Neuroimaging and the Vegetative State

Resolving the Behavioral Assessment Dilemma?

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The accurate assessment of patients with impaired consciousness following a brain injury often remains a challenge to the most experienced clinician. A diagnosis of vegetative or minimally conscious state is made on the basis of the patient's clinical history and detailed behavioral examinations, which rely upon the patient being able to move or speak in order to demonstrate residual cognitive function. Recently, the development of noninvasive neuroimaging techniques has fostered a rapid increase in the exploration of residual cognitive abilities in these patient populations. However, while this body of literature is growing rapidly, at present the enterprise remains one of scientific endeavor with no inclusion in standard clinical practice. Correctly administered behavioral testing in survivors of brain injury may provide sufficient information to identify patients who are aware and are able to signal that this is the case via a recognized motor output. However, it remains possible that a subgroup of these patients may retain some level of awareness, but lack the ability to produce any motor output and are therefore mistakenly diagnosed as vegetative. It is in this latter situation that functional neuroimaging may prove to be most valuable, as a unique clinical tool for probing volition and residual cognition without necessarily assuming that the patient is able to produce any motor output.

Key words: **fMRI; disorders of consciousness; vegetative state; minimally conscious state; clinical assessment; Sensory Modality Assessment and Rehabilitation Technique (SMART); Coma Recovery Scale (CRS)**

Introduction

From a medical and scientific standpoint, disorders of consciousness, such as coma, vegetative state, and minimally conscious state, are among the most mysterious and least understood neurological conditions of the human brain. These conditions can arise as a consequence of a traumatic or a nontraumatic brain injury. A state of *coma* typically occurs as a consequence of focal lesions to brainstem structures or diffuse white matter and/or cortical damage (see Young, this volume, for a comprehensive review). Comatose patients are characterized by complete lack of arousal,[1] displaying, at most, reflexive behavior, and are assumed to have no awareness whatsoever of themselves or of their environment. Some coma patients may regain their sleep–wake cycles, as indexed by cyclic eye opening and closing, which typically marks their progression to a vegetative state (VS)[2,3] or minimally conscious state (MCS).[4] Although awake, and retaining sufficient hypothalamic and brainstem functions for survival, VS patients are considered, by definition, to be neither conscious nor aware.[1] Indeed, while some patients exhibit reflexive movements and occasionally display spontaneous "behaviors" such

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as smiling, teeth grinding, or crying, they show no signs of purposeful or voluntary behavior in response to stimulation. While the etiology is variable, VS patients with traumatic brain injuries typically exhibit diffuse brain changes, especially in subcortical white-matter fibers. VS patients with nontraumatic brain injuries, on the other hand, show various degrees of thalamic and cortical cell death.[3] In time, a small number of VS patients may go on to regain some degree of awareness, progressing to MCS, while others may progress directly from a comatose state directly to MCS. In contrast to the vegetative state, minimally conscious patients show inconsistent, but reproducible evidence of awareness of themselves and their environment, in as much as they can exhibit sustained, reproducible, or voluntary behavioral responses to sensory stimulation (e.g., visual, auditory, tactile, or nociceptive).

From a diagnostic point of view, progression from a state of coma is marked by the return of signs of wakefulness. Discriminating VS from MCS patients, on the other hand, is not always as clear-cut. This difficulty may reflect a number of problems including discrepancies in the diagnostic guidelines between countries and a lack of consistency in patient assessment. There is currently no standard protocol for the assessment of such patients, and the practice, knowledge, and skills of the examiner vary considerably between centers. Indeed, several clinical audits preformed by specialist centers found up to 43% of patients referred to them with a diagnosis of VS were in fact misdiagnosed.[5,6] Although no single reason was highlighted for such alarming error rates, the reliance upon the patient being able to move or speak in order to demonstrate cognitive function during behavioral assessments, has been widely cited. For this reason, many authors have advocated using additional techniques, such as functional neuroimaging, which does not rely upon a motor output to identify residual cognitive function, as a supplement to current clinical and behavioral assessments.[7–9]

The remainder of this chapter is organized in four parts. First, we focus on the definition of VS and the (flawed) logic that underlies the current behavioral assessment and diagnosis. Second, we define those scenarios in which we believe functional neuroimaging may offer a valuable and crucial supplement to the behavioral assessment of patients with impairments of consciousness. Following this, we discuss the role that functional neuroimaging may play in the diagnosis of VS and MCS, in the context of the available evidence. Finally, we highlight the current challenges that neuroimaging faces when employed in the clinical setting.

