Chapter 5
Identifying Covert Cognition in Disorders of Consciousness

Laura E. González-Lara and Adrian M. Owen

Abstract Several recent studies examining different aspects of residual cognitive function in patients with disorders of consciousness (DOC) have shown that multiple tasks and modalities provide the best opportunity for patients to demonstrate covert awareness where it exists. With a wide range of etiologies and comorbidities, this is a very diverse population with variable cognitive and behavioral abilities. Additional challenges include the availability of specific technology as well as the eligibility of individual patients to be assessed with functional magnetic resonance imaging (fMRI) or electroencephalography (EEG). A number of paradigms, in different modalities, have been developed in recent years to assess aspects of residual cognitive function in DOC patients. These include basic auditory, visual, and tactile processing, speech-specific processes, selective attention, executive function, and command following. The results confirm that preserved brain function in DOC may take a wide variety of forms, from basic auditory processing all the way up to preserved command following and communication.

Introduction

Improvements in emergency medicine and critical care have resulted in more patients surviving severe brain injuries. Some of these patients will have a significant functional recovery, albeit with different degrees of physical and/or cognitive impairments. Others will remain in a vegetative state (VS) or a minimally conscious state (MCS), following a period in coma. Assessment of this latter group, patients with disorders of consciousness (DOC), is extremely difficult, and the formal diagnosis relies on subjective interpretation of observed behavior. Moreover, this is a very diverse population of patients with variable cognitive and behavioral abilities that result from a wide range of etiologies and comorbidities. The difficulty of the

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L.E. González-Lara • A.M. Owen (✉)
Department of Psychology, The Brain and Mind Institute, The University of Western Ontario, London, ON, Canada, N6A 5B7
e-mail: uwocerc@uwo.ca

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assessment, coupled with inadequate experience and knowledge due, in part, to the relative rarity of these complex conditions, contributes to an alarmingly high rate of misdiagnosis (up to 43%) in these patient groups [1–3].

In recent years, a number of studies have used functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) to investigate different aspects of cognitive function and search for evidence of covert awareness in patients that are behaviorally nonresponsive at the bedside. In this chapter, we will review some of the EEG and fMRI techniques that have been used in this context, as well as a number of new methodological approaches that have focused on peripheral physiological signals of emotion. Together, these tools have allowed a range of cognitive functions to be probed in DOC, from basic auditory, visual, and tactile processing to speech-specific processes, selective attention, executive function, and command following. By combining different technologies and paradigms, it has been possible to explore the depth and breadth of preserved cognitive function in DOC patients.

The results suggest an urgent need for a reevaluation of the existing diagnostic guidelines for behaviorally nonresponsive patients and for the development and formal inclusion of validated, standardized, neuroimaging procedures into those guidelines.

Identifying Covert Cognition With fMRI

Mental Imagery

Following a severe brain injury, when the request to move a hand or a finger is followed by an appropriate motor response, the diagnosis can change from VS (no evidence of awareness) to MCS (some evidence of awareness). Neuroimaging techniques have provided a means for identifying unique brain activation patterns that can be used as a proxy for behavioral responses to command. For example, if a patient can reliably activate their supplementary motor area in response to being asked to imagine moving their hand, then that neural response carries exactly the same explanatory weight as if the person were actually able to move their hand to command [4–6]. Skeptics may argue that brain responses are somehow less physical, reliable, or immediate than motor responses but, as is the case with motor responses, all of these arguments can be dispelled with careful measurement, replication, and objective verification [7–12]. For example, if a patient who was assumed to be unaware raised his/her hand to command on just one occasion, there would remain some doubt about the presence of awareness given the possibility that this movement was a chance occurrence, coincident with the instruction. However, if that same patient were able to repeat this response to command on ten occasions, there would remain little doubt that the patient was aware. By the same token, if that patient was able to activate his/her supplementary motor area in response to command (e.g., by being told to imagine hand movements) and was able to do this on every one of ten trials, there would remain little doubt that this patient was consciously aware.

In one large study by Boly and colleagues, 34 healthy volunteers were asked to imagine hitting a tennis ball back and forth to an imaginary coach when they heard the word “tennis” (thereby eliciting vigorous imaginary arm movements) and to imagine walking from room to room in their house when they heard the word “house” (thereby eliciting imaginary spatial navigation) [8]. Imagining playing tennis was associated with robust activity in the supplementary motor area in each and every one of the participants scanned. In contrast, imagining moving from room to room in a house activated the parahippocampal cortices, the posterior parietal lobe, and the lateral premotor cortices, all regions that have been shown to contribute to imaginary, or real, spatial navigation [13]. By simply examining the responses elicited during the imagery tasks, Boly and colleagues were able to decipher which task was being mentally “performed.” Moreover, the robustness and reliability of fMRI responses across individuals meant that activity in these regions could be used to confirm that the participants retained the ability to understand instructions and to carry out different mental tasks in response to those instructions and, therefore, were able to exhibit voluntary brain behavior in the absence of any overt action. On this basis, Boly and colleagues argued that, like any other form of action that requires a choice between one of several possible responses, these brain responses are indicative of *awareness*, that is, to say, awareness of the various contingencies that govern the relationship between a given stimulus (in this case, the cue word for one of two possible imagery tasks) and a response (in this case, imagining a type of action). To put it simply, fMRI responses of this sort can be used to measure awareness because awareness is necessary for them to occur [8].

