Original Investigation

Making Every Word Count for Nonresponsive Patients

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IMPORTANCE Despite the apparent absence of external signs of consciousness, a significant small proportion of patients with disorders of consciousness can respond to commands by willfully modulating their brain activity, even respond to yes or no questions, by performing mental imagery tasks. However, little is known about the mental life of such responsive patients, for example, with regard to whether they can have coherent thoughts or selectively maintain attention to specific events in their environment. The ability to selectively pay attention would provide evidence of a patient's preserved cognition and a method for brain-based communication, thus far untested with functional magnetic resonance imaging in this patient group.

OBJECTIVE To test whether selective auditory attention can be used to detect conscious awareness and communicate with behaviorally nonresponsive patients.

DESIGN, SETTING, AND PARTICIPANTS Case study performed in 3 patients with severe brain injury, 2 diagnosed as being in a minimally conscious state and 1 as being in a vegetative state. The patients constituted a convenience sample.

MAIN OUTCOMES AND MEASURES Functional magnetic resonance imaging data were acquired as the patients were asked to selectively attend to auditory stimuli, thereby conveying their ability to follow commands and communicate.

RESULTS All patients demonstrated command following according to instructions. Two patients (1 in a minimally conscious state and 1 in a vegetative state) were also able to guide their attention to repeatedly communicate correct answers to binary (yes or no) questions.

CONCLUSIONS AND RELEVANCE To our knowledge, we show for the first time with functional magnetic resonance imaging that behaviorally nonresponsive patients can use selective auditory attention to convey their ability to follow commands and communicate. One patient in a minimally conscious state was able to use attention to establish functional communication in the scanner, despite his inability to produce any communication responses in repeated bedside examinations. More important, 1 patient, who had been in a vegetative state for 12 years before the scanning and subsequent to it, was able to use attention to correctly communicate answers to several binary questions. The technique may be useful in establishing basic communication with patients who appear unresponsive to bedside examinations and cannot respond with existing neuroimaging methods.

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Editorials

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A proportion of patients who survive severe brain injury are rendered behaviorally nonresponsive or exhibit very limited responsivity to commands administered at the bedside by the clinical staff. At the most extreme end of this spectrum, patients appear to be awake but show no signs of awareness of themselves or of the environment in repeated clinical examinations. Patients with this behavioral profile, particularly signs of wakefulness (ie, periodic eye opening and closing) in the absence of signs of awareness of themselves or of the environment, are clinically diagnosed as being in a vegetative state. Some patients may remain indefinitely in a vegetative state. Other patients, as they recover their ability to demonstrate inconsistent but reproducible signs of awareness, are said to progress to a minimally conscious state.[1] The clinical assessment of both patient groups is particularly difficult because of its reliance on the subjective interpretation of inconsistent behaviors, which are often limited by motor constraints.[2,3] It is well established that misdiagnosis occurs frequently in this patient group, with up to 40% of patients being diagnosed as in a vegetative state when they are, in fact, (minimally) aware.[4-6]

Although a clinical vegetative state diagnosis implies lack of consciousness and cognition, this is not necessarily always the case. Several recent neuroimaging studies have demonstrated that, despite the apparent absence of external signs of consciousness, a significant small proportion of behaviorally nonresponsive patients with disorders of consciousness can respond to commands by willfully modulating their brain activity according to instruction.[7-11]

Despite these advances, little is known about the mental life of such patients with regard to whether they can have any coherent thoughts. One fundamental mental function, critical for coherent thinking, is the ability to pay attention. Two different aspects of attention, *selective attention* (the ability to attend selectively to a stimulus while ignoring other potentially irrelevant ones) and *sustained attention* (the ability to maintain attention on a set of stimuli for prolonged periods), are often intertwined in the execution of everyday tasks. Attention fluctuates widely over time in patients with disorders of consciousness,[12,13] but to our knowledge, these 2 dimensions of attention have not been tested directly with functional magnetic resonance imaging (fMRI) in individual patients. More important, any given nonresponsive patient who can selectively sustain attention to events in his or her environment may be able to use it to convey conscious awareness and communicate answers to questions by simply attending to specific words (eg, yes or no), as has been shown for healthy controls.[14]

