

Auditory processing in the vegetative state

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Summary

$H_2^{15}O$ -PET was used to investigate changes in regional cerebral blood flow in response to auditory stimulation in patients in the vegetative state. Five patients in a vegetative state of hypoxic origin were compared with 18 age-matched controls. In addition, the cerebral metabolism of these patients and 53 age-matched controls was studied using [^{18}F]fluorodeoxyglucose. In control subjects, auditory click stimuli activated bilateral auditory cortices [Brodmann areas (BA) 41 and 42] and the contralateral auditory association cortices (BA 22). In the patients, although resting metabolism was decreased to 61% of normal values, bilateral auditory areas 41 and 42 showed activation as seen in the controls, but the temporoparietal junction cortex (BA 22) failed to be activated. Moreover, the auditory

association cortex was functionally disconnected from the posterior parietal association area (BA 40), the anterior cingulate cortex (BA 24) and the hippocampus, as revealed by psychophysiological interaction analysis. Thus, despite altered resting metabolism, the auditory primary cortices were still activated during external stimulation, whereas hierarchically higher-order multimodal association areas were not. Such a cascade of functional disconnections along the auditory cortical pathways, from the primary auditory areas to multimodal and limbic areas, suggests that the residual cortical processing observed in the vegetative state cannot lead to the integrative processes that are thought to be necessary for the attainment of the normal level of awareness.

Keywords: vegetative state; consciousness; functional neuroimaging; statistical parametric mapping; positron emission tomography

Abbreviations: BA = Brodmann area; rCBF = regional cerebral blood flow; rCMRGlu = regional cerebral metabolic rate for glucose; SPM = statistical parametric mapping; STG = superior temporal gyrus; STS = superior temporal sulcus; TTG = transverse temporal gyrus

Introduction

The vegetative state is a clinical condition characterized by recurring and prolonged periods of arousal with no sign of awareness (ANA Committee on Ethical Affairs, 1993; Multi-Society Task Force on PVS, 1994). Patients in the vegetative state have complete or partial preservation of brainstem and hypothalamic autonomic functions, but show no evidence of sustained, reproducible, purposeful or voluntary behavioural responses to auditory, visual, tactile or noxious stimuli, or evidence of language comprehension or expression. The most common causes of the vegetative state are severe hypoxic-ischaemic encephalopathy and head trauma. The vegetative state can occur a few days after the cerebral insult, but if it persists for >1 month it is called the 'persistent vegetative state'.

The diagnosis of the vegetative state is delicate. It remains

difficult to recognize infallibly unambiguous signs of conscious perception by the patient of his environment and of his self. This complication is reflected in the frequent misdiagnosing of the vegetative state (Childs *et al.*, 1993; Andrews *et al.*, 1996). First, there is a theoretical limitation to the certainty of the diagnosis, since we can only infer the presence or absence of conscious experience in another person (Bernat, 1992). This is even more so because consciousness is not an all-or-none phenomenon but part of a continuum (Wade and Johnston, 1999). Secondly, some spontaneous and stimulus-induced behaviour is disconcerting in patients in the vegetative state. They are usually not motionless: they chew, grind their teeth, swallow, and move their head, limbs and trunk in meaningless ways. Occasionally, they smile or shed tears and even utter grunts, moan or scream without

discernible reason. Their grasp reflex may be preserved, and painful stimulation can provoke an extensor or flexor response. They are often aroused by prominent stimuli, as evidenced by an increase in the breathing rate, grimaces or limb movement. Distressingly, they sometimes turn their head and eyes towards a loud sound or a moving object but, importantly, not in a consistent and reproducible manner. All these abilities are believed to be mediated through subcortical and brainstem structures, as they can also be observed in infants with anencephaly (Medical Task Force on Anencephaly, 1990). Thirdly, given that motor capacities may be severely impaired in these patients, careful, prolonged and repeated clinical examination is needed before it can be concluded that a patient's wakefulness is truly devoid of any behaviourally detectable expression of awareness.

Functional neuroimaging cannot replace the clinical assessment of patients in the vegetative state. Nevertheless, it can describe objectively how deviant from normal is the cerebral activity and its regional distribution, at rest and under various conditions of stimulation. A better understanding of the vegetative state can be expected from such studies. Most previous PET studies of patients in the vegetative state have measured resting brain metabolism, and have demonstrated a mean global reduction in the cerebral metabolic rate for glucose (CMRGlu) ranging from 40 to 60% below normal (Ingvar, 1973; Levy *et al.*, 1987; De Volder *et al.*, 1990; Tommasino *et al.*, 1995; Rudolf *et al.*, 1999). We have shown previously that the metabolically most impaired regions are the frontal and parietal associative cortices (Laureys *et al.*, 2000b) and that distant cerebral areas are functionally disconnected in the vegetative state (Laureys *et al.*, 1999a, 2000a). Measurement of residual cognitive processing in the vegetative state, using H₂¹⁵O-PET (de Jong *et al.*, 1997; Menon *et al.*, 1998; Owen *et al.*, 1999) or magnetoencephalography (MEG) (Ribary *et al.*, 1998) has so far been limited to anecdotal case reports. The present study is the first that measures prospectively changes in regional cerebral blood flow (rCBF) and functional cerebral connectivity during auditory processing in a group of patients in the vegetative state.

Material and methods

Subjects

The study was approved by the Ethics Committee of the Faculty of Medicine of the University of Liège. Written informed consent was obtained from the families of all patients and from all control subjects according to the Declaration of Helsinki.

