Uncovering Consciousness and Revealing the Preservation of Mental Life in Unresponsive Brain-Injured Patients

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Abstract

In the last few years, functional neuroimaging and electroencephalography-based techniques have been used to address one of the most complex and challenging questions in clinical medicine, that of detecting covert awareness in behaviorally unresponsive patients who have survived severe brain injuries. This is a very diverse population with a wide range of etiologies and comorbidities, as well as variable cognitive and behavioral abilities, which render accurate diagnosis extremely challenging. These studies have shown that some chronic behaviorally unresponsive patients harbor not only covert consciousness but also highly preserved levels of mental life. Building on this work, although in its infancy, the investigation of covert consciousness in *acutely* brain-injured patients could have profound implications for patient prognosis, treatment, and decisions regarding withdrawal of care. The body of evidence on covert awareness presents a moral imperative to redouble our efforts for improving the quality of life and standard of care for all brain-injured patients with disorders of consciousness.

Keywords
► covert consciousness
► brain injury
► mental life

Improvements in emergency medicine and critical care have led to an increasing number of patients surviving severe brain injuries. Long-term patient outcome is highly variable. Some pass away, others go on to make a good recovery, and a third group progresses into states of behavioral unresponsivity,[1–3] such as the vegetative state (VS; the Multi-Society Task Force, 1994), also known as the "unresponsive wakefulness syndrome" (UWS).[4] Clinical diagnosis in patients with such disorders of consciousness (DoC) is extremely difficult,[5] not least because it relies on subjective interpretation of observed behavior. Moreover, this is a very diverse population with a wide range of etiologies and comorbidities, as well as variable cognitive and behavioral abilities. The difficulty of the assessment, coupled with the limited clinical experience and knowledge due to the relative rarity of these complex conditions, leads to a high rate of misdiagnosis (up to 43%) in these patient groups.[6,7]

Although a clinical diagnosis of VS/UWS implies lack of consciousness and cognition, this is not necessarily the case. Neuroimaging studies using functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) have shown that some patients, who behaviorally appear to be entirely vegetative, are able to follow commands by modulating their brain activity, thereby indicating that they are consciously aware despite their clinical diagnosis.[8–15]

Identifying Covert Cognition and Consciousness with Command-Following Paradigms

Functional Magnetic Resonance Imaging

Owen and colleagues[15] were the first to employ an fMRI paradigm based on mental imagery to assess command-following in a patient who had been unresponsive for

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5 months and fulfilled all the internationally agreed criteria for VS/UWS (the Multi-Society Task Force, 1994). During two different scanning sessions, the patient was instructed to perform two mental imagery tasks, either imagining playing a game of tennis or moving from room to room in her house. Specifically, she was asked to imagine playing tennis/move around her home for 30 seconds when she heard the word "tennis" or "house" and to relax for 30 seconds when she heard the word "relax." When she was asked to imagine playing tennis, the patient's supplementary motor area repeatedly showed significant fMRI activity that was indistinguishable from that observed in the healthy volunteers.[16] Moreover, when she was asked to imagine walking through her home, her parahippocampal gyrus, the posterior parietal cortex, and the lateral premotor cortex showed significant activity that, again, was indistinguishable from that of the healthy volunteers (►**Fig. 1**).[15,17] 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 seconds), and repeated over each 5-minute session. On this basis, it was concluded that, despite fulfilling all of the clinical criteria for a diagnosis of VS/UWS, 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, 23 patients who were behaviorally diagnosed as VS/UWS, Monti et al showed that two (9%) were able to generate reliable responses of this sort in the fMRI scanner.[14] Furthermore, they extended this approach to demonstrate that fMRI could also be used to communicate with an unresponsive patient who was assumed to be in a VS/UWS. One type of imagery (tennis or spatial navigation) was mapped to a "yes" response, and the other to a "no" response. A single neutral word, "answer," was used to cue each response to a question. Monti et al successfully decoded three "yes"/"no" responses from 16 healthy individuals with 100% accuracy, by using only the online changes in each individual's supplementary motor area and the parahippocampal place area. Furthermore, in one traumatic brain injury patient who was consistently diagnosed as vegetative during a 5-year period, answers to similar questions were successfully decoded with the same approach. In this manner, this patient conveyed biographical information that was later verified as factually correct, including his father's name and the last place that he had visited before his accident. Following the fMRI scan, the patient was reclassified as being in a minimally conscious state; nevertheless, they could not establish any form of communication at the bedside.[14]