The most successful fMRI methods deployed to date to detect awareness in patients with disorders of consciousness have used mental imagery tasks (ie, motor and spatial navigation imagery) to elicit brain-based communication responses.[7-11] Patient cohort studies[9,10] have found that a small proportion (9%-19%) of nonresponsive patients were able to generate meaningful brain responses that confirmed that they were, in fact, performing the mental imagery task as requested. Apart from a genuine lack of awareness, other factors may explain the lack of response in some patients. Specifically, it is possible that some patients who are misdiagnosed as being in a vegetative state and are, in fact, conscious are nevertheless unable to perform the mental imagery tasks.[10] Indeed, a proportion of the healthy population is not able to produce robust brain activity with motor imagery tasks.[15] Another possibility is that, due to the brain injury, a patient may lose the ability to perform mental imagery and/or related precursory mental processes.[10]

In summary, although a large proportion (approximately 40%) of behaviorally nonresponsive patients are routinely misdiagnosed with bedside assessments,[4-6] only some of these patients have been shown to respond with existing neuroimaging methods. Thus, complementary tests that elicit volitional brain responses by recruiting alternate mental functions, such as attention, are needed to maximize the chances that any nonresponsive patient who retains covert awareness will be able to achieve brain-based communication. In this study, we tested whether selective auditory attention can be used as a proxy for behavior in nonresponsive brain-injured patients. As a proof of principle, we asked whether 2 patients in a minimally conscious state and 1 patient in a vegetative state could selectively pay attention, thereby conveying their ability to follow commands and communicate answers to binary (yes or no) questions.

Methods

Patients

The study was performed on 3 patients with severe brain injury. Ethical approval was obtained from Western University's Health Sciences Research Ethics Board. Informed consent was obtained from each patient's surrogate decision makers. The patients were selected based on their clinical diagnoses (ie, vegetative state or minimally conscious state) to form a convenience sample of the population with disorders of consciousness. No previous fMRI data were available for any patient at the time of scanning. Their demographic and clinical data, as well as the results of our fMRI assessments, are summarized in the **Table**. (For detailed narrative clinical histories, see the Supplement.)

fMRI Paradigm

The paradigm was validated in 15 healthy controls[14] before patient testing (eFigures 1 and 2 in the Supplement).

Stimuli

The stimuli were 11 single words (*one*, *two*, *three*, *four*, *five*, *six*, *seven*, *eight*, *nine*, *yes*, and *no*) and 4 sentences: "Is your name Scott?" "Is your name Steven?" "Is your name Mike?" "Are you in a hospital?" and "Are you in a supermarket?"

Command Following

The patient had to either count or relax as he heard a sequence of the sounds. The word *count* instructed the patient to count the occurrences of a target word (*yes* or *no*). In the subsequent trial, the word *relax* instructed the patient to simply relax and pay no attention at this time. The target word (*yes* or *no*) was counterbalanced across the count and relax trials.

Table. Patients' Demographic, Clinical, and fMRI Assessment Data

Patient No./ Sex/Age, y	Diagnosis	Interval Since Ictus, mo	Score on Coma Recovery Scale-Revised	Etiology	Behavior		Imaging	
					Communication and Following	Communication	Communication and Following	Communication
1/M/34	Minimally conscious state	184	9	Hypoxic brain injury	No	No	Yes	Not tested
2/M/25	Minimally conscious state	67	7	TBI	Yes	No	Yes	Yes
3/M/38								
Visit 1	Vegetative state	147	7	TBI	No	No	Yes	Yes
Visit 2	Vegetative state	152	6		No	No	Yes	Yes

Abbreviations: fMRI, functional magnetic resonance imaging; TBI, traumatic brain injury.

