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DOCs include the vegetative state, the minimally conscious state, and coma. Special attention requires the locked-in syndrome.

The assessment of such patients is extremely difficult and depends on subjective interpretations of the observed spontaneous and volitional behavior.

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The term “DISORDERS OF CONSCIOUSNESS” implies that they are all linked by disruption to some common, underlying, clearly defined system known as consciousness.

Unfortunately, there is, as yet, no universally agreed definition of *consciousness*.

At present, consciousness cannot be measured by any machine.

Widely accepted definitions often refer to *awareness* of the self and the environment (Plum & Posner 1966).

Accordingly, patients with DOCs are often described as lacking awareness of self or environment.

What constitutes *awareness?*

What level of awareness is sufficient for a patient to be described as *consciously aware*? Can it be estimated only by expert clinical interpretation of ‘motor responsiveness’?

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COMA

Coma is a state of pathologic unconsciousness in which the eyes remain closed and the patient cannot be aroused (MRC, 1941)

The defining feature of coma is that the eyes remain continuously closed (even when noxious stimuli are applied) as a manifestation of the complete loss of sleep/wake cycles.

There is also no behavioral evidence of purposeful motor activity, response to command or expressive language ability.

The comatose state almost always resolves within 2–4 weeks. (Plum and Posner, 1982)

VEGETATIVE STATE

The return of spontaneous eye-opening marks the onset of vegetative state in an otherwise comatose individual.

Eyes are open but there is no evidence of sustained or reproducible, purposeful behavioral responses to stimuli, and no evidence of language comprehension or expression (AAN, 1995).

Vegetative state lasting at least 1month is called persistent. Vegetative state persisting for at least 3 months following nontraumatic brain injury, or 12 months following traumatic injury, is considered irreversible and the term permanent VS is applied.

This definition, however is widely criticized (International Working Party on VS, 1996), because, although highly improbable after these periods of time, recovery cannot be excluded with absolute certainty.

MINIMALLY CONSCIOUS STATE

Distinguished from coma and VS by the presence of at least one clearly discernible behavioral sign of self or environmental awareness (Giacino et al, 2002).

Most individuals recovering from coma or vegetative state transition through MCS en route to higher levels of consciousness. MCS may also be observed during the course of progressive decline in neurodegenerative disease.

It is essential to recognize MCS during the acute phase of recovery as outcome is known to be significantly more favorable, relative to vegetative state.

MCS (2)

Diagnosis of MCS is based on clear-cut behavioral evidence of one or more of the following behaviors:

1. simple command following;

2. intelligible verbalization;

3. recognizable verbal or gestural ‘yes/no’ responses (without regard to accuracy);

4. movements or emotional responses that are triggered by relevant environmental stimuli and cannot be attributed to reflexive activity. Examples include:

smiling or crying following exposure to emotionally salient (e.g. family photographs) but not neutral stimuli (e.g. photographs of objects);

vocalizations or gestures that occur in direct response to attempts to prompt speech;

accurate reaching toward objects placed in the immediate visual field;

manipulation of objects placed in the hand;

sustained visual fixation or pursuit.

MCS (3)

MCS patients cannot be considered vegetative becuase they show signs of voluntary behaviour, but remain unable to communicate functionally

Emergence from MCS is signaled by the recovery of reliable and consistent communication or functional object use, as these behaviors permit meaningful interaction with the environment and enable assessment of higher cognitive functions.

Other authors suggested that when simple command following and yes/no responses reemerge, regardless of their consistency or accuracy, these behaviors no longer represent ‘minimal’ evidence of consciousness, but rather an ability to actively engage in environmental interactions. (Taylor et al., 2007)

LOCKED-IN SYNDROME (Plum & Posner 1966)

may be mistaken for VS

Patients who are locked-in are unable to speak or move

Limited eye movements and blinks are usually possible.

Due to lesions of the pons disrupting the descending motor pathways: sensation and consciousness entirely intact, while disrupting almost all forms of motoric behavior.

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The burden of proof for establishing conscious awareness lies in behavioral assessment.

Behavior represents indirect evidence of consciousness and reliance on behavioral markers may lead to misdiagnosis.

Differentiating reflexive or involuntary movement from intentional behavior at the bedside is often difficult and typically requires repeated assessment.

Even when purposeful, behavioral performance in this population is inconsistent since often fluctuates.

Errors may arise from complicating factors related to the patient, the examiner or the environment.

Recent advances in behavioral assessment of individuals with disorders of consciousness

Joseph T. Giacino and Colette M. Smart Curr Opin Neurol 20:614–619. 2007

Behavioral assessment methods remain the ‘gold standard’ for patients with DOC.

The effectiveness of a given instrument rests on its capacity to measure the construct of interest, replicate results over time and across examiners, and relate the findings to diagnosis, prognosis and treatment.

Despite the availability of a wide range of standardized behavioral rating scales (SRS), their psychometric properties and clinical utility in individual cases varies considerably.

Individualized Quantitative Assessment Procedures (IQBA) strategies, designed to address case-specific questions, serve an important complementary role but are underutilized in the clinical setting.

NEUROPHYSIOLOGY

A lot of ERP metaanalyses demonstrated that the absence of cortical somatosensory evoked potentials (SEPs) are good predictors of unfavourable outcome.
Systematic reviews confirmed the superior predictive value of SEPs compared with other tests. For example, a meta-analysis of 25 studies confirmed that SEPs are superior, with few exceptions, to pupillary responses, motor responses, GCS, EEG and CT for the prediction of outcome after acute severe brain damage (Carter and Butt, 2005).

IMAGING

Promising results of MRS, volumetry and DTI in the evaluation of traumatic or anoxo-ischaemic brain lesions, detecting damage of the brainstem, basal ganglia and white matter tracts not visible on conventional sequences.

