Auditory Processing in Severely Brain Injured Patients

Differences Between the Minimally Conscious State and the Persistent Vegetative State

Mélanie Boly, BS; Marie-Elisabeth Faymonville, MD, PhD; Philippe Peigneux, PhD; Bernard Lambermont, MD, PhD; Pierre Damas, MD, PhD; Guy Del Fiore, PhD; Christian Degueldre, PhD; Georges Franck, MD, PhD; André Luxen, PhD; Maurice Lamy; MD, PhD; Gustave Moonen, MD, PhD; Pierre Maquet, MD, PhD; Steven Laureys, MD, PhD

Background: The minimally conscious state (MCS) is a recently defined clinical condition; it differs from the persistent vegetative state (PVS) by the presence of inconsistent, but clearly discernible, behavioral evidence of consciousness.

Objective: To study auditory processing among patients who are in an MCS, patients who are in a PVS, and healthy control subjects.

Methods: By means of ^{15}O-radiolabeled water–positron emission tomography, we measured changes in regional cerebral blood flow induced by auditory click stimuli in 5 patients in an MCS, 15 patients in a PVS, and 18 healthy controls.

Results: In both patients in an MCS and the healthy controls, auditory stimulation activated bilateral superior temporal gyri (Brodmann areas 41, 42, and 22). In patients in a PVS, the activation was restricted to Brodmann areas 41 and 42 bilaterally. We also showed that, compared with patients in a PVS, patients in an MCS demonstrated a stronger functional connectivity between the secondary auditory cortex and temporal and prefrontal association cortices.

Conclusions: Although assumptions about the level of consciousness in severely brain injured patients are difficult to make, our findings suggest that the cerebral activity observed in patients in an MCS is more likely to lead to higher-order integrative processes, thought to be necessary for the gain of conscious auditory perception.

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From the Cyclotron Research Center (Ms Boly and Drs Peigneux, Del Fiore, Degueldre, Maquet, Luxen, and Laureys), and the Departments of Neurology (Drs Franck, Moonen, Maquet, and Laureys), Anesthesiology and Reanimation (Drs Faymonville, Damas, and Lamy), Intensive Care Medicine (Drs Faymonville, Lambermont, Damas, and Lamy), Neuropsychology (Dr Peigneux), and Internal Medicine (Dr Lambermont), University of Liège, Liège, Belgium.

THE *MINIMALLY CONSCIOUS state* (MCS) has recently been defined as "a condition of severely altered consciousness in which minimal but definite behavioral evidence of self or environmental awareness is demonstrated".[1(pp350-351)] Bedside evaluation of residual cognitive function in patients in an MCS is difficult because they are rapidly exhausted and may show fluctuating levels of arousal, attention, and motor responsiveness. We used ^{15}O-radiolabeled water–positron emission tomography (PET) to objectively measure cerebral activation patterns in response to auditory stimuli in patients in an MCS and compared it with that observed in healthy control subjects and in patients in a persistent vegetative state (PVS). Given that our previous studies have stressed the role of functional cerebral integration deficits in unconscious patients in a PVS,[2,3] we also looked for differences in cortico-cortical functional connectivity[4] during auditory processing in patients in an MCS compared with patients in a PVS.

METHODS

SUBJECTS

We prospectively studied 5 patients in an MCS (2 females and 3 males; age range, 46-74 years), 15 patients in a PVS (3 females and 12 males; age range, 19-75 years), and 18 healthy volunteers (10 females and 8 males; age range, 19-64 years). Patients' conditions were diagnosed according to internationally established criteria for MCS[1] and PVS.[5] Demographic data of patients in an MCS are summarized in **Table 1**. Demographic data of patients in a PVS have been reported previously[2]; causes were cardiorespiratory arrest (n=5), diffuse axonal injury (n=3), drug overdose (n=2), prolonged respiratory insufficiency (n=2), encephalitis with diffuse white matter lesions (n=2), and carbon monoxide intoxication (n=1). All patients had preserved pupillary, corneal, and vestibulo-ocular reflexes.

