REVIEW ARTICLE

Functional Neuroimaging Applications for Assessment and Rehabilitation Planning in Patients With Disorders of Consciousness

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ABSTRACT. Giacino JT, Hirsch J, Schiff N, Laureys S. Functional neuroimaging applications for assessment and rehabilitation planning in patients with disorders of consciousness. Arch Phys Med Rehabil 2006;87(12 Suppl 2):S67-76.

Objective: To describe the theoretic framework, design, and potential clinical applications of functional neuroimaging protocols in patients with disorders of consciousness.

Data Sources: Recent published literature and authors' own work.

Study Selection: Studies using functional neuroimaging techniques to investigate cognitive processing in patients diagnosed with vegetative and minimally conscious state.

Data Extraction: Not applicable.

Data Synthesis: Positron-emission tomography activation studies suggest that the vegetative state represents a global disconnection syndrome in which higher order association cortices are functionally disconnected from primary cortical areas. In contrast, patterns of activation in functional magnetic resonance imaging studies of patients in the minimally conscious state show preservation of large-scale cortical networks associated with language and visual processing.

Conclusions: Novel applications of functional neuroimaging in patients with disorders of consciousness may aid in differential diagnosis, prognostic assessment and identification of pathophysiologic mechanisms. Improvements in patient characterization may, in turn, provide new opportunities for restoration of function through interventional neuromodulation.

Key Words: Magnetic resonance imaging, functional; Minimally conscious state; Persistent vegetative state; Rehabilitation.

FUNCTIONAL NEUROIMAGING PROCEDURES are increasingly used in the clinical domain. Recent applications include protocols designed to monitor the natural history of recovery from acquired brain injury and assess the effects of neurorehabilitative interventions. In this article, we discuss the use of functional neuroimaging procedures intended to characterize the integrity of residual cortical networks and the search for neural evidence of cognitive function in patients with disorders of consciousness.

Comparisons between patients with disturbances in consciousness and healthy subjects aim to inform clinical judgments of the potential to sustain awareness when behavioral evidence is lacking or ambiguous. An underlying assumption is that assessment of recovery potential can be enhanced by neuroimaging techniques that show the status of neural systems specialized for essential cognitive and volitional tasks in individual patients. Thus, development of imaging techniques that assess the functional status of unresponsive patients is a primary goal and requires a renewed focus on single-subject neuroimaging studies.

The structural integrity of the injured brain often depends on the specific mechanism of injury, and, therefore, images cannot be grouped across patients as is standard practice for investigations of cognitive systems in healthy volunteers using either positron-emission tomography (PET) or functional magnetic resonance imaging (fMRI) techniques. We address these challenges and discuss technique adaptations associated with passive stimulation, paradigm selection, and individual patient assessments to achieve "zero tolerance for error" and confidence in the results that meets the highest standards of care.

In the sections that follow, we describe our current work involving the development of PET and fMRI protocols for the study of patients diagnosed with the vegetative state and minimally conscious states. We discuss the theoretic framework guiding the design of these studies and review our preliminary results with emphasis on their implications for neurorehabilitation and neurorecovery.

STUDIES OF AUDITORY, VISUAL AND SOMATOSENSORY PROCESSING IN THE VEGETATIVE STATE AND MINIMALLY CONSCIOUS STATE

The Vegetative State as a "Disconnection Syndrome"

In 1987, fluorine-18–labeled deoxyglucose PET studies by Levy et al[1] first showed that patients in a vegetative states suffer from a massive cerebral metabolic dysfunction, estimated to be 40% to 50% of normative values. These results have been confirmed by many other groups in vegetative states of different etiology and duration.[2-6] Compared with cerebral glucose metabolism, cerebral blood flow seems to have a larger interpatient variability in the vegetative state.[1] Cortical metabolism is lower in long-lasting vegetative state than in acute vegetative state,[5] probably because of progressive Wallerian and transsynaptic degeneration. There is no established correlation between cerebral metabolic depression and patient outcome, and brain metabolism may be close to normal in well-documented vegetative patients. It remains controversial

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Supported in part by the National Institute on Disability and Rehabilitation Research (grant no. H133A031713-04), National Cancer Institute Cancer Center Support, Charles A. Dana Fund, National Institute of Neurological Disorders and Stroke (grant no. R21 NS43451), the University Hospital of Liège, Belgium, and the Mind Science Foundation.

No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit upon the author(s) or upon any organization with which the author(s) is/are associated. Laureys is Research Associate at the Belgian National Funds for Scientific Research.

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0003-9993/06/8712S-10981$32.00/0

doi:10.1016/j.apmr.2006.07.272

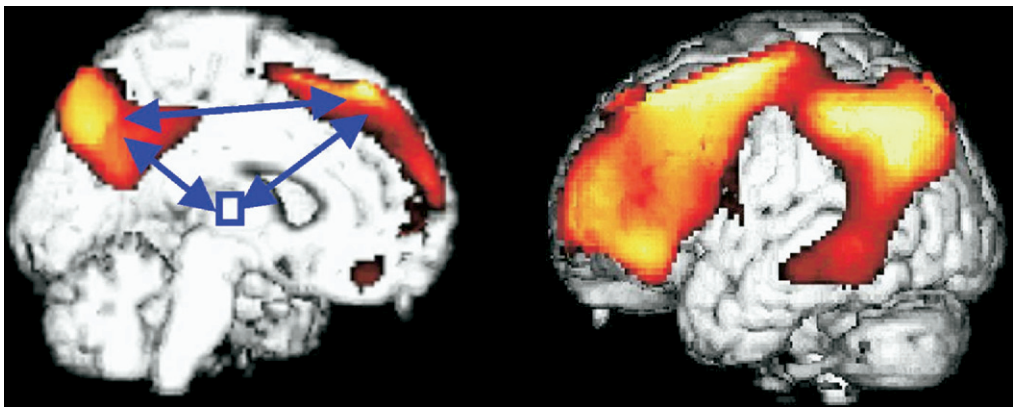

Fig 1. The vegetative state as a "disconnection syndrome." Characteristic of the vegetative state is the metabolic impairment in a wide frontoparietal cortical network encompassing medial and lateral prefrontal and parietal multimodal associative areas. This might be due to either direct cortical damage or to cortico-cortical or cortico-thalamo-cortical disconnections (schematized by blue arrows; the square represents nonspecific thalamic nuclei). Adapted from Laureys et al.[2,30]