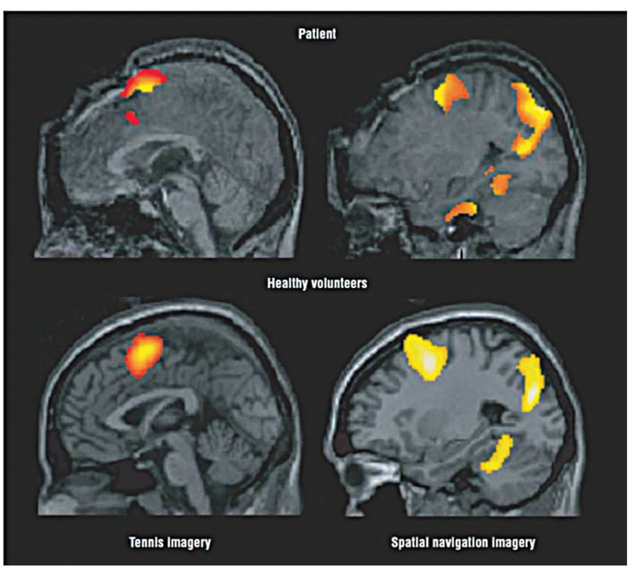

Fig. 1 Conscious responses to stimuli in a patient who fulfilled all the clinical criteria defining the vegetative state/unresponsive wakefulness syndrome, revealed by functional MRI. The top panel shows the brain activation in the supplementary motor area (SMA) during tennis imagery (left), and the parahippocampal gyrus (PPA), posterior parietal-lobe (PPC), and lateral premotor cortex (PMC) during imagery of spatial navigation (right), in a patient who fulfilled all the internationally agreed criteria for the vegetative state. These responses were indistinguishable from that of a group of healthy volunteers (bottom panel). (Image adapted from Owen et al.[15])

A later study by Bardin and colleagues[10] demonstrated that although a behaviorally unresponsive patient could follow commands by using motor imagery (in that case, swimming) on two different occasions, they could not use the motor imagery task to produce robust brain activity for binary (yes/no) communication. The patient's profile of cognitive deficit, in particular her short-term memory reserve, may have compromised her inability to communicate. A patient with a pronounced memory deficit may not be able to remember the correct answer and/or to maintain in short-term memory the abstract link between the arbitrary response function (i.e., a specific form of motor imagery) and answer (yes or no). This case highlighted the need for more intuitive paradigms[18] to maximize the chance that patients with very limited cognitive reserves can be reached.

To this end, Naci and colleagues developed a paradigm based on selective attention—whereby individuals could demonstrate covert consciousness by selectively attending to the word "yes" or "no" when specifically asked to do so, or freely select "yes" or "no" to answer questions when asked.[19] In the first study, 15 healthy volunteers initially followed commands to either "count" or "relax" as they heard a sequence of words, including "yes" or "no," interspersed with "distractor" stimuli (the digits 1–9). Activity was consistently observed in the attention network of the brain after the word "count" relative to the word "relax," demonstrating that individual participants could follow commands by selectively deploying their attention according to commands. Subsequently, healthy volunteers answered questions (e.g., "Do you have brothers or sisters?") by freely attending to the word ("yes" or "no"), which induced changes in activity that could be decoded from the fMRI signal. Ninety percent of the answers were decoded correctly based on activity changes within the attention network.[19] Moreover, most volunteers conveyed their answers with less than 3 minutes of scanning, a significant time saving compared with the mental imagery methods described earlier.[10,14–16]

Naci and Owen[8] extended this study to develop a novel tool for communicating with behaviorally unresponsive patients. Three patients (1 MCS –, 1 MCS –/+,[20] 1 VS/UWS) were able to demonstrate that they were able to follow commands using fMRI by selectively deploying their attention as described earlier. In stark contrast, either extremely limited and inconsistent or a complete lack of behavioral responsivity was observed in repeated bedside assessments of all three patients. These results confirmed that selective attention is an appropriate vehicle for detecting covert awareness in some behaviorally unresponsive patients who are presumed to lack all cognitive abilities, based on a diagnosis of VS/UWS. In subsequent fMRI sessions, communication was attempted with two of the patients. 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 willfully choose which word ("yes" or "no") to attend to 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 (1 MCS, 1 VS/UWS) were able to use selective attention to repeatedly communicate correct answers to binary questions. Despite a diagnosis of VS/UWS maintained for 12 years, one patient's brain responses within specific regions of the attention network were remarkably consistent and reliable across two different scanning visits, 5 months apart (►**Fig. 2**). For all four questions asked, the patient produced a robust neural response that yielded the correct answer in each case.[8]

Electroencephalography

Translation of the aforementioned paradigms to cost-effective and portable techniques, such as EEG, has been sought to facilitate their widespread clinical use. Motor imagery, in particular, has been found to produce a clear modulation of EEG sensorimotor rhythms akin to those elicited by motor execution, which has motivated several attempts to detect conscious awareness after severe brain injury.[21,22] For example, Cruse and colleagues developed a novel EEG-based classification technique by using this principle. They successfully decoded offline in 9 of 12 healthy individuals two mental imagery responses (squeezing the right hand or wiggling the toes), with an accuracy of 60 to 91%.[12] Subsequently, they used same approach to investigate command-following in the absence of overt behavior, in VS/UWS 16 patients. Three of these patients (19%) were repeatedly and reliably able to generate appropriate EEG responses to the two distinct commands (►**Fig. 3**), despite being behaviorally entirely unresponsive, indicating that they were aware and following the task instructions.