A DTI study raised the possibility of detecting ongoing axonal regrowth many years after the initial injury in 2 patients in a MCS for many years after a severe TBI (Voss et al., 2006). The first patient, who underwent a first MRI when he spontaneously emerged from a MCS, 19 years after the trauma, showed an increased anisotropy in the parieto-occipital white matter that normalized on a follow-up scan performed 18 months later, with a synchronous improvement in language and motor functions and increased metabolism in FDG PET. The second showed aberrant connections in R hemisphere while still in MCS.

Variations in anisotropy could be related to axonal regrowth and could occur many years after a severe TBI.

Significant improvement of superior functions, observed many years after the acute brain injury, could be related to the ‘rewiring’ of the brain structure through white matter tracts regrowth (Laureys et al. 2006).

Quantitative imaging could lead to a more objective evaluation of destruction or preservation of critical brain areas at the acute phase of brain injury, which could be integrated in multi-parametric decisional strategies for these patients.

FUNCTIONAL NEUROIMAGING

Until recently, based only on measurement of resting CBF and glucose metabolism with SPECT and FDG PET.

Widespread reductions in metabolic activity of up to 50% reported in **VS**, although normal metabolism (Schiff et al. 2002) and blood flow (Agardh et al. 1983) is possible.

Isolated islands of metabolism identified in circumscribed regions of cortex, suggesting the potential for cognitive processing in a subset of patients (Schiff et al. 2002).

Significantly higher metabolic levels in **LIS** compared to **VS** (Levy et al. 1987).

No greymatter areas show reduced metabolism in acute or chronic **LIS** compared to age-matched healthy **controls** (e.g., Laureys et al. 2004).

Longitudinal PET examinations revealed increases in resting metabolism coincident with marked clinical improvements in motor function in a case of recovery from **MCS** (Voss et al. 2006).

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NEUROPHYSIOLOGY

A very promising candidate for predicting (good) outcome is the mismatch negativity (MMN), a component which appears in auditory oddball paradigms. MMN has high specificity (91% of patients not regaining consciousness had no MMN) but low sensitivity (only 33% of patients regaining consciousness had a MMN). A very high proportion of patients (89%) evoking this component later regained consciousness (Fischer et al., 2004, Luaute et al., 2005).

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NEUROPHYSIOLOGY

Long-latency ERPs to words were used to estimate the integrity of language comprehension in brain damaged non communicative patients. Schoenle and Witzke (2004) recorded ERPs in response to sentences ending with semantically congruent and incongruent words. An N400 response to incongruous words was reported in nearly all (90%) of the patients who are not in a VS, in a majority (77%) of ‘near-vegetative state’ patients, but also in some VS patients (12%),.

P300 wave was observed to the patient’s first name in the MCS (Laureys et al., 2004). Perrin et al., however, observed that P300 responses to patients’ own names can also be observed in a well-documented chronic vegetative state, showing no subsequent recovery (unpublished).

Long-latency ERPs (P300 and N400 responses) were also observed in some VS patients with EEG-background activity above 4 Hz (Kotchoubey et al., 2005; Hinterberger et al., 2005).

These studies suggest that P300 or N400 responses cannot be used to differentiate VS from MCS patients, although do not necessarily reflect conscious perception.

FUNCTIONAL NEUROIMAGING

Metabolic studies can only identify functionality at the most general level, mapping cortical and subcortical regions that are *potentially* recruitable, but cannot relate neural activity within such regions to specific cognitive processes.

Methods such as $H_2{}^{15}O$ PET and fMRI can be used to link distinct and specific physiological responses (changes in regional CBF or changes in regional cerebral hemodynamics) to specific cognitive processes, in the absence of any overt response (e.g., a motor action or a verbal response) on the part of the patient.

FUNCTIONAL NEUROIMAGING

Recently, new **activation studies** have been used to assess cognitive functions in DOCs without the need for any overt response of the patient.

This approach has been used to identify residual brain functions in patients who behaviorally meet all of the standard clinical criteria for VS yet retain cognitive abilities that have evaded detection using standard clinical methods.

Similarly, in some MCSs, functional neuroimaging has been used to demonstrate residual cognitive capabilities even when there is no clear and consistent external behavioral evidence to support this conclusion.

Early activation studies in DOCs used $H_2{}^{15}O$ PET, in part because the technique was more available and in part because of the yet unresolved logistic difficulties in using the strong magnetic fields for fMRI in critically ill patients.

However, also $H_2{}^{15}O$ PET studies are limited by issues of radiation burden (precluding essential longitudinal or follow-up studies or examination of multiple cognitive processes within any one session).

FUNCTIONAL NEUROIMAGING

De Jong et al. (1997). used $H_2{}^{15}O$ PET to measure rCBF in a posttraumatic VS during an auditorily presented story told by his mother. Compared to nonword sounds, activation was observed in the anterior cingulate and temporal cortices, reflecting emotional processing of the contents, or tone, of the mother's speech.

In another VS patient, Menon et al. (1998) used PET to study covert visual processing in response to familiar faces. When the patient was presented with pictures of the faces of family and close friends, robust activity was observed in the right fusiform gyrus, the so-called human face area.

Both of these studies involved single, well-documented cases;

However, the statistical power of individual PET studies is also low, requiring group studies, whose results are limited by heterogeneity in terms of individual diagnosis, residual functions, and potential for recovery.

In cohort PET studies of VS patients, normal brain activity in response to external stimulation has generally been the exception rather than the rule.

For example, in one PET study of 15 VS patients with high-intensity noxious electrical stimulation, the patients, unlike control subjects, did not activate secondary somatosensory, insular, posterior parietal, or anterior cingulate cortices (Laureys et al. 2002).