whether the observed metabolic impairment in the vegetative state reflects functional and potentially reversible damage or irreversible structural neuronal loss.[3] Rudolf et al[7] argued for the latter, using ^{11}C-flumazenil as a marker of neuronal integrity in evaluating acute postanoxic vegetative patients. However, PET studies in reversible unconscious states such as deep sleep[8,9] and pharmacologic coma (ie, general anesthesia)[10-12] show similar, albeit transient, decreases in cortical metabolism. In the rare patients who have been studied while in a vegetative state and after subsequent recovery of consciousness, PET studies have shown that global cortical metabolic rates for glucose often do not show substantial increases.[4,13,14] Hence, the relation between global levels of brain function and the presence or absence of awareness is not absolute; rather, some areas in the brain seem more important than others for the emergence of awareness.

Voxel-based analyses have identified the common regional pattern of metabolic impairment in the vegetative state and reported systematic dysfunction in a wide cortical network encompassing polymodal associative areas: bilateral prefrontal regions, Broca's area, parietotemporal and posterior parietal areas, and precuneus.[2] This frontoparietal network is known to be important in various functions underlying consciousness such as attention, memory, and language.[15] Interestingly, these brain areas have also been shown to be dysfunctional in other states of wakefulness without awareness characterized by merely "automatic" behavior—albeit transient and much briefer—such as absence seizures,[16,17] complex partial seizures,[18,19] and somnambulism.[20] Not surprisingly, the areas that remain relatively well preserved in the vegetative state are the brainstem's pedunculopontine reticular formation, hypothalamus, and basal forebrain,[21] underlying patients' preserved arousal and autonomic functions. Compared with conscious controls, locked-in patients, and minimally conscious patients, the brain regions that differentiate most from vegetative patients are posterior midline structures (ie, precuneus, posterior cingulate cortex).[22] These areas are among the most active in the "conscious waking state"[23] and are the least active in altered states of consciousness such as general anesthesia,[10,24,25] deep sleep,[8] dementia,[26,27] and Wernicke-Korsakoff's or postanoxic amnesia.[28] This richly connected area is part of the neural network involved in voluntary movement and self-consciousness.[29]

PET studies assessing vegetative patients during and after recovery of consciousness conclude that some patients are unconscious not just because of a global loss of neuronal function but rather because of an altered activity in the frontoparietal cortical network.[13,14] Hence, the number of surviving neurons is not the only critical parameter on which the outcome of vegetative patients depends. As important are the functional integrity of long-range cortico-cortical and cortico-thalamo-cortical connections. Indeed, "functional disconnections" between lateral prefrontal and midline posterior cortices[2] and between nonspecific thalamic nuclei and midline posterior cortices[21] were identified (as shown in fig 1) when patients in a vegetative state were compared with healthy controls. Most important, these altered cortico-thalamo-cortical loops restored near normative values after recovery of consciousness.[30] The mechanisms that underlie this normalization—occurring sometimes after many weeks of massive neuronal metabolic dysfunction—remain putative but could include axonal sprouting and neurogenesis. In our view, the vegetative state is not necessarily characterized by structural cortical damage but should rather be seen a functional cortical disconnection syndrome.

The terms *apallic syndrome* and *neocortical death* have previously been used to describe patients in a vegetative state.[31] It is important to stress that recent functional imaging studies have shown that vegetative patients are not apallic—that is, they still may show preserved activation in islands of functional "pallium" or cortex. In the next section, we summarize the results of recently completed PET studies of changes in regional cerebral blood flow (rCBF) using the oxygen-15–labeled water technique and we demonstrate evidence of important functional disconnections during visual, auditory, and noxious somatosensory stimulation.

Visual Activation

In 1998, Menon et al[32] were the first to use $H_2{}^{15}O$-PET to study visual processing in the vegetative state. They presented photographs of familiar faces and meaningless pictures to an upper-boundary vegetative or lower-boundary minimally conscious postencephalitic patient who subsequently recovered. Although there was no evidence of behavioral responsiveness except occasional visual tracking of family members, the visual fusiform face area showed significant activation. The assessment of complex visual processing in vegetative patients is, however, confronted by a supplementary difficulty with regard to (the absence of) visual fixation in these patients. Hence, visual stimulation needs to be triggered online by infrared eye tracking devices in the scanner. To circumvent this problem, we passively presented simple visual stimuli via goggles through closed eyelids to 5 patients unequivocally meeting the clinical diagnosis of the vegetative state after traumatic (n=2) and nontraumatic (n=3) brain damage. Patients were studied 1 to 3 months after the acute brain insult. The rCBF increases

