Functional Neuroimaging of Disorders of Consciousness

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An accurate and reliable evaluation of the level and content of cognitive processing is of paramount importance for the appropriate management of severely brain-damaged patients with disorders of consciousness.[1] Objective behavioral assessment of residual cognitive function can be extremely challenging in these patients, as motor responses may be minimal, inconsistent, and difficult to document, or may be undetectable because no cognitive output is possible. This difficulty leads to much confusion and a high-level of misdiagnoses in the vegetative state (VS), minimally conscious state, and locked-in syndrome.[2,3] Recent advances in functional neuroimaging suggest a novel solution to this problem; so-called "activation" studies can be used to assess cognitive functions in altered states of consciousness without the need for any overt response on the part of the patient.

In several recent studies, this approach has been used to detect residual cognitive function and even conscious awareness in patients who behaviorally meet the criteria defining the VS.[4–6] Similarly, these techniques have been used in other studies to guide therapeutic interventions and track recovery processes.[7,8] Such studies suggest that the future integration of emerging functional neuroimaging techniques with existing clinical and behavioral methods of assessment will be essential in reducing the current rate of misdiagnosis. Moreover, such

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efforts may provide important new prognostic indicators, helping to disentangle differences in outcome on the basis of a greater understanding of the underlying mechanisms responsible and better guiding therapeutic choices in these challenging populations.[9,10]

■ Positron Emission Tomography

Until recently, the majority of neuroimaging studies in patients with disorders of consciousness used either flurodeoxyglucose positron emission tomography (PET) or single photon emission computed tomography to measure resting cerebral blood flow and glucose metabolism.[11–15] Typically, widespread reductions in metabolic activity of up to 50% were reported, although, in some studies, normal cerebral metabolism or blood flow in patients in a VS has also been reported.[16,17] In some cases, isolated ''islands'' of metabolism were identified in circumscribed regions of cortex, suggesting residual cognitive processing in a subset of patients.[16] In 1 recent and remarkable case of late recovery from minimally conscious state, longitudinal PET examinations revealed increases in resting metabolism coincident with marked clinical improvements in motor function.[8] Although metabolic studies are useful in this regard, they can only identify functionality at the most general level; that is, mapping cortical and subcortical regions that are potentially recruitable, rather than relating neural activity within such regions to specific cognitive processes. On the other hand, methods such as $H_2^{15}O$ PET and functional magnetic resonance imaging (fMRI) can be used to link distinct and specific physiologic responses (changes in regional cerebral blood flow or changes in regional cerebral hemodynamics) to specific cognitive processes in the absence of any overt response (eg, a motor action or a verbal response) on the part of the patient.[18]

Early activation studies in patients with disorders of consciousness used $H_2^{15}O$ PET, in part because the technique was more widely available and in part because the multiple logistic difficulties of scanning critically ill patients in the strong magnetic field that is integral to fMRI studies had yet to be resolved. In the first of such studies, $H_2^{15}O$ PET was used to measure regional cerebral blood flow in a posttraumatic vegetative patient during an auditorily presented story told by his mother.[19] Compared with nonword sounds, activation was observed in the anterior cingulate and temporal cortices, possibly reflecting emotional processing of the contents, or tone, of the mother's speech. In another patient diagnosed as vegetative, Menon et al[20] used PET to study covert visual processing in response to familiar faces. When the patient was presented with pictures of the faces of family and close friends, robust activity was observed in the right fusiform gyrus, the so-called human "face area." Importantly, both of these studies involved single, well-documented cases; in cohort PET studies of patients unequivocally meeting the clinical diagnosis of the VS, normal brain activity in response to external stimulation has generally been the exception rather than the rule. For example, in 1 study of 15 VS patients, high-intensity noxious electrical stimulation activated midbrain, contralateral thalamus, and primary somatosensory cortex in every patient.[21] However, unlike control subjects, the patients did not activate secondary somatosensory, insular, posterior parietal, or anterior cingulate cortices.

$H_2^{15}O$ PET studies are limited by issues of radiation burden that may preclude essential longitudinal or follow-up studies in many patients or even a comprehensive examination of multiple cognitive processes within any one session. The power of PET studies to detect statistically significant responses is also low and group studies are often needed to satisfy standard statistical criteria.[18] Given the heterogeneous nature of disorders of consciousness and the clinical need to define each individual in terms of their diagnosis, residual functions, and potential for recovery, such limitations are of paramount importance in the evaluation of these patients.