Recently, shift of emphasis from PET activation studies using $H_2{}^{15}O$ PET to fMRI:

- more widely available than PET
- increased statistical power
- improved spatial and temporal resolution
- no associated radiation burden.

Cerebral response to patient's own name in the vegetative and minimally conscious states

H.B. Di, MS; S.M. Yu, BSc; X.C. Weng, PhD; S. Laureys, MD, PhD; D. Yu, BSc; J.Q. Li, BSc; P.M. Qin, MS; Y.H. Zhu, PhD; S.Z. Zhang, MS; and Y.Z. Chen, MD

NEUROLOGY 2007;68:895–899

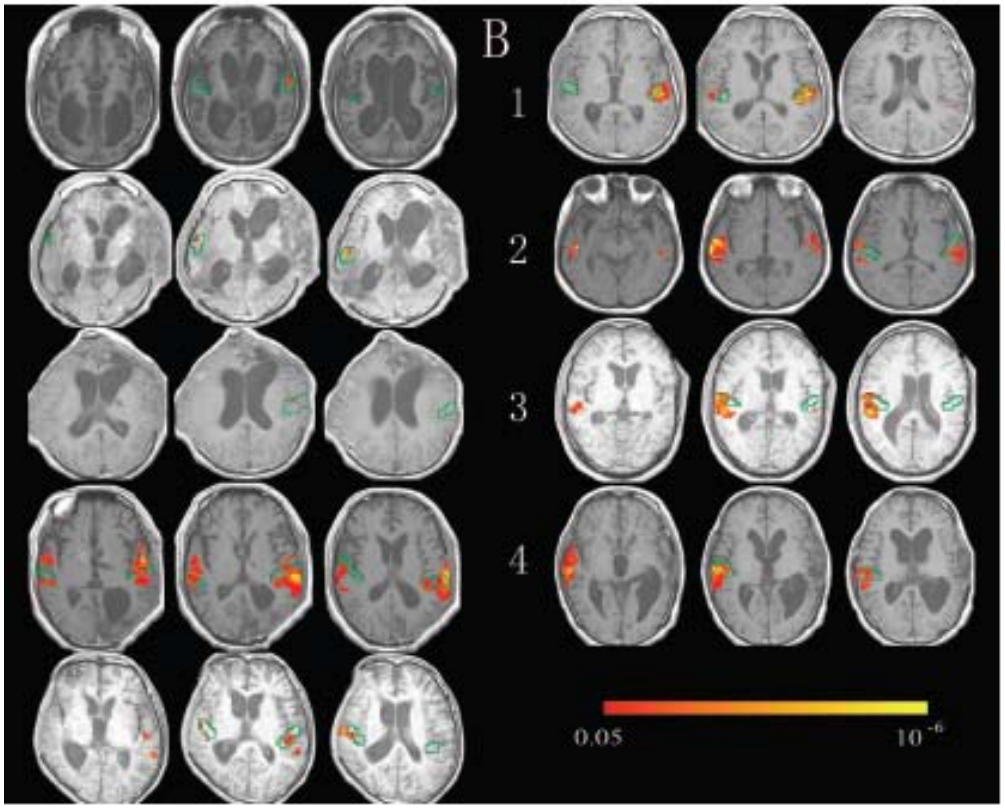


Figure. Areas showing significant ($p < 0.05$, corrected) activation in patients in a vegetative state (VS) (Patients 3, 4, 5, 6, and 7) (A) and patients in a minimally conscious state (MCS) (B). Green contours denote the boundary of the primary auditory areas as defined by anatomic landmarks (see text for details). The patients with VS (Patients 6 and 7), and all four patients with MCS showed activation in associative areas beyond the primary auditory cortex. Left is on the right of the image.

SELECTIVE CORTICAL PROCESSING OF ONE'S OWN NAME

Event-related fMRI study comparing sentences containing the patient's own name (e.g., "James, hello James"), spoken by a variety of unfamiliar voices, with sentences containing another first name, in a 10- months VS patient.

Differential cortical processing was observed to the patient's own name in a region of the medial prefrontal cortex, similar to that observed in three healthy volunteers. Staffen et al. (2006)

Differential P3 responses to patient's own names (compared to other names) in LIS, MCS, and some VS patients in ERPs (Perrin et al. 2006).

A HIERARCHICAL APPROACH TO STUDYING DISORDERS OF CONSCIOUSNESS

(Owen et al., 2005)

Table 2. Hierarchical strategy to evaluate cognition in non-communicative severely brain-damaged patients

Level of processing	Question posed	Contrast used	Regions involved
Acoustic	Basic response to any sound?	Noise bursts, silence	Auditory superior and middle temporal gyri
Perceptual	Discrimination between different categories of sound (i.e. recognise speech as more than a sound?)	Speech sounds, signal correlated noise	Superior temporal gyri, extending ventro-laterally into superior temporal sulcus
Phonological	Recognise words in absence of overall meaning (i.e. content of words)?	3 increasing levels of intelligibility (depending on signal-to-noise ratios)	Left anterior and superior temporal lobe
Semantic	Understand meaning of sentence?	Ambiguous sentences (containing words with more than one meaning), unambiguous sentences	Left posterior inferior temporal cortex and bilateral inferior frontal gyri

Strategy proposed by Owen *et al.* [46•] for neuroimaging, but also applicable to event related potentials studies [15••,33•].

ACOUSTIC LEVEL OF PROCESSING

It is important to establish normal or near-normal sensory perception in any candidate patient for functional neuroimaging studies of higher cognitive functions (e.g., language processing).

