fMRI reveals large-scale network activation in minimally conscious patients

N.D. Schiff, MD; D. Rodriguez-Moreno, MS; A. Kamal, MD; K.H.S. Kim, MD, PhD; J.T. Giacino, PhD; F. Plum, MD; and J. Hirsch, PhD

Abstract—*Background:* The minimally conscious state (MCS) resulting from severe brain damage refers to a subset of patients who demonstrate unequivocal, but intermittent, behavioral evidence of awareness of self or their environment. Although clinical examination may suggest residual cognitive function, neurobiological correlates of putative cognition in MCS have not been demonstrated. *Objective:* To test the hypothesis that MCS patients retain active cerebral networks that underlie cognitive function even though command following and communication abilities are inconsistent. *Methods:* fMRI was employed to investigate cortical responses to passive language and tactile stimulation in two male adults with severe brain injuries leading to MCS and in seven healthy volunteers. *Results:* In the case of the patient language-related tasks, auditory stimulation with personalized narratives elicited cortical activity in the superior and middle temporal gyrus. The healthy volunteers imaged during comparable passive language stimulation demonstrated responses similar to the patients' responses. However, when the narratives were presented as a time-reversed signal, and therefore without linguistic content, the MCS patients demonstrated markedly reduced responses as compared with volunteer subjects, suggesting reduced engagement for "linguistically" meaningless stimuli. *Conclusions:* The first fMRI maps of cortical activity associated with language processing and tactile stimulation of patients in the minimally conscious state (MCS) are presented. These findings of active cortical networks that serve language functions suggest that some MCS patients may retain widely distributed cortical systems with potential for cognitive and sensory function despite their inability to follow simple instructions or communicate reliably.

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The minimally conscious state (MCS) refers to a subcategory of patients with severe brain damage who demonstrate unequivocal, but intermittent, behavioral evidence of awareness of self or their environment.[1] The episodic nature of the interactions of patients in MCS presents diagnostic challenges for physicians and increases emotional burdens for families and caregivers. Herein we report the first fMRI maps of brain activity of two MCS patients in response to language and sensory stimulation paradigms. Recent observations of fragments of cerebral activity in persistent vegetative state (PVS) patients provide evidence that at least some partially functional cerebral regions can remain in catastrophically injured brains.[2-4] Such remaining cerebral activity in PVS, however, appears isolated to small regions of the forebrain that retain limited anatomic and functional connection. Whereas patients in PVS remain behaviorally unconscious, inconsistent evidence of higher integrative brain function demonstrated in some MCS patients invites further investigation of potential residual cerebral function. Moreover, comparisons of lesion volume and location in patients remaining in a vegetative state after a traumatic brain injury with other patients remaining severely disabled suggest that wide differences in structural injury patterns are present in patients with behavioral evidence of consciousness.[5]

Evidence for conscious awareness is indirectly inferred from behavior, and investigations of underlying brain function utilizing fMRI provide a unique opportunity to characterize the neurobiological correlates of MCS. Emergence from MCS is contingent in part on demonstration of a reliable communication system.[1] Methods for interrogation of cortical sensory and language systems are therefore of considerable potential importance, as evidence of residual functional substrates that could support communication would motivate and guide further efforts at rehabilitation. Based on previous findings in PVS patients, we hypothesized that MCS patients would fail to activate the complete cerebral network identi-

From the Department of Neurology and Neuroscience (Drs. Schiff, Kamal, and Plum) and Graduate School of Medical Sciences (D. Rodriguez-Moreno), Weill College of Medicine, Cornell University, and Departments of Radiology and Psychology, fMRI Research Center (Dr. Hirsch), Center for Neurobiology and Behavior, Columbia University, New York, Center for Functional and Molecular Imaging, Division of Clinical Pharmacology (Dr. Kim), Georgetown University Medical Center, Washington, DC, and JFK Johnson Rehabilitation Institute (Dr. Giacino), Edison, NJ.

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Address correspondence and reprint requests to Dr. J. Hirsch, Functional MRI Research Center, Neurological Institute, Columbia University, 710 W. 168 St., Box 108, New York, NY 10032; e-mail: jh2155@columbia.edu

Table 1 *Healthy volunteers: Biographic information*

Subject	Age, y	Gender	Handedness	Laterality quotient
A	24	M	Right	100
B	29	F	Right	100
C	32	M	Right	100
D	29	M	Right	50
E	28	F	Right	56
F	37	M	Right	47
G	32	F	Right	82
Average	30.1			76.43
SD	4.06			24.76

fied in normal subjects in response to similar passive listening paradigms. However, we rule out this hypothesis for these two patients in favor of the alternative hypothesis that the networks remain largely intact but show significant differences in their level of responsiveness.

Methods. *Control subjects and patients.* Seven healthy volunteers without history of neurologic disorders or chronic disease were recruited according to institutional informed consent procedures and performed language-related tasks similar to those performed by the MCS patients. All subjects were right handed as assessed by the Edinburgh Handedness Inventory (average laterality quotient 76.43 ± 24.76)[6] with mean age of 30 ± 4.06 years (table 1). One volunteer who was age and gender matched to the patients also participated in a tactile study performed similarly to the patients. Structural MRI revealed no abnormalities in any of the healthy subjects.