After admission to the hospital and while in awake periods (as demonstrated by simultaneous polygraphic recordings) patients underwent scanning a mean (SD) of 33 (11) days for those in an MCS and 36 (9) days for those in a PVS. Informed consent was obtained from the persons having legal responsibility for the

Table 1. Clinical, Electrophysiological, and Structural Imaging Data of Patients in the Minimally Conscious State

	Patients				
Variable	**1**	**2**	**3**	**4**	**5**
Sex/age, y	F/46	M/51	M/74	F/46	M/50
Cause	Respiratory arrest	Trauma	Encephalitis	Hypertensive encephalopathy	Diffuse axonal injury
GCS on admission (maximum score 15)	3	3	14	3	6
Time of PET, No. of days after admission	124	20	40	46	37
Outcome at 6 mo	Markedly dependent	Moderately dependent	Died	Independent in special environment	Markedly dependent
Clinical evaluation at time of PET					
Interactive communication	Absent	Absent	Absent	Absent	Absent
Functional use of ≥2 objects	Absent	Absent	Absent	Absent	Absent
Best verbal response	Sporadic intelligible (prayers)	None	None	None	Incomprehensible sounds
Best gestural response to auditory stimuli	Reaching for objects	Finger flexion of left hand	Smiling in relation to relevant verbal stimuli	Vertical gaze movements, inconsistent tongue protrusion	Tongue protrusion
Eye opening	Spontaneous	Spontaneous	Spontaneous	Spontaneous	Spontaneous
Sleep-wake cycles	Present	Present	Present	Present	Present
Arousal level	Normal	Normal	Normal	Fluctuating	Fluctuating
Eye movements	Consistent tracking and fixation	Inconsistent fixation	Tracking of family members	Tracking	Inconsistent tracking and fixation
Eye blinking to visual threat	Present	Present	Present	Present	Present
Breathing	Normal	Normal	Normal	Normal	Normal
Gag reflex	Present	Present	Present	Present	Present
Deep tendon reflexes	Increased	Normal	Increased	Increased	Increased
Skeletal muscle tone	Flexor	Flaccid	Rigid	Extensor	Normal
Paralysis paresis	Bilateral	Bilateral	Bilateral	Bilateral	Bilateral
Babinski sign	Bilateral	Absent	Absent	Bilateral	Absent
Electroencephalographic finding					
Background activity	Disorganized theta	Reactive theta, moderate diffuse delta	Disorganized theta	Reactive, disorganized theta	Disorganized delta
Magnetic resonance imaging					
Increased intensity on T2	Basal ganglia, diffuse white matter	Left frontal contusion, diffuse white matter	Diffuse white matter	Diffuse white matter	Diffuse white matter

Abbreviations: GCS, Glasgow Coma Scale; PET, positron emission tomography.

patients and from all controls. The study was approved by the ethics committee of the University of Liège, Liège, Belgium.

DATA ACQUISITION

Changes in regional cerebral blood flow were measured using ^{15}O-radiolabeled water–PET as described elsewhere.[3] Scanning was performed during rest and left-sided and right-sided auditory stimulation (5.1-Hz, 95-dB monaural clicks with contralateral 55-dB white noise). The remaining scans were performed with median nerve stimulation (14 patients in a PVS and 4 patients in an MCS) or presentation of human voices (1 patient in a PVS and 1 patient in an MCS). Results regarding the other acquisitions will be reported elsewhere once a larger cohort of patients is included. Each condition was repeated 3 times and the presentation order was pseudorandomized. Patients' vital parameters and brainstem auditory evoked potentials were recorded throughout the procedure. Stimulation intensity was identical for all subjects. A high-resolution, T1-weighted, magnetic resonance image was obtained for coregistration to the PET data.