Owen and colleagues used this same logic to demonstrate that a young woman who fulfilled all internationally agreed criteria for VS was, in fact, consciously aware and able to make responses of this sort using her brain activity [7, 9]. The patient, who was involved in a complex road traffic accident and had sustained very severe traumatic brain injuries, had remained entirely unresponsive for a period of 6 months prior to the fMRI scan. During two different scanning sessions, the patient was instructed to perform the two mental imagery tasks described above. In each case, she was asked to imagine playing tennis/moving around the rooms of her home (for 30 s) when she heard the word *tennis/house* and to relax (for 30 s) when she heard the word *relax*. When she was asked to imagine playing tennis, significant activity was observed repeatedly in the supplementary motor area [7] that was indistinguishable from that observed in the healthy volunteers scanned by Boly et al. [8]. Moreover, when she was asked to imagine walking through her home, a significant activity was observed in the parahippocampal gyrus, the posterior parietal cortex, and the lateral premotor cortex which was again indistinguishable from that observed in healthy volunteers [7, 9]. The patient’s brain activity was statistically robust, reproducible, task appropriate (enhanced following the “tennis”/“house” cue and returning to baseline following the “relax” cue), sustained over long time intervals (30 s), and repeated over each 5-min session. On this basis, it was 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 that she was consciously aware of herself and her surroundings. In a follow-up study of 23 patients who were behaviorally diagnosed as vegetative, Monti/Vanhaudenhuyse and colleagues showed that four (17%) were able to generate reliable responses of this sort in the fMRI scanner [10].

Owen and Coleman extended the general principles discussed above, by which active mental rehearsal is used to signify awareness, to show that communication of "yes" and "no'" responses was possible using the same approach [14]. Thus, a healthy volunteer was able to reliably convey a "yes" response by imagining playing tennis and a "no'" response by imaging moving around his house, thereby providing the answers to simple questions posed by the experimenters using only his brain activity. This technique was further refined by Monti/Vanhaudenhuyse and colleagues who successfully decoded three "yes" and "no" responses from each of 16 healthy participants with 100% accuracy using only their real-time changes in the supplementary motor area (during tennis imagery) and the parahippocampal place area (during spatial navigation). Moreover, in one traumatic brain injury patient, who had been repeatedly diagnosed as vegetative over a 5-year period, similar questions were posed and successfully decoded using the same approach. Thus, this patient was able to convey biographical information that was not known to the experimenters at the time (but was later verified as factually correct) such as his father's name and the last place that he had visited on vacation before his accident 5 years earlier. In contrast, and despite a re-classification to a minimally conscious state following the fMRI scan, it remained impossible to establish any form of communication with this patient at the bedside [10].

Selective Attention

Although techniques like the ones described above require that the patient engages in rather specific types of mental imagery (playing tennis or moving from room to room through a house), that is not really the main point that allows consciousness to be detected and communication to occur. All that is required to detect consciousness is a reliable indicator that a patient can turn his or her attention to a specific scenario, because this then serves as a "neural proxy" for a physical "response to command." By extension, if it can be shown that the patient can turn his or her attention to two separate scenarios, then communication is possible because those two separate scenarios can be linked to "yes" responses and "no" responses, respectively. Thus, mental imagery is not necessary at all but serves as a simple vehicle for guiding a patient's attention one way or another.

A related and possibly simpler approach to detecting covert awareness after brain injury, therefore, is to target processes that require the willful adoption of "mind-sets" in carefully matched (perceptually identical) experimental and control conditions. For example, Monti and colleagues presented healthy volunteers with a series of neutral words and alternatively instructed them to just listen, or to count, the number of times a given word was repeated [15]. As predicted, the counting task revealed the frontoparietal network that has been previously associated with target detection and working memory. When tested on this same procedure, a severely brain injured patient produced a very similar pattern of activity, confirming that he could wilfully adopt differential mind-sets as a function of the task conditions and could actively maintain these mind-sets across time. These covert abilities were entirely absent from his documented behavioral repertoire. As in the tennis/spatial navigation examples described earlier, because the external stimuli (a series of words) were identical in the two conditions, any difference in brain activity observed cannot reflect an "automatic" brain response (i.e., one that can occur in the absence of consciousness). Rather, the activity must reflect the fact that the patient has performed a particular action (albeit a "brain action") in response to the stimuli on one (but not the other) presentation; in this sense, the brain response is entirely analogous to a (motor) response to command and should carry the same weight with respect to evidence of awareness.

Naci and colleagues took this general principle even further and developed a novel tool for communicating with nonresponsive patients based on how they selectively directed their attention to sounds while in the fMRI scanner [11, 12]. It is well established that selective attention can significantly enhance the neural representation of attended sounds [16], although most previous studies have focused on group-level changes rather than individual responses that are crucial for work with (individual) brain-injured patients. In the first study by Naci and colleagues, 15 healthy volunteers answered questions (e.g., "Do you have brothers or sisters?") in the fMRI scanner, by selectively attending to the appropriate word ("yes" or "no"), which was played to them auditorily, interspersed with "distractor" stimuli (digits 1–9). Ninety percent of the answers were decoded correctly based on activity changes within the attention network of the brain [11]. Moreover, the majority of volunteers conveyed their answers with less than 3 min of scanning, which represents a significant time saving over the mental imagery methods described above [7–9]. Indeed, a formal comparison between the two approaches revealed improved individual success rates and an overall reduction in the scanning times required to correctly detect responses; 100% of volunteers showed significant task-appropriate activity in the selective attention task, compared to 87% in the motor imagery tasks. This result is consistent with previous studies showing that a proportion of healthy volunteers do not produce reliable brain activation during mental imagery tasks [8].