Two right-handed male MCS patients, ages 21 (Patient 1) and 33 (Patient 2), were recruited for this study. Legally authorized surrogates for both patients were contacted by medical personnel not directly involved in the current studies. Informed consent was obtained according to institutional guidelines on two occasions, allowing for a period of evaluation and opportunity for additional information. The patients had no history of neurologic disorder prior to the episodes that led to their severe brain injuries. The durations of the MCS at the time of the study were 18 (Patient 1) and 24 (Patient 2) months. Serial bedside examinations conducted by multiple examiners over a period of months were consistent with the diagnosis of MCS.

Patient 1 experienced a spontaneous intracranial hemorrhage in the left temporoparietal region with brainstem compression injury. Vegetative state was diagnosed at 3 months and progressed over the course of first year to MCS. Neurologic evaluation at the time of the study indicated right hemiparesis, intact oculocephalic and optokinetic responses, visual tracking, and saccades to stimuli. A large area of encephalomalacia over the left temporoparietal region was seen in structural MRI. Resting fluorodeoxyglucose (FDG) PET demonstrated 38.6% of normal regional cerebral metabolic rate. The highest-level behavioral responses observed for this patient were one-step command following, inconsistent identification of objects via eye gaze, and intelligible single-word verbalizations.

Patient 2 received blunt head trauma to the right frontal region that led to bilateral subdural hematomas and associated brainstem compression injury. Neurologic evaluation at the study time revealed released oculocephalic responses with intact visual tracking and both saccades to stimuli and to command, marked increased motor tone bilaterally, and frontal release signs. Right frontal lobe encephalomalacia and a small right-sided paramedian thalamic infarction were seen on structural MRI. Resting FDG-PET demonstrated 40.6% of normal regional cerebral metabolic rate. The highest-level behavior observed in this patient was his ability to inconsistently follow complex commands including go/no-go and countermanding tasks and occasional verbalization.

Image acquisition. A 1.5-T General Electric MR scanner (Milwaukee, WI) was used to obtain T2*-weighted images with a gradient echo pulse sequence that was sensitive to MR signal changes induced by alteration in the proportion of deoxyhemoglobin in the local vasculature accompanying neuronal activation (repetition time = 4,000 seconds, echo time = 60 seconds, flip angle = 60°). The in-plane resolution was 1.5 × 1.5 mm, and slice thickness was 4.5 mm. Twenty-one contiguous axial slices of the brain, which covered the entire cortex, were taken parallel to the anterior–posterior commissural plane. Thirty-six images were acquired for each run: a baseline (resting) period of 14 images (56 seconds), a stimulation period of 10 images (40 seconds), and a baseline (recovery) period of 12 images (48 seconds). The initial three images of each run were not included in the analysis to allow the magnetic signal to reach a steady state. Conventional high-resolution (T1-weighted) images were also acquired along the same plane locations as the T2*-weighted images and served as anatomic references.

Tasks. Three passive stimulation tasks were performed: light touch of both hands, auditory narratives of familiar events presented by a familiar person, and the same auditory passages without language-related content. Each condition was performed twice for a total of six runs per subject. During the first two runs, patients "listened" to a narrative prepared by a familiar relative through headphones (Gradient Muff Headset; Resonance Technology, Northridge, CA). A similar task was employed for the healthy volunteers, where the narrative consisted of four 20-second English paragraphs chosen for neutral emotional content without personally meaningful content.[7] The neutral content was employed to minimize cross-subject variability and was intended to influence a response restricted to the essential language areas. Similar methods to study passive language function are employed for neurosurgical planning prior to tumor resection[8] and for assessment of language function in unresponsive infants and children.[9] In the subsequent scans, the narratives were played in time reverse (backward) so that they were recognizable as speech, but content, propositional, and prosodic information were absent. Reversed speech is acoustically matched to normal speech in terms of duration, amplitude, and power spectrum but lacks the temporal attributes contained in the phase relationships in the forward signal. The final task consisted of two runs of passive tactile stimulation of the two hands simultaneously by gently rubbing the subject's palm and fingers with a coarse-textured plastic surface. These methods are routinely employed to localize sensory and motor-related cortex for patients in preparation for neurosurgical procedures[8] and were selected for this study because of the inflexible hand positions of the patients.

Image processing and data analysis. Prior to statistical analysis, images were computationally aligned using the Woods algorithm,[10] and a two-dimensional Gaussian filter (approximately 3 voxels, at half-height) was applied. The last image of the resting baseline and the first two images of the recovery baseline corresponding to transitions between epochs were also not part of the statistical analysis. Each analyzed epoch consisted of 10 images (40 seconds). Activation of each voxel was determined by a multistage statistical process that compared mean amplitudes of signals acquired during stimulation and baseline periods (voxel × voxel t maps) and identified voxels with signal changes between baseline and activity epochs on two identical runs. This conjunction yielded an empirically determined false-positive rate of $p < 0.0008$ for each condition.[11] Because of the descriptive goal of this study, patient images were analyzed as "fixed effects," meaning that the observations are valid for the subjects studied, but the investigation is without the benefit of a sufficient patient sample size to statistically generalize beyond the single subjects who participated in the study. However, the small sample size is assumed to be justifiable in these extraordinary and high-impact cases where the experimental design relies on the internal consistency of multiple measurements and comparison with matched healthy volunteers.