The 2 trial types presented the same stimuli and differed only in the instructions. There were 4 trial pairs consisting of a count trial followed by a relax trial or vice versa. Each trial had an on-and-off design: sound (approximately 22.5 seconds) followed by silence (10 seconds) (eFigure 2 in the Supplement). The sound sequence consisted of pseudorandom repetitions of the target word interspersed with repetitions of the digits *one* to *nine*. The digits served as close distractors to the number to be counted. They increased task difficulty during the count trials and aided suppression of any automatic task activity during the relax trials. The scan lasted 5 minutes, including instructions.

Communication

The trials in the communication scan were similar to those in the command-following scan, with 1 exception. Instead of an instruction (count or relax), a binary question preceded each sound sequence. Thus, each patient could willfully choose which word to attend to (count) and which to ignore, depending on his answer to the specific question. One communication scan presented 3 yes or no trials for 5 minutes, including instructions. There were 4 communication scans, each involving a different question.

fMRI Data Acquisition

Patient 1 underwent only the command-following and not the communication scans because of time limitations. Patient 2 underwent all 5 scans (1 command-following scan and 4 communication scans) in the same visit. Patient 3 underwent 3 scans in 1 visit (1 command-following scan and 2 communication scans) and 2 communication scans in a second visit 5 months later.

Patient data were acquired on a 3-T Siemens Tim Trio system at the Robarts Research Institute in London, Ontario, Canada. The paradigm was validated in healthy controls with the same scanner and identical scanning parameters.[14] Task instructions were delivered aurally by using noise cancellation headphones (Sensimetrics, S14; www.sens.com). Functional echo-planar images were acquired (32-channel coil, 33 slices, 3 × 3 × 3-mm voxel size, interslice gap of 25%, repetition time of 2000 milliseconds, echo time of 30 milliseconds, matrix size of 64 × 64, and flip angle of 75°). In total, 150 volumes were acquired for either scan. An anatomic volume was obtained using a T1-weighted 3D MPRAGE sequence (32-channel coil, 33 slices, 1 × 1 × 3-mm voxel size, interslice gap of 50%, repetition time of 2300 milliseconds, echo time of 4.25 milliseconds, matrix size of 64 × 64, and flip angle of 75°).

fMRI Data Analyses

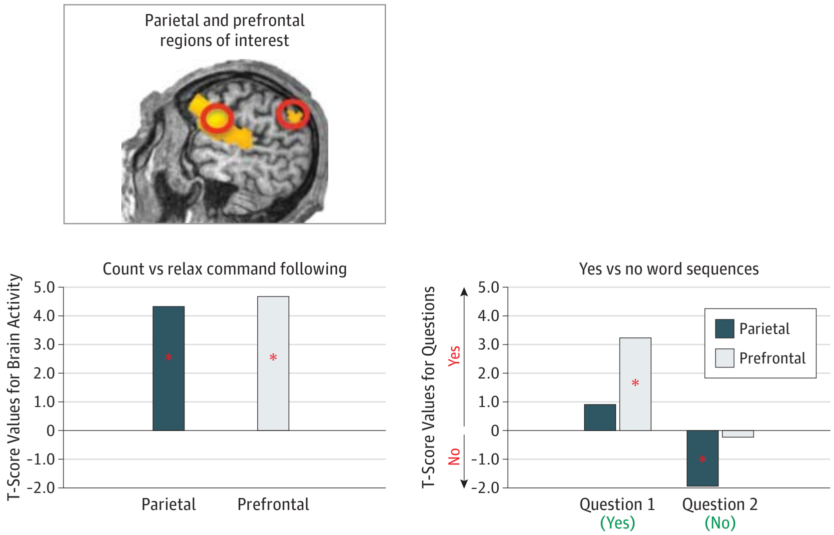
Before the analyses, the first 5 volumes of each scan were discarded to account for the T1 relaxation and the patients' adjustment to the noise of the scanner. The imaging data were analyzed using SPM8 (Wellcome Institute of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Preprocessing was performed with the AA software (www.cusacklab.org) (gaussian smoothing kernel = 8 mm full-width at half-maximum[16]). The data were kept in native space for each patient and not normalized to a template because of large brain morphologic differences between patients.

