Article

Behavior in the Brain

Using Functional Neuroimaging to Assess Residual Cognition and Awareness After Severe Brain Injury

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Abstract. Recent evidence has suggested that functional neuroimaging may play a crucial role in assessing residual cognition and awareness in brain injury survivors. In particular, brain insults that compromise the patient's ability to produce motor output may render standard clinical testing ineffective. Indeed, if patients were aware but unable to signal so via motor behavior, they would be impossible to distinguish, at the bedside, from vegetative patients. Considering the alarming rate with which minimally conscious patients are misdiagnosed as vegetative, and the severe medical, legal, and ethical implications of such decisions, novel tools are urgently required to complement current clinical-assessment protocols. Functional neuroimaging may be particularly suited to this aim by providing a window on brain function without requiring patients to produce any motor output. Specifically, the possibility of detecting signs of willful behavior by directly observing brain activity (i.e., "brain behavior"), rather than motoric output, allows this approach to reach beyond what is observable at the bedside with standard clinical assessments. In addition, several neuroimaging studies have already highlighted neuroimaging protocols that can distinguish automatic brain responses from willful brain activity, making it possible to employ willful brain activations as an index of awareness. Certainly, neuroimaging in patient populations faces some theoretical and experimental difficulties, but willful, task-dependent, brain activation may be the only way to discriminate the conscious, but immobile, patient from the unconscious one.

Keywords: functional magnetic resonance imaging (fMRI), consciousness, disorders of consciousness, vegetative state, minimally conscious state

Disorders of consciousness such as coma, the vegetative state (VS) and the minimally conscious state (MCS) are among the most mysterious and least understood conditions of the human brain. Following a severe traumatic or nontraumatic brain injury, patients may enter an acute state of *coma*, as a consequence of focal lesions to brainstem structures or diffuse white matter and/or cortical damage. Comatose patients typically show no sign of arousal, are considered to be unconscious (Laureys, 2005), and only exhibit reflexive movement. If a comatose patient regains some basic level of sleep-wake cycles, as indexed by eye-opening and closing periods, without also regaining consciousness, they are said to enter VS (Jennett, 2002; Jennett & Plum, 1972). Although awake, and retaining sufficient hypothalamic and brainstem functions for survival, VS patients are considered to be neither conscious nor aware (Laureys, 2005). Indeed, while they exhibit reflexive movements and some spontaneous behaviors such as crying, smiling, and teeth grinding, they exhibit no sign of purposeful or voluntary behavior. The underlying etiology is highly variable. Traumatic brain injuries typically exhibit diffuse brain changes, especially in subcortical white-matter fibers, while nontraumatic brain injuries show various degrees of thalamic and cortical cell death (Jennett, 2002). Chances of recovery from VS rapidly decrease with time, and are considered to be minimal if the patient doesn't regain awareness within 1 year for traumatic brain injury, or 3 months for nontraumatic brain injury (Multi-Society Task Force on PVS, 1994). Some patients will, thus, remain in VS permanently. Other patients, however, regain some level of (fluctuating) awareness, and are, thus, said to progress to a MCS (Giacino et al., 2002). In contrast to VS, MCS patients do show inconsistent, but reproducible, signs of awareness of themselves and their environment, by exhibiting sustained, reproducible, or voluntary behavioral responses to sensory stimulation.

From a diagnostic point of view, the transition from coma to VS is indexed by a relatively objective marker; namely, the return of eye-opening and closing cycles. Disentangling VS from the MCS, however, is not as clear cut. In fact, assessing the transition from the former state to the latter requires assessing the return of (periods of) consciousness. In the absence of an agreed definition of what consciousness is, or a satisfactory measure of its presence