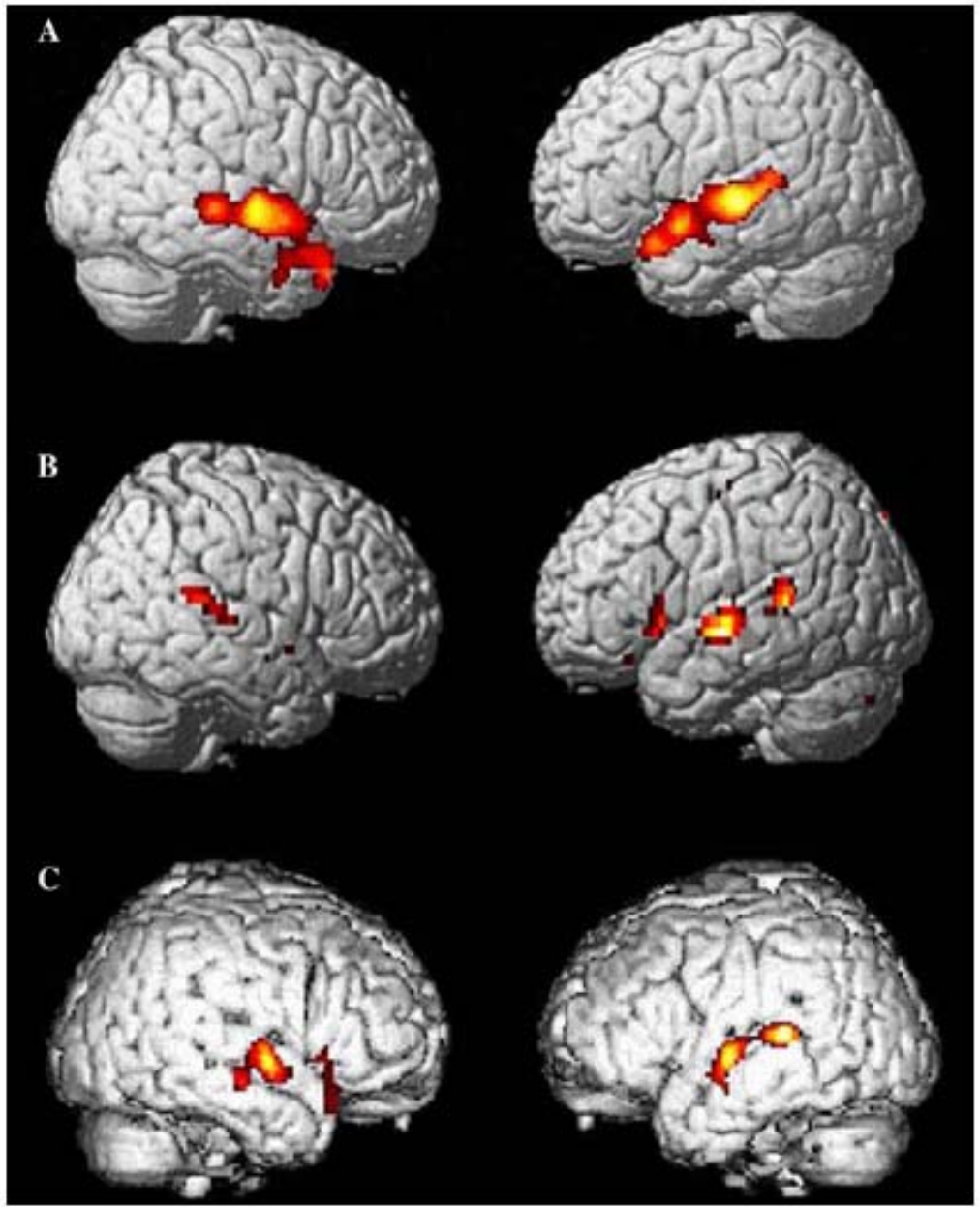
Auditory or visual evoked potentials are usually sufficient to establish that the respective neural pathways are intact.

The integrity of the auditory neural axis can be assessed using a BAEPs and passive mismatch negativity (MMN).

MMN is thought to reflect a precognitive response generated from a comparison between the deviant input and a neural memory trace encoding the physical features of the repetitive sound (Naatanen 2003).

MMN ha been successfully applied to the assessment of vegetative patients, although with considerable variability in results (Jones et al. 2000; Kotchoubey et al. 2001).

PERCEPTUAL LEVEL OF PROCESSING



(Owen et al. 2005)

Brain activity when speech is compared with signal-correlated noise
in healthy volunteers **(A)**
and
in two patients **(B, C)** meeting the clinical criteria for V.S.
The speech-specific bilateral superior temporal-lobe activity observed in the two patients is similar to that observed in controls.

PHONOLOGICAL LEVEL OF PROCESSING

At perceptual level, processing do not allow any conclusions about comprehension (is speech is processed beyond the point at which it is identified as speech???).

Answer can be approached at phonological level, by documenting responses to a set of stimuli of graded complexity.

During the task, healthy volunteers listen passively to sentences that have been distorted by adding noise such that they produce a graded range of intelligibility (as a measure of speech comprehension. Intelligibility (the amount of a sentence that is understood) was found to correlate with fMRI study activation in a region of the left anterior and superior temporal lobe (Davis & Johnsrude 2003).

These findings suggest that activity in the left anterior and superior temporal lobe reflects processing of the linguistic content of spoken sentences, rather than their acoustic properties.