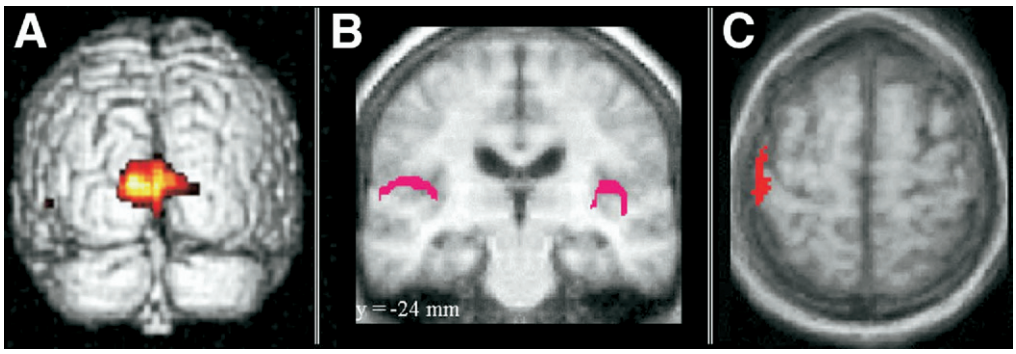

Fig 2. Brain regions, shown in red, that activated during (A) visual, (B) auditory, and (C) noxious stimulation in patients in the vegetative state.

were measured by means of $H_2{}^{15}O$-PET during presentation of pattern flashes (3 scans) compared with darkness (3 scans). Flashes were presented using home-made goggles taped to a thermoplastic face mask adapted to each patient. Goggles contained within each eyepiece a rectilinear grid (8×4cm) of 15 monochromatic red light–emitting diodes, mean peak of 655nm, resulting in maximal retinal field stimulation. Flashes were delivered by a square wave pulse of 5ms in duration at a frequency of 7Hz. Activation profiles were analyzed using statistical parametric mapping. Results showed significant ($P<.001$) stimulation-induced activation in striate cortices in each patient. There was, however, no concomitant activation of higher-order association areas, suggesting that these regions were functionally disconnected from spared primary cortex (S. Laureys et al, unpublished data, 2005). We illustrate these findings in figure 2A.

Auditory Stimulation

In a second study, we[33] presented simple auditory stimuli (loud clicks) to 5 patients in a vegetative state of anoxic origin. In line with the results of the visual activation study described above, auditory stimulation induced bilateral activation of primary, but not associative, auditory cortices as shown in figure 2B. Moreover, functional connectivity assessment showed that the auditory association cortex was disconnected from posterior parietal cortex, anterior cingulate cortex, and hippocampus.[34] Thus, despite a massively reduced resting metabolism (ie, less than half of normative values), primary cortices still seem to activate during external stimulation in vegetative patients, whereas hierarchically higher-order multimodal association areas do not. The observed cortical activation was isolated and dissociated from higher-order associative cortices, suggesting that the observed residual cortical processing in the vegetative state is insufficient to lead to integrative processes thought to be necessary to attain the normal level of awareness.

Noxious Somatosensory Stimulation

The study of pain perception in the vegetative state is not only clinically but also ethically of major importance, especially with regard to end-of-life decisions. Appropriate attention to pain control during withdrawal of artificial hydration and nutrition[35,36] is a common concern of family members. To explore somatosensory processing capacity in the vegetative state, we selected 15 nonsedated unequivocally vegetative patients and administered high-intensity electric stimulation of the median nerve at the wrist. The same level of stimulation was perceived as unpleasant to painful in 15 control subjects. As shown in figure 2C, all 15 patients showed activation of midbrain, contralateral thalamus, and primary somatosensory cortex.[37]

Traditionally, primary somatosensory cortex is considered to be involved in the sensory-discriminative component of pain perception.[38] The affective-motivational and cognitive evaluative components of pain are only partly understood but have been proposed to depend on insular, anterior cingulate, and posterior parietal cortices.[39] None of these regions activated in the 15 vegetative patients during noxious stimulation. Functional connectivity analyses indicated that the observed activation of primary somatosensory cortex existed as an island, isolated from downstream associative areas (ie, secondary somatosensory, polysensory superior temporal, posterior parietal, prefrontal and premotor cortices) considered necessary to subtend conscious awareness.[15] Acknowledging the methodologic limitations of functional neuroimaging, these results provide objective evidence for the absence of pain perception in the vegetative state.[37]

Implications for Neurorehabilitation

Functional neuroimaging cannot (and should not) replace bedside clinical evaluation as the criterion standard for assessment of patients with disorders of consciousness. Nevertheless, it offers an objective method of differentiating brain activity measured at rest and (preferably) during external stimulation. PET[40] and fMRI[41] case reports incorporating complex auditory stimuli have shown large-scale network activation in the minimally conscious state that is not observed in unconscious vegetative patients.

Future studies, using more powerful (and nonionizing) techniques such as fMRI, are needed to assess the temporal evolution of individual patients' somatosensory and cognitive processing. Functional neuroimaging strategies may also aid in the clinical quest to define the upper borders of the vegetative state so that this condition can more reliably be distinguished from the minimally conscious state.[42] At present, much more research and methodologic validation are required before functional neuroimaging can be considered to have evidence-based value in establishing diagnosis or predicting irreversibility in the vegetative state.

Development of Single-Subject fMRI Protocols

Because of risks associated with injections of radioactive tracers, limitations to the number of times a subject can be studied, the relatively coarse spatial resolution, the need for registration to high resolution structural images, and the relatively few PET facilities available for research, imaging of cortical activity associated with cognitive processes has ad-

vanced most rapidly using noninvasive, higher-resolution, and more widely available fMRI techniques.

Functional maps for individual patients aim to identify critical functional specializations specific to that patient. For example, in the case of functional mapping before a surgical procedure, the goal is to identify regions of the individual patient's brain that are used for functions such as motor movements, tactile sensation, language, vision, and audition, which might be at risk because of the location of the surgery. The presence of a space-occupying lesion, long-term epileptogenic condition, or acquired brain injury can modify the foci of functional brain tissue, and normal assumptions of functional specificity do not necessarily apply. In these cases, functional brain maps are acquired at the highest possible resolution to locate eloquent cortex, and this information is integrated into the appropriate treatment plan for the patient.