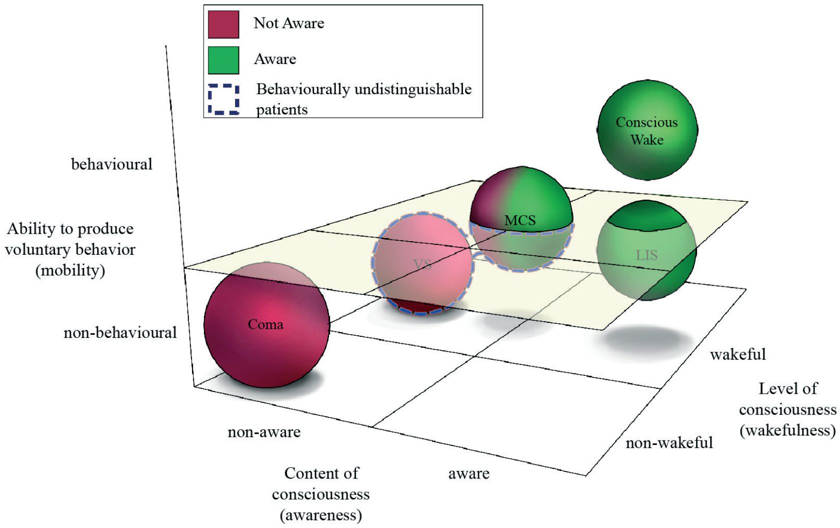

Figure 1. Characterization of different patient groups (including coma, vegetative state (VS), minimally conscious state (MCS), and locked-in patients (LIS)) and healthy individuals along three traits: contents of consciousness (awareness), level of consciousness (wakefulness), and ability to produce voluntary behavior (mobility) (from Monti et al., 2009b).

(Seth, Dienes, Cleeremans, Overgaard, & Pessoa, 2008), its clinical assessment relies on bedside observation of the patient's elicited and spontaneous behavior. These observations, aimed at detecting the presence of any sign of nonreflexive behavior, are recorded following standardized, although subjective, procedures (e.g., Giacino, Kalmar, & Whyte, 2004, JFK Coma Recovery Scale; Gill-Thwaites & Munday, 2004, Sensory Modality Assessment and Rehabilitation Technique; Shiel et al., 2000, Wessex Head Injury Matrix). In particular, discriminating MCS from VS patients requires finding evidence of (1) awareness of the self or the environment; (2) sustained, reproducible, purposeful or voluntary response to auditory, tactile, or noxious stimuli; or (3) language comprehension and/or expression (Royal College of Physicians, 1996; Multi-Society Task Force on PVS, 1994). If the patient can exhibit any form of nonreflexive behavior, thereby implying a state of consciousness, the patient is diagnosed MCS. If no evidence of (1)–(3) can be found, the patient is considered unconscious and, therefore, diagnosed VS.

In the reminder of this paper we will argue that functional neuroimaging should be included in the guidelines for the assessment of patients with disorders of consciousness as a source of diagnostically relevant information. Three main points underlie this argument. First, in the face of an alarming misdiagnosis rate, there is an urgent need for novel assessment tools that may detect residual cognition and awareness without requiring patients to produce motoric behavior. For example, a patient could fulfill, at the bedside, all criteria for a VS diagnosis while being conscious, yet be unable to produce motor output. It is possible, however, that such a patient may well be able to signal a state of awareness by willfully modulating their own brain activity (see Owen et al., 2006). Second, some kinds of brain activity should be considered as a form of "behavior"; that is, in terms of assessment of consciousness, informationally equipollent to motoric behavior. For, "motor" and "brain" behavior, when willful, can equally reveal the presence of consciousness. The main advantage of neuroimaging, however, is its ability to dispense with requiring patients to produce motoric output. Third, as is the case for motor behavior, the use of functional neuroimaging as a source of diagnostically relevant information requires the ability to tease apart voluntary brain activity from automatic response to stimulation. Many experiments, to date, have proven that it is possible to develop neuroimaging protocols in which positive results unambiguously reveal the presence of awareness.

Diagnostic Use of Functional Neuroimaging: The Need for New Patient Assessment Tools

One of the major limitations of our current understanding of "consciousness" is the fact that we have no objective means for detecting its presence and are, thus, bound to relying on others' self-report. With respect to patient assessment, inasmuch as motoric responses are clearly voluntary and appropriate, awareness can be confirmed behaviorally. This strategy, however, relies on the assumption that motor behavior can accurately index the level of available brain processing in a patient. An unwanted consequence of such an assumption is the fact that should a patient be entirely conscious, but unable to signal so by producing voluntary motoric output, they would appear vegetative when assessed at the bedside (Monti, Coleman, & Owen, 2009b; Owen & Coleman, 2008). To clarify, consider the three-dimensional graph in Figure 1.