Assignments of anatomic labels and coordinates for active regions were based on correspondence between the patient's brain anatomy and the human brain atlas.[12] These assignments were made without registration of the acquired brains to a normalized brain owing to atypical morphology secondary to brain injury. The stages of assignment included identification of the brain slice passing through the anterior–posterior commissural line, assign-

ment of an atlas plate to each acquired brain slice, and assignment of corresponding anatomic labels, the indicated Brodmann areas (BAs), and coordinates for each active cluster. Because of the marked trauma-related variations in brain anatomy for these patients, this process included subjective judgments of corresponding labels to brain areas. This process was achieved in the same manner for all subjects and yielded a summary tabulation containing anatomic regions and BAs for each of the clusters of activated voxels in the regions of interest for each task. These assignments were made independently by three experienced investigators, and discrepancies were reconciled by detailed scrutiny of the anatomic structures. Volumes of activation for the whole brain and active clusters in specific anatomic areas were based on the number of active voxels and computationally calculated with the same software used for the statistical analysis.

Images acquired from control subjects were analyzed individually as for the patients and as a group (Statistical Parametric Mapping [SPM2]; Welcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk). Images were preprocessed for the analysis by first correcting for slice timing acquisition delay and then realigning them to correct head motion. The functional images were normalized to the Montreal Neurological Institute echoplanar imaging template and smoothed with a Gaussian kernel of $3 \times 3 \times 9$ mm full width at half-maximum. The data from the seven control subjects were used for a fixed-effects analysis as implemented in SPM2. Functional activity related to passive listening was modeled using two regressors per subject: one for the forward speech runs and the other for the reversed speech runs. All the regressors were obtained by convolving the vector of stimulus onsets with a canonical hemodynamic response. Data were filtered in the time domain using both a high-pass filter (cut-off period of 128 seconds) and a low-pass filter (convolution with a standard hemodynamic response function) before estimating the model. Proportional scaling was used to correct for volume-to-volume fluctuations in the global signal. After model estimation, t contrasts were performed (family-wise error correction, threshold $p = 0.05$, with extent thresholds of 5 voxels) for each passive listening condition for all subjects. WFU_pickatlas software was employed to transform the Montreal Neurological Institute coordinates of active areas to Talairach coordinates and to label the clusters.[13,14]

Results. *Language-related activation.* All brain slices for the patients (figure 1, A and B), three representative slices for each of the seven healthy subjects (figure 1C), and group data for all of the healthy subjects (figure 1D) indicate regions active during presentation of the recorded narratives played forward (yellow) and time reversed (blue). Red indicates the overlapping regions associated with the forward and time-reversed tasks. These images indicate activity associated with passive listening to forward narratives in known language-sensitive areas as well as primary auditory cortical areas in both patients (arrows) and the control subjects. Superior temporal or middle temporal gyrus activations are identified in the left hemisphere for Patient 2, in the right hemisphere for Patient 1, and across all healthy volunteers.

Percentages of total brain volume activated by the two language conditions, forward speech and reversed speech, are shown for whole brain and right and left hemisphere temporal lobes in figure 2. In the case of forward speech, the volume of activation for the left temporal gyrus of Patient 2 (red) is similar to that in control subjects (black). As Patient 1 (blue) experienced extensive damage to the left temporal region, minimal activation on the left is consistent with the clinical findings. Superior and middle temporal gyrus activations are also observed in the right hemisphere for both patients and in all volunteers. The number of active voxels in healthy volunteers is similar for both hemispheres. However, the volume of activation in the right temporal lobe for both patients is markedly reduced with respect to control subjects and also in relation to the left hemisphere for Patient 2.

Average human brain atlas coordinates (tables 2 and 3) for the areas active during the narrative forward condition show that the locations for the activity clusters in middle and superior temporal lobe are similar for patients and control subjects. Averages of individual control subjects (see table 2) show patient and control coordinates within the estimated error of spatial determination. For example, the putative Wernicke area, superior temporal gyrus (BA 22) in the left hemisphere, is represented at (57, −22, 7) for the averaged individual (see table 2), at (56, −21, 7) for Patient 2, and at (−53, −24, 8) for Patient 1 (right hemisphere homologue area). These results are consistent with the SPM2 group data registered to a common stereotactic coordinate system,[12] where one of the clusters in the superior temporal gyrus is centered at (63, −17, 6) (see table 3).

Activity in the transverse temporal cortex corresponding to the Heschl gyrus (primary auditory cortex) is identified bilaterally in six of the seven normal subjects performing the passive auditory forward task and in the left hemisphere in the remaining subject (see figure 1C). Auditory cortex activations appear primarily in the right hemisphere of Patient 1 (see figure 1A), presumably owing to the large regions damaged in the left temporal lobe and surrounding areas; auditory cortex activity is similarly restricted to the left hemisphere of Patient 2 (see figure 1B), possibly related to right hemisphere injury in this patient. Active centroid locations for the averaged individual controls (see table 2) are within estimated spatial errors of patient data and consistent with the SPM2 group analysis (see table 3).