The general linear model (SPM8) was used to explore effects of interest. Two event types were defined, corresponding to the on-and-off periods in the command-following (count or relax; approximately 22.5 seconds, or vice versa) and communication (no or yes sequence; approximately 22.5 seconds each) scans. The silent period (10 seconds) served as an implicit baseline for all trials. Events for these regressors were modeled by convolving boxcar functions with the canonical hemodynamic response function. Also included in the general linear model were nuisance variables: the movement parameters in the 3 directions of motion and 3 degrees of rotation, as well as the mean of each scan. Linear contrasts were used to obtain subject-specific estimates for the effect of interest.

Region-of-Interest Analyses

For patients 2 and 3, native activations at the fixed-effects level from the count > relax contrast (command-following scan) were used to derive 2 regions of interest for each patient. Each region of interest was defined as a 5-mm sphere with center coordinates at the peak voxel of each of the 2 most strongly activated significant clusters (eTable in the Supplement). These independently defined, patient-specific regions of interest were used to test for significant activations in each communication scan at the fixed-effects level of the yes-no and no-yes contrasts. Contrasts in both directions were performed since we did not have a priori hypotheses about which word the patient would attend. The Marsbar SPM toolbox (http://marsbar.sourceforge.net/) was used to test significance in the region-of-interest activations.[17]

Figure 1. Region-of-Interest Data for 1 Patient in a Minimally Conscious State



The parietal and prefrontal regions of interest are displayed on the patient's native anatomic volume. From left to right, in purple or light purple are the T-score values for the brain activity in the 2 regions of interest during the command-following and localizer scan. By default, these were significant. In black and gray are the T-score values for question 1 and question 2 (contrast yes-no). Positive values represent higher brain activity for yes than for no word sequences and vice versa. Significant T-score values are indicated by a red asterisk. The direction of significant functional activation (ie, yes > no or no > yes) indicated an answer of yes or no. These are displayed at the bottom of the graph. Green indicates a correct match to the factual answers.

Results

Command Following

All 3 patients showed significantly more activation following the instruction to count than to relax (eFigure 3B-D and eTable in the Supplement). Patient 1 showed significant brain activity in the temporal cortex bilaterally, patient 2 in the left frontotemporal and parietal cortex, and patient 3 in the right temporal and precentral or premotor cortex (all results were familywise error corrected). The lateralization observed in patient 3 most likely reflects the extensive cortical atrophy in the patient's left hemisphere. Formally identical stimuli were presented during the count and relax trials. Hence, the significantly different activations between the 2 trial types do not reflect basic sound perception or any other automatic processes; rather, they must reflect the effects of willful allocation of attention. Indeed, in each patient, the significantly active regions observed during basic sound perception differed from those during auditory attention (compare eFigure 3 and eFigure 4 in the Supplement). In summary, each patient's brain activations were task specific (ie, as predicted based on task commands), spatially consistent with (a subset of) activations observed in the healthy controls,[14] and sustained for sufficiently long periods (5 minutes). The significant brain activity observed for each patient during the command-following task confirmed that he understood and followed the commands and was able to pay attention to some words while ignoring others that were irrelevant for the task.