On the horizontal plane, we plot the two major components of consciousness (Laureys, 2005; Laureys, Perrin, & Bredart, 2007): content (awareness) and level (wakefulness). Even though each dimension is best understood as representing a continuum, we mark a conventional qualitative boundary, on the contents-of-consciousness axis, separating what most people would consider to be aware from what most people would consider to be not aware. Similarly, on the level-of-consciousness axis, we mark a conventional boundary between a state of wakefulness and one of nonwakefulness, demarcating whether a patient exhibits eye opening and closing cycles or any other comparable index of arousal. Finally, on the elevation axis, we characterize the ability of an individual to produce voluntary motor output. Also on this axis, we mark a conventional point (represented by the white plane) separating "behavioral individuals," capable of producing voluntary motor output, from "nonbehavioral individuals," unable produce voluntary output.

In this three-dimensional space, comatose patients fall close to the origin of the three axes, exhibiting no signs of wakefulness or awareness and being unable to producing any voluntary motor output. Healthy (awake) individuals, on the other hand, lie at the symmetric opposite of the graph. Patients with locked-in syndrome (Smith & Delargy, 2005) sit in the proximity of healthy individuals, retaining comparable levels of awareness and wakefulness. However, this group is divided into complete locked-in patients (below the white plane), entirely unable to produce any motor output, and incomplete locked-in patients (above the white plane), who retain some ability to produce voluntary motor output (e.g., eye-blink). VS patients distinguish themselves from comatose patients because they exhibit signs of wakefulness and, thus, sit beyond the threshold line on the levels-of-consciousness axis. However, similar to coma patients, they are by definition unconscious and, thus, unable to produce any voluntary behavior. Hence, VS patients sit below both the awareness and the mobility thresholds. Finally, MCS patients lie beyond the wakefulness threshold and, for the most part, also beyond the awareness threshold (thus allowing for periods of lost consciousness; cf. Laureys, Owen, & Schiff, 2004). With respect to mobility, however, it is possible that some patients may be unable to produce any motor output, as a consequence of the brain injury. This subgroup of "nonbehavioral" MCS patients, thus, sits below the mobility threshold (i.e., the white plane). As a consequence, inasmuch as motor output is a central requirement for signaling consciousness, VS patients and nonbehavioral MCS patients are indistinguishable at the bedside (i.e., the area enclosed within the dashed blue line) since in both cases clinical evaluation will yield no evidence of consciousness. It is this segment of nonbehavioral MCS patients that is, therefore, highly at risk of being misdiagnosed as VS.

This implicit limit of clinical assessments may indeed be one of the major contributors to the estimated rate of about 40% by which MCS patients are misdiagnosed as being vegetative (Andrews, Murphy, Munday, & Littlewood, 1996; Childs, Mercer, & Childs, 1993; Schnakers et al., 2009). In the face of the important medical (Elliott & Walker, 2005), as well as legal and ethical (Fins et al., 2008), consequences of an incorrect VS diagnosis, novel techniques able to overcome such limitations are urgently needed. As we will argue below, noninvasive neuroimaging techniques may be particularly suited to complement bedside testing by providing a nonmuscle-dependent means to covertly detecting signs of residual cognition and awareness.

Brain Activity as a Form of Behavior

In the past 10 years, an increasing amount of evidence has highlighted the ability of functional neuroimaging techniques such as PET and fMRI to detect aspects of preserved cognition and awareness that remained undetected at bedside testing (e.g., Laureys, Giacino, Schiff, Schabus, & Owen, 2006; Menon et al., 1998; Owen et al., 2006). The possibility to directly observe patients' brain activity without relying on their motoric capabilities has lead many authors to advocate the use of functional neuroimaging as part of the diagnostic decision-making process (Laureys et al., 2006; Owen & Coleman, 2008; Schiff, 2006). At present, however, despite the increasing amount of research on the topic, the use of functional neuroimaging remains a scientific endeavor, and has no impact on the assessment and diagnosis of this patient group.

For functional neuroimaging to be considered diagnostically relevant with respect to the guidelines mentioned above, one must allow for brain activations to be considered as a form of behavior, albeit nonmotoric. If this were the case, voluntary brain activity, similarly to voluntary motor behavior, could be taken to reveal the presence of awareness. To accept brain activation as a form of behavior, it suffices to observe the causal role of brain function to motoric output. Trivially, where any output is seen, be it automatic or voluntary, there must be an underlying brain activity. Thus, it is perfectly conceivable, and possible, to directly observe the underlying brain activity in lieu of its behavioral manifestation. By extension, if observation of voluntary motor behavior can be taken as evidence of a state of awareness, observation of its underlying (voluntary) brain activity must also lead to the same conclusion. Therefore, inasmuch as it is possible to distinguish voluntary brain activity from an automatic response to sensory stimulation, the observation of voluntary brain behavior should be regarded as informationally equivalent to the observation of voluntary motor output. Employing functional neuroimaging in this clinical setting, then, reduces to the same problem faced by behavioral assessment: Is it possible to distinguish voluntary brain behavior from automatic responses?