DATA ANALYSIS

Positron emission tomographic data were realigned, spatially normalized,[6] smoothed (16 mm), and analyzed using statistical parametric mapping (SPM99).[7] Data obtained during left-sided auditory stimulation and rest were flipped as reported previously.[3] A random effect[8] analysis identified brain areas that activated during auditory stimulation. We calculated 1 contrast (stimulation-rest) per subject (accounting for the within-subject component of the variance) and used these contrast images in a second design matrix (accounting for the between-subject component of the variance) separating the data into 3 groups (controls, patients in an MCS, and patients in a PVS). We then performed 2 conjunction analyses looking for activation (1) common to controls and those in a PVS and (2) common to controls and those in an MCS. We also looked for the groups (MCS-PVS) × condition (stimulation-rest) interaction, searching for areas less activated in patients in a PVS than in patients in an MCS. Given our a priori[3] activation in superior temporal areas, results were thresholded at small-volume–corrected $P<.05$ (20-mm-diameter sphere centered on peak voxels).

Finally, a psychophysiological interaction analysis[2-4] looked for differences in functional connectivity between MCS and PVS. Our hypothesis was that patients in an MCS and patients in a PVS would differ in their degree of functional integration of auditory stimuli. We identified areas in which activity was modulated by secondary auditory cortex (ie, peak activation in controls; Brodmann area 42) differently in those in an MCS vs those

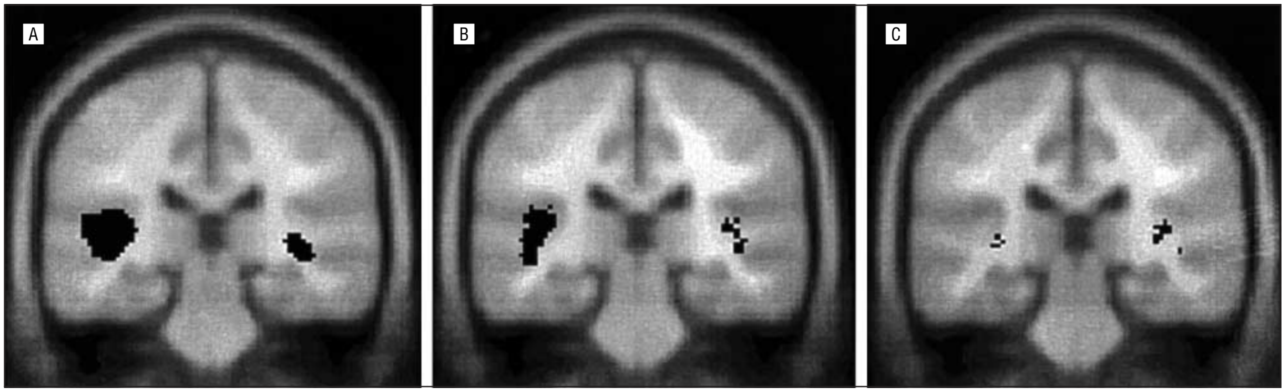

Figure 1. Brain regions showing activation during auditory stimulation in healthy control subjects (A), patients in a minimally conscious state (B), and patients in a persistent vegetative state (C). Coronal section 28 mm behind the anterior commissural line.

Table 2. Areas That Became Activated During Auditory Stimulation in Healthy Control Subjects and in Patients in an MCS

Region	BA	Coordinates*	*T* Value	*P* Value
Healthy Control Subjects				
TTG				
Contralateral	41	–40, –28, 12	5.14	<.001
Ipsilateral	41	39, –32, 10	3.71	.01
Superior surface of STG				
Contralateral†	42	–44, –31, 7	6.68	<.001
Ipsilateral	42	44, –32, 13	4.25	.002
Lateral and inferior part of STG				
Contralateral	22	–54, –34, 16	3.67	.03
Ipsilateral	22	38, –30, 0	4.45	.002
Patients in an MCS				
TTG				
Contralateral	41	–42, –31, 7	3.02	.001
Ipsilateral	41	38, –30, 16	2.84	.002
Superior surface of STG				
Contralateral	42	–44, –28, 14	2.60	.004
Ipsilateral	42	42, –33, 9	2.87	.001
Lateral and inferior part of STG				
Contralateral	22	–44, –29, 0	2.58	.005
Ipsilateral	22	42, –33, 3	3.16	.001
Patients in a PVS				
TTG				
Contralateral	41	–34, –25, 5	2.21	.04
Ipsilateral	41	34, –25, 7	2.84	.02
Superior surface of STG				
Contralateral	42	–38, –29, 1	2.07	.04
Ipsilateral	42	42, –34, 11	3.77	.01