Price et al[43] developed a battery of fMRI tasks designed to target cortical regions critical to tactile, motor, language, and visual processing. In this battery all functions are repeated using both "active" (volitional) and "passive" (receptive) modes, to ensure that it is applicable to patients with a wide range of symptoms and abilities to comply with task directions. This feature facilitates use in patients with disorders of consciousness where passive stimulation is required. Any subset of these tasks may be selected for specific clinical objectives while retaining the advantages of the standardized procedures with validations based on responses of both healthy volunteers and patients. Thus, objectives of mapping residual cognitive functions with passive stimulation techniques in behaviorally unresponsive patients are served by these prior validations.

Passive stimulation methods can be adapted to study a broad array of somatosensory, linguistic, and cognitive functions and can be easily incorporated into both single-subject and group designs. The specific tasks selected for investigation of these functions are nearly universally applicable and use simple stimuli and both active and passive procedures including manual tactile stimulation, finger-thumb tapping, listening to words, naming objects, and viewing reversing checkerboard patterns.

The aims of these conditions include localization of primary and secondary visual, sensory, and motor cortices and by inference, determination of the integrity of the calcarine cortex, lingual and fusiform gyri, central sulcus, and Broca's and Wernicke's areas. The language areas are redundantly targeted by expressive (active) and receptive (passive) language tasks and by visual and auditory modalities that makes them suitable for use with patients with disorders of consciousness. Comparison of active and passive functional maps serves to validate the procedure.

The fundamental relevance of the language system to recovery from prolonged periods of behavioral unresponsiveness motivates focus on the underlying network for language. Models of the neural correlates for elementary language processes often include left-hemisphere regions involved in a variety of language functions, including Broca's and Wernicke's areas, and are generally consistent with a network model. This network is easily shown using an object naming task and multiple modalities including auditory, visual, and tactile stimuli.[44] A cross-modality conjunction technique is used in which the active neurologic substrate common to all 3 sensory modalities is identified. This technique isolates object naming effects that are observable in all cases and, therefore, not dependent on sensory processes.[43] Results are consistent with the view that the task of naming objects elicits activity from a set of areas within a neurocognitive system specialized for language-related functions. This simple "active" task is clearly similar to the results of the "passive" task of listening to spoken narratives by a familiar adult that can be used with sedated or underaroused patients and suggests that both approaches stimulate a common system.[45]

Pitfalls Associated With Scanning Patients With Disorders of Consciousness

In contrast to population-based studies, where grouped results are taken as evidence of generalizable findings and error is considered to represent variations largely because of individual differences and is thought to be a source of noise, clinical tests focus on the individual for diagnosis, treatment, and follow-up. Thus, the burden for accuracy for the "n-of-1" case is 100% and dictates methodologic adaptations to meet this standard. These adaptations include an extraordinary standard for high image quality as well as clarity, accuracy, and precision for interpretation.

The "zero tolerance for error" standard is further complicated by the special circumstances of many awake patients. Some key factors include functional deficits that challenge execution of the task, high levels of anxiety leading to claustrophobia, inability to remember or perform instructions, excessive head movements, probability of a seizure or other sudden event that interrupts a scan, the effects of therapeutic drugs, and susceptibility artifacts often resulting from a previous surgical bed, implant, or a vascular abnormality. All of these adaptations are relevant to the even more challenging task of imaging patients with disorders of consciousness where passive (rather than volitional) responses are required. They include standardized paradigms and tasks that map most relevant functions, short imaging runs, high-resolution grids, and least number of assumptions for data analysis.

Although a specific task elicits a specific brain map, interpretation of the function that each of the areas contributes usually requires careful follow-up attention and control experiments. For example, in the language listening task it is possible that the activity patterns use specific regions involved in attention, language, audition, imagery, associations, emotion, and memory. Even if each of the repetitions of the task elicit common responses, this diverse group of putative functions can not be disambiguated. Thus, interpretation of the factors that actually elicit the blood oxygenation level-dependent (BOLD) signal remains a pivotal issue.

In the case of patients with disorders of consciousness, the tasks must be limited to passive stimulations, and the most relevant questions center around inferences regarding cognition and awareness. The challenge is to elicit evidence that sheds light on the question of internal cognitive processes and potential for recovery. Options for testing with the advantage of prior validation procedures (above) are tasks that involve listening to spoken language and tactile stimulation of the hands. Tactile stimulation can serve as a procedural control whereas passive listening offers possible information regarding the status of language-related cognitive systems. However, the extent to which the BOLD response in unresponsive or minimally responsive patients can be interpreted similarly to the BOLD response in healthy volunteers must be examined carefully.

Procedure Adaptations: Multiple Short Runs

Under conditions where constant monitoring and assessments are necessary, as with patients who are unaware, imaging runs may need to be repeated because of unexpected events. In these instances the shorter the imaging epoch the better. The trade-off is accuracy and statistical confidence, and both are optimized by increased numbers of acquisitions. One technique that balances these procedural concerns is sometimes referred to as a "double-pass" strategy.[46] Short runs are per-

formed for each task consisting of an initial and ending baseline epoch (minimum of 10 acquisitions each) and a central "activity" epoch. Both runs are identical block designs and if not successfully implemented can be repeated without compromising the other. The optimal analysis rule is that 2 good runs must be acquired for standardized quality assurance. However, in the case that only 1 run is possible, then a map can be produced that offers meaningful results at a reduced level of certainty.

Analysis Adaptations: Confidence Based on Conjunction and Signal-to-Noise

The short-run, double-pass method uses an analysis strategy based on a combination of statistical signal-to-noise models and physiologic repeatability. Statistical analysis of BOLD imaging compares blood flow changes in each voxel during stimulation with changes that occur during baseline periods. Because results may be spurious because of statistical "noise," individual voxels may appear active when they are not. To avoid the possibility of a false positive result, multiple runs are performed and the results obtained on 1 run must be replicated on another. Probabilities of a false positive result using this technique are conventionally adjusted to be in the range of *P* less than .005 to less than .001.[53,47-49] Because of the extensive validation and ease of implementation, the short run, double-pass, method is well suited for imaging patients who are not responsive or cooperative.