Control population

The control population consisted of drug-free, healthy volunteers without any significant medical, surgical or psychiatric history. CMRGlu data were obtained from 53 subjects (18 females, 35 males; mean age 42 years, range

18–76 years). Data on rCBF were obtained from 18 subjects (10 females, eight males; mean age 33 years, range 19–45 years).

Patient population

We prospectively selected five patients in the vegetative state of hypoxic origin (mean age 44 years, range 28–63 years). Demographic data are summarized in Table 1. The vegetative state was diagnosed according to established criteria (ANA Committee on Ethical Affairs, 1993; Multi-Society Task Force on PVS, 1994): (i) spontaneous eye opening and behaviourally assessed sleep-wake cycles; (ii) preserved autonomic functions (respiratory, haemodynamic and thermoregulatory); (iii) no evidence of awareness of the environment; (iv) no evidence of reproducible voluntary behavioural responses to any stimuli; (v) no evidence of language comprehension or expression. None of the patients had a history of impaired auditory acuity. All patients had preserved pupillary, corneal and vestibulo-ocular reflexes. Brainstem auditory evoked potentials showed preserved pontine and midbrain function in all patients. Somatosensory evoked potentials obtained by stimulation of the median nerve showed the presence of primary somatosensory cortex potentials (N20) in all patients except patient 2, from whom only medial lemniscus potentials (P14) were recorded.

All patients except patient 5 had frequent spontaneous head and trunk movements necessitating muscular blockade during scanning. These patients were already intubated or tracheostomized before PET scanning (some needed assisted ventilation during their hospital stay but all of them triggered the respirator by themselves). Patient 5 was scanned while receiving low doses of intravenous midazolam (0.025 mg/kg per hour), which did not interfere with spontaneous respiration. Patient 4, a heroin addict who was receiving methadone substitution, needed low doses of alfentanil (4.7 µg/kg per hour) and midazolam (0.09 mg/kg per hour) during scanning.

Data acquisition

PET

PET data were obtained with a Siemens CTI 951 16/32 scanner (Siemens, Erlangen, Germany). A transmission scan was performed to allow measured attenuation correction. Data were reconstructed using a Hanning filter (cut-off frequency 0.5 cycle/pixel) and corrected for attenuation and background activity.

Resting metabolism. CMRGlu was studied after intravenous injection of 5–10 mCi (185–370 MBq) [¹⁸F]fluorodeoxyglucose. Sequential arterial blood samples were drawn during the whole procedure as described elsewhere (Maquet *et al.*, 1990). The operational equation of (Phelps *et al.*, 1979) with a lumped constant of 0.418 was

Table 1 Summary of clinical, electrophysiological and structural imaging data of the patients

	Patient				
	1	2	3	4	5
Clinical features					
Sex (age, years)	Female (42)	Male (37)	Female (52)	Male (28)	Female (63)
Cause	Respiratory arrest	Cardiorespiratory arrest	Respiratory arrest	Cardiorespiratory arrest	Respiratory arrest
Time spent in VS before PET	38 days	3 days	19 days	13 days	36 days
Clinical status after 3 months	VS	VS	Moderate disability	Moderate disability	Good recovery
Neurological symptoms					
Verbal response	None	None	None	None	None
Eye opening	Spontaneous	Spontaneous	Spontaneous	Spontaneous	Spontaneous
Pupillary reactions	Normal	Normal	Normal	Normal	Normal
Spontaneous eye movements	Roving conjugate	Roving conjugate	Roving conjugate	Roving conjugate	Dysconjugate
Oculocephalic responses	Normal	Normal	Normal	Normal	Normal
Oculovestibular responses	Normal	Normal	Normal	Normal	Normal
Corneal reflexes	Present	Present	Present	Present	Present
Respiratory reflex	Present	Present	Present	Present	Present
Best motor response	Extensor	None	Grimacing	Extensor	Extensor
Deep tendon reflexes	Increased	Normal	Absent	Increased	Increased
Skeletal muscle tone	Flexor	Flaccid	Flaccid	Extensor	Normal
Paralysis/paresis	Right	Bilateral	Bilateral	Bilateral	–
Babinski's sign	Absent	Absent	Absent	Bilateral	Bilateral
EEG					
Background activity	Non-reactive alpha	Disorganized theta	Disorganized theta	Disorganized theta	Disorganized delta
Evoked potentials					
Auditory	Normal	Normal	Normal	Normal	Normal
Somaesthetic (median nerve)	N20 present	P14 present, N20 absent	N20 present	N20 present	N20 present
MRI					
Increased intensity on T ₂	None	None	None	Centrum ovale	Diffuse white matter
Atrophy	None	None	None	None	None

VS = vegetative state.

used for the calculation of absolute CMRGl_u. Data acquisition was performed in two-dimensional mode. In patients, CMRGl_u data were obtained after acquisition of rCBF data.

Activation study. Fifteen H₂¹⁵O scans were acquired at 8-min intervals in three-dimensional mode. Each scan consisted of two frames: a 30-s background frame and a 90-s frame. The slow intravenous water infusion began just before the second frame in order to observe the head curve rising within the first 10 s of this frame. Six to eight millicuries (222–296 MBq) was injected for each scan, in 5 ml saline, over a period of 20 s. The infusion was totally automated.

MRI

High-resolution T₁-weighted structural MRI (voxel size 0.96 × 0.96 × 1.35 mm) was performed within 5 days after the PET study in each patient (1.5 T Magnetom imager; Siemens).