Disentangling the Automatic Form the Willful Brain

Initial evidence that functional neuroimaging could detect residual cognitive functioning beyond what is observable

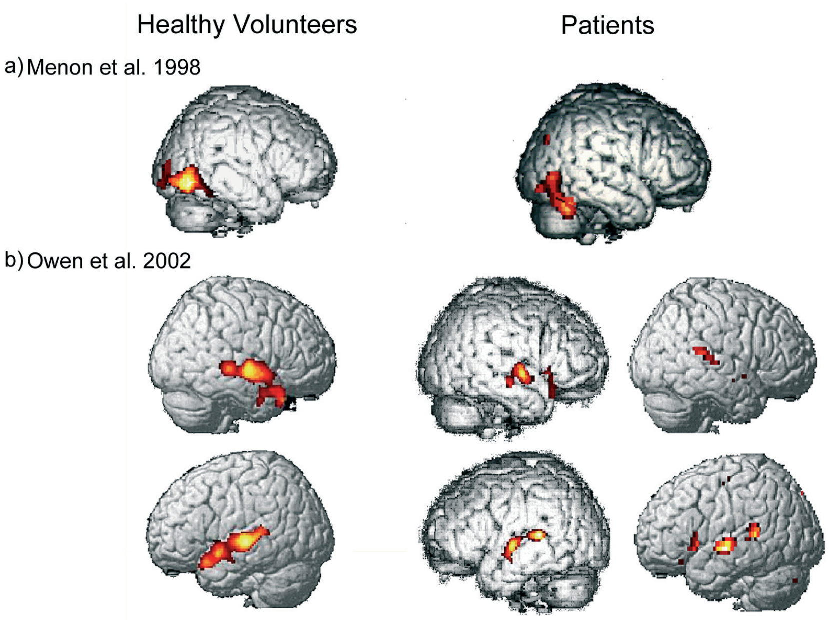

Figure 2. Brain activations observed in healthy volunteers and vegetative patients in response to (a) pictures of faces and (b) coherent speech sounds (adapted from Menon et al., 1998; Owen et al., 2002).

at the bedside was provided by Menon and colleagues (1998). In this report, the authors described the case of a VS patient exhibiting extensive activation in the temporal lobe in response to viewing pictures of faces (as detected with PET; see Figure 2a). In a similar report, Owen and colleagues (2002) described two VS patients exhibiting differential metabolic responses to speech sounds versus nonspeech sounds. As compared to signal-correlated noise, listening to coherent speech resulted in a bilateral increase in metabolic response in the superior temporal gyrus, the same pattern typically observed in healthy volunteers listening to similar stimuli (see Figure 2b).

These findings highlight the fact that some aspects of relatively high-level cognitive processing may be preserved in VS patients, despite the lack of responsiveness at the bedside. However, do these brain activations reveal that the patients consciously "saw" and "heard" the stimuli? On one hand, there is no question that coherent speech sounds and pictures of faces were processed differently, as revealed by metabolic response, than nonspeech sounds and scrambled pictures of faces. Thus, the cognitive processes underlying the relevant stages of vision and auditory processing were certainly intact in these patients. On the other hand, however, it is not clear whether such differential activations can be used as a marker of conscious perception and, thereby, consciousness. In fact, much sensory processing is rapid and automatic, and can happen in the absence of any conscious perception (see Dehaene et al., 1998). Furthermore, perceiving a set of lines and contours as a coherent face or a string of utterances as speech (in the case of a familiar language), is not subject to volition. A healthy individual, for instance, has no choice but to perceive a face as such (excluding sophisticated cases of ambiguity or other artificial circumstances). These results, then, while very informative with respect to residual cognitive functioning, cannot address the issue of whether the patients were conscious.