In a follow-up study, Naci and Owen used the same approach to test for residual conscious awareness and communication abilities in three behaviorally nonresponsive, brain-injured patients [12]. As in the previous study of healthy participants, the patients had to either "count" or "relax" as they heard a sequence of words. The word *count* at the beginning of the sequence instructed the patient to count the occurrences of a target word (*yes* or *no*), while the word *relax* instructed them to relax and ignore the sequence of words. Reliable activity increases in the attention network of the brain after the word *count* relative to the word *relax* were taken as evidence of command following. All three patients (two of whom were diagnosed as being in a MCS and one as being in a VS) were able to convey their ability to follow commands inside the fMRI scanner by following the instructions in this way. In a stark contrast, extremely limited or a complete lack of behavioral responsivity was observed in repeated bedside assessments of all three patients. These results confirm that selective attention is an appropriate vehicle for detecting covert awareness in some behaviorally nonresponsive patients who are presumed to mostly or entirely lack any cognitive abilities whatsoever [12].

In subsequent fMRI sessions, communication was attempted with two of the patients in that study [12]. During these sessions, instead of an instruction (to count or relax), a binary question (e.g., "Is your name John?") preceded each sound sequence. Thus, each patient then had to wilfully choose which word to attend to (count) and which to ignore, depending on which answer they wished to convey to the specific question that had been asked. Using this method, the two patients (one diagnosed as MCS and one diagnosed as VS) were able to use selective attention to repeatedly communicate correct answers to questions that were posed to them by the researchers [12]. In the absence of external cues as to which word the patient was attending to, the functional brain activation served as the only indicator of the patient's intentions—and in both cases led to the correct answers being decoded. For example, when asked "Are you in a supermarket?" one patient showed significantly more activation for "no" than "yes" sequences in a network of brain areas that had been previously activated when that patient was focusing attention on external cues. Conversely, when asked "Are you in a hospital?" the patient showed significantly more activation for "yes" than "no" sequences in those same brain regions. Despite his diagnosis (VS for 12 years), the fMRI approach allowed this patient to establish interactive communication with the research team in four different fMRI sessions. The patient's brain responses within specific regions were remarkably consistent and reliable across two different scanning visits, 5 months apart, during which the patient maintained the long-standing VS diagnosis. For all of the four questions, the patient produced a robust neural response and was able to provide the correct answers with 100% accuracy. The patient's brain activity in the communication scans not only further corroborated that he was, indeed, consciously aware but also revealed that he had far richer cognitive reserves than could be assumed based on his clinical diagnosis. In particular, beyond the ability to pay attention, these included autobiographical knowledge and awareness of his location in time and space [12].

Identifying Covert Cognition Through EEG

Performing fMRI in severely brain-injured patients is enormously challenging; in addition to considerations of cost and scanner availability, the physical stress incurred by patients as they are transferred to a suitably equipped fMRI facility may be significant. Movement artifacts often occur in imaging datasets from patients who are unable to remain still, while metal implants, including plates and pins which are common in many traumatically injured populations, may rule out fMRI altogether. EEG measures the activity of groups of cortical neurons from scalp electrodes and is far less expensive than fMRI, both in terms of initial cost and maintenance. EEG recordings are unaffected by any resident metallic implants and, perhaps most importantly, can be used at the bedside [17]. In brain-injured patients, EEG recordings are typically made in the acute period and allow for broad assessments of cortical damage including the occurrence of brain death. However, uncertainty about the causes of abnormal raw EEG patterns (i.e., damage to the cortex itself or to subcortical structures which influence cortical activity) provides challenges for its use as a more precise tool for the assessment of awareness [18].

Motor imagery produces clearly distinguishable modulation of EEG sensorimotor rhythms similar to those seen during motor execution and has been the basis of several recent attempts to detect conscious awareness after severe brain injury [19, 20]. For example, Cruse and colleagues developed a novel EEG-based classification technique in which two mental imagery responses (squeezing the right hand or squeezing the toes) were successfully decoded offline in 9 out of 12 healthy individuals with accuracy rates varying between 60 and 91% [21]. The same approach was then used to attempt to detect evidence of command following the absence of any overt behavior in a group of 16 patients who met the internationally agreed criteria for a diagnosis of VS. Three of these patients (19%, two traumatic brain injury and one nontraumatic brain injury) were repeatedly and reliably able to generate appropriate EEG responses to the two distinct commands (“squeeze your right hand” or “squeeze your toes”), despite being behaviorally entirely unresponsive, indicating that they were aware and following the task instructions. Indeed, on the basis of such data, far broader conclusions about residual cognition can be drawn. For example, performance of this complex task makes multiple demands on many cognitive functions, including sustained attention (over 90-s blocks), response selection (between the two imagery tasks), language comprehension (of the task instructions), and working memory (to remember which task to perform across multiple trials within each block), all aspects of “top-down” cognitive control that are usually associated with—indeed, could be said to characterize—normal conscious awareness [22].

In a follow-up study, 23 minimally conscious state patients (15 traumatic brain injury and 8 nontraumatic brain injury) completed the same motor imagery EEG task. Consistent and robust responses to command were observed in the EEG of 22% of the minimally conscious state patients (5/23) [23]. Etiology had a significant impact on the ability to successfully complete this task, with 33% of traumatic patients (5/15) returning positive EEG outcomes, compared with none of the nontraumatic patients (0/8). However, the link between etiology and projected neuroimaging outcomes remains poorly understood and must be interpreted with caution where individual patients are concerned, as patients in both traumatic and nontraumatic groups vary widely in etiologies, neuropathology, and clinical features. Indeed, in some cases, nontraumatic brain-injured patients have returned positive outcomes, including one of the three patients in the aforementioned study [21].