Diagnosing Vegetative State: The Logic of the Consciousness Conundrum

A diagnosis of VS is currently based on two main sources of information: detailed clinical history, including structural brain imaging, and careful (albeit subjective) behavioral observation by trained personnel. The behavioral assessment typically relies on repeated daily examinations over a period of weeks. Spontaneous and elicited behavior in response to multisensory stimulation (visual, auditory, tactile, olfactory, and gustatory) is recorded on multiple occasions, at different points of the circadian rhythm, in accordance with specific scales such as the Sensory Modality Assessment and Rehabilitation Technique (SMART),[10] the JFK Coma Recovery Scale-Revised[11] or the Wessex Head Injury Matrix (WHIM).[12] Regardless of the specific scale used, a diagnosis of VS is only made when a state of "wakefulness without awareness"[2] is observed, which in turn depends crucially on three defining features:[13,14] (1) no evidence of awareness of the self or the environment; (2) no evidence of sustained, reproducible, purposeful, or voluntary response to auditory, tactile, or noxious stimuli; and (3) no evidence of language comprehension or expression.

In the absence of an agreed definition of consciousness and/or awareness,[15] the line between what most people would regard as "consciousness" (or awareness) and what most people would regard as "unconsciousness" (or lack of awareness) must ultimately rely on the pragmatic principle that a person can only be considered to be unequivocally conscious if they can signal that this is the case. Thus, the discrimination between VS and MCS, and (by extension) the discrimination between a patient who is considered to be unconscious and one who is considered to be conscious, hinges upon the (in)ability of any given patient to signal their awareness by a sustained, reproducible, purposeful, or voluntary (motor) response. At face value, this approach is seriously flawed and represents a central conundrum in our understanding of consciousness and the consequences of its impairment.[16]

To illustrate this faulty logic, consider the following conditional statement: "If it rains, then Sarah takes the umbrella." It is subjectively trivial to accept that if we are then told that it rains, we can conclude that Sarah takes the umbrella. From a formal point of view, this inference—typically referred to as *modus poenens*—hinges on the fact that the antecedent of the conditional implicature (i.e., "it rains") is a sufficient condition for the consequent (i.e., "Sarah takes the umbrella") to be true. This is the very logic that justifies the clinical inference by which if a patient exhibits purposeful and reproducible behavior then she or he must be aware, and thus (at the very least) minimally conscious. Now consider the case in which you were told, following the preceding conditional statement, that "it does not rain." What could you conclude? As tempting as it may be to conclude that "Sarah does not take the umbrella," this would be an unwarranted inference—often referred to as the "fallacy of negating the antecedent." The invalidity of this conclusion becomes obvious when one considers the fact that, even if there is no rain, there may well be other reasons to want to take an umbrella; a blazing sun, for example. From a formal standpoint, what renders the conclusion just drawn unwarranted is the fact that it incorrectly assumes that a *sufficient* condition (i.e., "it rains") is also *necessary*, while this is not the case. By the same token, if a patient exhibits no movement during the behavioral examination, the conclusion that he or she is not conscious is unwarranted and thus invalid. Indeed, the patient could be aware but unable to produce a motor output (as was clearly the case, for example, in the patient described recently by Owen and colleagues[17]). Thus, from a logic standpoint, no conclusion can be inferred when a patient fails to produce any response as a signal of his or her state of awareness. Yet, the diagnosis of vegetative state relies crucially on interpreting the absence of evidence as evidence of absence.