Evoked potentials

For auditory evoked potentials, electrodes were positioned on each earlobe; Cz served as a reference. Auditory stimulation consisted of 95 dB HL rarefaction clicks (0.1 ms duration) presented monaurally by earphones at a rate of 5.1 Hz, with masking white noise (55 dB) presented to the other ear (Nicolet Viking system 4.0; Nicolet Biomedical, Madison, Wis., USA). Stimulation intensity was identical for all subjects.

Polysomnography

In patients 1–4, further electrodes were placed for monitoring the EEG (C3-A2 and C4-A1), horizontal electro-oculogram and chin-EMG.

Experimental conditions

The patients' vital parameters (temperature, electrocardiogram, blood pressure, O₂ saturation, respiratory rate,

tidal volume, airway pressures, inspired O₂ fraction and PCO₂ capnography) were monitored permanently throughout the scanning procedure.

Scanning was performed during five conditions: resting state; right auditory stimulation; left auditory stimulation; right median nerve stimulation; and left median nerve stimulation. Each condition was repeated three times. The presentation was pseudorandomized using a Latin square design. Stimulation started 10 s before the second scan frame. Control subjects kept their eyes closed and the patients' eyes were taped during scanning. Ambient light and noise were kept to a minimum. Results of somatosensory stimulation will be reported elsewhere.

Data analysis

Data were analysed using statistical parametric mapping (SPM96; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>) implemented in MATLAB (Mathworks, Sherborn, Mass., USA). Data obtained during left-sided auditory stimulation and during the rest condition were flipped. Scans from each subject were realigned using a least-squares approach and the first scan as a reference (Friston *et al.*, 1995a). Images were then transformed into standard stereotaxic space (Talairach and Tournoux, 1988) using a symmetrical template (Montreal Neurological Institute; Ashburner *et al.*, 1999) and smoothed using a 16 mm full-width-half-maximum isotropic kernel (Friston, 1997). In patients, PET data were coregistered to their T₁-weighted MRI scan (Friston *et al.*, 1995a).

The condition and subject (block) effects were estimated according to the general linear model at each voxel (Friston *et al.*, 1995b). Global flow normalization was performed by proportional scaling. The design matrix included scans from 60 patients and 216 control subjects; for each subject there were six resting scans (three flipped and three non-flipped) and six activation scans (three flipped scans obtained during left-sided stimulation and three non-flipped scans obtained during right-sided stimulation). The scans obtained during somatosensory stimulation are not considered here.

Two separate statistical analyses were performed. The first used a multi-study design and assessed the effect of auditory stimulation in the control group and in the patient group. To test hypotheses about regionally specific condition effects, the estimates were compared using linear compounds or contrasts. Contrasts first identified the main effects of auditory stimulation in the control group. Then, a conjunction analysis searched for activations common to the patient and the control groups. Similarly, we looked for the group (patient versus controls) × condition (auditory stimulation versus rest) interaction, looking for brain areas that were less activated by auditory stimulation in patients than in controls. The resulting set of voxel values for each contrast, constituting an SPM of the *t* statistic (SPM{*t*}), was transformed to the unit normal distribution (SPM{*Z*}) and thresholded at *P* =

Table 2 Cerebral metabolic rate for glucose (mg/100 g per minute) in primary auditory cortex (area 41; coordinates ±40, -28, 12) and auditory association cortex (area 22; coordinates ±68, -36, 16) in patients and controls

	Area		
	BA 41	BA 22	Average grey matter
Patients			
1	1.7	1.3	2.1
2	3.0	2.4	3.7
3	1.7	0.9	2.0
4	3.0	1.9	3.1
5	2.8	1.8	2.3
Mean (± SD)	2.4 ± 0.7*	1.7 ± 0.6*	2.6 ± 0.7*
Normal controls	6.3 ± 1.2	4.7 ± 0.9	7.1 ± 1.3

**P* < 0.001, two-tailed unpaired Student's *t*-test.

0.001. Given the a priori hypothesis of superior temporal lobe activation during non-speech stimulation in healthy subjects (Lauter *et al.*, 1985; Zatorre *et al.*, 1992; Binder *et al.*, 1994a, b; Engelien *et al.*, 1995; Millen *et al.*, 1995; Hirano *et al.*, 1997; Strainer *et al.*, 1997), results in this region were considered significant at uncorrected *P* < 0.005 (*Z* > 2.50).

The second statistical analysis used psychophysiological interaction analysis (Buchel and Friston, 1997; Friston *et al.*, 1993, 1995c, 1997) to test the hypothesis of altered cerebral connectivity in the vegetative state compared with controls (Laureys *et al.*, 1999a, 2000a, b, c). The design matrix included the same scans as described above and took into account group differences in mean levels of brain activity. The analysis looked for brain regions whose activity was modulated differently in patients compared with controls, with the following selected cortical areas, which were activated during auditory stimulation in normal subjects: primary auditory cortex [Brodmann area (BA) 41] (stereotaxic coordinates: *x* = -40, *y* = -28, *z* = 12; 40, -30, 12); auditory association cortex (BA 22) (-68, -36, 16). Here, the number of anatomically related regions was expected to be large (Kaas, 1993) and no specific a priori hypothesis could be suggested. In consequence, results were considered significant at a voxel-level-corrected *P* value of <0.05 (*Z* > 4.4).

For comparison between patients and controls of rCMRGlucose in the auditory cortices and overall grey matter, a two-tailed Student's *t*-test was used.