In a more recent study, Cruse and colleagues refined their EEG approach using a simpler and more clinically viable paradigm that required participants to actually try to move their hands, and, unlike the two previous studies [21, 23], 100% of the healthy volunteers showed reliable event-related desynchronization and event-related synchronization responses [24]. Moreover, in one of the patients studied previously by Naci and Owen [12], who had been repeatedly diagnosed as vegetative for 12 years, reliable modulations of sensorimotor beta rhythms were observed following commands to try to move, and these could be classified significantly at a single-trial level [24]. This patient is the first published case of a clinically vegetative patient in whom awareness has been demonstrated using two independent imaging methods (fMRI and EEG) in the absence of any supportive evidence from clinical (behavioral) examination [6].

Is it possible that appropriate patterns of activity could be elicited in patients like this in the absence of awareness? Could they somehow reflect an "automatic" response to aspects of the task instructions, such as the words "right hand" and "toes," and not a conscious and overt "action" on the part of the patient? This is extremely unlikely for a number of reasons. First, the task instructions were delivered once at the beginning of each block of tones that signaled the time to begin each imagery trial. Any "automatic" response to the previously presented verbal instruction would then have to abate and recur in synchrony with these tones/cues that carried no information in themselves about the task to be performed. Indeed, 75% of the healthy control participants tested in the study by Cruse and colleagues returned positive EEG outcomes when completing this motor imagery task. However, when these same individuals were instructed *not* to follow the commands—i.e., not to engage in motor imagery—not one participant returned a positive EEG outcome [21]. Evidently, any automatic brain responses generated by listening to the instructions are not sufficient for significant task performance; rather, an act of consistently timed, volitional command following is required. In this context then, it is clear that successful performance of these EEG tasks represents a significant cognitive feat, not only for those patients who were presumed to be vegetative but also for healthy control participants. That is to say, to be deemed successful, each respondent must have consistently generated the requested mental states to command for a prolonged period of time within each trial and must have consistently done so across numerous trials. Indeed, one behaviorally vegetative patient was able to produce EEG responses that were classified with a success rate of 78% [21]. In other words, consistently appropriate EEG responses were generated across approximately 100 trials. Conversely, when assessed behaviorally using accepted standard clinical measures that were administered by experienced specialist teams, none of these patients exhibited any signs of awareness, including visual fixation, visual pursuit, or localization to pain. These results demonstrate that consistent responses to command—a reliable and universally accepted indicator that a patient is not vegetative—need not be expressed behaviorally at all but, rather, can be determined accurately on the basis of EEG responses [24].

The success of recent EEG techniques for detecting awareness in nonresponsive patients [21, 23, 24] paves the way for the development of a true "brain-computer interface" (BCI) [25]—or simple, reliable communication devices—in this patient group. It seems likely that such devices will provide a form of external control and communication based on mappings of distinct mental states—for example, attempting right-hand movements to communicate "yes" and toe movements to communicate "no" [24]. Indeed, the degrees of freedom provided by EEG have the potential to take this beyond the sorts of binary responses that have worked well using fMRI [6, 10–12], to allow methods of communication that are far more functionally expressive. The development of techniques for the real-time classification of these forms of mental imagery [21, 23, 24] will open the door for a routine two-way communication with some of these patients, ultimately allowing them (within the constraints of BCI technologies) to share information about their inner worlds, experiences, and needs.

Emerging Approaches

False-negative findings in functional neuroimaging studies are common, even in healthy volunteers, and they present particular difficulties in this patient population. For example, a patient may fall asleep during the scan or may not have properly heard or understood the task instructions, leading to an erroneous negative result. Indeed, in the study by Monti/Vanhaudenhuyse and colleagues, no wilful fMRI responses were observed in 19 of 23 patients—whether these are *true* negative findings (i.e., those 19 patients were indeed vegetative) or *false-negative* findings (i.e., some of those patients were conscious, but this was not detected on the day of the scan) cannot be determined [10]. Accordingly, negative fMRI and EEG findings in patients should never be used as evidence for impaired cognitive function or lack of awareness.

Furthermore, inconsistent responses, either through behavioral or neuroimaging assessments, add to the challenge of assessing patients who may have varying degrees of awareness over time. In the first study to evaluate convergence and divergence of fMRI and EEG findings in this group of patients, Gibson and colleagues concluded that the application of multiple paradigms gives patients the best opportunity for demonstrating covert awareness [26]. In that study, six patients were evaluated using standard clinical behavioral assessments, EEG, and fMRI. During the fMRI assessments, patients were asked to perform either a motor imagery task (playing tennis) or a spatial navigation imagery task (moving through a familiar place) as previously described [6, 7, 10, 27]. During the EEG assessments, two types of motor imagery were used, a conventional one (i.e., squeezing a hand) [21, 24] and a familiar one (an action the patients had experience with prior to their injury) [28]. Event-related desynchronizations were only observed in some of the patients during the conventional imagery task but were not produced by any patients during the familiar task. One patient demonstrated command following using both fMRI and EEG. Two patients showed significant and anatomically appropriate fMRI activation during the spatial navigation task, although there was no evidence of activation during the motor imagery tasks with either fMRI or EEG. Conversely, one patient produced EEG event-related desynchronizations during conventional motor imagery task, but no significant activation was observed during any of the fMRI tasks. In the last two patients, there was no evidence of reliable activation during any of the tasks using either fMRI or EEG [26]. The results of this study emphasize the importance of using a battery of assessments to investigate covert awareness. The exact source of the variability observed in this group is not entirely clear, although the locus of injury in each patient is a likely factor, as is daily variations in arousal level and motivation. By using multiple tools, all patients have the best opportunity to demonstrate residual cognitive abilities (where they exist) via one or more of these methods.