A significant development in this rapidly evolving field has been the relative shift of emphasis from PET "activation studies" using $H_2^{15}O$ methodology to fMRI. Not only is magnetic resonance imaging more widely available than PET, it offers increased statistical power, improved spatial and temporal resolution, and has no associated radiation burden.

■ fMRI

Event-related fMRI has so far been used to reveal various degrees of retained speech comprehension in patients with disorders of consciousness.[4,22–24] However, fMRI is not without its complexities and challenges when applied to this patient group. Although it is possible to present visual, tactile, and noxious stimuli in the magnetic resonance imaging environment, to date only auditory stimuli have been used in this context. Work in a strong magnetic field has well-known safety and logistical constraints, but the behavioral portfolio of patients with disorders of consciousness also creates challenges. For example, many vegetative patients only have transient periods of eye opening precluding the use of visual paradigms. Similarly, scanning a patient who is unable to communicate presents numerous ethical dilemmas, particularly when they are unable to tell you if they are in pain.

Where these difficulties are overcome, however, the design of fMRI paradigms and their interpretation must also be carefully planned to ensure that a specific cognitive process is targeted and where neural activation is observed this is known to be anatomically and physiologically appropriate in healthy volunteers. Unfortunately, many neuroimaging paradigms are let down by the use of a reverse inference approach, whereby a given cognitive process is inferred solely on the basis of an observed activation in a particular brain region. For instance, a patient is presented with his/her name spoken by the voice of his/her mother in 1 condition and the sound of scanner noise in another condition. Using a simple subtraction analysis, the experimenters observe greater cortical activation in the primary auditory cortex when the patient hears his mother's voice versus the scanner noise. One conclusion could be that the patient recognized his/her name, but the activation observed could equally reflect a low-level orienting response to speech in general or an emotional response to the mother's voice. Consequently, such a paradigm lacks cognitive specificity and, therefore, provides limited information about the retained cognitive function of a patient with impaired consciousness. fMRI paradigms, therefore, require careful planning to ensure that they are appropriately counter-balanced and can be directly attributed to a specific cognitive process under study. Using mother's voice as an example, a study by Staffen et al[23] compared the response of a patient to hearing their own name versus another name. In this case, because identical speech stimuli were used that differed only with respect to the name itself, activations can be confidently attributed to cognitive processing that is specifically related to the patient's own name. Staffen and colleagues found activation in the medial prefrontal cortex in response to the patient's own, but not in response to other names. This pattern of activation was similar to that observed in 3 healthy volunteers and corresponds closely to the findings of an electrophysiologic study, which reported P3 responses to patients own names (compared with other peoples names) in locked-in, minimally conscious, and some vegetative patients.[25]

Although knowing that a patient recognizes their own name or the voice of a family member is often comforting to their relatives, a response to one's own name is one of the most basic forms of language and may not depend on the higher-level linguistic processes that are assumed to underpin comprehension. We have, therefore, previously proposed a hierarchical approach to the fMRI assessment of language comprehension in patients with disorders of consciousness, beginning with the simplest form of auditory processing and progressing sequentially through more complex cognitive operations.[6,26] In a recent study of 7 vegetative and 5 minimally conscious patients, we assessed each patient's response at 3 levels of auditory processing to 4 conditions (sentences containing ambiguous words, sentences containing unambiguous words, signal correlated noise, and silence) presented pseudo-randomly.[4] At the lowest level, we determined whether these patients retained basic primary auditory processing in response to hearing sound (both intelligible speech and unintelligible noise) in contrast to a silent, interscan baseline. This level of analysis identifies those brain regions that process the acoustic properties of sound that is common to both speech and nonspeech stimuli. In healthy controls, this contrast produces activation in primary auditory regions on the superior temporal plane centered on Heschl gyrus.[27]

The second level of analysis assesses speech-specific perceptual processing by comparing fMRI responses to intelligible speech versus acoustically matched unintelligible noise stimuli. It, therefore, goes further than our first level of analysis because it specifically isolates the brain's response to intelligible speech, whereas the first level of analysis was designed to identify the brain's response to sound in general (ie, both intelligible and nonintelligible sounds) when compared with silence.

At the third level of analysis, sentences containing ambiguous words (eg, bark or rain/reign) are contrasted with sentences containing no ambiguous words. In healthy volunteers, this comparison reveals distributed higher-order processing in the left inferior frontal and left temporal cortex reflecting the retrieval of semantic information that is essential to process the intended meaning of the ambiguous words. The presence of appropriate activations in this contrast provides strong evidence that some high-level semantic aspects of speech comprehension are preserved.