During the normal speech conditions, we observed activations of the inferior frontal, prefrontal, and parietal cortices in all healthy volunteers. Activations of the left inferior frontal gyrus appeared in six of the seven normal subjects. The MCS patients also showed small clusters of activity in this area. In the healthy control subjects, the right hemisphere homologue region also activated in response to the normal speech. Prefrontal cortex activations in the right hemisphere are seen in all control subjects and Patient 1 and in the left hemisphere for three of the control subjects and Patient 2. Parietal cortex activations are observed in the right hemisphere in all seven healthy subjects and Patient 2. Left hemisphere parietal cortical activations are observed in three healthy subjects. Primary or secondary visual areas, on the other hand, were active in four of the seven healthy volunteers and in Patient 2.

Passive listening to backward (time-reversed) narratives elicited most of the same clusters of activity in the temporal lobe that passive listening to forward narratives elicited in the healthy volunteers (red), as indicated by the similitude of coordinates (see figure 1, C and D; tables 4 and 5). Moreover, the pattern of activation for the normal subjects is similar in both the time-reversed and the forward conditions, suggesting that many of the same processing mechanisms were engaged. During this task, normal subjects reported that they recognized the time-reversed stimuli as speech and realized that it was meaningless. On the other hand, MCS patients show a very little activation during the backward speech condition (see figure 1, A and B; tables 4 and 5), indicating a difference in

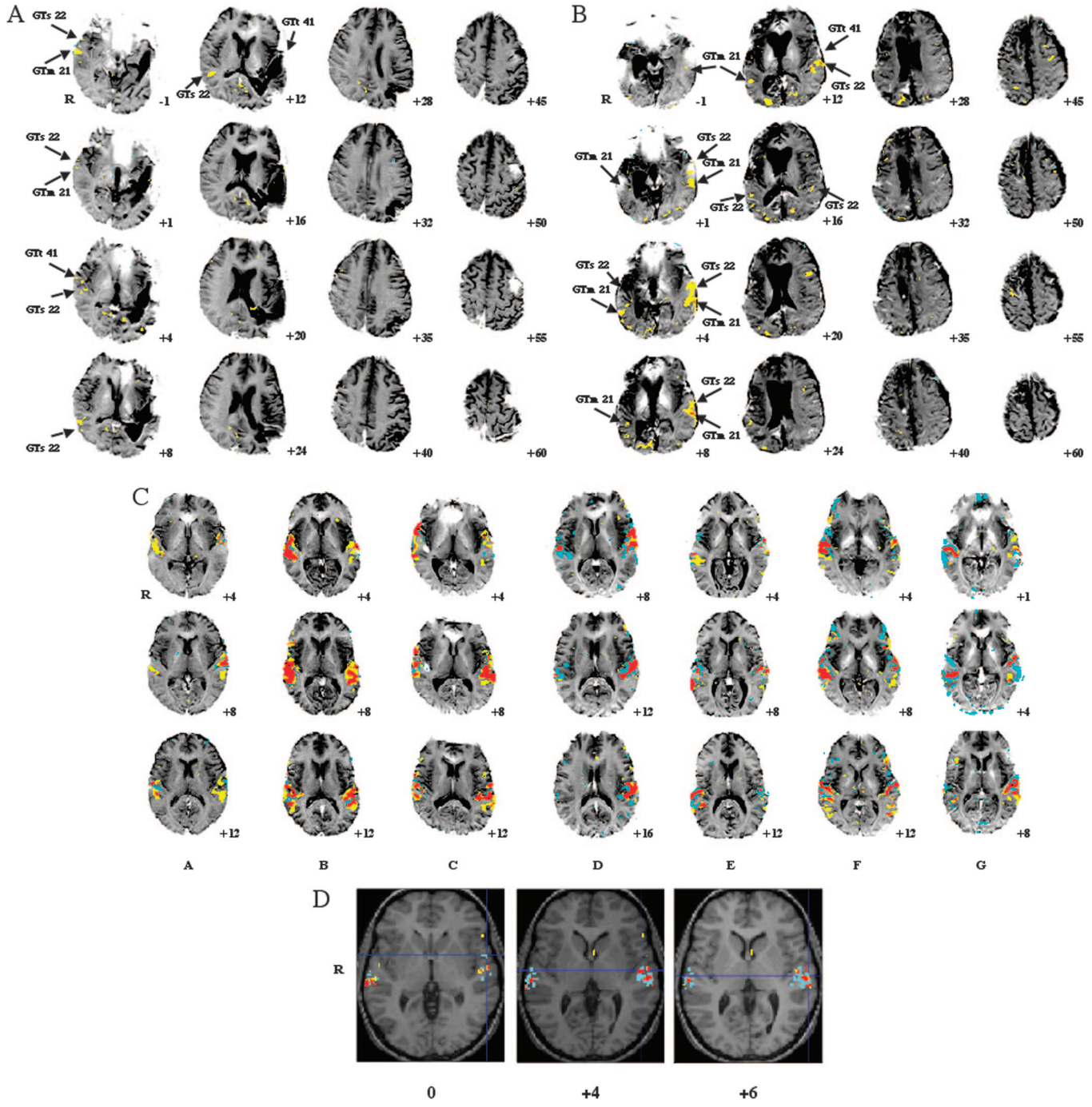

Figure 1. Functional maps obtained during listening to narratives. (A) Patient 1; (B) Patient 2; (C) individual healthy subjects; (D) group analysis of healthy subjects. Blood oxygenation level–dependent signal increases during forward and reversed speech conditions are shown on the T2-weighted images for A, B, and C and on the high-resolution T1 image of a single subject for D. The numbering of slices indicates approximate distance (mm) from the anterior–posterior commissural line and corresponding planes in the human brain atlas.[12] Activations associated to passive listening of the forward speech are shown in yellow; those associated with passive listening of reversed speech are shown in cyan; and the overlap between them is shown in red. R = right hemisphere; GTs 22 = superior temporal gyrus (Brodmann area [BA] 22); GTm 21 = middle temporal gyrus (BA 21); GTt 41 = transverse temporal gyrus (BA 41).*

processing of the time-reversed stimuli. As illustrated in figure 2, healthy volunteers (black) showed similar volumes of activation for the time-reversed condition compared with the forward condition, whereas both patients showed a marked reduction in the total active volume.