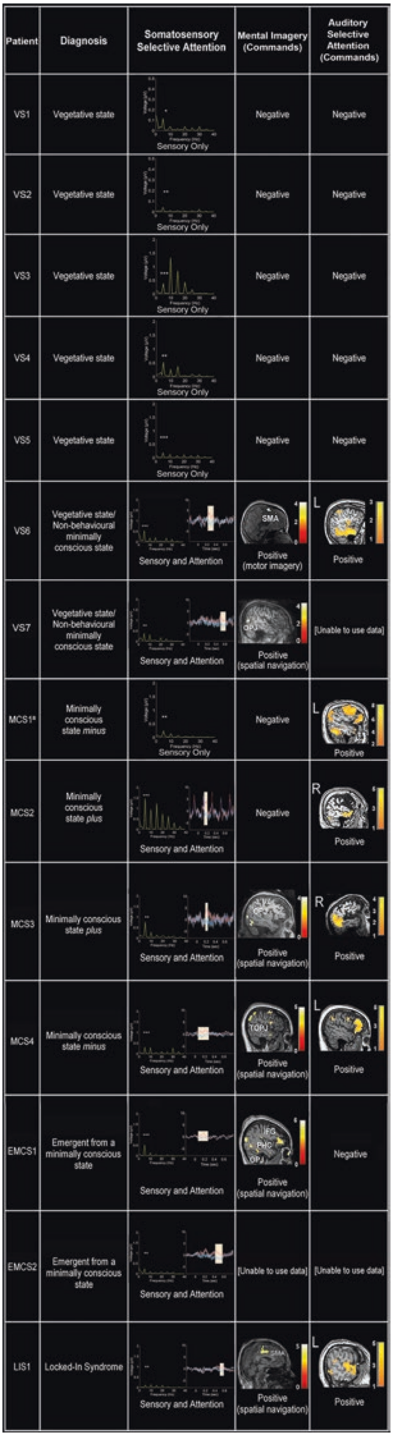
The approaches discussed so far all illustrate the use of active (e.g., wilful) tasks in the assessment of covert awareness after serious brain injury. The neural responses required are not produced *automatically* by the eliciting stimulus but, rather, depend on time-dependent and sustained responses generated by the participants themselves. Such behavior (albeit neural "behavior") provides a proxy for a motor action and is, therefore, an appropriate vehicle for reportable awareness [29].

To further investigate alternative approaches to this problem, Gibson and colleagues recently developed a paradigm that does not use visual stimuli nor depend solely on auditory stimuli [30]. They assessed somatosensory-selective attention by eliciting steady-state evoked potentials (SSEP) and measuring event-related potentials (ERP) in 14 patients using a vibrotactile stimulus. A hierarchical approach was used to probe SSEP, bottom-up attention (P3a ERP), and top-down attention (P3b ERP) using an oddball paradigm; the results were compared to those obtained through the fMRI motor imagery, spatial navigation [4, 5, 7, 8, 10], and selective auditory attention [11, 12] paradigms, described above. Gibson and colleagues found SSEPs in all 14 patients, indicating a basic sensory response to the vibrotactile stimulus. Furthermore, bottom-up attention ERPs (P3a) were detected in eight patients. While top-down ERPs (P3b) were not detected in any of the patients; all of the patients who showed P3a effects also demonstrated evidence of command following, either through behavioral or fMRI responses (Fig. 5.1). The relationship between P3a and command following suggests an overlap of the neural attention networks responsible for these different types of output. However, the fact that the P3a can be elicited without the patient being required to follow any instructions suggests that this paradigm may serve as a passive assessment with lower cognitive demands than active orienting of attention.

Passive Paradigms

While "active" paradigms have proven themselves to be an effective means for assessing residual awareness in some nonresponsive patients, it remains likely that many patients will lack the necessary cognitive resources for carrying out these

Fig. 5.1 Fourteen patients with diagnosis of VS, MCS, EMCS, and LIS were assessed using a vibrotactile stimulus. The results were compared to those obtained through the fMRI motor imagery, spatial navigation, and selective auditory attention paradigms. SSEPs were present in all 14 patients. Bottom-up attention ERPs (P3a) were detected in eight patients who also demonstrated evidence of command following either through behavioral or fMRI responses. Reprinted from Gibson RM, Chennu S, Fernández-Espejo D, Naci L, Owen AM, and Cruse D. Somatosensory attention identifies both overt and covert awareness in disorders of consciousness. Ann Neurol 80(3):412–23 2016, with permission from John Wiley & Sons, Inc.



Patient	Diagnosis	Somatosensory Selective Attention	Mental Imagery (Commands)	Auditory Selective Attention (Commands)
VS1	Vegetative state	Sensory Only	Negative	Negative
VS2	Vegetative state	Sensory Only	Negative	Negative
VS3	Vegetative state	Sensory Only	Negative	Negative
VS4	Vegetative state	Sensory Only	Negative	Negative
VS5	Vegetative state	Sensory Only	Negative	Negative
VS6	Vegetative state/ Non-behavioural minimally conscious state	Sensory and Attention	Positive (motor imagery)	Positive
VS7	Vegetative state/ Non-behavioural minimally conscious state	Sensory and Attention	Positive (spatial navigation)	[Unable to use data]
MCS1[a]	Minimally conscious state minus	Sensory Only	Negative	Positive
MCS2	Minimally conscious state *plus*	Sensory and Attention	Negative	Positive
MCS3	Minimally conscious state *plus*	Sensory and Attention	Positive (spatial navigation)	Positive
MCS4	Minimally conscious state minus	Sensory and Attention	Positive (spatial navigation)	Positive
EMCS1	Emergent from a minimally conscious state	Sensory and Attention	Positive (spatial navigation)	Negative
EMCS2	Emergent from a minimally conscious state	Sensory and Attention	[Unable to use data]	[Unable to use data]
LIS1	Locked-In Syndrome	Sensory and Attention	Positive (spatial navigation)	Positive