Results

Resting metabolism

Resting metabolism in BA 41 and 22 (peak voxels activating during auditory stimulation in controls) was 61 and 64%, respectively, lower in patients than in controls (Table 2). This decrease paralleled the diminution of the average CMRGlucose

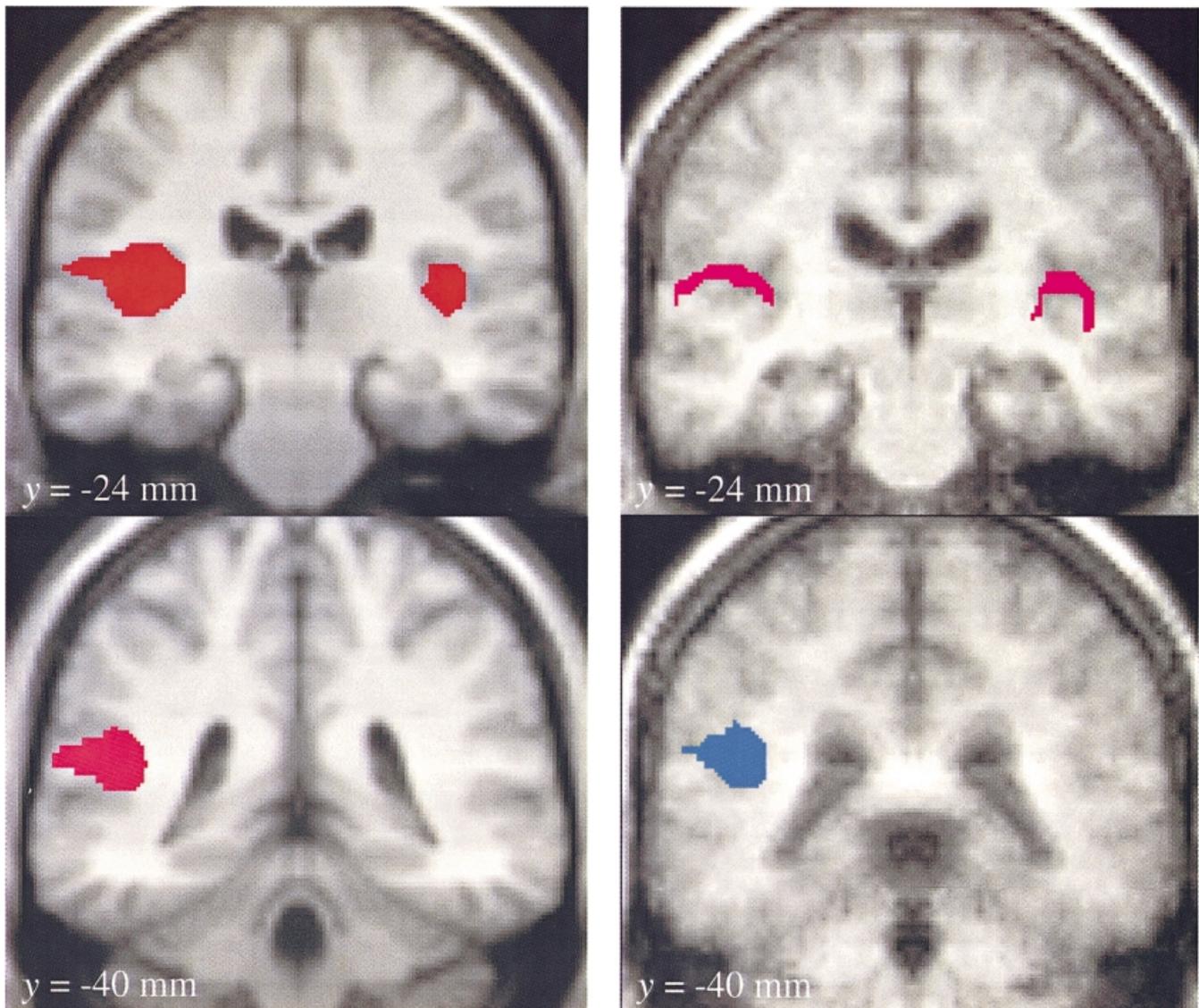


Fig. 1 *Left panels:* areas showing an increase in regional blood flow (rCBF) during auditory stimulation in controls, shown in red. Projected on a coronal section of a normalized brain MRI template, 24 and 40 mm behind the anterior commissural line. *Right panels:* areas of increase in rCBF during auditory stimulation that are common to patients and controls, shown in red, and areas where rCBF showed significantly less activation compared with controls, shown in blue. Projected on the mean normalized MRI of the patients. For display, results are thresholded at $P < 0.01$.

(7.1 ± 1.3 mg/100 g per minute in controls and 2.6 ± 0.7 mg/100 g per minute in patients, i.e. a 63% decrease).

Auditory stimulation

Normal subjects

In the control group, auditory stimulation compared with the resting condition resulted in an increase in rCBF in both the transverse temporal gyri (TTG) of Heschl (BA 41) and in the superior temporal gyrus (STG) on its superior surface (BA 42). Only on the side contralateral to the auditory stimulation did the activation area extend to the lateral surface of the STG (BA 22) and to the temporoparietal junction of the superior temporal sulcus (STS) (BA 22/40) (Table 3, Fig. 1A).

Vegetative state patients

During auditory stimulation, patients showed a significant increase in rCBF in both TTG (BA 41) and on the superior surface of the STG (BA 42), as seen in controls (Table 3, Fig. 1B). The temporoparietal STS contralateral to the side of click presentation (coordinates $-42, -46, 20$; $Z = 2.83$; uncorrected $P = 0.002$; BA 22/40) significantly failed to activate in patients compared with controls.