In both patients, the total number of activated voxels for the forward condition exceeded the total number of activated voxels in the reverse condition (see figure 2). Although the extent of the activation during the forward condition for Patient 1 is not robust, the amount of activation for Patient 2 is comparable with that of some of the normal subjects. This indicates some variability of activa-

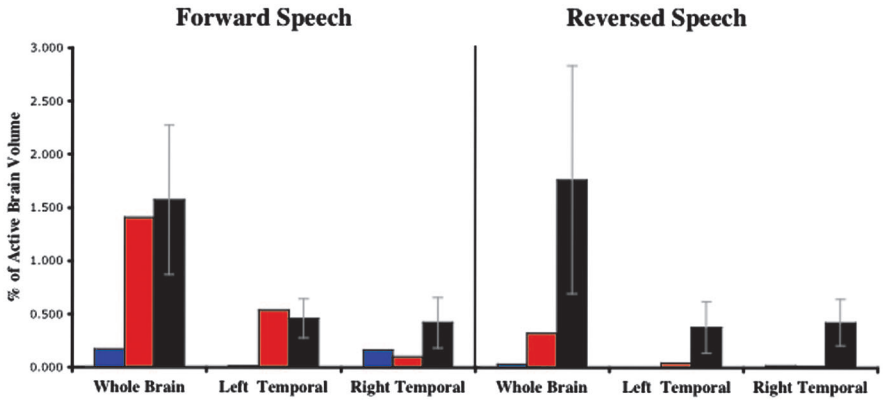

Figure 2. Volumes of activation during the passive listening tasks. Histogram of the percentage of brain volume that is active during the forward (left) and reversed (right) speech conditions for the 1) the whole brain and 2) the right and left temporal lobes for Patients 1 (blue) and 2 (red) in a minimally conscious state and the healthy control subjects (black). Error bars indicate the SD for the seven control subjects. Note that for Patient 1, damage in the left temporal region is consistent with no observation of activation in that area.

tion during passive listening in patients as well as in the control population. Similar to the forward speech condition, the overlap of locations of activity associated with the reversed speech was similar for patients and normal control subjects. For example, the two patients fall near the average coordinates of (51, −24, 11) for the left transverse temporal gyrus (see table 4) and the group coordinates of (45, −25, 6) (see table 5).

Tactile-related activation. Bilateral tactile stimulation of the hand elicited activation in the primary somatosensory area (SI) in the postcentral gyrus of both cerebral hemispheres in both patients and the control subject (figure 3). The activity is observed in the expected anatomic hand area as identified by its position in the postcentral gyrus posterior and lateral to the characteristic "Ω" shape in the precentral gyrus, which constitutes the landmark for the motor hand area in the axial plane.[15,16] Previous reports show good correlation between the location of the anatomic hand landmark and the location of activity elicited by tactile stimulation.[17] The corresponding brain atlas coordinates and the volumes of activation for each subject are shown in table 6. Although all individuals showed activity in both hemispheres, the volume of activation for the hand area in the right hemisphere of Patient 2 was considerably smaller, presumably related to structural injury of the right hemisphere.

Stimulation of the hands also evoked bilateral activation of the parietal operculum (SII), precentral gyrus, parietal cortex, superior temporal gyrus, occipital gyrus, and calcarine sulcus in our healthy age-matched control subject. Interestingly, hand stimulation produces activity clusters in many of these same areas in the MCS patients. Indeed, Patient 1 exhibited activity in the right parietal operculum, posterior insula, precentral gyrus, superior temporal gyrus, and middle frontal gyrus and bilateral activation of parietal cortex, occipital gyrus, and calcarine sulcus. Patient 2 showed activity clusters in the left precentral gyrus, superior temporal gyrus, superior frontal gyrus, and occipital gyrus and bilaterally in the parietal cortex. Overall, the control subject had similar volumes of

Table 2 *Human brain atlas[12] coordinates for active areas in temporal lobe during passive listening to forward narrative*

	Right hemisphere			Left hemisphere		
	X	*Y*	*Z*	*X*	*Y*	*Z*
Middle temporal gyrus (BA 21)						
Patient 1	−59.5	−38.8	2.0			
Patient 2	−46.8	−42.0	4.3	56.7	−46.8	3.5
Control subjects*	−56.9	−42.0	2.0	56.9	−46.5	2.9
SD	3.6	7.0	1.7	4.6	5.1	2.4
Superior temporal gyrus (BA 22)						
Patient 1	−53.1	−24.1	7.8			
Patient 2	−55.3	−31.6	7.8	55.7	−20.6	7.2
Control subjects*	−56.5	−19.9	5.8	56.5	−21.6	7.1
SD	1.7	6.2	2.2	1.6	4.8	1.8
Transverse temporal gyrus (BA 41)						
Patient 1	−51.0	−11.8	8.0			
Patient 2				42.5	−22.1	12.0
Control subjects*	−49.8	−19.2	10.0	51.3	−25.0	11.0
SD	3.2	7.3	3.3	5.6	7.8	1.5

* Average coordinates are expressed as the mean and SD of seven individual subject images.