tasks in the scanner and will therefore fail to exhibit signs of awareness even when it may exist. To further address this issue, Naci and colleagues have used a richly evocative stimulus—a highly suspenseful movie—to capture attention naturally in the absence of structured instruction [31]. In order to establish whether some DOC patients experience the world in a way that is similar to healthy individuals (despite their outward appearance), Naci and colleagues investigated whether a common neural basis can account for how different individuals form similar conscious experiences, and if so, whether it could be used to interpret those experiences without recourse to self-report in behaviorally nonresponsive patients. They reasoned that executive function, in particular, might provide an empirical window by which the cognitive aspect of human conscious experience can be quantified. By their very nature, engaging movies are designed to give viewers a shared conscious experience driven, in part, by the recruitment of similar executive processes, as each viewer continuously integrates their observations, analyses, and predictions while filtering out any distractions, leading to an ongoing involvement in the movie's plot [31].

When healthy participants viewed a highly engaging short movie by Alfred Hitchcock—the so-called Master of Suspense—in the fMRI scanner, they displayed highly synchronized brain activity in supramodal frontal and parietal regions, which support executive function [32, 33]. The movie's executive demands, assessed quantitatively with a dual-task procedure [34] in an independent group, predicted activity in frontal and parietal regions of the healthy participants, who had watched the movie without a secondary task in the scanner. Also, the movie's suspense ratings, provided by a third independent healthy group, demonstrated that individual participants had a similar qualitative experience of the movie, which also predicted activity in the frontal and parietal regions. Together, these results suggested that the movie's executive demands drove brain activity in frontal and parietal regions and, furthermore, that the synchronization of this activity across individuals underpinned their similar experience. By extension, the degree to which each individual's frontoparietal brain activity could be predicted from the rest of the group's represented a reliable neural index of how similar his/her cognitive experience was to the others'.

Naci and colleagues then applied this approach to two entirely behaviorally nonresponsive patients with unknown levels of consciousness, in order to examine and quantify their experience of the world. fMRI data was acquired from the two patients, as they freely viewed the same Hitchcock movie [31]. One patient, who had remained behaviorally nonresponsive for a 16-year period prior to scanning, demonstrated a highly similar brain response to that of the three independent control groups. The patient's brain activity in frontal and parietal regions was tightly synchronized with the healthy participants' over time, and crucially, it reflected the executive demands of specific events in the movie, as measured both quantitatively and qualitatively in healthy individuals. This suggested that the patient could continuously engage in complex thoughts about real-world events unfolding over time and, thus, that he was consciously aware. Moreover, the patient's brain response suggested that his conscious experience was highly similar to that of each and every healthy participant, including his moment-to-moment perception of the movie content, as well as his executive engagement with its plot. These processes are likely to include updating the contents of working memory (e.g., to follow the plot), relating events in the movie to past experiences (e.g., to appreciate that a gun is a dangerous weapon), and coding the foreshadowing cues (i.e., events that might have future relevance to the plot) characteristic of movies of this type [31]. No such responses in frontal and parietal regions were observed in the second patient, despite similar behavioral and clinical profiles.

A problem with this approach is that sustained visual fixation and tracking are not preserved in most patients who have a VS diagnosis [35]. To address this challenge, Naci and colleagues developed an auditory-only task using the composite soundtrack from an early and suspenseful scene from the movie "Taken" to investigate executive function [36]. In this short audio story, both speech and other sound effects are important for the development of the plot. Like the previous study, this auditory paradigm does not require that participants follow instructions but engage attention naturally through lifelike sounds and speech. Highly correlated activity patterns, including frontoparietal regions, were recorded across the brain of 15 healthy individuals suggesting that this audio-story paradigm is suitable for investigating executive function in behaviorally nonresponsive patients who may have impaired vision but preserved auditory function [36]. Indeed, in a remarkable case of recovery from the vegetative state, a patient who had been vegetative for several months following an anoxic brain injury produced responses in frontal and parietal regions during this auditory task that were very similar to those of healthy controls (Fig. 5.2). At the time, this data was the only information available to the investigators that the patient was anything other than vegetative. Yet 7 months later, the patient had recovered to the point that he was able to talk and walk (with assistance) and was preparing to return to school. At that time, he was able to report a remarkably detailed account of his evaluation 7 months earlier (when he had appeared to

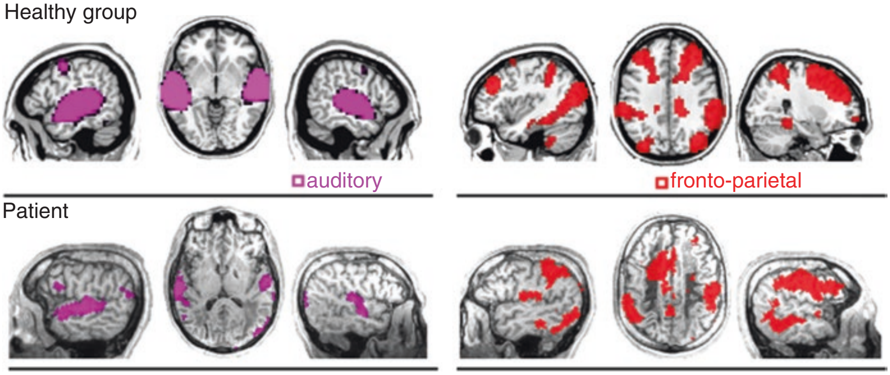


Fig. 5.2 (*Top row*) Fifteen healthy volunteers show highly correlated activity patterns, including frontoparietal regions while listening to a suspenseful short audio story. (*Bottom row*) A patient, who at the time the data was acquired had a VS diagnosis though later had a remarkable recovery, produced responses in frontal and parietal regions very similar to those of healthy controls

be entirely vegetative), including details of the plot of the movie soundtrack that he had been exposed to during the fMRI scan.