Abbreviations: BA, Brodmann area; MCS, minimally conscious state; PVS, persistent vegetative state; STG, superior temporal gyrus; TTG, transverse temporal gyrus.

*Coordinates are defined in stereotaxic space.[10]

†This area was used for further connectivity assessment.

in a PVS. As we expected a large diversity of areas[9] and no a priori areas could be suggested; results were thresholded at cluster- or voxel-level–corrected $P<.05$.

RESULTS

Brainstem auditory evoked potentials were normal, showing preserved function of the auditory periphery to the inferior colliculus in all patients. In controls, auditory stimulation activated auditory cortex contralateral and ipsilateral to the side of stimulation (mean volumes of activation were 6.4 and 1.6 mL, respectively; **Figure 1** A). The activated areas encompassed bilateral transverse temporal gyri (TTG) (Brodmann area 41) and superior temporal gyrus (STG) (Brodmann areas 42 and 22) (**Table 2**). In patients in an MCS, auditory stimulation activated bilateral auditory cortex (mean volumes were 2.8 mL contralateral and 1.6 mL ipsilateral to the side of stimulation; Figure 1B). Peak voxels were located in bilateral TTG (Brodmann area 41) and STG (Brodmann

Table 3. Areas Where Functional Connectivity With Secondary Auditory Cortex Was Different in Patients in MCS Compared With Patients in PVS

Region	BA	Coordinates	*T* Value	*P* Value
Posterior part of STG	22	−57, −44, 17	4.75	.03*
Middle temporal gyrus	21	−61, −49, 3	5.66	<.001*
Inferior frontal gyrus	44/45	−57, 18, 1	3.92	.008†
Middle frontal gyrus	9	−32, 44, 33	4.45	<.001†
Middle frontal gyrus	46	−48, 40, 15	4.29	.001†
Superior frontal gyrus	10	−12, 68, 8	4.49	.04†

Abbreviations: BA, Brodmann area; MCS, minimally conscious state; PVS, persistent vegetative state; STG, superior temporal gyrus.
**P* value corrected for multiple comparisons at the voxel level.
†*P* value corrected for multiple comparisons at the cluster level.