BA = Brodmann area.

Table 3 *Human brain atlas[12] coordinates* for active areas in temporal lobe during passive listening to forward narrative obtained in fixed effects group analysis*

	Right hemisphere					Left hemisphere				
	X	*Y*	*Z*	*z* Score	*k* Extent	*X*	*Y*	*Z*	*z* Score	*k* Extent
Middle temporal gyrus (BA 21)	−67.3	−27.2	0.3	7.84	68					
Superior temporal gyrus	−53.5	−5.8	0.3	6.11	6	53.5	−11.4	4.3	7.37	23
(BA 22)						61.4	−9.7	0.5	7.26	21
						63.4	−17.2	6.4	7.13	53
						53.5	−2.2	−4.9	5.94	6
Transverse temporal gyrus (BA 42)	−63.4	−9.1	11.5	6.24	9	63.4	−32.3	20.0	6.57	57

* Coordinates are expressed as the average across subjects based on registration of all normal control images to a common atlas prior to analysis.

BA = Brodmann area.

activation for both hemispheres in responses to bilateral somatosensory stimulation, whereas both MCS patients showed reduced volumes of activation in the damaged hemisphere.

Discussion. During both passive listening and tactile stimulation tasks, the MCS patients studied here showed remarkably similar brain activity to that evoked in healthy control subjects. Thus, our original hypothesis that the MCS patients would demonstrate only partial activation of the normal language network was not supported. Moreover, the reduced activation for the time-reversed passive language condition in the MCS patients constitutes a significant difference compared with normal control subject responses.

Passive listening to normal (forward) narratives robustly activates superior and middle temporal gyri in healthy subjects.[18-23] We observed a similar pattern of activation for the MCS patients. Conventionally, based on lesion and neuroimaging studies, these areas are linked to language comprehension. Brain damage encompassing dominant superior and middle temporal gyrus is associated with Wernicke aphasia, which is characterized by loss of speech comprehension and production of meaningful speech.[25] Imaging studies have confirmed the in-

Table 4 *Human brain atlas[12] coordinates for active areas in temporal lobe during passive listening to reversed narrative*

	Right hemisphere			Left hemisphere		
	X	*Y*	*Z*	*X*	*Y*	*Z*
Middle temporal gyrus (BA 21)						
Patient 1	−59.5	−32.5	2.5			
Patient 2				59.5	−51.5	6.7
Control subjects*	−58.4	−44.3	2.6	57.3	−47.0	2.8
SD	2.2	7.7	1.7	2.6	6.5	1.7
Superior temporal gyrus (BA 22)						
Patient 1	−59.5	−11.8	1.0			
Patient 2	−59.5	9.0	−1.0	53.8	−8.3	4.0
Control subjects*	−56.4	−21.9	6.5	56.6	−21.3	6.6
SD	1.8	5.4	2.5	2.3	4.8	1.3
Transverse temporal gyrus (BA 41)						
Patient 1				59.5	−11.8	12.0
Patient 2				42.5	−32.5	12.0
Control subjects*	−49.1	−19.0	10.9	50.7	−24.3	11.3
SD	3.4	6.2	3.0	5.3	6.7	1.5

* Average coordinates are expressed as the mean and SD of seven individual subject images acquired on the original T2* grid.

BA = Brodmann area.

Table 5 *Human brain atlas[12] coordinates for active areas in temporal lobe during passive listening to reversed narrative obtained in fixed effects analysis*

	Right hemisphere					Left hemisphere				
	X	*Y*	*Z*	*z* Score	*k* Extent	*X*	*Y*	*Z*	*z* Score	*k* Extent
Middle temporal gyrus (BA 21)	−59.4	1.6	−6.8	6.72	8					
Superior temporal gyrus	−67.3	−25.3	−0.4	10.45	162	59.4	3.9	0.2	6.5	10
(BA 22)	−59.4	−15.3	4.5	5.69	6	61.4	−5.4	7.6	6.08	14
						55.4	9.4	−5.5	5.30	6
BA 42						59.4	−21.0	6.6	10.33	271
Transverse temporal gyrus (BA 41)						45.5	−24.8	8.6	6.22	12
BA 42	−65.3	−9.2	9.7	8.65	32					

* Coordinates are expressed as the average across subjects based on registration of all normal control images to a common atlas prior to analysis.

BA = Brodmann area.

volvement of temporal cortex in speech perception and syntactic and semantic processing.[11,16,18-23]

As all healthy volunteers reported understanding the sentences played forward, we assume that activation of left superior and middle temporal gyri reflects processing of the serially ordered presentation of words in standard syntax or possibly the semantic content of the sentences themselves. As MCS patients cannot communicate, the interpretation of their results is less clear. Activation of the dominant temporal gyrus in Patient 2 suggests that the forward narratives may be recognized as speech. On the other hand, right temporal lobe activation in response to language stimuli has been associated with prosody and the processing of vocal sounds for the recognition of speaker identity, gender, and emotional state.[15,24] Therefore, the right temporal activation observed in all subjects and the two patients could be related to voice perception irrespective of the semantic content or rudimentary right hemisphere word recognition.