Imaging Adaptations: Field Strength and Resolution

Although high field scanners promise advantages in sensitivity, the increased susceptibility to artifacts within the field of view in some cases favors the 1.5-T field strength scanners for patients with implants, surgical beds, and vascular abnormalities for functional maps. These postsurgical conditions often apply to patients with head trauma, thus favoring the conventional strength scanners. Nonetheless, high-quality descriptions of functional systems on individual patients requires high resolution acquisitions for the functional images. In basic science applications, images from multiple subjects are registered together, enabling the anatomy of each brain to be "warped" (ie, structurally modified) into a common space. In traditional group studies with healthy subjects, increased anatomic homogeneity facilitates data analysis and interpretation. However, for a single person with brain injury, this normalization process may smooth out injury-induced distortions in anatomy, increasing the probability that active areas may be missed or misidentified. Images obtained using high-resolution T2* acquisition reduce the need to display the functional maps on an alternative (such as T1) acquisition for anatomic detail. This further avoids misinterpretation caused by image registration and preserves the best description of structure and function for each patient. In patients with traumatic brain injury (TBI) and altered cortical topography, these advantages have particular relevance.

Functional MRI Interrogation of Language and Visual Processing in Minimally Conscious State

In 2002, the Aspen Workgroup established a case definition and diagnostic criteria for the *minimally conscious state* to promote research on the epidemiology, pathophysiology, prognosis, and rehabilitation potential of patients in this condition.[50] Among other priorities, the Workgroup recommended that research efforts investigate the residual cognitive capacity and pathophysiologic substrate underlying minimally conscious state. In this context, 3 of the authors (JTG, JH, NS) established a collaborative partnership with the overarching aim of examining the neurophysiologic and neurocognitive underpinnings of minimally conscious state using specialized fMRI paradigms.

In the initial phase of the research, a modified version of the passive stimulation paradigm described by Hirsch et al[46] was developed to compare the integrity of the language processing network in minimally conscious-state patients with a group of healthy controls. A related objective was to examine the relation between the pattern of cortical activation observed in individual minimally conscious-state patients and behavioral findings obtained at the bedside. Seven healthy volunteers and 2 patients in minimally conscious state, all of whom were right-handed, completed a passive listening paradigm in which subjects listened to audiotaped narratives while undergoing fMRI. Patient 1 suffered a spontaneous left temporoparietal intracerebral hemorrhage approximately 18 months before the study. Patient 2 sustained a large right frontal subdural hematoma and a right-sided paramedian infarct after an assault that occurred 24 months before participation in the study. Both patients occasionally followed commands and demonstrated verbal or gestural communicative responses, but these behaviors were always inconsistent or unreliable.

fMR images were acquired using passive language stimulation. Image acquisition procedures have been previously described.[49] The minimally conscious-state patients listened to the voice of a family member who was instructed to recount a familiar past event such as a vacation or wedding while the healthy volunteers listened to emotionally neutral, paragraph-length prose passages read by nonrelatives. Familiar voices and events were used for the minimally conscious-state patients to facilitate sustained attention. Emotionally neutral content was used with the healthy controls to decrease intersubject variability and constrain activation to language-related structures. Subjects were subsequently exposed to a second condition in which the narratives were time-reversed, rendering them unintelligible. Postscan interviews with the volunteers confirmed that the linguistic content of the reversed narratives was incomprehensible, aprosodic, and apropositional, even though subjects were able to recognize the stimuli as speech. Loci of activation and activation volumes were compared in patients and controls under both conditions.

Summary of Language Processing Studies

Patterns of activation were surprisingly similar between the patients and healthy volunteers. In the forward narrative condition, activation loci clustered in the middle and superior temporal gyri, and in Heschl's gyrus, corresponding to Wernicke's area and primary auditory cortex, respectively. These regions have previously been shown to participate in speech perception and comprehension.[51-53] Controls tended to show bilateral activation of these areas whereas the patients showed primarily unilateral activation conforming to their individual lesion profiles. Activation of the inferior frontal, prefrontal, and parietal cortices was also noted, although more variably and to a lesser degree in the minimally conscious-state patients. Of interest, activation patterns were notably different between the healthy volunteers and the patients in the backward narrative condition. The volunteers activated most of the same temporal lobe structures observed during the forward condition; however, both patients showed very little activation during the backward condition. Figure 3 displays regions of activation in the 2 patients (A, B) and in the healthy volunteers (C) during the