A follow-up study assessed 23 MCS patients (15 traumatic brain injury and 8 nontraumatic brain injury) with this motor imagery EEG task: 22% of the MCS patients (5/23) showed consistent and robust EEG responses to the experimenter's commands[23]; 33% of the traumatic injury patients (5/15) returned positive EEG outcomes, in stark contrast to the nontraumatic patients (0/8), suggesting that etiology has a significant impact in determining these responses. However, the link

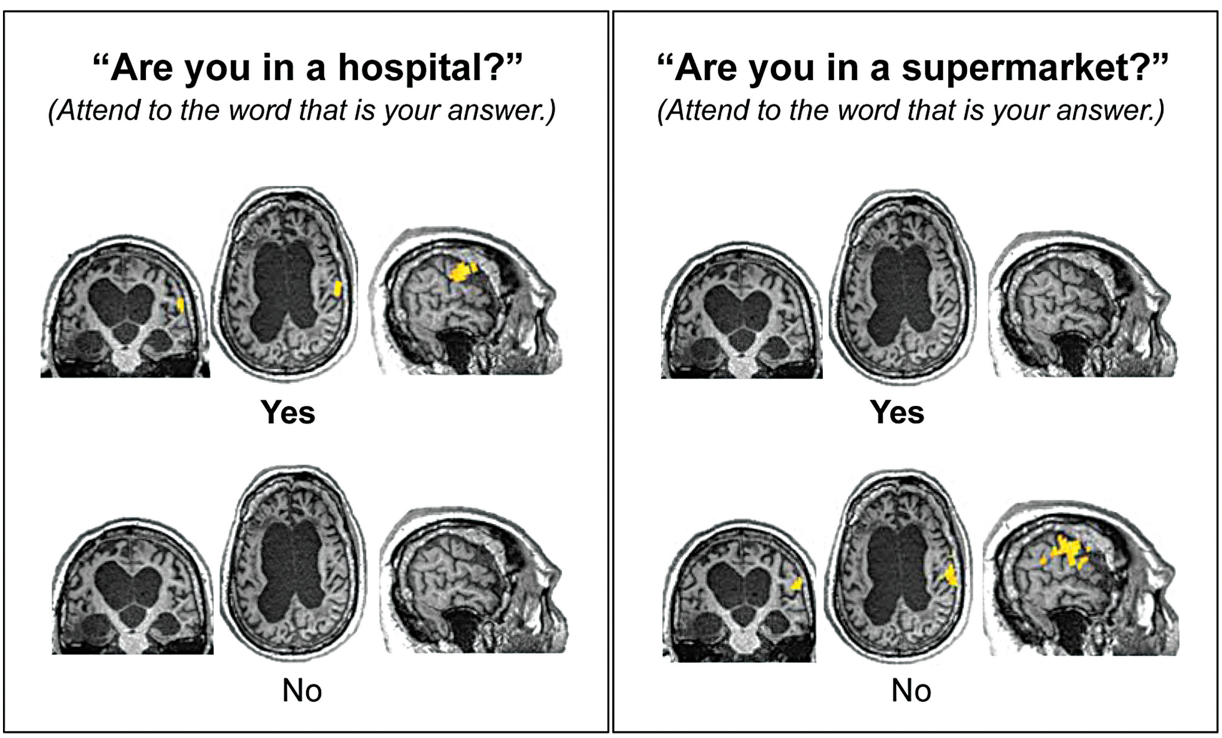

Fig. 2 Command-following and communication scans in a patient clinically diagnosed as being in a vegetative state/unresponsive wakefulness syndrome. Brain activity is overlaid on the patient's native anatomical volume. Selective attention to the answer word (either "yes" [left panel] or "no" [right panel]) during each communication scan was observed within regions of the patient's attention network, particularly the precentral or motor region. (Image adapted from Naci et al.[19])