Communication

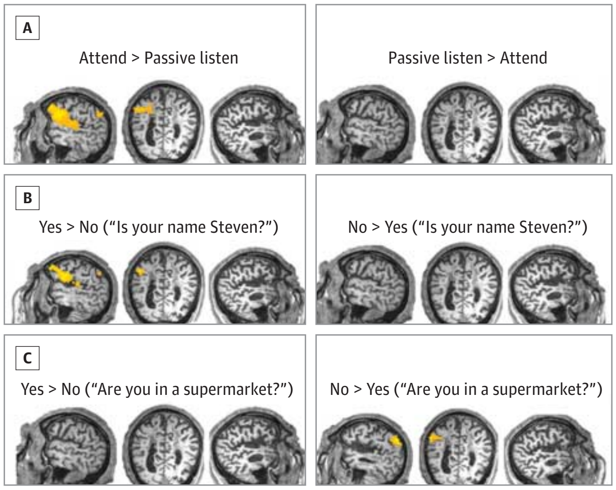
Two of the 3 patients (patients 2 and 3), who were entirely behaviorally nonresponsive in repeated bedside examinations, were tested further with the communication task. In these scans, the patient was asked to willfully determine his focus of attention. In the absence of external cues as to which word the patient would attend to, the functional brain activation served as the only indicator of the patient's intentions. Hence, it was especially important to achieve a high level of confidence in the results to avoid false positives. To ensure conservative testing, we assessed the presence of attention against an a priori hypothesis. This was based on each patient's previously established attention response, on the independent data from his command-following scan. This scan also served to localize each patient's brain attention network and drive the hypothesis that the patient would recruit all or parts of this network when he volitionally attended to answering (yes or no) a question during a communication scan. To maximize detection power, we tested this hypothesis on 2 regions of interest in the 2 most active foci of attention native to each patient.

Patient 2

The patient's functional activation in 2 of 4 communication scans satisfied the region-of-interest analysis (**Figure 1**). For example, when asked, "Is your name Steven?" the patient answered yes by showing significantly more activity for yes than no sequences in the prefrontal region of interest (T-score value = 3.2; $P < .001$). When asked, "Are you in a supermarket?" the patient answered no by showing significantly more activity for no than yes sequences (T-score value = 1.9; $P = .03$) in the parietal region of interest (**Figure 2**B and C; the activations were consistent with the attention foci observed during the command-following scan, Figure 2A). The direction of significant activation (ie, yes > no or no > yes) successfully decoded the answers to each of the 2 questions.

The patient's functional activation in the other 2 communication scans did not satisfy the region-of-interest analysis, not because the incorrect pattern of activation was observed but because no differential activity for the yes and no sequences was found within the predetermined regions of interest. However, for each of these 2 scans, independent whole-brain analysis revealed significant activation consistent with the correct answer to the question, in attention-related brain regions,[14] with different foci from those observed during the command-following scan. In these communication scans, the directions of significant activation in the inferior prefrontal, temporal, and parietal cortices (eFigure 5B and C in the Supplement) correctly decoded the answer to each question.

Figure 2. Command Following and Communication for 1 Patient in a Minimally Conscious State



Command-following (A) and communication (B and C) scans in patient 2, who was clinically diagnosed as being in a minimally conscious state. The brain activity is overlaid on the patient's native anatomic volume. The opposite directions of each contrast (ie, *a* > *b* or *b* > *a*) are shown on the left and right sides of each panel. A, The command-following scan also served to localize the brain foci of attention, unique to the patient. B and C, Selective attention to one of the answer words (either yes or no) during each communication scan was investigated within these regions. Attention to answering questions B (yes) and C (no) significantly activated the frontotemporal and parietal regions, respectively.