Neuroimaging and Vegetative State: The Relevant Space of the Parameter

Let us first make clear the circumstances in which patient assessment may benefit maximally from the contributions of neuroimaging. It is obvious that patients who are able to produce motor output would only benefit to a limited extent from such techniques. Inasmuch as their responses are clearly voluntary and appropriate, awareness can be confirmed behaviorally. Similarly, the integrity of those neurocognitive systems that support audition, vision, and linguistic comprehension also can be probed using behavioral examinations, as long as the patient is able to produce a motor response. On the other hand, when behavioral observation yields no positive result, then functional neuroimaging can provide an additional layer of information by probing for signs of awareness without necessarily requiring the patient to produce any motor output. To clarify, consider the three-dimensional graph in Figure 1.

On the horizontal plane, we plot the two major components of consciousness:[1,18] its content (awareness) and its level (wakefulness). Even

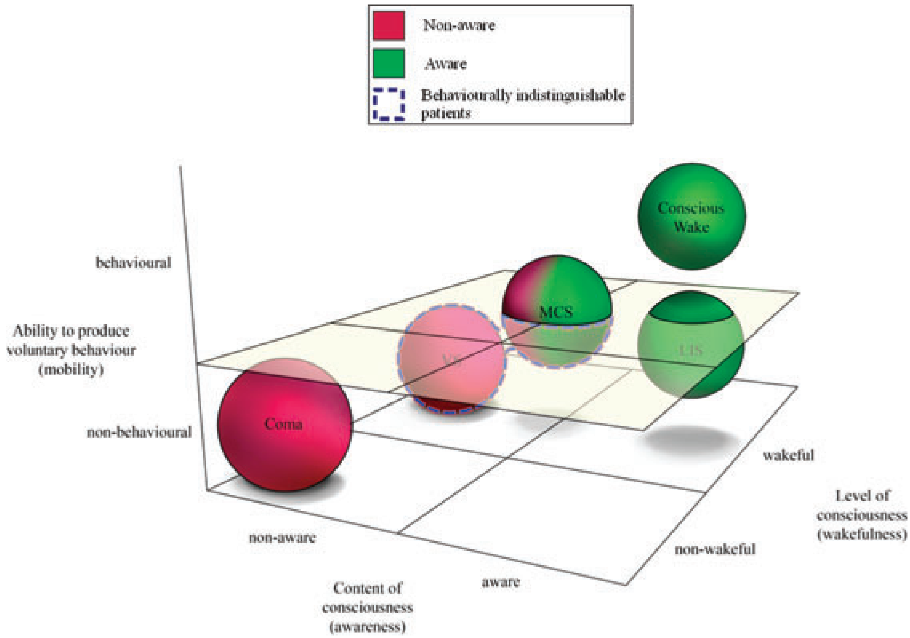

Figure 1. Characterization of different patient groups [coma, vegetative state (VS), minimally conscious state (MCS), and LIS)], and healthy individuals, along three traits: contents of consciousness (awareness), level of consciousness (wakefulness), and ability to produce voluntary behavior (mobility).

though it is understood that each dimension represents a continuum, on the contents of consciousness axis, we mark a conventional qualitative boundary 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, representing whether a patient exhibits cycles of eye opening and closing or any other similar index of arousal. Finally, we add a third dimension, on the elevation axis, representing the ability of an individual to exhibit voluntary behavior. Also along this axis we mark a conventional point (the white plane) separating behavioral individuals, capable of producing *voluntary* motor output, from nonbehavioral individuals, who are unable produce any voluntary output.

In this three-dimensional space, comatose patients fall close to the origin of the axes, exhibiting no signs of wakefulness or awareness and producing no motoric output other than some reflexive movement. Healthy (awake) individuals, on the other hand, lie symmetrically opposite, at the top right point of the graph. Patients with locked-in syndrome[19] (LIS) sit in the proximity of healthy individuals, retaining comparable levels of awareness and wakefulness. However, this group is split into complete locked-in patients (the part of the sphere below the threshold on the mobility axis), who are entirely unable to produce any motor output, and incomplete locked-in patients (above that same threshold), who typically retain some very limited motor output such as the ability to blink an eye to command. VS patients distinguish themselves from coma patients because they exhibit signs of wakefulness, and thus sit beyond the threshold line on the level of consciousness axis. On the other hand, like coma patients, VS patients are defined as unconscious and unable to produce any voluntary behavior, and therefore sit below both the awareness and the mobility thresholds. Finally, minimally conscious patients lie beyond the wakefulness threshold and, for the most part, also beyond the awareness threshold, allowing for periods of lost consciousness.[20] With respect to mobility, minimally conscious patients sit both above and below the threshold, reflecting the fact that this group may include behavioral patients (able to produce sustained voluntary output) and nonbehavioral patients (conscious and awake, but unable to produce any output).