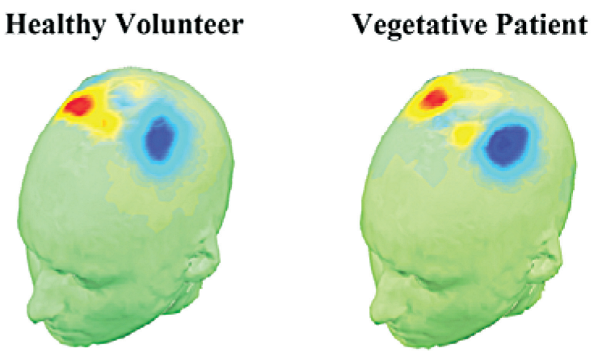

Fig. 3 Conscious responses to stimuli in a patient who fulfilled all the clinical criteria defining the vegetative state/unresponsive wakefulness syndrome, revealed by electroencephalography (EEG). The EEG response during a motor imagery task shows clear foci over the hand and toe motor areas, which are formally identical to a healthy control participant and a vegetative/unresponsive state patient. (Image adapted from Cruse et al.[12])

between etiology and neuroimaging outcomes must be interpreted with caution for individuals, as patients in both traumatic and nontraumatic groups vary widely in etiologies, neuropathology, and clinical features and some nontraumatic brain-injured patients have returned positive outcomes in other studies.[12,24,25]

In a further refinement of their paradigm, Cruse et al required participants to simply try to move their hands.[12,23] Hundred percent of the healthy volunteers showed reliable event-related desynchronization and event-related synchronization responses.[13] Moreover, one of the patients who had been repeatedly diagnosed as VS/UWS for 12 years[8] showed reliable modulations of sensorimotor β rhythms in response to commands to try to move, which were classified at a single-trial level.[13] This is the first published case of a clinically VS/UWS patient who has demonstrated awareness with two independent brain-based technologies (fMRI and EEG), in the absence of any behavioral/clinical evidence of awareness.[9] Other teams[11] and more recent studies[26,27] have continued to demonstrate the feasibility of bedside EEG paradigms for detecting covert consciousness.

These studies have demonstrated that willful brain activity can serve as a proxy for command-following. Indeed, cohort studies show that a significant minority of patients (14–19%)[13,28] clinically diagnosed as VS/UWS can, nevertheless, demonstrate covert awareness through cognitive brain responsivity in neuroimaging tasks. The nosological distinction of "cognitive motor dissociation" (CMD) has been proposed to describe this subset of patients, who meet the behavioral criteria for the diagnosis of VS/UWS but show neuroimaging evidence of conscious awareness.[29] Alternative labels include "covert" or "hidden" consciousness and "functional locked-in syndrome."[21,30] However, even in such responsive patients, the extent of preserved mental life—or the contents of conscious experience including sensations, emotions, and cognitive abilities—that can be ascertained from performing mental imagery tasks or answering binary "yes/no" questions is limited.

Identifying Covert Cognition and Consciousness with Naturalistic Paradigms

Naci at al[25] developed an entirely different approach for understanding the preservation of mental life in patients with DoC. They used a plot-driven naturalistic narrative—a highly suspenseful brief movie—to capture attention without instruction. This richly evocative stimulus that engages the brain of healthy individuals in similar cognitive processes enabled Naci and colleagues to investigate whether a common neural basis underlies similar conscious experiences in different individuals, and, if so, whether it could serve as a template to examine and interpret such experiences, without recourse to self-report, in behaviorally unresponsive patients. They focused on executive function during the movie as empirical window by which the cognitive aspect of human conscious experience can be quantified. Executive function during the movie was quantified by independent behavioral investigations to track its neural processing in individual participants.[25]

During viewing of a highly engaging short movie by Alfred Hitchcock inside the MRI scanner, healthy participants displayed highly synchronized brain activity in frontal and parietal cortical areas that support executive function.[30,31] The movie's executive demands, that assessed quantitatively in an independent behavioral group with a dual-task procedure,[32] were found to predict activity in frontal and parietal brain regions of the control group who watched the movie inside the scanner.[25] The movie's suspense ratings were obtained from a third independent healthy group, and showed that different individuals had a significantly similar qualitative experience during movie-viewing. Critically, the behavioral descriptor of suspense also predicted activation in the frontoparietal regions. Together, these results provided strong evidence that the synchronization of brain activity in frontal and parietal regions across individuals underpinned their similar experience. In order words, the typical frontoparietal brain activity that could be predicted in each individual from the rest of the group represented a reliable neural signature of the individuals' similar cognitive experiences during the movie.

