis of the vegetative state: Retrospective study in a rehabilitation unit. *BMJ* 313:13–16.
- Beauchamp MS, Haxby JV, Jennings JE, DeYoe EA (1999): An fMRI version of the Farnsworth-Munsell 100-Hue test reveals multiple color-selective areas in human ventral occipitotemporal cortex. *Cereb Cortex* 9:257–263.
- Beckmann CF, Jenkinson M, Smith SM (2003): General multilevel linear modeling for group analysis in FMRI. *Neuroimage* 20:1052–1063.
- Bekinschtein TA, Coleman MR, Niklison J III, Pickard JD, Manes FF (2008): Can electromyography objectively detect voluntary movement in disorders of consciousness? *J Neurol Neurosurg Psychiatry* 79:826–828.
- Bekinschtein TA, Dehaene S, Rohaut B, Tadel F, Cohen L, Naccache L (2009): Neural signature of the conscious processing of auditory regularities. *Proc Natl Acad Sci USA* 106:1672–1677.
- Bekinschtein TA, Manes FF, Villarreal M, Owen AM, Della-Maggiore V (2011): Functional imaging reveals movement preparatory activity in the vegetative state. *Front Hum Neurosci* 5:5.
- Bernat JL (2002): Questions remaining about the minimally conscious state. *Neurology* 58:337–338.
- Boly M, Coleman MR, Davis MH, Hampshire A, Bor D, Moonen G, Maquet PA, Pickard JD, Laureys S, Owen AM (2007): When thoughts become action: An fMRI paradigm to study volitional brain activity in non-communicative brain injured patients. *Neuroimage* 36:979–992.
- Childs NL, Mercer WN, Childs HW (1993): Accuracy of diagnosis of persistent vegetative state. *Neurology* 43:1465–1467.
- Coleman MR, Bekinschtein T, Monti MM, Owen AM, Pickard JD (2009): A multimodal approach to the assessment of patients with disorders of consciousness. *Progr Brain Res* 177:231–248.
- Coleman MR, Rodd JM, Davis MH, Johnsrude IS, Menon DK, Pickard JD, Owen AM (2007): Do vegetative patients retain aspects of language comprehension? Evidence from fMRI. *Brain* 130:2494–2507.
- Dehaene S, Changeux JP, Naccache L, Sackur J, Sergent C (2006): Conscious, preconscious, and subliminal processing: A testable taxonomy. *Trends Cogn Sci* 10:204–211.
- Elliott L, Walker L (2005): Rehabilitation interventions for vegetative and minimally conscious patients. *Neuropsychol Rehabil* 15:480–493.
- Epstein R, Kanwisher N (1998): A cortical representation of the local visual environment. *Nature* 392:598–601.
- Faugeras F, Rohaut B, Weiss N, Bekinschtein TA, Galanaud D, Puybasset L, Bolgert F, Sergent C, Cohen L, Dehaene S, Naccache L (2011): Probing consciousness with event-related potentials in the vegetative state. *Neurology* 77:264–268.
- Fins JJ, Illes J, Bernat JL, Hirsch J, Laureys S, Murphy E. (2008): Neuroimaging and disorders of consciousness: Envisioning an ethical research agenda. *Am J Bioeth* 8:3–12.
- Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, Kelly JP, Rosenberg JH, Whyte J, Zafonte RD, et al. (2002): The minimally conscious state: Definition and diagnostic criteria. *Neurology* 58:349–353.
- Giacino JT, Hirsch J, Schiff N, Laureys S (2006): Functional neuroimaging applications for assessment and rehabilitation planning in patients with disorders of consciousness. *Arch Phys Med Rehabil* 87:S67–S76.
- Giacino JT, Kalmar K, Whyte J (2004): The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. *Arch Phys Med Rehabil* 85:2020–2029.
- Giacino JT, Schnakers C, Rodriguez-Moreno D, Kalmar K, Schiff N, Hirsch J (2009): Behavioral assessment in patients with disorders of consciousness: Gold standard or fool's gold? *Progr Brain Res* 177:33–48.
- Giesbrecht B, Camblin CC, Swaab TY (2004): Separable effects of semantic priming and imageability on word processing in human cortex. *Cereb Cortex* 14:521–529.
- Gill-Thwaites H, Munday R (2004): The Sensory Modality Assessment and Rehabilitation Technique (SMART): A valid and reliable assessment for vegetative state and minimally conscious state patients. *Brain injury* 18:1255–1269.

- Hadjikhani N, Liu AK, Dale AM, Cavanagh P, Tootell RB (1998): Retinotopy and color sensitivity in human visual cortical area V8. *Nat Neurosci* 1:235–241.
- Hampshire A, Owen AM. (2006): Fractionating attentional control using event-related fMRI. *Cereb Cortex* 16:1679–1689.
- Henson R (2005): What can functional imaging tell the experimental psychologist? *Q J Exp Psychol A* 58:193–233.
- Jenkinson M, Bannister P, Brady M, Smith S (2002): Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage* 17:825–841.
- Jenkinson M, Smith S (2001): A global optimisation method for robust affine registration of brain images. *Med Image Anal* 5:143–156.
- Jennett B, Plum F (1972): Persistent vegetative state after brain damage. A syndrome in search of a name. *Lancet* 1:734–737.
- Kanwisher N, McDermott J, Chun MM (1997): The fusiform face area: A module in human extrastriate cortex specialized for face perception. *J Neurosci* 17:4302–4311.
- Kircher T, Sass K, Sachs O, Krach S (2009): Priming words with pictures: Neural correlates of semantic associations in a cross-modal priming task using fMRI. *Hum Brain Mapp* 30:4116–4128.