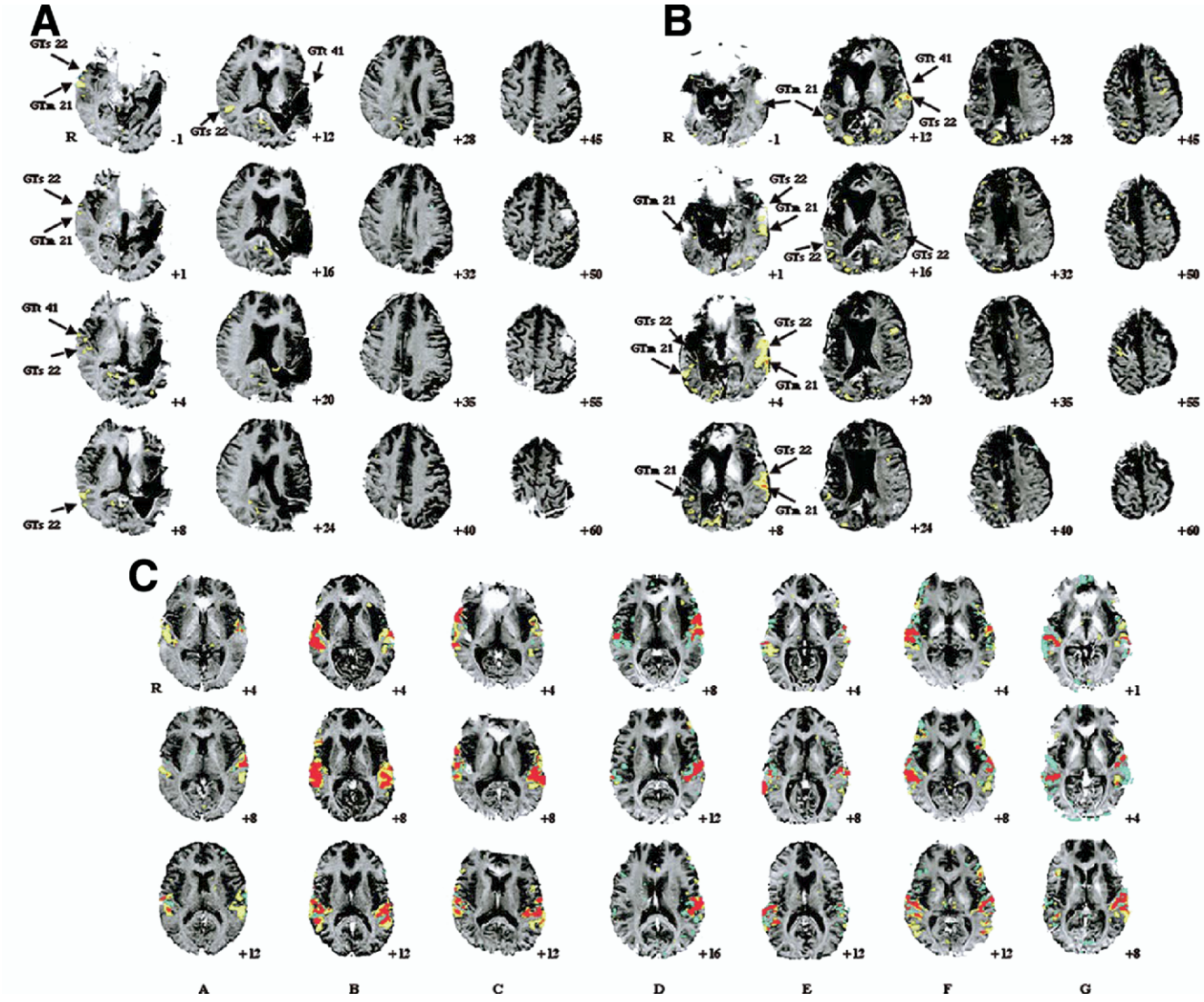

Fig 3. BOLD signal increases during the forward (yellow) and backward (blue) conditions, and with the forward and backward conditions superimposed (red) in (A) patient 1, (B) patient 2, and (C) and healthy volunteers. Arrows indicate active language network foci in the 2 minimally conscious state patients. Adapted with permission from Schiff et al.[49]

forward and backward conditions, and with the forward and backward conditions superimposed. These results suggest that, unlike the healthy volunteers, the minimally conscious-state patients failed to recruit downstream temporal and frontal structures necessary to process the speech-like but unintelligible backward narratives.

Summary of Visual Processing Studies

In the second arm of our research plan, we extended our investigation of residual neural and cognitive processes in minimally conscious state to the visuoperceptual system. As this work has only recently begun, we limit our discussion to the methods used and provide an illustrative case study. In the passive viewing paradigm, subjects are presented with a series of back-projected visual images comprising 3 conditions. Condition 1 consists of a combination of familiar (ie, family members and close friends) and unfamiliar faces, condition 2 includes pictures of hands in various postures, and condition 3 is composed of landscape scenes. Landscapes and hands were selected as contrast stimuli because prior studies with healthy volunteers indicate that these stimuli activate cortical regions distinct from those activated by faces[54,55] and because they are emotionally neutral relative to the familiar faces.

The index case for the passive viewing paradigm was a 38-year-old, right-handed man who sustained a severe TBI after being struck by a car as a pedestrian. The injury occurred approximately 3 months before the patient underwent fMRI scanning. A conventional T1 MRI scan obtained before the fMRI study showed a left frontal subdural hematoma with hypodensities noted in the left anterior and superior frontal, and left temporal lobes. Clinically, the patient met diagnostic criteria for minimally conscious state and showed no evidence of object recognition on standardized bedside assessment of visual function. fMRI images were acquired in a block paradigm that mirrored the one used in the passive language study.

Results showed significant activation of the calcarine and extrastriate cortex (right greater than left) in response to faces and hands, and in the right calcarine cortex and fusiform gyrus during exposure to the landscapes. The selective activation of