Naci and colleagues used this approach to examine conscious experiences in two behaviorally unresponsive patients, as they viewed the same Hitchcock movie.[25] One of the patients, who had remained largely behaviorally unresponsive (i.e., exhibiting only intermittent visual pursuit) for 16 years, demonstrated a highly similar brain response to that of the three independent control groups. Behaviorally, the patient has received a diagnosis of either VS or MCS− (when visual pursuit could be detected), in repeated bedside assessments with the JFK Comma Recovery Scale – Revised (CSR–R).[33] By contrast to these clinical diagnoses, the patient's brain activity in frontal and parietal regions was tightly synchronized to the executive demands of specific events in the movie (►**Fig. 4**, Patient 2). The patient's brain activity suggested that he could consciously and continuously engage in complex thoughts about real-world events unfolding over time. Critically, it suggested that his moment-to-moment perception of the movie content, as well as his executive function during the plot, was highly similar to that

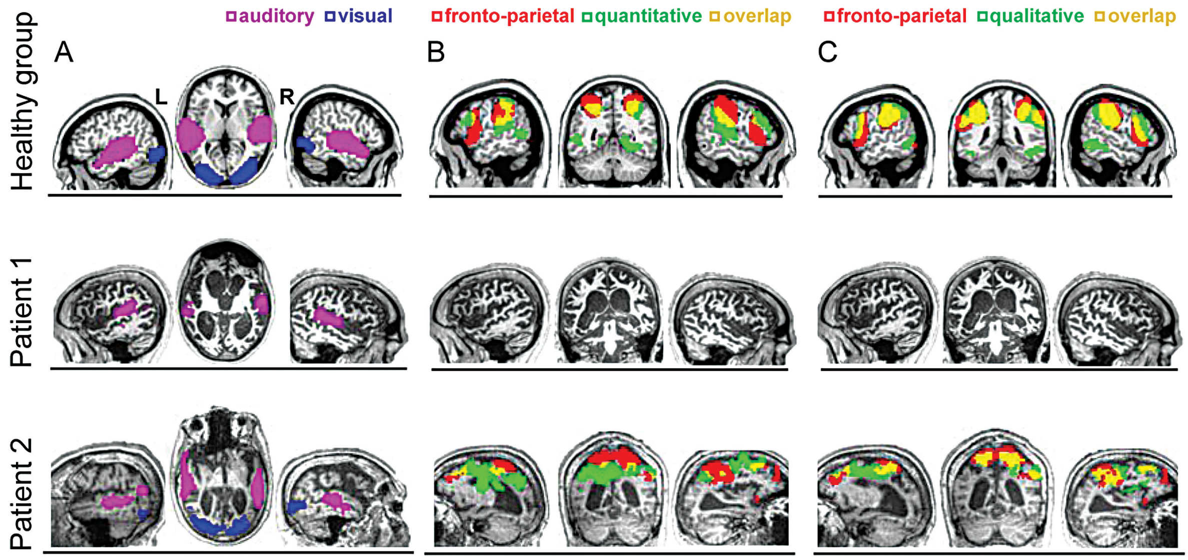

Fig. 4 Decoding executive function in one patient thought to lack consciousness. *Healthy group*: (**A**) Group-level auditory (purple) and visual (blue) responses while watching a suspenseful movie. (**B–C**) The healthy group's activity predicted by the quantitative (**B**)/qualitative (**C**) executive measure (green) is overlaid on the group frontoparietal responses (red); overlap areas are displayed in yellow. *Patients*: (**A**) The healthy group's auditory and visual responses predicted significant activity in Patient 1' and Patient 2's auditory (purple) cortex, and Patient 2's visual (blue) cortex, respectively. The quantitative (**B**) and qualitative (**C**) executive measures predicted activity (green) in Patient 2's frontal and parietal regions. Overlap with activity predicted by the healthy group's frontoparietal responses (red) is displayed in yellow. (Image adapted from Naci et al.[25])

of each and every healthy participant. Despite a similar behavioral profile, similar responses were not observed in the second patient (►**Fig. 4**, Patient 1).

A limitation of this audiovisual paradigm is that sustained visual fixation and tracking are not preserved in most patients who have a VS/UWS diagnosis[34] and this is required to fully experience a movie. To address this limitation, Naci and colleagues[34] developed an auditory-only task, using the auditory excerpt from an early and suspenseful section of the movie "Taken," to investigate executive function. 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 rather that they engage attention naturally to understand the unfolding narrative. Highly correlated activity patterns, including frontoparietal regions, were recorded at the single-subject level in 15 healthy participants. In a different study, Naci and colleagues[24] showed that story-related activity in these frontoparietal regions was extinguished when consciousness was abolished with deep anesthesia, demonstrating that activity in these regions required conscious awareness. Together, these results provided strong evidence that this audio story paradigm is suitable for investigating executive function in behaviorally unresponsive patients, who may have impaired vision but preserved auditory function.[34]