The activity in inferior frontal gyrus during passive listening of the narratives is consistent with the emerging view that inferior frontal gyrus is also recruited during receptive language functions.[26,27] Prefrontal cortex activations were seen in the right

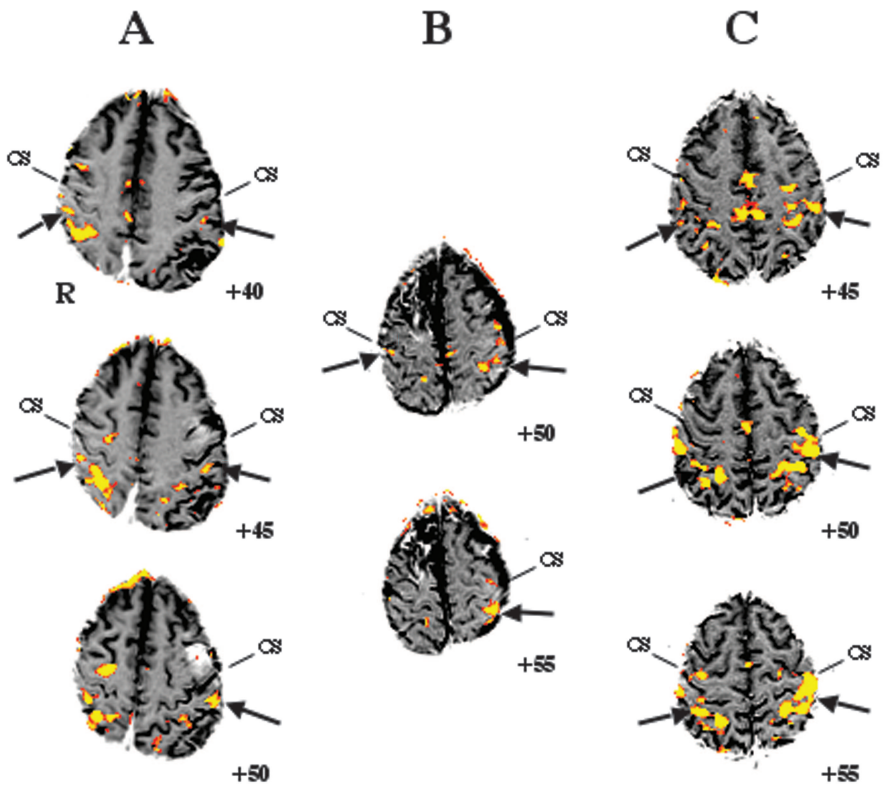

Figure 3. Bilateral tactile stimulation of hands. (A) Patient 1; (B) Patient 2; (C) control subject. Percentage change statistical maps are shown on the T2-weighted images. The arrows indicate activity during bilateral hand tactile stimulation in the postcentral gyrus. The numbering of slices indicates approximate distance (mm) from the anterior–posterior commissural line and corresponding planes in the human brain atlas. Central sulcus is indicated by a black line. R = right hemisphere.*

Table 6 *Human brain atlas[12] coordinates for active areas in the postcentral gyrus during bilateral tactile stimulation of hands*

Subject	Right hemisphere			Volume, mm^3	Left hemisphere			Activated volume, mm^3
	X	*Y*	*Z*		*X*	*Y*	*Z*	
Patient 1	38.3	−22.1	47.5	648	39.7	−25.6	50.0	587
Patient 2	42.5	−11.8	50.0	91	38.3	−32.5	52.5	871
Control	36.8	−29.0	50.0	840	39.7	−25.6	50.0	1,185

hemisphere in all control subjects and Patient 1 and in the left hemisphere of three of the control subjects and Patient 2. Parietal activation was observed in the left hemisphere in all seven healthy subjects, whereas right hemisphere activation was observed in four subjects and Patient 2. Parietal cortex activation is also associated with some aspects of language as well as conscious awareness.[28,29]

One haunting aspect of these findings is the selective activation of occipital cortical regions in the forward condition of the passive language paradigm. Primary or secondary visual areas, on the other hand, were active in only four of the seven healthy volunteers but showed robust activation in Patient 2. Activation of these regions may reflect individual differences in the patient's narrative content that described personally meaningful events and possibly triggered episodic memories that elicited visual imagery. In addition, the familiarity of the narrator may also have generated an imaginal representation of the person speaking. Visual cortex activity in the absence of visual stimulus is suggestive of visualization processes organized by either automatic or controlled cognitive processes.[30-32] We cannot rule out the possibility that the bilateral occipital activations are an "anomalous response" and reflect some failure of a top-down gating mechanism as identified in fMRI studies of aphasic patients[33]; the lack of visual input, however, tends to mitigate this possible interpretation.