PHONOLOGICAL LEVEL OF PROCESSING

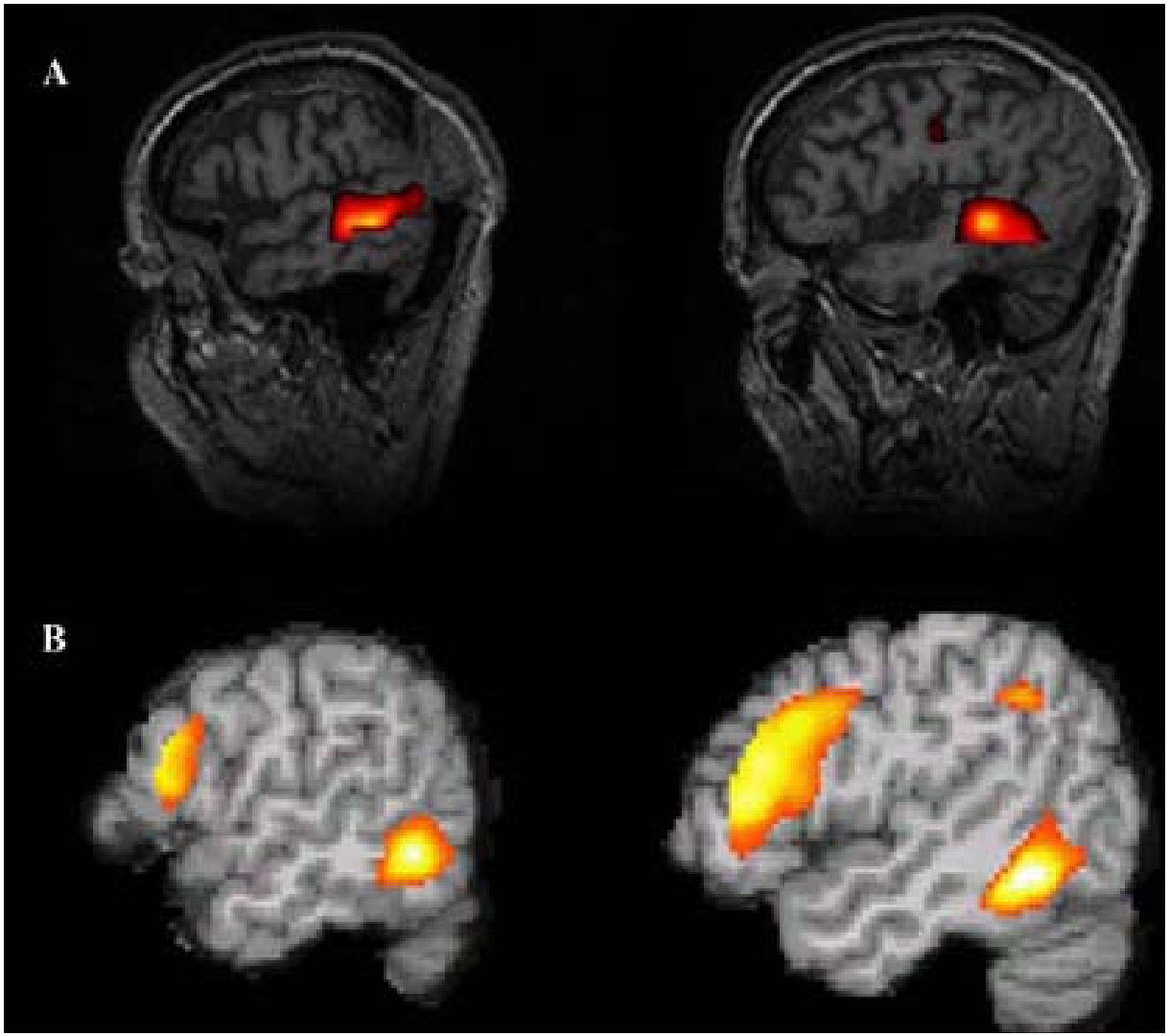
This auditory comprehension paradigm has been adapted for use in patients with disorders of consciousness (Owen et al. 2005).

While the left superior temporal sulcus responds to the presence of phonetic information in general, its anterior part appears to respond only when the stimuli become intelligible (Scott et al. 2000).

Whether the responses observed reflect speech comprehension per se (i.e., understanding the contents of spoken language) or a more basic response to the acoustic properties of intelligible speech that distinguish it from less intelligible speech cannot be determined on the basis of these data.

SEMANTIC LEVEL OF PROCESSING

Owen et al., 2005; Coleman et al., 2007)