It should be clear from the graph that vegetative and nonbehavioral minimally conscious patients are indistinguishable by the means of behavioral testing alone (the area enclosed within the dashed blue line in Fig. 1). Inasmuch as motor output is a central requirement for signaling consciousness, these two groups will show equivalent lack of evidence for purposeful behavior and therefore awareness of themselves or the environment. Furthermore, we are unaware of any evidence indicating that additional sources of information such as patient history and structural imaging may unequivocally discriminate between these groups.

In the broader context, there may then be two quite different situations in which MCS patients can be misdiagnosed as vegetative. On the one hand, human error due to lack of training, appropriate behavioral methodology, and exclusion of alternative causes or confounding factors (such as sedative medication, poor seating, range of movement, or inadequate nutrition) may affect the ability to detect awareness when the signal-to-noise ratio (in this case, very few clear behavioral responses) is particularly small.[5,6] On the other hand, as we have argued earlier in the chapter, it is simply not possible with standard clinical (i.e., behavioral) tools to distinguish nonbehavioral MCS from VS. In both cases, functional neuroimaging may play a crucial diagnostic role by allowing the detection of volition and other cognitive activity in the absence of any behavioral output. The importance of this issue becomes clear when one considers that the long-term care support for these patients is partly funded on the basis of diagnosis, including any referral for specialist rehabilitation. Additionally, accurate diagnosis has legal ramifications concerning applications for withdrawal of nutrition and hydration.[5]

Neuroimaging and Vegetative State: Informing the Behavioral Assessment with Functional Magnetic Resonance Imaging

In the last 10 years, various functional neuroimaging techniques have been used to probe physiological characteristics as well as residual cognitive abilities in patients suffering from disorders of consciousness. Fluorodeoxyglucose (FDG), positron emission tomography (PET) and single-photon emission computerized tomography (SPECT) have all been used, for example, to measure resting-state metabolism[21,22] and its change over time relative to clinical improvement.[23] PET and, more recently, functional magnetic resonance imaging (fMRI) have been used to explore the level and the type of cognitive processing that may still be available in some of these patients.[24–28] This ever-growing contribution of functional neuroimaging has been reviewed exhaustively elsewhere,[8,16,20] so we will restrict our attention to studies and methods that have been used to identify the defining features of VS and MCS, and are therefore of direct relevance to patient assessment and diagnosis.

Can neuroimaging detect signs of awareness in patients who are conscious, yet unable to signal that this is the case using a motor output? To address this question, Owen and colleagues[17] used fMRI to detect volition in a patient who fulfilled all behavioral criteria for a diagnosis of VS. Following 1-s-long auditory cues, the patient was instructed to produce either of two types of imagery (motor vs. spatial) for 30-s-long epochs in alternation with rest periods. Comparison of each type of imagery to rest yielded activations, in appropriate neuroanatomical locations, that were virtually indistinguishable from those obtained from

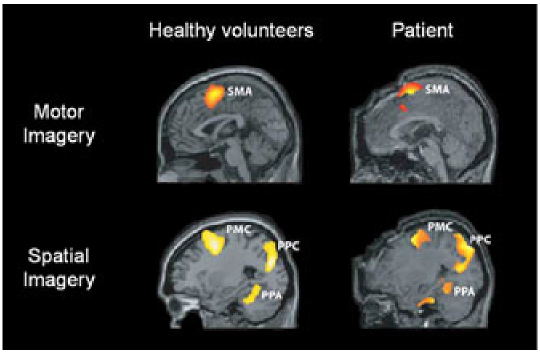

Figure 2. Brain activations for two imagery tasks (motor vs. spatial) in a group of healthy individuals and a patient behaviorally meeting the criteria defining the VS. (From Owen *et al.*[17] Used by permission.)

a group of healthy volunteers performing the same task (see Fig. 2).