Fiacconi and Owen have recently used an entirely different approach to examine peripheral physiological signals of emotional functioning in 36 healthy controls and 2 behaviorally nonresponsive patients [37]. They measured facial electromyography (EMG) while participants listened to sentences, half of which were jokes and half of which were non-jokes. Greater zygomatic and reduced corrugator muscle activity was observed when comparing jokes to non-jokes in 31 of the healthy volunteers (86%). Using EMG to detect peripheral changes in this way has clinical and practical advantages over techniques like fMRI and EEG, as it is relatively inexpensive and very portable. Accordingly, one of the patients, who had been behaviorally nonresponsive for almost 17 years, exhibited an increased zygomatic response and decreased corrugator response, similar to healthy volunteers, when comparing jokes and non-jokes (Fig. 5.3). Because high-level language processes are required to

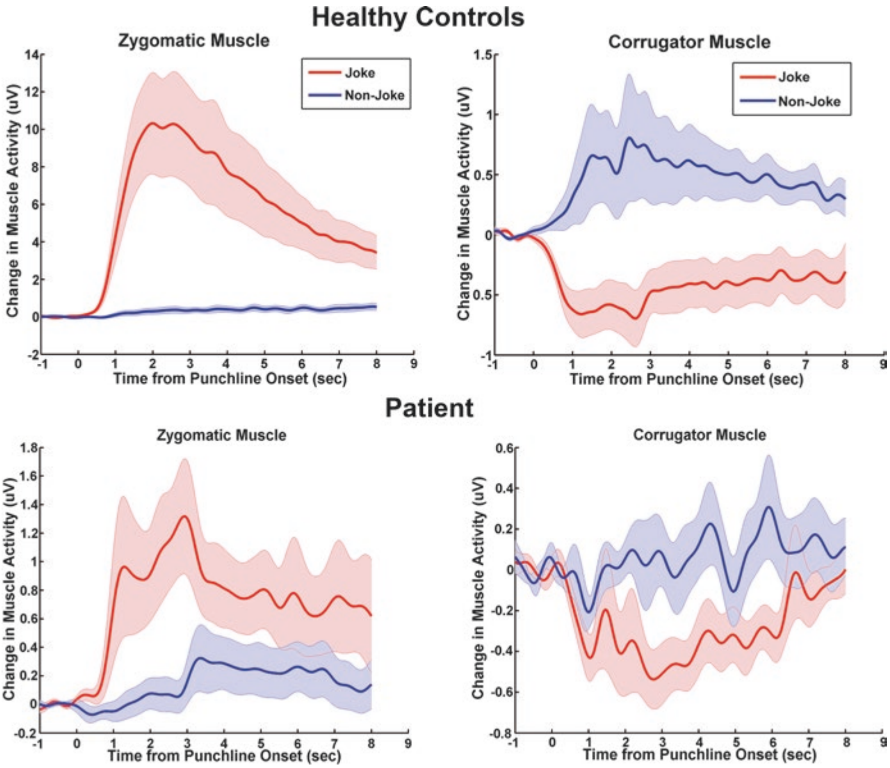


Fig. 5.3 (*Top row*) Facial EMG of healthy participants shows greater zygomatic and reduced corrugator muscle activity when comparing jokes to non-jokes. (*Bottom row*) A patient, who had been behaviorally nonresponsive for almost 17 years, exhibited an increased zygomatic response and decreased corrugator response, similar to healthy volunteers, when comparing jokes and non-jokes. Adapted from Fiacconi CM and Owen AM. Using facial electromyography to detect preserved emotional processing in disorders of consciousness: A proof-of-principle study. Clin Neurophysiol 127(9):3000–6 2016, with permission from Elsevier

"get" a joke, the peripheral changes in muscle activity observed can be used to confirm that both speech perception and language comprehension are preserved in behaviorally nonresponsive patients. Moreover, the preservation of the zygomatic muscle responses to jokes implies that the emotional processes involved in appreciating humor remain intact despite the patient's brain injury.