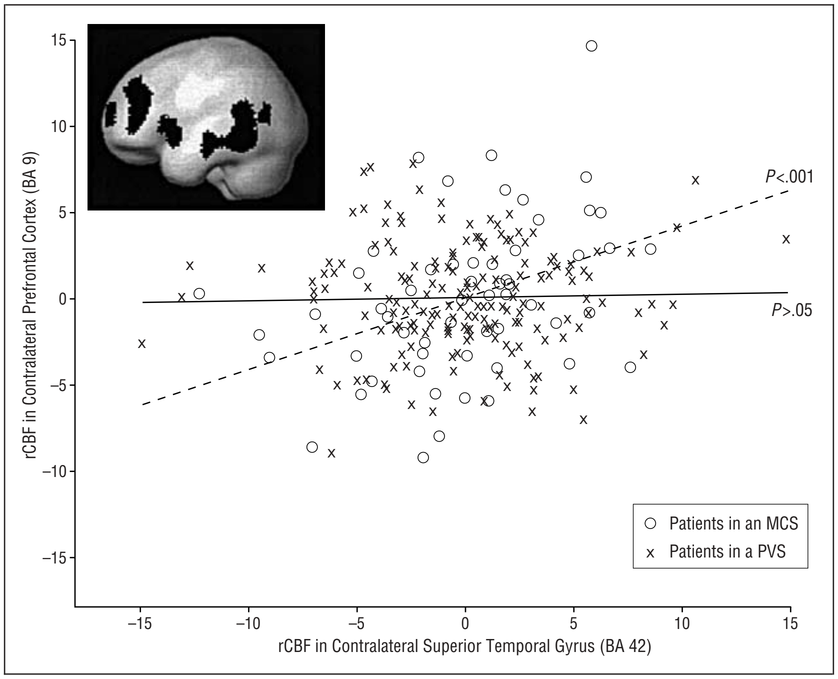

Figure 2. Cross-correlation of neural activity in auditory cortex (coordinates −44, −31, and 7) and prefrontal cortex (coordinates −42, 35, and 4) in patients in a minimally conscious state (MCS) vs patients in a persistent vegetative state (PVS). Inset, View of the the brain areas that remain functionally connected with auditory cortex in patients in an MCS but not in patients in a PVS. BA indicates Brodmann area; rCBF, regional cerebral blood flow.

areas 42 and 22) (Table 2). In patients in a PVS, auditory stimuli also activated the bilateral auditory cortex, but the extent of this activation was much smaller (mean volumes were 0.4 mL contralateral and 0.7 mL ipsilateral; Figure 1C). The peak voxels were located in bilateral TTG (Brodmann area 41) and STG (Brodmann area 42) (Table 2). In controls, patients in a PVS, or patients in an MCS, activation patterns were not significantly different for left- or right-sided auditory stimulation. The group (those in an MCS vs those in a PVS) × task (stimulation vs rest) interaction did not reveal significant differences in cerebral activation between our 2 patient groups.

Finally, we observed a significantly tighter functional connectivity[2-4] in patients in an MCS than in patients in a PVS between Brodmann area 42 contralateral to the stimulation and a network of brain areas including contralateral posterior temporal areas (Brodmann areas 21 and 22) and several prefrontal regions: bilateral middle frontal gyri (Brodmann areas 9 and 46), contralateral inferior frontal gyrus (Brodmann area 44-45), and contralateral frontal pole (Brodmann area 10) (**Table 3** and **Figure 2**).

COMMENT

In response to auditory stimulation, patients in an MCS activated spatially larger areas of auditory cortex than did patients in a PVS. Functional connectivity[2-4] between the secondary auditory cortex and the posterior temporal and prefrontal areas, involved in higher levels of auditory processing, was significantly more effective in patients in an MCS than in patients in a PVS. In agreement with our previous results,[3] controls activated bilateral temporal Brodmann areas 41, 42, and 22. Patients in a PVS activated bilateral Brodmann areas 41 and 42, but not higher-order associative Brodmann area 22. These results extend to a larger population of patients then our previous work about auditory processing in a PVS.[3] Moreover, using a random effect analysis, we identified the common denominator of cortical activation in response to these auditory stimuli in the patient in a canonical PVS.

In patients in an MCS, the activation pattern was spatially more extended than in patients in a PVS and encompassed not only Brodmann auditory areas 41 and 42 but also higher-order Brodmann area 22. A direct comparison between MCS and PVS, however, showed no significant difference in activation. This might be due to (1) an intermediate level of activation in patients in an MCS compared with controls and patients in a PVS, (2) power limitations of the design (large variance in patient populations), or (3) lack of emotional valence of the auditory stimuli. Indeed, clinical experience shows that patients in an MCS are often more responsive to stimuli with high emotional content. Nevertheless, the activation of higher-order associative temporal cortices found in patients in an MCS probably corresponds to a more elaborate auditory processing, allowing further cognitive integration of the stimuli.