It is impossible to explain these results without accepting that this patient retained the ability to comprehend verbal instructions, to remember them from the time they were given (before scanning began) to the appropriate time during the scan itself, and to act on those instructions, thereby willfully producing specific mental/neural states.[16,17,29] It may be tempting to dismiss this as a simple case of error in the behavioral assessment, but examination of the exhaustive case report reveals that was not the case. Indeed, at testing, the patient exhibited no evidence of sustained or reproducible purposeful behaviors consistent with the criteria defining the MCS. The diagnosis of VS was thus entirely appropriate, given the current criteria that rely on the behavioral assessment. The fundamental problem is that the functional neuroimaging data revealed that this patient was not VS, but presumably fell in that subgroup of nonbehavioral minimally conscious patients who, being unable to produce any motor output, are unable to signal their state of awareness.

A series of recent papers have made a strong case that neuroimaging is also capable of assessing high-level components of linguistic comprehension based solely on patterns of brain activation. Using a hierarchical approach[30] and adopting tasks well characterized in healthy volunteers,[31–33] it has been possible to assess high-level features of language comprehension in groups of patients with disorders of consciousness.[26,27] VS and MCS patients were first tested for acoustic processing, speech perception, and phonological processing using speech and nonspeech sounds. In a subset of these patients, the results were indistinguishable from the activations seen in a group of volunteers performing the same tasks.[31,32] At the top of this hierarchy, a semantic ambiguity task was used,[27] comparing brain activation while hearing sentences that included semantically ambiguous words (e.g., "there were 'dates' and 'pears' in the fruit bowl") with well-matched sentences that presented little ambiguity (e.g., "there was 'beer' and 'cider' on the kitchen shelf").[33] While the two types of sentences have similar acoustic, phonological, syntactic, and prosodic features, the high-ambiguity ones require additional processing to identify and select the appropriate meaning, in the context, of ambiguous words.

A subset of VS and MCS patients tested on this task exhibited the same activations that have been observed in posterior temporal and inferior frontal cortices in healthy volunteers (Fig. 3).[33] It is difficult to interpret such differences between the activation observed during highly ambiguous sentences and that observed during low-ambiguity sentences in any way other than inferring that high-level linguistic processes, such as activating, selecting, and integrating contextually appropriate word meanings, are operational. Unless the patients are able to perceive some difference among the two sets of sentences, there should be no reason to expect any differential activation across the two conditions, especially in light of the careful matching of stimuli (e.g., acoustic, phonological, syntactic properties), and the appropriate neuroanatomical location of activations as compared to healthy volunteers. These results provide a compelling case for fMRI being able to detect residual high-level components of linguistic comprehension in the absence of any motor response by the patient indicating that this is the case.