Our fMRI investigation of 7 vegetative and 5 minimally conscious patients found that 3 vegetative patients and 2 minimally conscious patients retained significant temporal lobe responses in the first and second level of analysis, that is, basic primary auditory cortex responses to sound, but also more elaborate responses to intelligible speech versus nonintelligible noise stimuli.[4] However, of particular importance, our investigation also found evidence of high-level language function (ie, retrieval of semantic information) in 2 of the vegetative patients. This striking finding not only reveals that some vegetative patients with negative behavioral markers retain aspects of normal speech processing, but specifically unravels the level of cognitive function that is retained in the auditory domain. Contrary to the diagnostic criteria defining the VS, this fMRI paradigm reveals that these patients retain aspects of speech comprehension, which are dependent on a higher-order distributed cortical network. Moreover, the activation patterns demonstrated in these vegetative patients were highly consistent with those observed in healthy volunteers.

■ Using Neuroimaging to Detect Awareness

Unfortunately, our speech processing paradigm does not unequivocally tell us whether these patients are aware—although it does give a strong impetus for further investigation in patients who demonstrate higher-order distributed cortical processing. To address this problem, we have recently turned our attention to creating a paradigm that demonstrates that a patient is able to understand an instruction and perform it, without requiring them to move or speak. To do this, we instructed a patient to perform 2 mental imagery tasks when cued by the instructions "imagine playing tennis" or "imagine visiting the rooms in your home." Importantly, these particular tasks were chosen, not because they involve a set of fundamental cognitive processes that are known to reflect conscious awareness, but because imagining playing tennis and imagining moving around the house elicit extremely reliable, robust, and statistically distinguishable patterns of activation in specific regions of the brain.[28] Indeed, a recent analysis of these paradigms in a large group of healthy volunteers has shown that they permit the identification of volitional brain activity (and thus of consciousness) at the single-subject level, without the need for any motor response.[28]

We have recently used this approach to demonstrate that a young woman who fulfilled all internationally agreed criteria for the VS was, in fact, consciously aware and able to make responses using her brain activity, despite her clinical diagnosis.[5] In July 2005, the 23-year-old woman sustained a severe traumatic brain injury as a result of a road traffic accident. During the 5 months between her accident and the fMRI scan, she was assessed by a multidisciplinary team employing repeated standardized assessments consistent with the procedure described by Bates[29] and her condition was entirely consistent with a diagnosis of VS. During the fMRI scan, the patient was instructed to perform the 2 mental imagery tasks described above. When she was asked to imagine playing tennis, significant activity was observed in the supplementary motor area (SMA)[5] that was indistinguishable from that observed in the healthy volunteers scanned.[28] In contrast, when she was asked to imagine walking through her home, significant activity was observed in the parahippocampal gyrus, the posterior parietal cortex, and the lateral premotor cortex,[5] which was again indistinguishable from that observed in healthy volunteers.[28] We concluded that, despite fulfilling all of the clinical criteria for a diagnosis of VS, this patient retained the ability to understand spoken commands and to respond to them through her brain activity, rather than through speech or movement, confirming beyond any doubt that she was consciously aware of herself and her surroundings.

This particular patient was also assessed with the speech comprehension task described above and not only did she demonstrate significant temporal lobe activation to intelligible speech, but she also demonstrated left inferior frontal gyrus activation consistent with speech comprehension.[4,5] Our hierarchical fMRI approach, therefore, provides an additional source of information to the clinical assessment of patients with disorders of consciousness. In patients unable to move, these paradigms are able to reveal neural markers of key cognitive processes, such as speech comprehension, but they are also able to reveal whether patients are able to exhibit willed, voluntary behavior in the absence of any overt action. As demonstrated, a hierarchical approach pays significant dividends; rather than concluding simply that a patient shows no response to a command (as a purely behavioral approach might suggest), the level of language processing can be precisely tracked from basic primary cortical response through to higher-order distributed cortical processing.