Whereas the aforementioned analyses of cerebral segregation related to simple auditory processing did not show significant differences between patients in an MCS and patients in a PVS, the study of functional connectivity[2-4] showed significant differences in cortical integration of the stimuli between patients in an MCS and patients in a PVS. Indeed, only patients in an MCS showed preserved functional connections between Brodmann area 42 and posterior temporal and prefrontal associative areas. Posterior temporal cortices (Brodmann area 22-21) have been involved in high-order auditory perception.[11,12] The unimodal part of this auditory associative area (Brodmann area 22) is thought to be involved in the analysis of temporal acoustic features of speech and other highly modulated sounds.[13] Whereas its temporoparietal junction area is known to receive inputs from caudal parabelt areas,[14] many of its neurons are heteromodal and participate in cognitive aspects of auditory processing.[15] Functional imaging studies have reported activation of this area during auditory attention and perception.[16-18] Lesions in this region lead to contralateral hemi-inattention, neglect, or extinction of auditory stimuli in both monkeys[19] and humans.[20] The posterior part of the middle temporal gyrus (Brodmann area 21) is a multimodal associative area. Its neurons do not code for specific acoustic features (eg, do not exhibit frequency tuning), but are thought to be closely related to auditory selective attention[16] and aware perception.[17] Therefore, the observed preservation in corticocortical connectivity within different regions of the auditory associative Brodmann areas in the MCS compared with the PVS could be related to differences in attentional state and conscious perception.

Our findings also showed preserved functional connections in patients in an MCS between Brodmann area 42 and dorsolateral prefrontal (Brodmann areas 9 and 46), posterior inferior frontal (Brodmann areas 44 and 45), and frontopolar (Brodmann area 10) cortices. The role of the frontal lobe in auditory processing and its connections with auditory association cortices are not yet as precisely determined as for the visual domain. However, studies in primates demonstrate connections between the temporal and prefrontal cortex.[12] Recent work also suggests the involvement of frontal processing in successful normal auditory perception.[21] Prefrontal cortex is also known to be involved in auditory attention[16,22] and conscious perception of auditory stimuli.[17]

Apart from their clinical interest, our findings also contribute to the study of the neural correlates of consciousness. It is, however, of major importance to stress that our results should be used with appropriate caution regarding clinical decisions in individuals in a PVS or an MCS. Our data describe canonical PVS and MCS but do not rule out that some individuals might have cortical activation above the identified common denominator of cortical activation. For instance, some patients in a PVS may show a relatively preserved isolated cortical activity,[23,24] which may express itself through isolated nonpurposeful behavior.[24] Also, the present ^{15}O-radiolabled water–PET studies are only snapshot assessments of residual brain function, even if they were acquired during continuous electroencephalographic monitoring to assure the highest possible level of vigilance in each patient. It is well known from clinical experience that repetitive evaluations are mandatory in the evaluation and categorization of severely brain injured patients.

CONCLUSIONS

We showed preserved activation in bilateral auditory cortices (Brodmann areas 41 and 42) in patients in a PVS during simple auditory click stimuli, which probably reflects a residual neural encoding of basic sound attributes without further high-order processing or functional integration.[3] In patients in an MCS, a more widespread activation was observed, encompassing bilateral auditory associative areas (Brodmann area 22), suggesting a more elaborate level of processing. Moreover, we identified differences in cortico-cortical functional connectivity between auditory cortex and a large network of temporal and prefrontal cortices in patients in an MCS compared with patients in a PVS. These findings encourage ongoing developments of neuromodulatory and cognitive revalidation therapeutic strategies in patients in an MCS.[10] As a next step, more complex auditory stimuli should be used to better characterize the residual cognitive faculties of patients in an MCS.

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Corresponding author: Steven Laureys, MD, PhD, Cyclotron Research Center and Department of Neurology, University of Liège, Sart Tilman B35, 4000 Liège, Belgium (e-mail: steven.laureys@ulg.ac.be).