Previous studies report activation of overlapping temporal lobe clusters by passive listening to forward and time-reversed narratives.[15,22,34,35] These results suggest that the clusters of activity present in response to both forward and time-reversed speech might be related to fundamental language processing prior to semantic encoding. The MCS patients, however, fail to recruit the same language-responsive networks when exposed to unintelligible but physically identical auditory stimuli (as characterized by the power spectrum of the signal). It is possible that this finding reflects a failure of the MCS patients to "recognize" the backward stimuli as speech. Thus, the lack of primary auditory cortex activation could be due to loss of a top-down, "anticipatory" modulation of the auditory and language system, resulting in failure of stimuli to actually engage cognitive processing per se. Whether the patients perceive the reversed speech as white noise or the forward speech as meaningful is unknown. In healthy volunteers, passive listening to time-reversed narratives activates temporal regions with the same or greater spread than in the forward condition. The higher volume of activation in some of these subjects suggests that the time-reversed task may demand more processing resources. This view would suggest that these subjects attempted to form associations and engaged attentional resources aimed at signal detection, despite being instructed to passively listen to the reversed speech stimuli. Indeed, some of the subjects reported interpreting the time-reversed speech as a "kind of foreign language."

The activation of a complex of cortical regions during bilateral hand stimulation in both patients and control subjects is consistent with previous studies that indicate stimulation of the hand activates the contralateral primary somatosensory cortex (SI) as a part of a large-scale cortical network that also includes secondary somatosensory cortex (SII), posterior insula, precentral gyrus, parietal gyrus, and posterior cingulate cortex.[36-38] The activation of cortical areas outside the somatosensory system per se suggests that somatosensory stimulation may trigger other additional processing steps. Both MCS patients demonstrate at least partial preservation of distributed networks for processing of somatosensory information, including evidence of cortical activity beyond primary and secondary somatosensory areas as observed in healthy subjects. Although this distributed system for the processing of incoming tactile information was observed in both patients and the control subject, there was a difference in the lateralization pattern consistent with hemispheric injuries in each patient.

Taken together with the inconsistent evidence of receptive and expressive language skills evident in the bedside examinations of these patients, the fMRI findings demonstrate an unexpectedly consistent language-responsive network. Importantly, both patients show low resting cerebral metabolic rates (38.6% of normal in Patient 1 and 40.6% of normal in Patient 2) based on PET studies, comparable with levels measured in patients remaining in a vegetative state following traumatic brain injuries.[3] Direct comparisons of changes in cerebral metabolism, blood oxygenation level–dependent (BOLD) signal, and neuronal activity indicate correspondence of these measures.[39] Thus, severely reduced neuronal firing rates at rest throughout the cerebrum are likely in both patients. The failure of the time-reversed narratives to activate the widely distributed language-responsive networks seen with the

forward presentations in normal control subjects may reflect a failure to provoke a global change in neuronal firing patterns based on stimulus salience. As we did not measure regional cerebral metabolism during stimulation with forward narratives, we cannot be certain that metabolic increases would accompany the wide activation of BOLD response elicited by these stimuli. The measured relationship between these modalities[39] suggests that regional increases would be expected near the locations of BOLD activation and the further possibility that global increases in metabolism not reflected in the BOLD signal per se might also arise in conjunction with the observed wide bilateral activation. This interpretation suggests that the MCS patients may have a severe deficit of "baseline" or "default self-monitoring" brain activity proposed to account for high resting cerebral metabolic rates in the normal human brain.[28] The dissociation of widely recruitable networks and resting global metabolic rates producing values consistent with the vegetative state can thus provide a potential mechanistic insight into the basis of MCS. In our subjects, the resting MCS brain preserves an ability to recruit cerebral networks necessary for cognition and interaction despite a failure to spontaneously drive these networks, possibly as a result of a lack of ongoing brain activity associated in normal subjects with high metabolic demands. Compression of the thalamus and brainstem during the acute phase of brain injuries for both patients may be a key underlying physiologic mechanism producing chronically low neuronal activity at rest. These paramedian mesodiencephalic regions help to establish sustained cortical activations supporting intentional behaviors that contribute significantly to the activation of wide territories of cerebral cortex.[40]

Finally, several specific fMRI regional activation patterns are proposed to correlate with awareness. Studies of visual awareness in normal subjects and patients with parietal extinction phenomena implicate co-activation across prefrontal, parietal, and occipitotemporal cortical areas for seen as opposed to unseen stimuli.[41,42] These differences in activation patterns have been identified with both significant elevations of regional BOLD signal or in the strength of effective connectivity (increases in measured signal covariance). Both loss of parietal activations and alteration in strength of occipitotemporal covariation are identified with unconsciousness in vegetative patients utilizing simple auditory stimulation paradigms and functional PET.[4] In this context, the observed activation of prefrontal, parietal, and occipital regions in our patients is suggestive of awareness but potentially consistent with other interpretations. Nonetheless, the validity and reliability of behavioral indexes for discerning level of consciousness are also challenged by these findings that suggest functional imaging may provide evidence of cerebral integrative activity not available at the bedside. These concerns amplify the need to improve diagnostic clarity in disorders of consciousness.[1] Our data provide further evidence that the underlying physiology of the MCS brain is distinct from the vegetative state brain. Thus, these findings raise important questions related to whether MCS patients have a greater capacity to experience subjective states but also to benefit from therapeutic interventions. Given the wide public health dimensions of the problem of traumatic brain injuries, this possibility presents a humanitarian imperative to further investigate the state of consciousness of these and other brain-injured patients.[43]

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