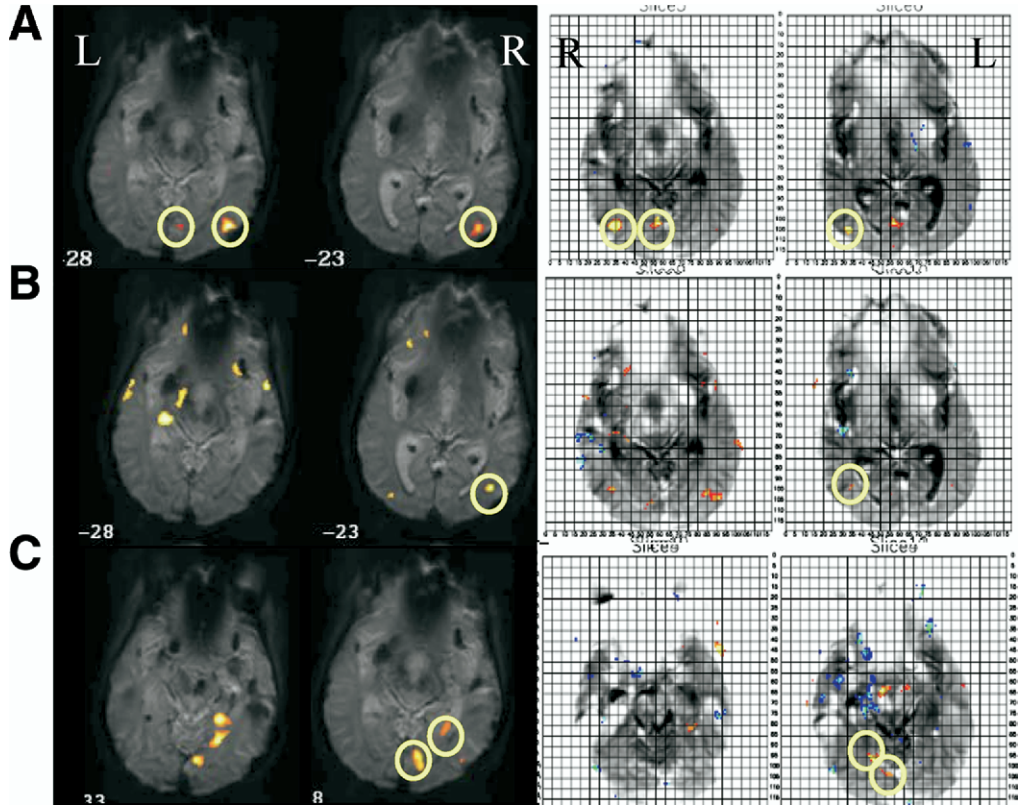

Fig 4. Viewing pictures: Patient 3. BOLD signal increases observed in a minimally conscious-state patient during passive viewing of the (A) faces, (B) hands, and (C) landscapes. Images on the black background were analyzed with Statistical Parametric Mapping. Images on the grid background were identified by a multistage statistical analysis that compared average signals acquired during baseline and stimulation epochs. Circles indicate areas of activation common to both analyses. Abbreviations: L, left; R, right.

these regions is consistent with previously reported findings in face-processing studies.[55,56] Figure 4 shows the visual activation profile by condition as depicted by the results of 2 different data analyses.

Implications for Diagnosis, Prognosis, and Treatment Planning

The results of these studies, although preliminary, suggest a number of potential clinical applications. Although bedside clinical examination remains the criterion standard for establishing diagnosis, fMRI activation profiles may serve an adjunctive diagnostic role when behavioral findings are limited or ambiguous. Patients who demonstrate activation of language network loci in response to linguistic stimulation may be more likely to retain receptive and expressive language functions than those who fail to selectively activate these structures. In such cases, clinicians should be particularly cautious before rendering a diagnosis of vegetative state. fMRI activation profiles may also inform prognosis in patients who show no behavioral evidence of language or visual processing. In such patients, robust activation of cortical networks that mediate language or visuoperception may presage subsequent recovery of these functions. Interestingly, patients 1 and 2 described above both eventually regained expressive speech as well as the ability to consistently follow basic commands. Our third patient, who initially showed no evidence of object recognition, regained the ability to identify and use common objects in a functional manner before hospital discharge. Similar findings were reported by Menon et al[32] who found significant activation of the fusiform face area in a patient in vegetative state who later showed clearly discernible signs of visual recognition of objects and people.

The fMRI findings may also provide guidance in rehabilitation planning. In patients with disorders of consciousness, it is often difficult to determine if the absence of command-following is due to impaired arousal, aphasia, akinesia, or motor impairment. The approach to treatment may differ considerably depending on which of these disorders accounts for the failure to follow commands. If one were to find significant activation of left temporal structures involved in language processing, but minimal activation of mesial frontal structures linked to behavioral initiation, it would be reasonable to assume that akinesia was the principal factor in the command-following deficit. Consequently, rehabilitative interventions would likely include aggressive behavioral prompting strategies and neurostimulants[57,58] rather than aphasia therapy.

As the sensitivity and specificity of fMRI methodologies improve, there will be a greater mandate to incorporate these procedures into routine clinical care. The future of diagnostic and prognostic assessment of patients with disorders of consciousness envisions a battery of neurobehavioral and neuroimaging techniques that serve as complementary clinical tools that may help differentiate the effects of underarousal, sensory impairment, motor dysfunction, and cognitive disturbance in the search for potential causes of behavioral unresponsiveness.

Putative Pathophysiologic Mechanisms of Impaired Consciousness and Neuroplasticity

The provocative finding that patients who exhibit minimal behavioral signs of consciousness sometimes retain large-scale cortical network activity naturally leads to the question of what mechanisms may limit further behavioral recovery in these patients. A systematic approach to this question is necessary and will require consideration of several potential pathophys-

iologic mechanisms. Imaging studies alone cannot adequately identify fluctuations in the resting brain state, which may strongly influence the likelihood of a response at that time and confound interpretation of the activation task. In patients with widely varying responsiveness, these limitations suggest the need for more careful consideration of ongoing brain dynamics and the development of more sensitive diagnostics that can identify dynamic signatures of several abnormal processes that may arise in the setting of severe brain injuries and limit recovery.[49]