Preservation of Mental Life Revealed by Neuroimaging Paradigms

The successful completion of the movie/audio-story tasks provides evidence for covert narrative capacity—or the ability to understand complex, real-world stories that evolve over time.[35] This can reveal a great deal about the preserved cognition and conscious experience of behaviorally unresponsive patients thought to be in a VS/UWS.[36–39] The command-following paradigms that we have discussed, whether mental imagery or selective attention, tap into several preserved functions including language comprehension, working memory, long-term memory, and selective and sustained attention to external stimuli. Covert narrative capacity, in addition to the capacities shared with the command-following paradigms, provides evidence for preserved executive function. Furthermore, other complex composite mental faculties can be inferred from covert narrative capacity. In the brief movie by Alfred Hitchcock,[25] we see a young boy playing with his uncle's revolver in public, unaware of his power and danger. Naci and colleagues[25] found that the brain responses of one patient to the movie suspense ratings provided by healthy controls were the same as that of every healthy individual, suggesting that the patient was having an affective experience similar to that of a healthy participant. Additionally, comprehension of complex narratives frequently relies on "moral reasoning" or the process of determining whether a particular action is right or wrong.[40] Naci and colleagues found that the suspense ratings in scenes where the gun was pointed at the boy's mother was higher than in those portraying other characters, suggesting that participants attributed a higher moral salience to the child's mother, perhaps reflecting an appreciation of the moral significance of the familial relationship that was absent in the character's other interactions. Like those of the healthy participants, the patient's brain response was highly sensitive to the plot's moral implications, suggesting that his experience of the film may have been shaped by similar moral considerations. Finally, the experience of suspense is supported by future-directed cognitive processes, including anticipation and prediction about uncertain future outcomes.[41] If a patient is capable of conceiving a series of events as a cohesive narrative, or perceiving one event as following from another in a meaningful way, they may similarly be capable of organizing their own experiences according to a temporally coherent structure. Therefore, rather than existing merely "moment to moment," such a patient may be capable of reflecting on and interpreting the events of their own life in light of their past experiences and potential future experiences.[35] These composite mental faculties involved further abstraction from the study data, and therefore required direct investigation in follow-up studies. In summary, when compared with command-following paradigms,[8,12,13,15] the naturalistic paradigm allows for broader and further reaching inferences for understanding the preserved mental life of behaviorally unresponsive patients (►**Table 1**).

Methodological Considerations

A proportion of patients with DoC may not be able to demonstrate command-following or covert narrative capacity in neuroimaging tasks, and, indeed, clinical prevalence is a topic of current empirical investigation. It is likely that the determination of clinical prevalence will be susceptible to limitations in sensitivity and specificity endemic to neuroimaging-based assessment of mental content.[42] For example, of those patients who show negative results on neuroimaging tasks, a proportion will be false negatives, and, therefore, caution must be exercised when interpreting such results. Several factors can cause a negative result, and it is often impossible to determine whether any of these is relevant for any given patient. These include fatigue at the time of testing, and thus inability to engage with task instructions or stimuli, or impaired cognitive resources, leading to inability to perform the task. Notably, brain-injured patients often have impaired attention, which may limit their ability to comply with task instructions.[43–45] The discrepancy between the high proportion of unresponsive patients, who are routinely misdiagnosed through bedside assessments (~43%)[6] and those who are able to demonstrate brain-based command-following (14–19%),[12,46] suggests that command-following neuroimaging paradigms are subject to this limitation. By contrast, the naturalistic approach by Naci and colleagues[25] is unconstrained by any task commands; rather, it captures attention naturally, and, therefore, might be more effective for detecting conscious awareness in patients who lack the necessary cognitive resources for carrying out structured tasks in the scanner. Furthermore, multimodal assessments that tap into different sensory modalities (audiovisual, auditory, somatosensory[47]) will likely increase the chances of revealing spared cognition and reduce the rate of false-negative results.[48,49] It is also worth noting that, in some cases, an absence of activation to a specific task can be observed even in healthy individuals. Thus, a negative neuroimaging result provides no additional information beyond the patient's clinical assessment at their bedside.

Caution must also be exercised when interpreting significant positive results that do align with a priori predictions. Spurious positive results in patients can sometimes be generated from neuroimaging analyses, such as, for example, from the normalization of a patient's individual brain to the healthy controls' template.[50,51] Some of the aforementioned paradigms have been optimized to sidestep this issue. For example, the naturalistic paradigm[24,25,34,35] does not involve normalization to a healthy template, nor does it statistically constrain the patient's expected brain activity based on the localization of the effect in healthy controls. Instead, the time course of brain activity in healthy controls builds a strong prediction for the temporal evolution of brain activity in patients, should they retain covert awareness. Drawing comparisons in the temporal domain enables direct relation of the healthy controls' activation to that of brain-

Table 1 Covert cognitive faculties of behaviorally nonresponsive patients that can be revealed by fMRI paradigms