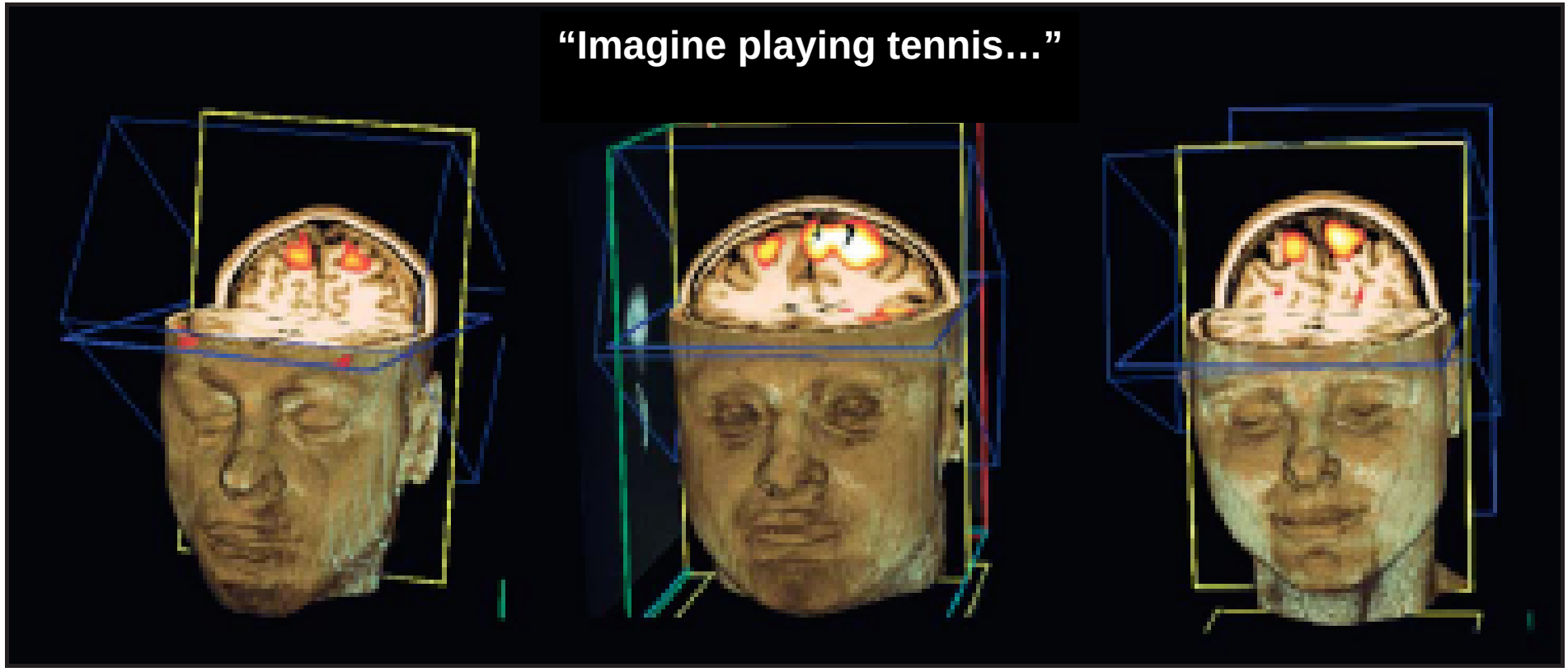


fMRI data for the ambiguous sentences versus unambiguous sentences comparison.
Like healthy volunteers (**B**; adapted from Rodd et al. 2005), this patient **(A)** exhibited significant signal intensity changes in the left posterior inferior temporal cortex, suggesting that some of the processes involved in activating, selecting, and integrating contextually appropriate word meanings may be intact, despite the clinical diagnoses.

Using Functional Magnetic Resonance Imaging to Detect Covert Awareness in the Vegetative State

Adrian M. Owen, PhD; Martin R. Coleman, PhD; Melanie Boly, PhD; Matthew H. Davis, PhD; Steven Laureys, MD, PhD; John D. Pickard, MD, PhD