Using a psychophysiological interaction analysis (Friston *et al.*, 1997), we demonstrated a significant alteration in functional connectivity between BA 41 opposite to the side of click presentation (coordinates $-40, -28, 12$) and contralateral areas 41 and 22 and ipsilateral posterior cingulate cortex and precuneus (BA 31 and 7). BA 41 on the same side as click presentation (coordinates $40, -30, 12$) also

Table 3 Cerebral areas that showed activation during auditory stimulation in normal controls and in vegetative patients

Region	BA	Coordinates			Z	P
		x	y	z		
<i>Normal controls</i>						
TTG						
Contralateral*	41	-40	-28	12	5.72	<0.001
Ipsilateral*	41	40	-30	12	4.97	<0.001
Superior surface of STG						
Contralateral	42	-58	-36	18	2.91	0.002
Ipsilateral	42	52	-34	16	2.66	0.004
Lateral surface of STG						
Contralateral*	22	-68	-36	16	2.76	0.003
Temporoparietal STS						
Contralateral	22/40	-42	-44	18	2.55	0.005
<i>Patients</i>						
TTG						
Contralateral	41	-30	-30	14	3.29	0.001
Ipsilateral	41	34	-30	12	3.12	0.001
Superior surface of STG						
Contralateral	42	-52	-32	16	2.89	0.002
Ipsilateral	42	48	-32	14	3.23	0.001

Results were thresholded at uncorrected $P < 0.005$ ($Z > 2.50$). Coordinates are defined in the stereotaxic space of Talairach and Tournoux (1988). Z scores are for the peak voxel in each region. The areas marked with an asterisk were used for further connectivity assessment. Contralateral is contralateral to the side of presentation of click stimuli.

showed a decrease in connectivity with the ipsilateral retrosplenial cortex (BA 31 and 7); however, statistical significance did not survive correction for multiple comparisons (voxel-level-corrected $P = 0.06$). Finally, BA 22 (coordinates -58, -36, 18) opposite to the side of click presentation showed altered connectivity with the contralateral hippocampus (Fig. 2), posterior parietal association cortex (BA 40) and anterior cingulate cortex (BA 24) (Table 4).

Discussion

Methodological considerations

Patients were in a vegetative state according to international criteria (ANA Committee on Ethical Affairs, 1993; Multi-Society Task Force on PVS, 1994). They were scanned while in awake periods, as no signs of sleep were demonstrated by polysomnography. The aim of our study was to assess cerebral processing objectively during a basic auditory activation task in the vegetative state independent of its duration or outcome. It is important to stress the difference between the vegetative state and the persistent vegetative state, the latter being defined as a vegetative state that has endured for at least 1 month. Three of our patients subsequently recovered to partial autonomy. When looking at the data obtained in each patient,

we did not see major differences in activation pattern between patients who did and those who did not recover awareness. However, given the small number of observations, we did not correlate our data with patient outcome. Further research is needed on a larger cohort of patients in order to evaluate the important issue of the prognostic value of brain activation studies in the vegetative state. On the basis of aetiology, clinical status and electrophysiological and structural imaging findings, the patients included in the present study represent a relatively homogeneous group: all were in a vegetative state of hypoxic origin; brainstem auditory evoked potentials showed preserved brainstem function and MRI showed no cortical or subcortical atrophy and no cortical lesions. Hence, to increase statistical power we performed a group analysis, comparing the patient group with the control group. In this study, we did not consider patients with structurally distorted brains (e.g. long-standing vegetative state with major brain atrophy or post-traumatic vegetative state with major focal lesions) as this complicates the coregistration of PET with MRI and spatial normalization to a standard stereotaxic space.

Patients 4 and 5 were studied while receiving light sedation. The doses used were very low: patient 5 needed light midazolam sedation but continued to breath spontaneously; patient 4, a heroin addict who was taking methadone before entering the vegetative state, needed small doses of alfentanil and midazolam sedation (3 months after PET scanning, after he had regained consciousness, he was given slightly higher doses of alfentanil (8.9 g/kg per hour) and midazolam (0.09 mg/kg per hour) for gastrostomy withdrawal, and he remained fully aroused and conscious). Our clinical experience in surgical patients also showed that similar small doses of midazolam and/or alfentanil do not produce loss of consciousness (Faymonville *et al.*, 1997). Midazolam, at higher doses than those used in our two patients, is known to decrease global CBF and metabolism by ~10% (Veselis *et al.*, 1997). Results concerning regional changes are more contradictory: some authors observed no regional differences (Forster *et al.*, 1982; de Wit *et al.*, 1991; Mathew and Wilson, 1991; Roy-Byrne *et al.*, 1993), others have reported decreases in the thalamus (Volkow *et al.*, 1995; Veselis *et al.*, 1997) and prefrontal cortex (Veselis *et al.*, 1997), but none have described changes in the auditory cortices. The effect of midazolam on rCBF activation during auditory stimulation is not known. Previous PET studies in healthy subjects have shown that sufentanil induces decreases in rCBF in some temporal and frontal areas and the cerebellum, while rCBF increases in the cingulate, orbitofrontal and medial prefrontal cortices and caudate nuclei (Firestone *et al.*, 1996). We are convinced that the changes described in the cerebral activation pattern and connectivity are the result of the vegetative state of our patients: the observed preservation of auditory cortex activation is unlikely to be influenced by light sedation, and the absence of temporoparietal junction activation in the patient group was also observed in a separate SPM analysis including only the three patients scanned without any sedative drugs.