REFERENCES

1. Giacino JT, Ashwal S, Childs N, et al. The minimally conscious state: definition and diagnostic criteria. *Neurology.* 2002;58:349-353.
2. Laureys S, Faymonville ME, Peigneux P, et al. Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. *Neuroimage.* 2002;17:732-741.
3. Laureys S, Faymonville ME, Degueldre C, et al. Auditory processing in the vegetative state. *Brain.* 2000;123:1589-1601.
4. Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ. Psychophysiological and modulatory interactions in neuroimaging. *Neuroimage.* 1997;6:218-229.
5. The Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state, 1. *N Engl J Med.* 1994;330:1499-1508.
6. Talairach J, Tournoux P. *Co-Planar Stereotaxis Atlas of the Human Brain.* Stuttgart, Germany: Georg Thieme Verlag; 1988.
7. Friston KJ. Analysing brain images: principles and overview. In: Frackowiak RS, Friston KJ, Frith CD, Dolan RJ, Mazziotta JC, eds. *Human Brain Function.* San Diego, Calif: Academic Press; 1997:25-41.
8. Peigneux P, Maquet P, Meulemans T, et al. Striatum forever, despite sequence learning variability: a random effect analysis of PET data. *Hum Brain Mapp.* 2000;10:179-194.
9. Kaas JH, Morel A. Connections of visual areas of the upper temporal lobe of owl monkeys: the MT crescent and dorsal and ventral subdivisions of FST. *J Neurosci.* 1993;13:534-546.
10. Schiff ND, Plum F, Rezai AR. Developing prosthetics to treat cognitive disabilities resulting from acquired brain injuries. *Neurol Res.* 2002;24:116-124.
11. Engelien A, Silbersweig D, Stern E, et al. The functional anatomy of recovery from auditory agnosia: a PET study of sound categorization in a neurological patient and normal controls. *Brain.* 1995;118:1395-1409.
12. Binder JR, Rao SM, Hammeke TA, et al. Functional magnetic resonance imaging of human auditory cortex. *Ann Neurol.* 1994;35:662-672.
13. Kaas JH, Hackett TA. Subdivisions of auditory cortex and processing streams in primates. *Proc Natl Acad Sci U S A.* 2000;97:11793-11799.
14. Hackett TA, Stepniewska I, Kaas JH. Subdivisions of auditory cortex and ipsilateral cortical connections of the parabelt auditory cortex in macaque monkeys. *J Comp Neurol.* 1998;394:475-495.
15. Hikosaka K, Iwai E, Saito H, Tanaka K. Polysensory properties of neurons in the anterior bank of the caudal superior temporal sulcus of the macaque monkey. *J Neurophysiol.* 1988;60:1615-1637.
16. Pugh KR, Shaywitz BA, Shaywitz SE, et al. Auditory selective attention: an fMRI investigation. *Neuroimage.* 1996;4:159-173.
17. Engelien A, Huber W, Silbersweig D, et al. The neural correlates of "deaf-hearing" in man: conscious sensory awareness enabled by attentional modulation. *Brain.* 2000;123:532-545.
18. Jancke L, Mirzazade S, Shah NJ. Attention modulates activity in the primary and the secondary auditory cortex: a functional magnetic resonance imaging study in human subjects. *Neurosci Lett.* 1999;266:125-128.
19. Heilman KM, Pandya DN, Karol EA, Geschwind N. Auditory inattention. *Arch Neurol.* 1971;24:323-325.
20. Heilman KM, Valenstein E. Auditory neglect in man. *Arch Neurol.* 1972;26:32-35.
21. Griffiths TD, Penhune V, Peretz I, Dean JL, Patterson RD, Green GG. Frontal processing and auditory perception. *Neuroreport.* 2000;11:919-922.
22. Tzourio N, Massioui FE, Crivello F, Joliot M, Renault B, Mazoyer B. Functional anatomy of human auditory attention studied with PET. *Neuroimage.* 1997;5:63-77.
23. Menon DK, Owen AM, Williams EJ, et al, for the Wolfson Brain Imaging Centre Team. Cortical processing in persistent vegetative state [letter]. *Lancet.* 1998;352:200.
24. Schiff ND, Ribary U, Moreno DR, et al. Residual cerebral activity and behavioural fragments can remain in the persistently vegetative brain. *Brain.* 2002;125:1210-1234.