In contrast to the studies described above, it is possible to employ functional neuroimaging to detect the presence of awareness in the absence of any overt motor behavior. One striking example was recently presented by Owen and colleagues (2006). In this report, a VS patient that didn't exhibit any voluntary behavior during clinical bedside testing was able to voluntarily modulate brain activity in response to short aural cues. Specifically, the patient was asked to alternate 30 s blocks of mental imagery with periods of rest. Compared to rest, motor and spatial imagery recruited medial sections of frontal and temporal cortices (supplementary motor area, and parahippocampal place area), respectively. Crucially, there was no sensory stimulation during either the imagery or the rest periods, except for a brief one-second cue (namely, the words "tennis" or "house" for motor and spatial imagery, and "relax" for rest) instructing the patient/participant which task to perform. Yet, the observed activations were sustained throughout the full duration of the imagery blocks, and closely resembled the activations observed in healthy volunteers performing the same task (Figure 3). While it is known that single-word stimuli may induce some automatic brain responses (Hauk, Johnsrude, & Pulvermuller, 2004), these only occur on the millisecond scale and, unsurprisingly, in regions known to be implicated in semantic processing. In fact, there is no reason to expect any activation whatsoever in this imagery paradigm unless the patient consciously decided to perform the task, in a sustained fashion and in response to each cue. This is because time-locked, sustained, and repeated activations in the appropriate neuroanatomical locations cannot be explained as automatic responses to the brief aural cues (Owen et al., 2007).

Using a different experimental approach, we have re-

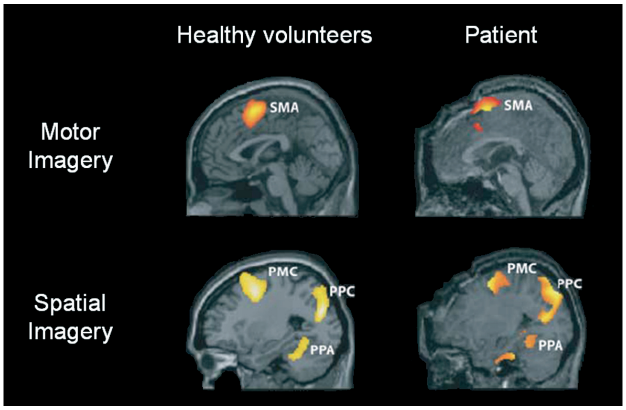

Figure 3. Brain activations for two imagery tasks (motor vs. spatial) in a group of healthy individuals and a patient behaviorally meeting the criteria defining the VS (adapted from Owen et al., 2006).

cently showed (Monti, Coleman, & Owen, 2009a) that it is possible to use functional neuroimaging to assess the presence of cognitive behaviors that are thought to require conscious awareness; namely, active maintenance of information through time, willful adoption of "mind-sets," and language comprehension (Dehaene & Naccache, 2001). In this paradigm, participants were presented with a series of neutral (i.e., not emotionally salient) words, and alternatively instructed to either listen to all the words, or to count the number of times a given target was repeated. Importantly, the perceptual stimulation in the passive listening and the counting tasks was carefully matched for the type of words used, their number, and repetition. Contrasted with passive listening, the counting task revealed a fronto-parietal network previously associated with target detection and working memory (see Naghavi & Nyberg, 2005). Remarkably, when tested on this same procedure, a minimally conscious patient presented a highly similar pattern of activations (Figure 4). Furthermore, the activity in these regions appeared sustained and highly synchronous to the onset and offset of the counting blocks. As for the Owen et al. (2006) study described above, the close matching of sensory stimulation across the experimental and the control tasks makes it very difficult to interpret the observed activations without assuming that the patient could willfully adopt differential "mind-sets" as a function of condition, and could actively maintain information through time.

Overall, this set of studies shows that functional neuroimaging is not only suited to assessing residual cognitive processing, but can also be employed to detect signs of covert voluntary brain behavior, and thereby the presence of consciousness.

Methodological Limitations

Despite the very encouraging work that has been carried out on neuroimaging in disorders of consciousness, it is important to stress that there are many issues that should be carefully considered when using functional neuroimaging in the clinical setting. First, it is not the case that all patients with impairments of consciousness will benefit from this approach, including patients that retain some ability to produce (convincingly voluntary) motoric output. Second, acquiring and analyzing fMRI data is especially difficult and complicated in this patient population (Giacino, Hirsch, Schiff, & Laureys, 2006). The coupling of hemodynamics and neuronal firing, which lies at the basis of the fMRI signal, may also be very different from that in healthy volunteers (Gsell et al., 2000; Rossini et al., 2004). In addition, both neuroanatomy and functional neuroanatomy may be severely altered and have undergone some amount of functional remapping after brain injury. Both issues are likely to affect the interpretability of neuroimaging data, especially when using healthy volunteer data as a benchmark. Finally, as for behavioral testing, it is important to consider the meaning of negative findings. While we have argued that neuroimaging may help in assessing cases