Patient 3

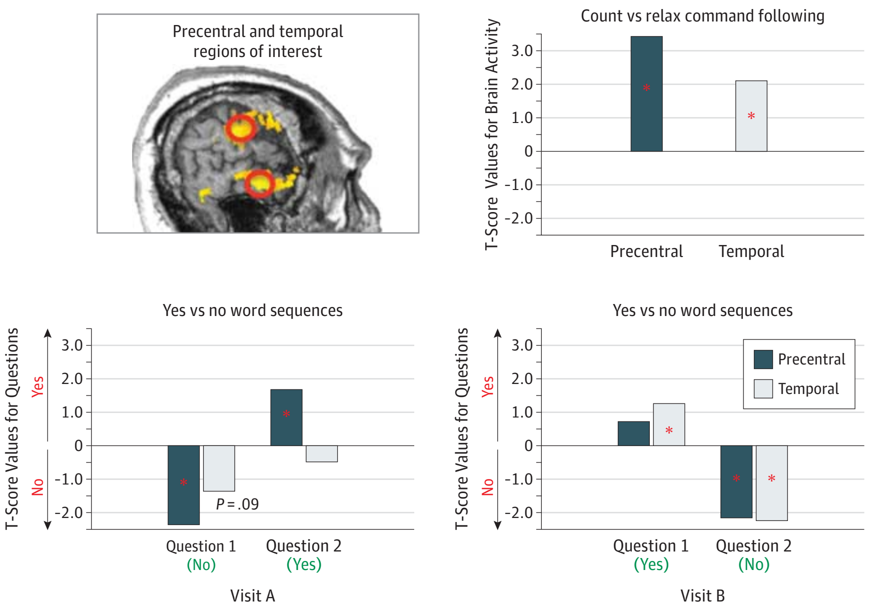
The patient's functional activation in all 4 communication scans satisfied the region-of-interest analysis (**Figure 3**). For example, when asked, "Are you in a supermarket?" the patient showed significantly more activation for no than yes sequences in the precentral region of interest. Conversely, when asked, "Are you in a hospital?" the patient showed significantly more activation for yes than no sequences in the same region (**Figure 4**B and C; the activations were consistent with the attention foci observed during the command-following scan, Figure 4A). The direction of activation (ie, yes > no or no > yes) successfully decoded the answers to all 4 questions.

Discussion

In this study, we present a novel fMRI technique that relies on selective auditory attention for detecting conscious awareness and communicating with behaviorally nonresponsive, brain-injured patients. We demonstrate that 3 patients with disorders of consciousness, 2 of whom were diagnosed as being in a minimally conscious state and 1 as being in a vegetative state, were able to convey their ability to follow commands inside the fMRI scanner by attending to some events while ignoring others, in accordance with instructions. By contrast, we observed extremely limited or a complete lack of behavioral responsivity in repeated bedside assessments of these patients (see the Supplement). These results suggest that some patients who are presumed to mostly or entirely lack cognitive abilities can have coherent thoughts about the environment that surrounds them.

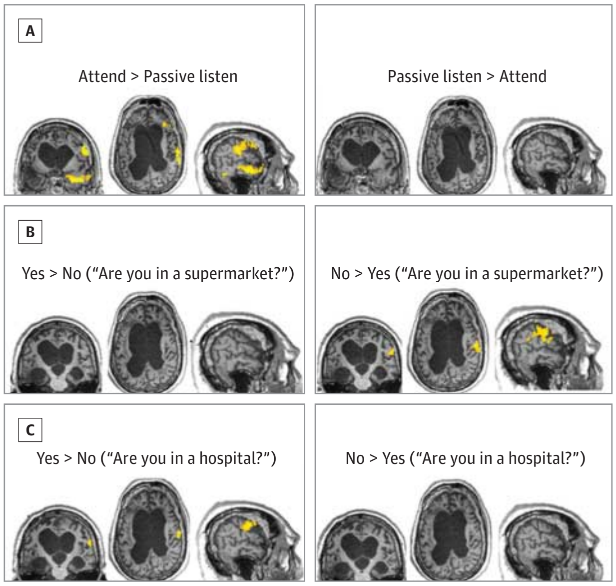
More important, 2 patients who were entirely behaviorally nonresponsive at the time of scanning (1 in a minimally conscious state and 1 in a vegetative state) were able to use selective attention to repeatedly communicate correct answers