Several different pathophysiologic mechanisms may produce abnormal dynamic changes across or within both cerebral hemispheres in the context of severe brain injuries. One relatively common finding after focal brain injuries is a reduction in cerebral metabolism in brain regions remote from the site of injury.[59] Disproportionately large reductions of neuronal firing rates are associated with modest reduction of CBF produced by these crossed-synaptic effects.[60] Recent studies show that the cellular basis of this effect is a loss of excitatory drive to neuronal populations producing a form of inhibition known as disfacilitation in which hyperpolarization of neuronal membrane potentials arises from absence of excitatory synaptic inputs allowing remaining leak currents to dominate.[61] Disfacilitation may play a pivotal role in changing resting brain activity levels, given recent evidence that cortical neurons may change fundamental firing properties based on levels of depolarization.[62] Multifocal brain injuries may therefore result in wide passive inhibition of networks because of loss of background activity, particularly if critical subcortical structures have been affected by the brain injury. Selective structural injuries to the paramedian thalamus can produce hemisphere-wide metabolic reductions presumably through this mechanism.[63,64] Damage to these structures from herniation injuries may generally produce some level of hemisphere-wide disfacilitation. As a result of severe brain injury, common thalamic driving inputs to the cerebral cortex may become abnormally synchronized or sufficiently down-regulated in output to produce global reductions in hemispheric function.[65]

A second important class of dynamic abnormalities are epileptiform or similar hypersynchronous phenomena that may arise in severe brain injuries without obvious traditional electroencephalographic markers. Williams and Parsons-Smith[66] described local epileptiform activity in the human thalamus that appeared only as surface slow waves in the electroencephalogram in a patient with a neurologic examination alternating between a state consistent with minimally conscious state and interactive communication, after encephalitis. A similar mechanism might underlie a case of episodic recovery of communication in a severely disabled patient that intermittently resolved after occasional generalized seizures.[67] Clauss et al[68] described emergence from a 3-year course of minimally conscious state after TBI after administration of the γ-aminobutyric acid agonist zolpidem, suggesting a role for some type of hypersynchrony, a process sharing circuit mechanisms with epilepsy or catatonia but arising on the basis of structural alterations in the corticothalamic or cortico-striatopallidal-thalamic systems. A similar case was reported by Cohen et al[69] in which there was transient improvement in aphasia after administration of zolpidem.

Experimental studies show increased excitability after even minor brain trauma that may support the development of epileptiform or different forms of hypersynchronous activity in both cortical and subcortical regions.[70] This mechanism may underlie other observed phenomena in severe brain injuries suggestive of hypersynchrony including several neurobehavioral syndromes such as oculogyric crises,[71] obsessive compulsive disorder,[72] paroxysmal autonomic phenomena,[73] and visuospatial neglect.[74] Similarly, these phenomena typically show specific pharmacologic response profiles.

Selective structural injuries can damage pathways of the brainstem arousal systems where the fibers emanate or run close together resulting in a consequent broad withdrawal of a neuromodulator that could produce significant dynamic effects on the electroencephalogram and behavior. Matsuda et al[75] described a small series of vegetative state patients with isolated MRI findings of axonal injuries near the cerebral peduncle (including substantia nigra and ventral tegmental area) and parkinsonism, who made significant late recoveries after administration of levodopa. Human anatomic studies show that the ascending cholinergic pathway travels in tight bundles at points along its initial trajectory to the cerebral cortex where it may be vulnerable to focal injury.[76]

At present, diagnostically specific physiologic signatures of such state-dependent, reversible phenomena arising from structural brain injuries are not systematically catalogued. Functional neuroimaging strategies coupled with quantitative electroencephalographic and magnetoencephalographic methods may pave the way for such a dynamic taxonomy.[77,78] Elucidation of these pathophysiologic substrates may clarify the underlying mechanisms that produce or contribute to prolonged disturbances in consciousness. Once these mechanisms are well-defined, therapeutic strategies can be developed to target dysfunctional systems. Neuromodulatory interventions including dopaminergic medications[79-81] and deep brain stimulation[82] hold therapeutic promise given their potential to activate down-regulated neural circuits and reverse diaschetic processes, and they may eventually lead to restoration of neurobehavioral function. Functional neuroimaging will also assume an important role in documenting longitudinal neural changes that may arise after institution of novel treatment interventions designed to promote cognitive and behavioral responsiveness.

CONCLUSIONS

In 1994, the Multi-Society Task Force on Persistent Vegetative State concluded that future studies of patients with disorders of consciousness should measure brain function in response to external stimulation.[83] More than 10 years later, disappointingly few such studies have been conducted. In part, this reflects the perception that vegetative patients are uniformly hopeless and the consequent difficulties encountered in obtaining grants and ethics committee approval for research in patients who cannot give consent.[84]

Research on disorders of consciousness is currently challenged by an extraordinary number of obstacles, including inadequate funding initiatives, lack of provisions to allow legally authorized representatives to provide consent, inconsistent regulatory guidelines across states and institutions that complicate necessary collaborative efforts, conventional biases that categorize this population of patients as beyond help, lack of billing codes for imaging procedures, and procedural complexities that require coordinated efforts from large numbers of collaborating specialists.[85] These imposing obstacles seem relatively minor when weighed against the potential benefits of a better understanding of mechanisms of recovery, improved neuroimaging, electrophysiologic, and behavioral assessment techniques and the development of effective neurorehabilitative interventions.[84,86] All in all, accelerated research efforts focused on investigations of disorders of consciousness, as well as resolution of the many obstacles to performing this research, could bring about a "quantum leap" in advantages for informed clinical practice serving severely brain injured patients. In our view, the time has come for a new conceptual framework for research involving patients with disorders of consciousness.

Acknowledgments: We are especially grateful for the critical contributions and support provided by the dedicated research teams at the JFK Johnson Rehabilitation Institute (Kathleen Kalmar, Caroline McCagg), Columbia University Center for Neurobiology and Behavior (Diana Rodriguez-Moreno, Jennifer Wydra, Steve Dashaw), Cornell-Weill College of Medicine (Erik Kobylarz), and the Belgian Fonds National de la Recherche Scientifique, which have been instrumental to the success of this unique collaboration.

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