ARCH NEUROL / VOL 64 (NO. 8), AUG 2007

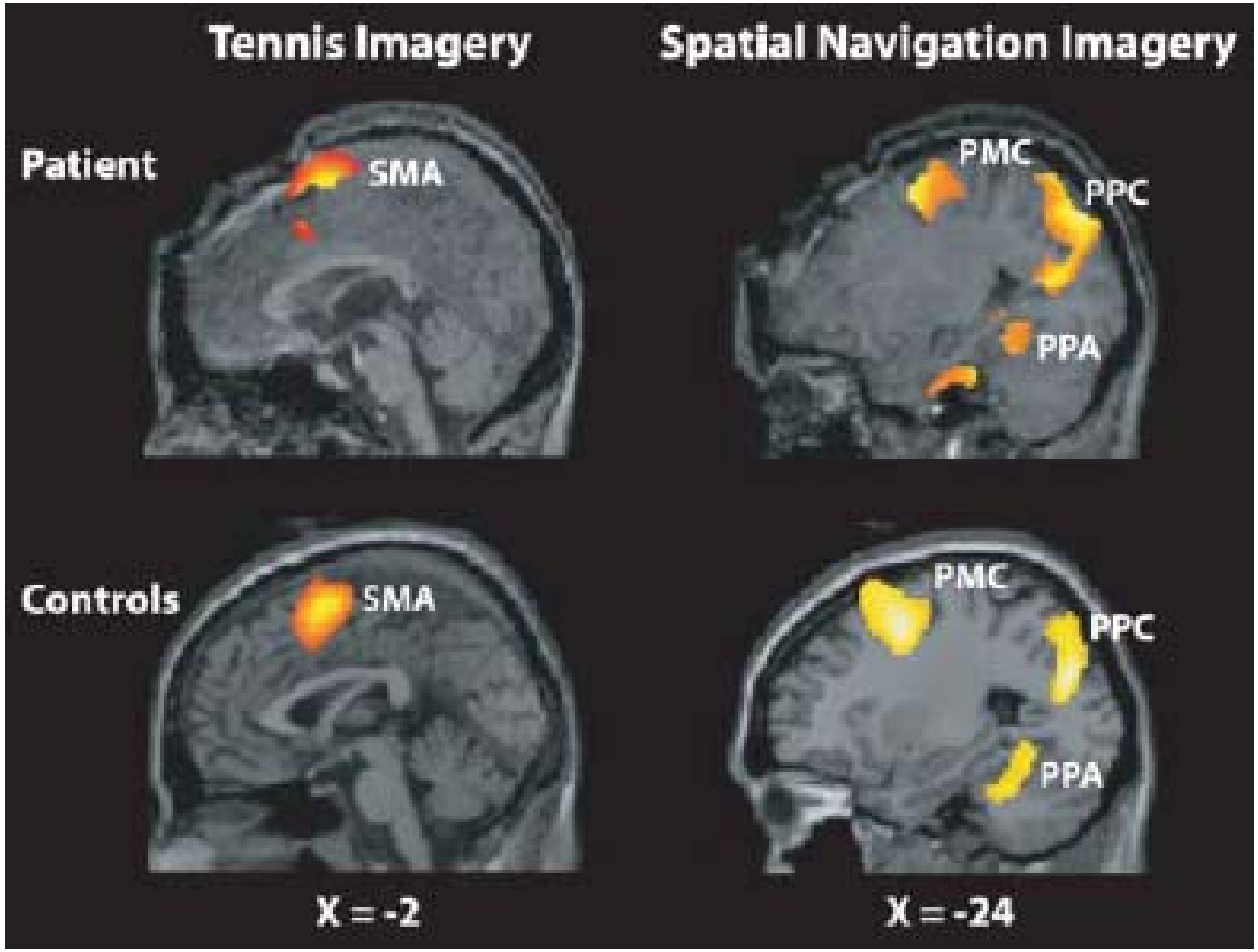


Three healthy volunteers imagine playing tennis during real-time functional magnetic resonance (MR) imaging at the Medical Research Council Cognition and Brain Sciences Unit, Cambridge, England. Functional MR imaging data are superimposed on 3-dimensional anatomical reconstructions of structural MR data for online examination of brain activity during the imaging period. Similar significant activation is observed in the supplementary motor area in all 3 volunteers.

Detecting Awareness in the Vegetative State

Adrian M. Owen,[1*] Martin R. Coleman,[2] Melanie Boly,[3] Matthew H. Davis,[1]
Steven Laureys,[3] John D. Pickard[2]

8 SEPTEMBER 2006 VOL 313 SCIENCE
1402



Supplementary motor area (SMA) activity during tennis imagery in a patient diagnosed as being in a vegetative state and a group of 12 healthy volunteers (controls).

Parahippocampal gyrus (PPA), posterior parietal-lobe (PPC), and lateral premotor cortex (PMC) activity while the patient and the same group of volunteers imagined moving around a house.

All results are thesholded at $P<0.05$ corrected for multiple comparisons. ***X*** values refer to distance in mm from the midline in stereotaxic space.

In dubio pro vita

- Problemi nella comprensione dello stimolo:

  - uditivo (problemi vie nervose, lesioni area primaria, afasie)

  - visivo (problemi vie nervose, lesioni area primaria, agnosie)

- Problemi nella traslazione dello stimolo in atto volitivo

- Problemi nell'output motorio

- Possibilità di una **Supra LIS?**

  (SHEWMON)

Problema interpretativo dell'idranencefalo

Using Functional Magnetic Resonance Imaging to Detect Covert Awareness in the Vegetative State

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Future integration of emerging functional neuroimaging techniques with existing clinical and behavioral methods of assessment will:

reduce diagnostic errors between these related conditions (Laureys et al. 2006; Schiff et al. 2006).

provide new prognostic indicators, helping to differentiate outcome on the basis of the underlying mechanisms responsible and thus improve therapeutic choices (Laureys et al. 2006).

contribute to our understanding of concepts such as awareness, arousal, volition, and even consciousness.

Consciousness without a cerebral cortex:
a challenge for neuroscience and medicine.

Merker B. *Behav Brain Scie* 2007 Feb;30(1):63-81; discussion 81-134

In vertebrate brain

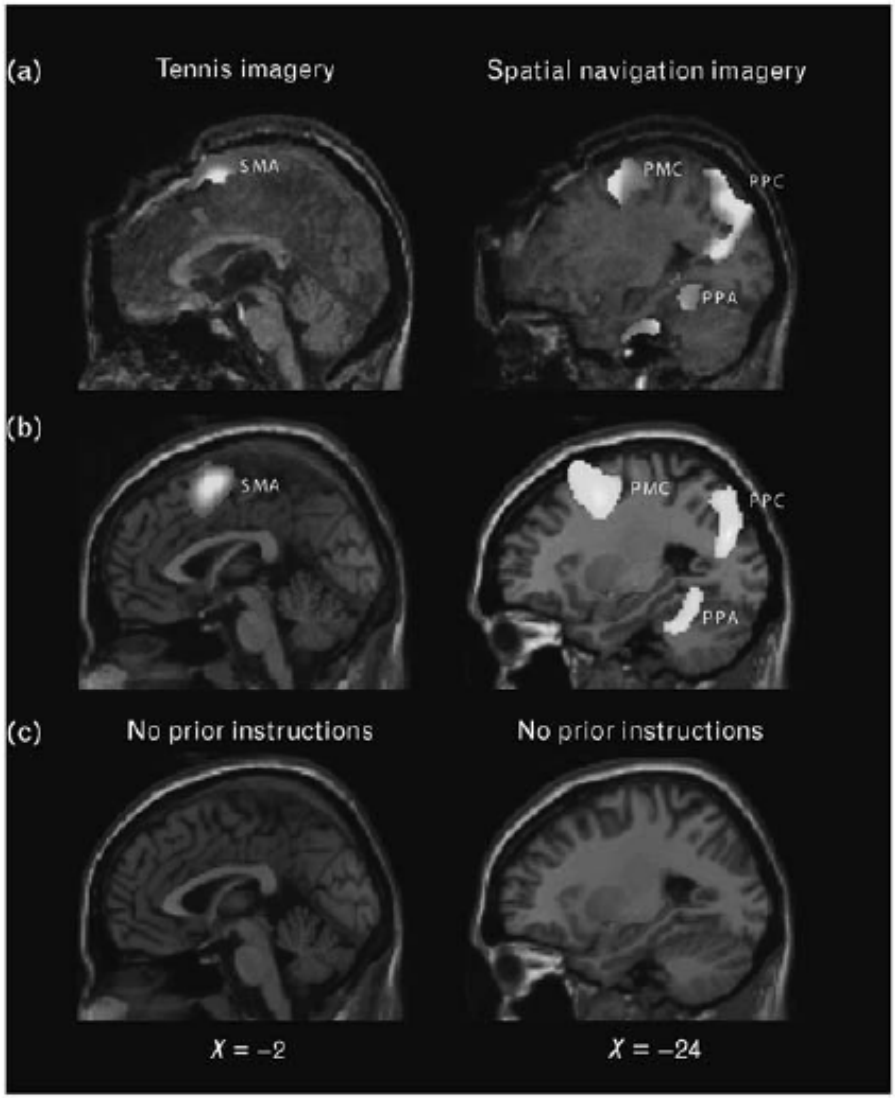
- … *upper brainstem system … integrates the massively parallel and distributed information capacity of the cerebral hemispheres into the limited-capacity, sequential mode of operation required for coherent behavior.*
- *It maintains special connective relations with cortical territories implicated in attentional and conscious functions,* ***but is not rendered nonfunctional in the absence of cortical input****.*
- *This helps explain the purposive, goal-directed behavior exhibited by mammals after* ***experimental decortication****, as well as the* ***evidence that children born without a cortex are conscious****.*
- *Brainstem mechanisms are integral to the constitution of the conscious state, and an adequate account of* ***neural mechanisms of conscious function cannot be confined to the thalamocortical complex alone****.*