■ Interpretation of fMRI Findings

As expected, the discovery of awareness in a patient meeting the behavioral criteria defining the VS has generated considerable debate. Among various commentaries, it was suggested that our patient's responses to the mental imagery instructions could have been automatic rather than acts of will. Many types of stimuli, including faces, speech, and pain, will elicit relatively "automatic" responses from the brain; that is, to say, they will occur without the need for active intervention on the part of the participant (eg, you can not choose to not recognize a face or to not understand speech that is presented clearly in your native language). However, such responses are transient and occur in the primary sensory cortex. In our patient, this was not the case. The instruction to imagine playing tennis produced activation in the SMA, consistent with motor planning and motor imagery in healthy volunteers.[28] We did not observe any activation in the primary auditory cortex. More importantly, however, the cortical activation seen in the SMA was sustained for a full 30 seconds before it ceased on command. Indeed, our motor imagery and spatial navigation paradigms require the participant to sustain mental imagery for a continuous period of 30 seconds. They are then asked to relax for 30 seconds and then to again perform the mental imagery task for a further 30 seconds. This routine requires the participant to imagine playing tennis or moving around the rooms of their home on 5 separate occasions for a full 30 seconds and each time to stop performing this imagery when they are cued to do so. We know of no data supporting the inference that such a paradigm can unconsciously elicit sustained hemodynamic responses in these anatomically specific regions of the brain. Indeed, noninstructive sentences containing the same key words (eg, "the man enjoyed playing tennis") produce no sustained activity in any of these brain regions in healthy volunteers.[30] Similarly, when the words "tennis" and "house" are presented to uninstructed participants, no activity is observed in either the SMA or the parahippocampal gyrus.

■ Limitations of Neuroimaging

Neuroimaging clearly has the potential to inform the clinical assessment of patients with disorders of consciousness. However, the acquisition, analysis, and interpretation of fMRI data from patients with severe brain damage are fraught with difficulties.[9] For example, in patients with brain damage, the coupling of neuronal activity, and local hemodynamics, essential for fMRI activation measurements, is likely to be different from that in healthy controls, making interpretation of such data sets extremely complex.[31–33] Notwithstanding this basic methodologic concern, the choice of the experiment is also crucial.[6,26] For example, if brainstem auditory evoked responses are abnormal, auditory stimuli may be inappropriate and alternative stimuli—such as visual stimuli—should be considered. The investigation should also be complex enough that the cognitive processes of interest will be studied (ie, preferably beyond stimulus perception), yet not so complex that the tasks could easily overload the cognitive capacities of a tired or inattentive patient. In order that the imaging data obtained from patients with disorders of consciousness can be interpreted, control studies are essential, which must produce well documented, anatomically specific, robust, and reproducible activation patterns in healthy volunteers. In patients with disorders of consciousness, episodes of low arousal and sleep are common and close patient monitoring—preferably through electroencephalogram recording—during activation scans is essential so that these periods can be avoided. Spontaneous movements during the scan itself may also compromise the interpretation of functional neuroimaging data, particularly with fMRI scans. Processing of functional neuroimaging data may also present challenging problems in patients with acute brain damage. For example, the presence of gross hydrocephalus or focal pathology may complicate the fitting of functional imaging data to structural imaging data, and the normalization of these images through reference to a healthy brain. Under these circumstances, statistical assessment of activation patterns is complex and interpretation of activation foci with standard stereotaxic coordinates may be impossible.

Finally and most importantly, negative fMRI findings in patients with disorders of consciousness should never be used as evidence for impaired cognitive function or lack of awareness.[34] For example, a patient may fall asleep during the scan or may not have properly heard or understood the task instructions, leading to so-called "false negative" results. False negative findings in functional neuroimaging studies are common, even in healthy volunteers. Nevertheless, positive findings, when they occur and can be verified by careful statistical comparison with data from healthy volunteers, can be used to detect conscious awareness in patients, without the need for conventional methods of communication such as movement or speech.

Conclusions

Clinical audits have revealed an alarmingly high rate of misdiagnosis in patients with disorders of consciousness.[2,3] Errors have been attributed to the reliance upon a patient being able to move or speak and the subjective nature of the assessment process. Neuroimaging techniques such as PET and fMRI are able to circumvent these problems using paradigms that do not require an overt motor output and which can be analyzed objectively. To date, PET and fMRI studies have revealed evidence of residual cognitive function in some patients behaviorally meeting the criteria defining the VS. However, so far data of this sort have only been collected from a small number of patients and neuroimaging studies are not without their own limitations. Paradigms must be carefully designed and great care must be exercised to accurately interpret the findings from this challenging patient group. Despite these caveats, neuroimaging presents an exciting and valuable approach to learning more about these complex conditions and ultimately a new source of information to improve diagnosis and rehabilitation efforts.

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