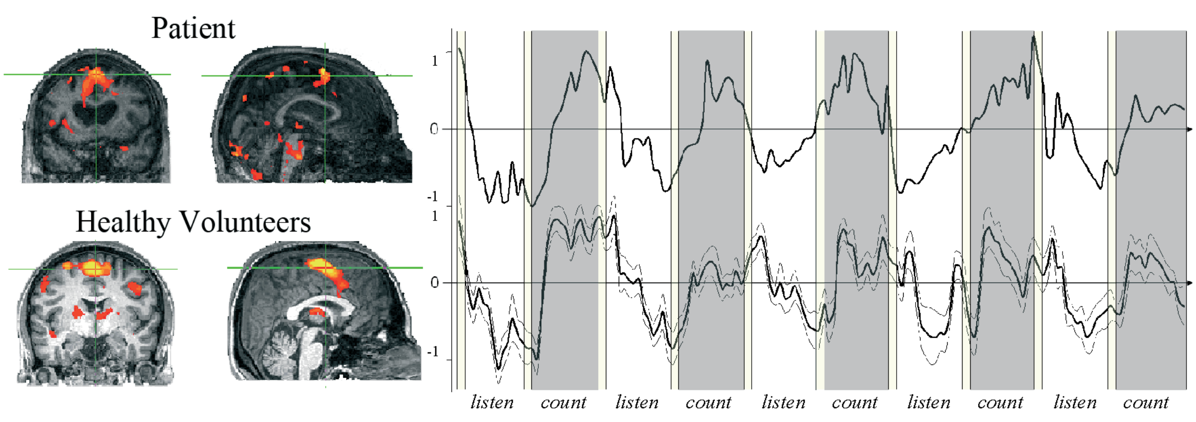

Figure 4. Brain activation observed in a group of healthy volunteers and a minimally conscious patient for the counting targets versus passive listening contrast (left). Activation time-course of a medial frontal cluster for the group of healthy volunteers (with standard error) and the patient (right) (from Monti et al., 2009a).

in which behavioral testing yields no results, it is also possible for neuroimaging tests to yield negative results. Indeed, this is a common finding in neuroimaging studies of healthy volunteers, especially with single subject data (where the signal-to-noise ratio is low). For this reason, negative findings should never be taken as evidence for a lack of mental activity. As with clinical testing, repeated scanning at different times of the day can help minimize this problem. Testing of different modalities in a broad neuroimaging assessment may also provide important clues to correctly interpreting negative results. A patient with significant damage to auditory cortex, for example, may yield negative findings in an auditory volition paradigm. When tested on a visual task, however, awareness may be detectable. In this regard, hierarchical paradigms can be very helpful by presenting two advantages (cf. Owen et al., 2005). On the one hand, they can provide a level of internal consistency when multiple tasks probing related cognitive processes all yield negative results. On the other hand, they provide useful information about cognitive specificity. For example, if activity is observed when comparing speech sounds to nonspeech sounds, but not when comparing ambiguous to nonambiguous sentences, then it is logical to conclude that the patient can perceive sound in general, and recognize speech, while nothing can be said about actual speech comprehension.

Conclusion

The recent technological developments in the field of noninvasive in vivo neuroimaging have greatly increased our ability to study the complex systems and interactions underlying cognitive behavior. Within the domain of patient assessment after severe brain injury, these tools may prove essential for reducing the alarmingly high rate by which conscious patients who unable to produce motoric output are misdiagnosed as vegetative when tested at the bedside. The possibility of detecting willful behavior by directly observing brain activity (i.e., "brain behavior") allows this approach to reach beyond what is observable at the bedside, via standard clinical testing. Importantly, the ability of neuroimaging tests to disentangle voluntary from automatic brain activity is embedded in the specific experimental protocols, and is not dependent on the subjective interpretation – by trained clinicians – of observed motor output. When test and control conditions are perfectly matched, in terms of sensory stimulation, and only differ in the mental task that has to be performed, differential brain activity can only be interpreted as reflecting a differential "mind set". Certainly, neuroimaging faces, especially in this patient population, presents theoretical, practical, and experimental difficulties, but the ability to detect task-dependent brain activation without relying on motor output may be the only means of discriminating the conscious, but nonbehavioral, patient from the unconscious one.

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