Thanks for your attention

Functional MRI in disorders of consciousness: advantages and limitations

Adrian M. Owen[a,b] and Martin R. Coleman[b]

Curr Opin Neurol 20:632–637.



Indistinguishable functional MRI (fMRI) activity in a vegetative state patient (a) and healthy controls (b) while imagining playing tennis (left column) or
moving around a house (right column) [Owen et asl. Science, 2006].
(c) The results from healthy volunteers when noninstructive sentences involving the same key words were
used [Owen et asl. Science, 2007].

Disorders of Consciousness

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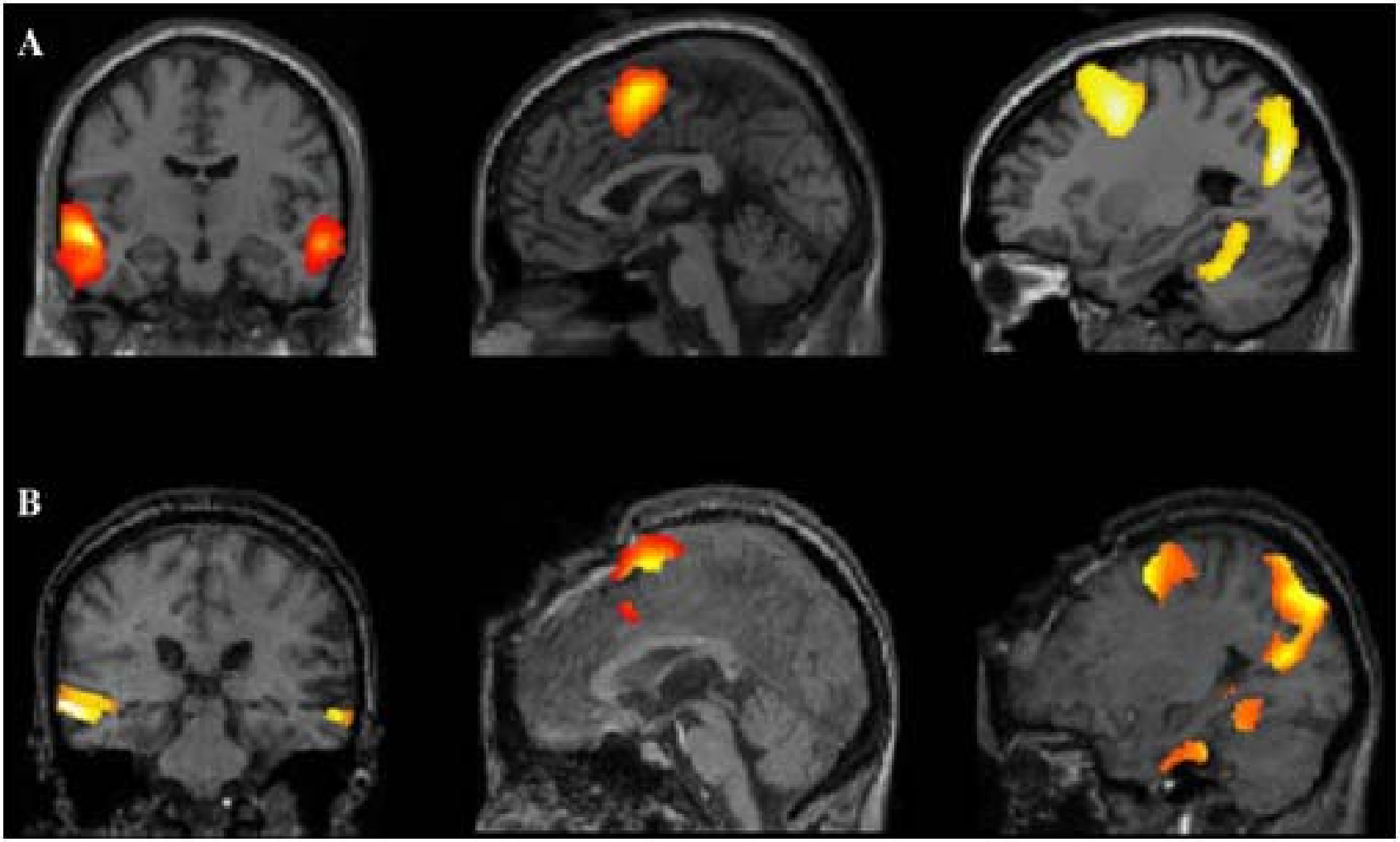
Ann. N.Y. Acad. Sci. 1124: 225–238 (2008)



Indistinguishable fMRI activity in healthy controls **(A)** and in a vegetative patient **(B)** while listening to speech versus signal-correlated white noise (left column), while imagining playing tennis (middle column), or while imagining walking around the house (right column). Adapted from Owen et al. (2006).