Paradigm	Task	Covert cognitive faculties
Command-following	Motor imagery instructions: Imagine playing tennis; imagine navigating; imagine swimming	Language working memory Long-term memory Mental imagery Sustained attention to internal imagery
	Selective attention instructions: attend to the word "yes" or "no"	Language working memory Long-term memory Selective attention to external stimuli Sustained attention to external stimuli
Covert narrative capacity	Movie watching instructions: pay attention to the movie on the screen	Language working memory Long-term memory Selective attention to external stimuli Executive function Affective experience Theory of mind Moral discrimination Future-oriented thinking

Source: Image adapted from Naci et al.[35]

injured patients, while reducing the likelihood of spurious positive results compared with other paradigms.[34] Although drawing conclusions from patients' brain activity localized in regions other than the controls' is challenging, significant activation that is constrained to an a-priory predicted temporal profile and that reflects stimulus-induced cognitive demands is likely to reflect reorganization after brain injury. Spatially displaced brain activation that does not meet these conditions is harder to interpret according to rigorous neuroscientific criteria and may be driven by noise.

The aforementioned factors behind false-negative and false-positive findings may manifest in different ways across studies using different paradigms, or even the same paradigm under different testing and analyses conditions in different laboratories. These challenges to replication are at the heart of current scientific debate about replication more broadly, pertaining to all sciences. In the DoC context, the development of consensus guidelines on standardizing testing parameters and data analyses pipelines will be instrumental for increasing the robustness of these assessment protocols for clinical use.

Noncognitive Approaches to Detecting Neural Correlates of Conscious Processing

A different approach to probing consciousness in unresponsive patients has focused on physiological signatures rather than the assessment of specific cognitive abilities that require consciousness. One prominent component of event-related potentials (ERPs; electrical potentials related to events/stimuli) that has been widely investigated in EEG studies of unresponsive DoC patients is the P300. This ERP component is often investigated in the context of the so-called oddball paradigm, in which rare deviant tones are presented among frequent standard tones and stand out as "oddballs" that generate a reliable P300, at local (within trial) or global (across trials) time scales. A key paradigm using this phenomenon in consciousness research is called the "Local-Global" paradigm.[52] Although detection of local regularity can occur without awareness, detection of global regularity is highly correlated with consciousness.[52–54]

A more recent approach has used direct stimulation of the brain using transcranial magnetic pulses delivered to the cortex. Using an EEG measure called the "perturbational complexity index" (PCI), the complexity of the response is captured, which can reveal the functional connectivity in its temporal dynamic dimension. Using the PCI index, it is possible to estimate the level of consciousness in single individuals with great accuracy in different settings (i.e., sleep, anesthesia, and following brain injury).[55,56] While the majority of patients clinically diagnosed as VS/UWS fall below a cut-off complexity value (indicating no consciousness), a significant minority are above, suggesting that these individuals are examples of CMD. While this approach cannot reveal cognitive capacities, follow-up with the aforementioned cognition-based fMRI and EEG paradigms could probe the preserved mental life in specific patients who show a high PCI value despite their VS/UWS diagnosis.

Detecting Consciousness in *Acutely* Brain Injured Patients

The body of research developed in the past 15 years has demonstrated that neuroimaging is a highly sensitive tool for uncovering covert cognition and awareness in behaviorally unresponsive patients with chronic DoC. Similarly, a proportion of patients with acute DoC may retain preserved covert cognition and awareness, despite their apparent unresponsiveness. Even though the exploration of consciousness in the acutely brain-injured patient is in its infancy, recent studies have shown that the detection of CMD is possible in the intensive care unit (ICU). For example, Edlow and colleagues[27] found that three patients in the ICU (7–15 days postinjury), who were clinically diagnosed as lacking consciousness, demonstrated the ability to follow commands via functional neuroimaging by willfully modulating their brain activity according to instruction (motor imagery of playing tennis or spatial navigation). A fourth patient, who had severely limited behavioral responsivity warranting a clinical diagnosis of MCS – , was also classified as CMD based on functional MRI responses consistent with command-following.

However, because imaging tests can be less easily repeated in acute patients and transport-related risks are present,[57] markers derived from resting-state EEG are another possibility for detecting covert awareness in the ICU context. One recent study found a correlation between EEG features (spectral, complexity, and connectivity measures) and level of consciousness in ICU patients.[58] In another study, Claassen and colleagues[59] applied machine learning to EEG recordings to detect brain activation in response to commands that unresponsive ICU patients were given to move their hands. In 15% of patients, such activation could be detected by EEG, and within that group, 50% improved to the point that they were able to follow commands before discharge. At 12 months, 42% of these patients had a Glasgow Outcome Score E[60] level of 4 or higher, denoting the ability to function independently for 8 hours. This study suggests that imaging in the ICU may have prognostic as well as diagnostic value. Further supporting this idea, Sokoliuk and colleagues[61] used a novel method, whereby the synchronization of EEG activity with the rhythm of phrases and sentences is indicative of speech comprehension, to show that the outcome of acutely brain-injured patients significantly correlated with the strength of their speech comprehension during the acute phase.