Implications

Diagnostic Implications

An obvious clinical consequence of the emergence of novel neuroimaging techniques that permit the identification of covert awareness and communication in the absence of any behavioral response is the possibility of improved diagnosis after severe brain injury. It is notable that in one of the cases described above, the patient was repeatedly and rigorously assessed by experienced teams and showed no behavioral sign of awareness on any of these occasions—indeed, this continued to be the case even after awareness had been established unequivocally with both fMRI and EEG [6, 12, 24]. Technically, however, he was not *misdiagnosed* (as VS), in the sense that any error of judgment was made, because the accepted diagnostic criteria are based on behavior, and no behavioral marker of awareness was missed. Nevertheless, the existing criteria did not accurately capture his actual state of awareness, and in this sense, his VS diagnosis was clearly incorrect. What then is the appropriate diagnostic label for such patients and who can follow commands with a measurable brain response but physically remain entirely nonresponsive? The term "nonbehavioral minimally conscious state" has been suggested [38], although because attention, language comprehension, and working memory are demonstrably preserved in these patients, we have argued that "minimally conscious" does not adequately describe their residual cognitive abilities [6, 12]. Indeed, the patient described above was consistently and reliably able to communicate (using fMRI), which places him well beyond the diagnostic criteria describing the minimally conscious state. The term "functional locked-in syndrome" has also been proposed for patients who demonstrate consistent and reliable communication using solely adjunctive technologies [39, 40]. In its classical clinical presentation, "locked-in syndrome" refers to patients who are left with only vertical eye movements and/or blinking, which often permits rudimentary communication. Cognitive function, however, is generally fully preserved, at least in those cases where the lesion is limited to the ventral pons [41]. Patients like the one described here are clearly "locked in" in the general sense of the term but do not have many of the same neuropathological and clinical features of the classic locked-in syndrome. Moreover, at present, there is still considerable uncertainty about the full extent of residual cognitive function in such patients and, thus, about the suitability of the term "functional locked-in syndrome." This is precisely the sort of question that can be explored with neuroimaging techniques.

Decision-Making

An obvious application for approaches of this sort is to begin to involve some of these patients in the decision-making processes involved in their own therapeutic care and management. To date, this has only been achieved successfully in one patient, who had been repeatedly diagnosed as vegetative for 12 years following a traumatic brain injury [6]. The patient was a male who, at the age of 26, had suffered a severe closed head injury in a motor vehicle accident. On admission to a hospital, he had a Glasgow Coma Scale [42] score of 4, meaning that he was unable to open his eyes or produce any sound, and his only response was extension to painful stimulation. Over the next 12 years, the patient was assessed regularly by experienced neurologists and multidisciplinary teams, and throughout this period, his behavior remained consistent with the internationally accepted criteria for the VS. Indeed, over a 14-month period, a total of 20 standardized behavioral assessments were performed by a multidisciplinary team, at different times of the day and in different postural positions, using the Coma Recovery Scale – Revised [43], and his diagnosis was unchanged throughout. Twelve years and 2 months after his accident, the patient was first scanned using the fMRI mental imagery approach described before [7, 10]. The patient was able to provide correct answers to multiple externally verifiable questions, including his own name, his whereabouts, the name of his personal support worker (who he had only encountered in the years following his accident), the current date, and other basic factual information (e.g., whether a banana is yellow). Two non-verifiable questions were then posed, including one pertaining to his care preferences (e.g., whether he liked watching (ice) hockey games on TV) and another to details about his current clinical condition (e.g., whether he was in any physical pain). Within the time constraints of the scanning visits, the majority of responses to these questions were verified in independent sessions that posed the reverse questions (e.g., “Is your name Mike?” vs. “Is your name Scott?”). In all, answers to 12 different questions were obtained across several sessions, despite the fact that the patient remained entirely physically nonresponsive at the bedside [6].

Schnakers developed a standardized neuropsychological assessment for locked-in syndrome that uses simple eye movements as responses (in most cases to provide “yes”/“no” answers to questions) [41]. There is no technical or theoretical reason why a similar approach could not be used with neuroimaging tools in entirely nonresponsive patients, although the data would take considerably longer to acquire. To this end, Hampshire and colleagues used fMRI to assess complex logical reasoning ability in a patient who was assumed to be in a vegetative state [44]. Adapting a verbal reasoning paradigm from Baddeley [45], Hampshire and colleagues presented participants with statements describing the ordering of two objects: a face and a house. Participants were instructed to deduce which of the objects was in front and to visualize the object in their mind. For example, if they heard the statement “the face is not followed by a house,” the correct answer would be “house.” Conversely, if they heard “the face precedes the house,” the correct answer would be “face.” The patient engaged the same brain regions as healthy individuals in response

Fig. 5.4 A patient (*right*) engaged the same brain regions as healthy individuals (*left*) in response to reasoning task demand during a verbal reasoning paradigm to assess complex logical reasoning

to the reasoning task demand (Fig. 5.4). This result was consistent with the patient's positive outcome in the fMRI command-following task [7, 8] and suggested that, despite the long-standing clinical diagnosis of vegetative state, he was not only consciously aware but, critically, retained capacity for higher-order cognition, in particular, for solving logically complex verbal problems.

In summary, using neuroimaging techniques, we are beginning to determine not only whether any given patient is conscious but also to infer what the contents of that conscious experience might actually be, thus revealing important practical and ethical implications for the patient's standard of care and quality of life [46].

Conclusions

In the last few years, neuroimaging methods—most notably fMRI and EEG—have been brought to bear on one of the most complex and challenging questions in clinical medicine, that of detecting residual cognitive function, and even covert awareness, in patients who have sustained severe brain injuries. The results demonstrate that responses need no longer be *physical* responses in the traditional sense (e.g., the blink of an eye or the squeezing of a hand) but can now include responses that occur entirely within the brain itself. The recent use of reproducible and robust task-dependent fMRI responses as a form of "communication" in patients who are assumed to be vegetative [6, 10, 12] represents an important milestone in this process. In some cases, these patients have been able to communicate information that was not known by the experimenters at the time, yet could be independently verified later, as being factually correct and true [10, 12]. More importantly perhaps, in one case, a patient has used these methods to answer clinically and therapeutically relevant questions (including "Are you in any pain?") that could not be answered in any other way, including via third party [6]. Further refinement of other tools such as EEG and EMG, which are relatively more portable and cost effective, will undoubtedly move this field even closer to a true brain-computer interface. Ultimately, this development may increase the opportunities for communication in behaviorally nonresponsive patients with covert awareness and potentially allow them to participate in quality-of-life decisions [46].

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