Figure 3. Region-of-Interest Data for the Patient in a Vegetative State



The precentral and temporal regions of interest are displayed on the patient's structural scan in the upper left of the figure. From left to right, in blue and light blue are the T-score values for the brain activity in the 2 regions of interest during the command-following and localizer scan. By default, these were significant. In black and gray are the T-score values for question 1 and question 2, for visits 1 and 2 (contrast: yes-no). The same regions of interest were used to decode the answers to the questions in the 2 visits. Positive values represent higher activity (T-score values) for yes than no and vice versa. Significant T-score values are indicated by a red asterisk. The direction of significant functional activation indicated an answer of yes or no. These are displayed at the bottom of the graph. Green indicates a correct match to the factual answers.

Figure 4. Command-Following and Communication Scans for the Patient in a Vegetative State



Command-following (A) and communication (B and C) scans in patient 3, clinically diagnosed as being in a vegetative state. Brain activity is overlaid on the patient's native anatomic volume. The opposite directions of each contrast (ie, *a* > *b* or *b* > *a*) are shown on the left and right sides of each panel. A, The command-following scan also served to localize the brain foci of attention unique to the patient. B and C, Selective attention to the answer word (either yes or no) during each communication scan was investigated within these regions. Attention to the answer in each question (B, no; C, yes) significantly activated the precentral or motor region.

to binary questions in the scanner. In particular, patient 2 had shown no behavioral responsivity before the scanning in repeated bedside assessments by the research team. Independent bedside assessments by the attending neurologist had shown highly limited and inconsistent command-following behavior, which had warranted a minimally conscious state diagnosis. However, bedside testing at the time of scanning again revealed no behavioral responsivity and a low score of 7 on the JFK Coma Recovery Scale–Revised,[18] consistent with a vegetative state diagnosis. Despite the variability of the behavioral response (or lack thereof) observed by the attending neurologist and the research team, it was impossible to establish any form of communication with the patient at his bedside. In contrast, fMRI enabled 2 independent communication sessions, in which the patient was able to use his selective attention to express autobiographical knowledge and awareness of his location in time and space.

The patient's behavioral variability was compatible with a minimally conscious state diagnosis, which, by definition, is marked by highly inconsistent behavior.[1] Furthermore, the patient's inconsistent but task-appropriate functional activation in 2 of the 4 communication scans aligned with this diagnosis and is best explained by his highly fluctuating levels of arousal and attention in the scanner, which are typical for minimally conscious patients.[12,13] These fluctuations in the patient's state may have led to variable task performance and possibly different strategies between the communication sessions.

More important, to our knowledge, we show for the first time that a patient who had been in a vegetative state for 12 years was able to selectively pay attention to some external events in his environment while ignoring others, according to command. Despite his diagnosis, the fMRI approach allowed the patient to establish interactive communication with the research team in 4 different sessions. The patient's brain responses within specific regions were remarkably consistent and reliable across 2 different scanning visits, 5 months apart, during which the patient maintained the long-standing vegetative state diagnosis. For all 4 questions, the patient produced a robust neural response and was able to provide the correct answer 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.

To our knowledge, in this study we establish for the first time that some entirely behaviorally nonresponsive patients can use selective attention to communicate. Future patient cohort studies will determine what proportion of nonresponsive patients can successfully use this technique. Previous electroencephalography methods have used auditory attention[19] to elicit communication responses from minimally conscious and locked-in state patients.[20] However, these have not been applied successfully to entirely nonresponsive patients, such as those in a complete locked-in state[21,22] or a vegetative state. Our results suggest that this fMRI technique may offer novel opportunities to entirely behaviorally nonresponsive patients who cannot use existing methods to communicate. Moreover, this technique assesses selective attention, a basic building block of human cognition, which underlies many complex faculties, including reasoning and, more broadly, information processing. Hence, for any behaviorally nonresponsive patient who can use selective attention as a means for communicating, this method may provide initial screening for more complex abilities, the presence of which may have important ethical and practical implications for the patient's standard of care and quality of life.[23]

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