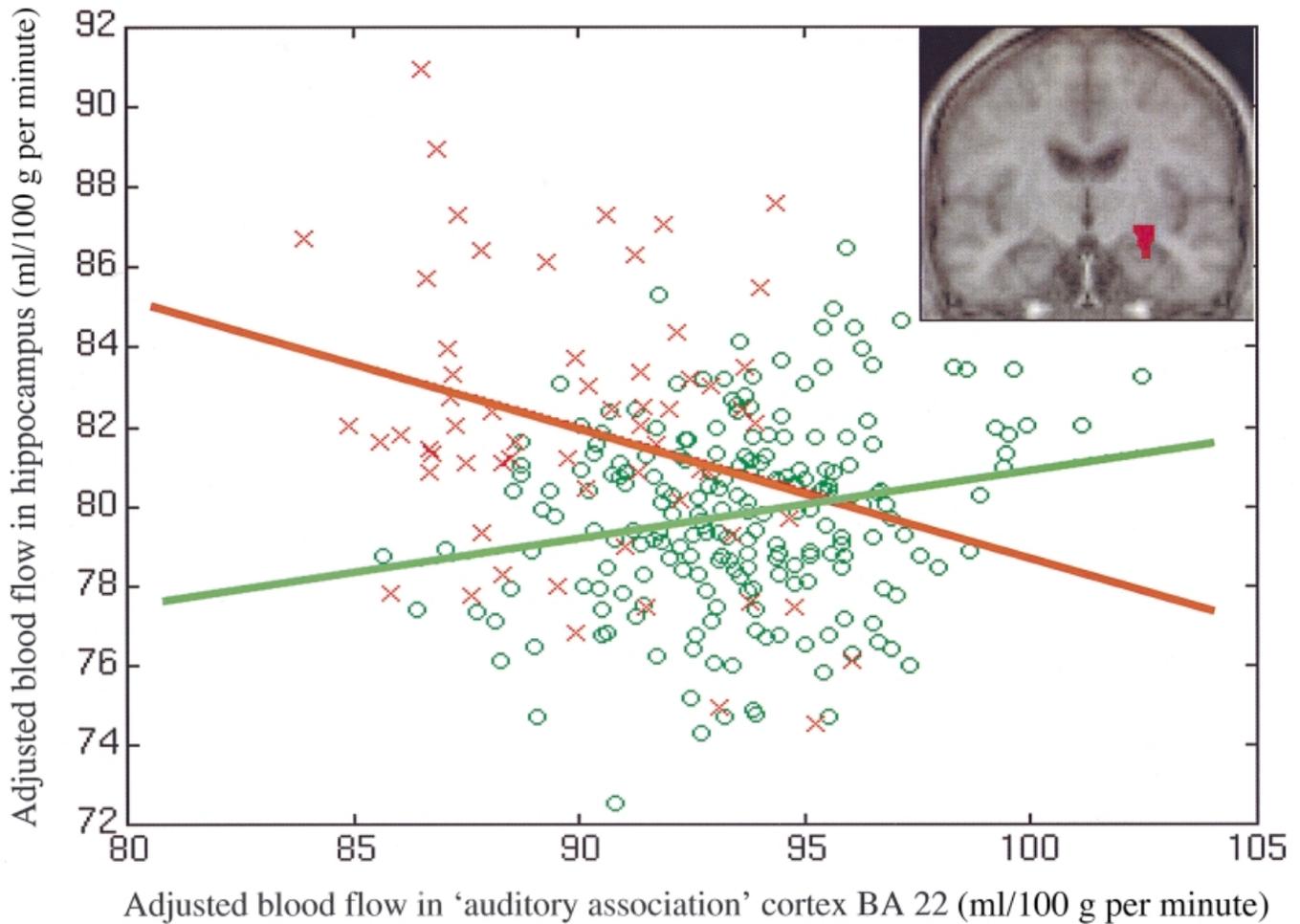


Fig. 2 Plot of the regression of blood flow in area 22 (coordinates $-68, -36, 16$) and hippocampus ($28 -10, -14$) in controls (green circles) and patients in the vegetative state (red crosses). Inset shows the hippocampal area (red) that demonstrated a significant difference in functional connectivity with auditory association cortex in patients relative to controls.

Table 4 Areas where functional modulation with primary and associative auditory cortices was impaired in patients compared with controls

Selected region (BA)	Identified region	BA	x	y	z	Z	P
Contralateral TTG (41)	TTG	41	42	-32	14	5.32	0.001
	STG	22	50	-38	20	5.05	0.004
	Posterior cingulate/ precuneus	31	-12	-38	30	5.98	<0.001
Ipsilateral TTG (41)	Posterior cingulate/ precuneus	7	-8	-60	48	5.04	0.004
	Posterior cingulate/ precuneus	31	8	-36	30	4.26	NS
Contralateral STG (22)	Hippocampus	7	8	-72	54	4.38	NS
	Inferior parietal lobule	40	42	-40	34	4.70	0.018
	Anterior cingulate	24	8	6	28	5.13	0.003

The selected voxels are marked with an asterisk in Table 3. Results were thresholded for significance at voxel-level-corrected $P < 0.05$ ($Z > 4.36$). Contralateral is contralateral to the side of click stimuli.