These studies have generated a renewed interest in using brain–computer interfaces (BCIs; ►**Fig. 5**) as a method for interacting with unresponsive ICU patients who harbor covert awareness. BCI technology has the potential to significantly increase patient autonomy,[62] allowing more efficient pain management, as well as better interaction with the external environment (e.g., bed position, call button, lights, and television). See the article by Rohaut et al[29] for a review of opportunities and challenges of BCI systems in the ICU context.

Ethical Implications

In the last few years, neuroimaging and EEG-based methods have been brought to bear on one of the most complex and

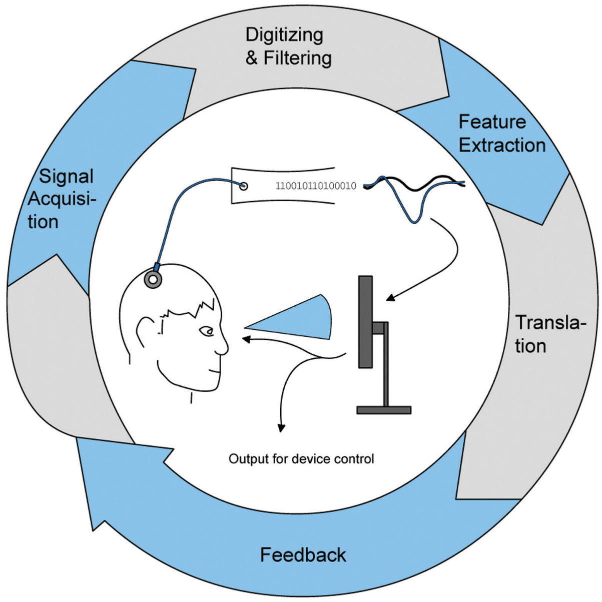

Fig. 5 Schematic representation of a brain–computer interface (BCI) system. The BCI cycle starts with the user engaging in a task in the presence or absence or sensory stimulation. The resulting output is preprocessed and analyzed for specific features that signal the user's intent, and translated into a command, which brings about a state change of the BCI system. This is fed-back to the user, for example, through a visual display. This cycle can be repeated iteratively to achieve online communication between the operator and BCI user. (Image adapted from Naci et al.[77])

challenging questions in clinical medicine, that of detecting residual cognitive function, and even covert awareness, in patients who have sustained severe brain injuries. Studies 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. This work is affecting clinical medicine and challenging the classical taxonomy of DoC.[1,63–65] The recent updating of the American Academy of Neurology (AAN) practice guideline,[66] with a recommendation that functional neuroimaging protocols be used to assess consciousness in severely brain-injured patients, when behavioral responses are ambiguous or absent, represents a significant milestone toward their widespread clinical use. Similarly, the European Academy of Neurology recently recommended that EEG-based techniques and functional neuroimaging should be used alongside and integrated with standardized clinical evaluation for multimodal evaluation of patients with DoC.[67]

This work underscores our moral obligations to probe residual consciousness and to seek the most accurate prognosis possible in all cases.[68] Furthermore, evidence of covert awareness in *some* patients presents a moral imperative to redouble our efforts for improving the quality of life and standard of care for *all* patients with DoC.[69–71] Recent work has proposed that both the patients' "subjective" well-being—how good or bad experience is on a moment-to-moment basis —and "evaluative" well-being—subsequent assessment of those experiences—should be considered and maximized to any extent possible.[72] Critically, detection of awareness should not be equated to changes in well-being in the absence of a clear understanding of the constituents of well-being for any particular patient. A novel assessment of quality of life, tailored to chronic DoC patients,[73] has identified physical pain, communication/inclusion in decision-making, and personal relationships as dimensions of primary importance that should be targeted in future interventions to facilitate recovery and quality of life in these patients.

For comatose patients, robust prognostic indicators of neurological recovery are desperately needed.[74] Neuroimaging research to ascertain the presence of covert awareness and its relationship to subsequent recovery of function could have profound implications for patient prognosis, treatment, and end-of-life decisions. However, any potential benefit to the patient arising from the acknowledgment of their current covert cognition, awareness, and any prognostic indicators is possible only if researchers can share and discuss the results of individual patients. Therefore, ethical guidelines for the dissemination of research results to surrogate decision makers and medical teams are urgently needed.[75,76] Additionally, as aforementioned, consensus guidelines for the standardization of testing parameters and data analyses pipelines across different groups are necessary to ensure reliability and robustness of these assessment protocols for clinical use.

Conflict of Interest
None declared.

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