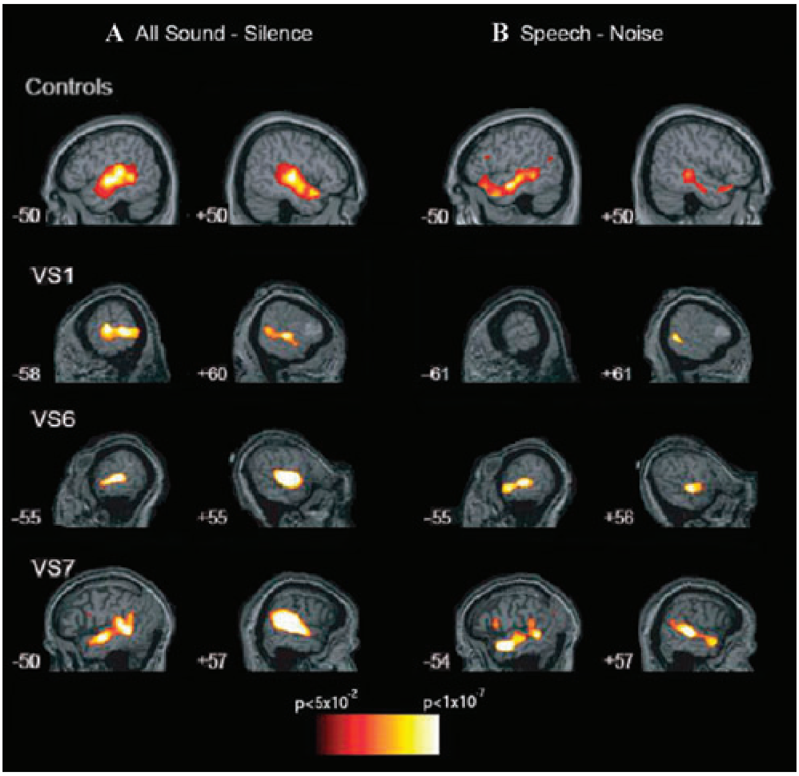

Figure 3. Brain activations for the comparison of sound minus silence and speech minus nonspeech in a group of healthy volunteers and three patients meeting the criteria defining the VS. (Adapted with permission from Coleman *et al.*[27])

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 considered carefully when using these tools in the clinical setting. First, as mentioned in the previous section, it is not the case that all patients suffering from an impairment of consciousness will benefit from this approach, and this includes patients that do retain some residual movement ability. Second, acquiring and analyzing fMRI data is especially difficult and complicated in this patient population.[34] The coupling of hemodynamics and neuronal firing, which lies at the basis of the fMRI signal, may be very different from that in healthy volunteers.[35,36] In addition, both neuroanatomy and functional neuroanatomy (the pattern of activation) may be severely altered and have undergone some amount of functional remapping in these patients. Both issues are likely to affect the interpretability of neuroimaging data, especially when using healthy volunteer data as a benchmark. The experimental design, when addressing issues such as language comprehension and volition, is also crucial. For example, it is difficult to argue that an activation reflects willful behavior unless the conditions that are being compared are carefully matched, ideally identical, except for the instructions that are given, and thus the patient's "mind-set." Finally, an important issue is how to deal with negative findings. While we have argued that neuroimaging may help to assess cases in which behavioral testing of patients yields no results, it is also possible for fMRI experiments to yield negative results. Indeed, this is a common finding in fMRI studies of healthy populations, especially when looking at single cases (where the power to detect differences 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 to alleviate this problem (for example, to rule out the possibility that the patient was asleep during the first, negative, scan). Testing of different modalities in a broad fMRI assessment may also provide important clues where negative results are observed. A patient with significant damage to auditory cortex, for example, may yield negative findings in an auditory volition paradigm. When tested on a visual analog of the same task, however, awareness may be detectable. In this regard, hierarchical paradigms can be very helpful by presenting two advantages. 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 also provide useful information about cognitive specificity. For example, if activity is observed when comparing speech sounds to non-speech 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 comprehension (e.g., whether the speech can be *understood*).

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. Beyond trying to tie cognitive processes to localized networks in the human brain, these techniques now allow for the assessment of perception,[37] category-specific recollection,[38] imaginary actions,[39,40] and intentions[41] by simply observing patterns of brain activation. Is it then the case that neuroimaging testing should be introduced as routine testing for all patients surviving brain injury? The answer is twofold. On one hand, assessment of consciousness via neuroimaging cannot (and should not) replace motor responses that are clear, appropriate and reproducible (e.g. the vocal answer to a question). On the other hand, however, in the many cases in which no evidence of consciousness is found by bedside clinical testing, neuroimaging may prove to be the only method able to detect residual cognition and even volition in patients that are aware but are unable to signal that is the case. Neuroimaging does face, especially in this patient population, many theoretical, practical, and experimental difficulties, but the ability to detect task-dependant fMRI activation to command with virtually no training[17,29] may, in some cases, be the only way to discriminate the unconscious patient from the conscious but nonbehavioral one.

Conflicts of Interest

The authors declare no conflicts of interest.

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