Complementary to the concept of functional segregation as a principle of organization in the human brain, more recent approaches have focused on the integration of functionally segregated areas by characterizing neurophysiological activations in terms of distributed changes (e.g. functional

connectivity). The concepts of functional connectivity were developed in the analysis of separable spike trains obtained from multi-unit electrode recordings. However, the neurophysiological measurements obtained from functional neuroimaging have a very different time-scale (seconds versus

milliseconds) and nature (haemodynamic or metabolic versus spike trains) compared with those obtained from electrophysiological studies. Psychophysiological interaction analysis explains the activity in one cortical area in terms of interaction between the influence of another area and some experimental condition (i.e. being a vegetative patient or a conscious control). A psychophysiological interaction means that the contribution (i.e. regression slope) of one area to another changes significantly with the experimental context, assessed with the general linear model as used in SPM (Friston *et al.*, 1997). Functional connectivity is defined as the temporal correlation of a neurophysiological index (i.e. rCBF) measured in different remote brain areas (Buchel and Friston, 1997). Put simply, our statistical analyses identified brain regions that showed condition-dependent differences in modulation with respect to another (chosen) area. It is important to stress that one cannot guarantee that these connections are direct (i.e. they may be mediated through other areas) and that the two regions can have a common input (a third area, which shows context-sensitive responses, may be providing input to the two areas involved in the psychophysiological interaction). These limitations should be taken into account when considering the biological significance of the psychophysiological interaction analyses that are presented.

Auditory stimulation

Normal subjects

Monastral clicks and contralateral continuous white noise caused an activation in bilateral areas 41 and 42. Contralateral to the clicks, the activated region encompassed BA 22. These results are in agreement with neurophysiological studies in primates. Neurons in the auditory core areas are highly responsive to pure tone stimuli and most neurons in the belt areas respond to more complex stimuli, such as modulated tones, noise bursts or clicks (Morel *et al.*, 1993). In alert monkeys, the core area encodes the spectral and temporal features of sound (deCharms *et al.*, 1998), whereas the belt area represents a higher hierarchical stage where spatial auditory representations are formed (Rauschecker *et al.*, 1995). The caudal parabelt is sensitive to motion and direction (Hikosaka *et al.*, 1988) and responds to sounds in contralateral space (Leinonen *et al.*, 1980). The temporoparietal junction area receives input from caudal parabelt areas (Hackett *et al.*, 1998); many of its neurons are heteromodal and participate in cognitive aspects of auditory processing (Benevento *et al.*, 1977; Hikosaka *et al.*, 1988). Accordingly, our results show an activation of the lateral surface of the STG and the temporoparietal junction area contralateral to the side of click presentation.

Previous functional neuroimaging studies have shown various patterns of activation of superior temporal cortices using different types of non-verbal auditory stimuli: white noise (Binder *et al.*, 1994b; Hirano *et al.*, 1997), pure tones

(Lauter *et al.*, 1985; Millen *et al.*, 1995; Strainer *et al.*, 1997), noise bursts (Zatorre *et al.*, 1992), clicks (Reite *et al.*, 1981; Pantev *et al.*, 1986) and pulsed tones (Strainer *et al.*, 1997).

Vegetative state patients

Despite a decrease in resting glucose metabolism of >60% below normal, temporal regions were bilaterally activated during auditory stimulation in the vegetative state, as in the control group. This finding confirms that some cortical areas may remain responsive to external auditory input in the vegetative state (de Jong *et al.*, 1997; Ribary *et al.*, 1998; Owen *et al.*, 1999; Schiff and Plum, 1999).

The activated area encompassed the TTG and the surrounding superior surface of the STG (BA 41 and 42). In non-human primates, lesions involving bilateral core and belt areas have been associated with a profound deficit in sound detection and with an altered perception of what is heard and where it is coming from (Heffner, 1997). Direct cortical stimulation of BA 41 and 42 in humans resulted in (most often contralateral) perception of elementary sounds (e.g. ringing, humming, clicking, rushing, chirping, buzzing, knocking and rumbling) but never of words or voices (Penfield and Jasper, 1954).

Regions that showed a significant lack of activation in patients compared with controls were localized in the contralateral temporoparietal STS. Destruction of this area results in contralateral hemi-inattention, extinction or frank neglect of auditory stimuli in both monkeys (Heilman *et al.*, 1971) and humans (Heilman and Valenstein, 1972).

Neuronal activity in auditory association cortices is influenced by the level of arousal, general attention and selective auditory attention in animals (Leinonen *et al.*, 1980; Benson *et al.*, 1981) and humans (Pugh *et al.*, 1996). Consequently, the observed deficit in activation of the temporoparietal junction area in vegetative patients might be explained partly by altered modulation by other brain areas just as readily as by severe neuronal loss in associative cortices, which are known to be particularly damaged in the vegetative state (Laureys *et al.*, 1999a, 2000b). It was to investigate the former possibility that psychophysiological interaction analyses were performed. In summary, the results of these analyses suggest disconnection between the auditory cortices and three critical sets of areas: the limbic system (hippocampal formation and cingulate cortex), the posterior polymodal associative cortices (inferior parietal lobule) and the anterior attentional system (anterior cingulate cortex).

We observed a significant alteration in functional connectivity between BA 22 and the hippocampus. Neuroanatomical studies in primates have suggested that auditory information is sent along the medial geniculate→core→belt→parabelt pathway (Kaas *et al.*, 1999); from here it is further sent serially to the hippocampus through the parahippocampal (Van Hoesen, 1982), entorhinal and subicular cortices (Amaral *et al.*, 1983; Yukie, 1995). In

the absence of a thorough understanding of the neural correlate of consciousness, it is very difficult to make any judgements about the possible level of conscious perception based on the present data. The hippocampus has been postulated to participate in conscious processes (Weiskrantz, 1997). Some authors have speculated that the hippocampal system receives as its input only information that is apprehended consciously (Moscovitch, 1995). At the very least, conscious recollection or recognition of facts and events, i.e. explicit or declarative memory, depends on hippocampal processing (Cohen and Squire, 1980; Clark and Squire, 1998). With these hypotheses in mind, it is possible that the disconnection between the auditory system (explored more specifically here) and the hippocampus hampers the emergence of conscious auditory perception in patients in the vegetative state.