- Kourtzi Z, Kanwisher N (2000): Cortical regions involved in perceiving object shape. *J Neurosci* 20:3310–3318.
- Lamme VAF (2010): How neuroscience will change our view on consciousness. *Cognit Neurosci* 1:204–240.
- Laureys S (2005): The neural correlate of (un)awareness: Lessons from the vegetative state. *Trends i Cognit Sci* 9:556–559.
- McKeefry DJ, Zeki S (1997): The position and topography of the human colour centre as revealed by functional magnetic resonance imaging. *Brain* 120:2229–2242.
- Menon DK, Owen AM, Williams EJ, Minhas PS, Allen CM, Boniface SJ, Pickard JD (1998): Cortical processing in persistent vegetative state. Wolfson Brain Imaging Centre Team. *Lancet* 352:200.
- Monti MM, Coleman MR, Owen AM (2009a): Executive functions in the absence of behavior: Functional imaging of the minimally conscious state. *Progr Brain Res* 177:249–260.
- Monti MM, Coleman MR, Owen AM (2009b): Neuroimaging and the vegetative state: Resolving the behavioural assessment dilemma? *Disorders of consciousness. Ann NY Acad Sci* 1157:81–89.
- Monti MM, Laureys S, Owen AM (2010a): The vegetative state. *BMJ* 341:c3765.
- Monti MM, Owen AM (2010): Behavior in the brain using functional neuroimaging to assess residual cognition and awareness after severe brain injury. *J Psychophysiol* 24:76–82.
- Monti MM, Vanhaudenhuyse A, Coleman MR, Boly M, Pickard JD, Tshibanda L, Owen AM, Laureys S (2010b): Willful modulation of brain activity in disorders of consciousness. *New Engl J Med* 362:579–589.
- Owen AM, Coleman MR (2008): Functional neuroimaging of the vegetative state. *Nat Rev Neurosci* 9:235–243.
- Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard JD (2006): Detecting awareness in the vegetative state. *Science* 313:1402.
- Posner JB, Saper JB, Schiff ND, Plum F (2007): *Plum and Posner’s Diagnosis of Stupor and Coma*. Oxford, New York: Oxford University Press.
- Puce A, Allison T, Gore JC, McCarthy G (1995): Face-sensitive regions in human extrastriate cortex studied by functional MRI. *J Neurophysiol* 74:1192–1199.
- Qin P, Di H, Liu Y, Yu S, Gong Q, Duncan N, Weng X, Laureys S, Northoff G (2010): Anterior cingulate activity and the self in disorders of consciousness. *Hum Brain Mapp* 31:1993–2002.
- Qin P, Di H, Yan X, Yu S, Yu D, Laureys S, Weng X (2008): Mismatch negativity to the patient’s own name in chronic disorders of consciousness. *Neurosci Lett* 448:24–28.
- Reinholz J, Pollmann S (2005): Differential activation of object-selective visual areas by passive viewing of pictures and words. *Cognit Brain Res* 24:702–714.
- Rissman J, Eliassen JC, Blumstein SE (2003): An event-related fMRI investigation of implicit semantic priming. *J Cognit Neurosci* 15:1160–1175.
- Ropper AH (2010): Cogito ergo sum by MRI. *New Engl J Med* 362:648–649.
- Schnakers C, Giacino J, Kalmar K, Piret S, Lopez E, Boly M, Malone R, Laureys S (2006): Does the FOUR score correctly diagnose the vegetative and minimally conscious states? *Ann Neurol* 60:744–745; author reply 745.
- Schnakers C, Perrin F, Schabus M, Majerus S, Ledoux D, Damas P, Boly M, Vanhaudenhuyse A, Bruno MA, Moonen G, et al. (2008): Voluntary brain processing in disorders of consciousness. *Neurology* 71:1614–1620.
- Schnakers C, Vanhaudenhuyse A, Giacino J, Ventura M, Boly M, Majerus S, Moonen G, Laureys S (2009): Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment. *BMC Neurol* 9:35.
- Smith SM (2002): Fast robust automated brain extraction. *Hum Brain Mapp* 17:143–155.
- The Multi-Society Task Force on PVS (1994a): Medical aspects of the persistent vegetative state (1). *New Engl J Med* 330:1499–1508.
- The Multi-Society Task Force on PVS (1994b): Medical aspects of the persistent vegetative state (2). *New Engl J Med* 330:1572–1579.
- Tong F, Nakayama K, Vaughan JT, Kanwisher N (1998): Binocular rivalry and visual awareness in human extrastriate cortex. *Neuron* 21:753–759.
- Tootell RB, Reppas JB, Kwong KK, Malach R, Born RT, Brady TJ, Rosen BR, Belliveau JW (1995): Functional analysis of human MT and related visual cortical areas using magnetic resonance imaging. *J Neurosci* 15:3215–3230.
- Tootell RBH, Hadjikhani NK, Mendola JD, Marrett S, Dale AM (1998): From retinotopy to recognition: fMRI in human visual cortex. *Trends Cognit Sci* 2:174–183.
- Vanhaudenhuyse A, Schnakers C, Bredart S, Laureys S (2008): Assessment of visual pursuit in post-comatose states: Use a mirror. *J Neurol Neurosurg Psychiatry* 79:223.
- Woolrich MW, Behrens TE, Beckmann CF, Jenkinson M, Smith SM (2004): Multilevel linear modelling for fMRI group analysis using Bayesian inference. *Neuroimage* 21:1732–1747.
- Worsley KJ, Evans AC, Marrett S, Neelin P. (1992): A three-dimensional statistical analysis for CBF activation studies in human brain. *J Cereb Blood Flow Metab* 12:900–918.