An alternative route for the delivery of highly processed auditory information to the hippocampus has been proposed, involving connections between the auditory cortices and the posterior cingulate cortex (Yukie, 1995), which in turn projects to the parahippocampal areas (Vogt and Pandya, 1987; Martin-Elkins and Horel, 1992). Interestingly, we observed a functional disconnection between the bilateral auditory sensory cortices and the retrosplenial cortex (although the level of significance did not survive correction for multiple comparisons on the side ipsilateral to stimulation). Functional imaging studies have shown the involvement of this region in various auditory tasks (Grasby *et al.*, 1993; Griffiths *et al.*, 1994; Shallice *et al.*, 1994; Lockwood *et al.*, 1999). We have proposed previously that the retrosplenial area might be involved in a neural network subserving conscious experience (Laureys *et al.*, 1999a). This area is the most active brain region, metabolically, in the awake state (Andreasen *et al.*, 1995; Raichle, 1998; Laureys *et al.*, 2000b) and shows a very low level of activity in states of absent or diminished consciousness, such as the vegetative state (Laureys *et al.*, 1999a, b), anaesthesia (Alkire *et al.*, 1999; Fiset *et al.*, 1999), slow-wave sleep (Maquet *et al.*, 1997) and paradoxical sleep (Maquet *et al.*, 1996), amnesia (Aupée *et al.*, 1999) and Alzheimer's dementia (Minoshima *et al.*, 1997). Neuropsychological studies in monkeys have demonstrated its involvement in auditory verbal memory and spatial orientation (for review see Vogt *et al.*, 1992), and clinical studies in humans have shown its role in anterograde and retrograde amnesia (Rudge and Warrington, 1991).

Another region that showed altered connectivity with the auditory association cortex in vegetative state patients was the inferior parietal lobule (BA 40). Neuroanatomical tracer studies in primates have shown projections from the auditory parabelt area to parietal cortex (Kaas *et al.*, 1999). The posterior parietal cortex is a polymodal association area that combines information from different sensory modalities (auditory, somatosensory, visual and vestibular). More specifically, it is involved in higher-order auditory processing, such as source localization (Andersen, 1997; Weeks *et al.*, 1999) and has been implicated in attention processes (Pugh

et al., 1996; Corbetta, 1998; Posner and Rothbart, 1998; Mesulam, 1999).

In addition to having many other cerebral deficits, patients in the vegetative state suffer from complete loss of attention to the external world. This clinical finding is in keeping with the impaired functional modulation between the auditory association cortex and the anterior cingulate cortex (BA 24). Neuroanatomical tracer studies in cats (Rouiller *et al.*, 1990) and monkeys (Pandya *et al.*, 1981) have demonstrated connections between the posterior auditory cortex and the anterior cingulate cortex. Physiological studies in monkeys have shown that neuronal discharge patterns in the STG are influenced by electrical stimulation of the anterior cingulate cortex (Muller-Preuss *et al.*, 1980). The involvement of the anterior cingulate cortex in selective auditory attention has also been reported by PET (Tzourio *et al.*, 1997). This area seems to play a critical role in tasks that require selective attention and response selection, independent of the modality engaged (Petersen *et al.*, 1988; Pardo *et al.*, 1990; Corbetta *et al.*, 1991; Paus *et al.*, 1993).

In vegetative state patients, BA 41 opposite to the side of click presentation was less tightly connected with contralateral BA 41 and 42. Tracer studies in primates indeed show numerous callosal connections from the auditory core area to the opposite core area and, to a lesser extent, to adjoining fields (Morel *et al.*, 1993). The functional implication of this impaired interhemispheric corticocortical connectivity is important, as the spatial location of sound is thought to be encoded through mechanisms of binaural integration. In awake macaques, frequency-selective neurons in the core and lateral belt area change their firing rate as a function of differences in the interaural intensity of sound (Brugge and Merzenich, 1973).

The observed preservation of activation in BA 41 and 42 could reflect residual neural encoding of basic sound attributes. However, the cascade of functional disconnections along the auditory cortical pathway, from the primary auditory areas to the multimodal and limbic areas, suggests that further cortical processing of sound is severely hampered.

Conclusions

The present study demonstrated that, in patients in the vegetative state, the TTG and the adjacent superior surface of the STG were activated during peripheral auditory stimulation (BA 41 and 42) despite their substantial metabolic impairment. However, patients did not activate the temporoparietal junction area of the STS, a higher-order stage in auditory processing. Using psychophysiological analysis, we then demonstrated that the primary auditory cortex was disconnected from the auditory cortices on the opposite side, the auditory association cortex was disconnected from the posterior parietal association cortex, anterior cingulate cortex and hippocampus, and the alternative route for auditory information to reach the hippocampal

system, which takes relay in the retrosplenial cortex, was also impaired.

It is difficult to make judgements about possible residual conscious auditory perception in our vegetative state patients. However, the absence of increases in rCBF in the heteromodal temporoparietal region and, more importantly, the cascade of functional disconnections along the auditory cortical pathway (including the limbic and attentional networks) make the persistence of higher levels of integration, let alone of consciousness, very unlikely.

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