

Cortical Processing of Noxious Somatosensory Stimuli in the Persistent Vegetative State

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The persistent vegetative state (PVS) is a devastating medical condition characterized by preserved wakefulness contrasting with absent voluntary interaction with the environment. We used positron emission tomography to assess the central processing of noxious somatosensory stimuli in the PVS. Changes in regional cerebral blood flow were measured during high-intensity electrical stimulation of the median nerve compared with rest in 15 nonsedated patients and in 15 healthy controls. Evoked potentials were recorded simultaneously. The stimuli were experienced as highly unpleasant to painful in controls. Brain glucose metabolism was also studied with [¹⁸F]fluorodeoxyglucose in resting conditions. In PVS patients, overall cerebral metabolism was 40% of normal values. Nevertheless, noxious somatosensory stimulation-activated mid-brain, contralateral thalamus, and primary somatosensory cortex in each and every PVS patient, even in the absence of detectable cortical evoked potentials. Secondary somatosensory, bilateral insular, posterior parietal, and anterior cingulate cortices did not show activation in any patient. Moreover, in PVS patients, the activated primary somatosensory cortex was functionally disconnected from secondary somatosensory, bilateral posterior parietal, premotor, polysensory superior temporal, and prefrontal cortices. In conclusion, somatosensory stimulation of PVS patients, at intensities that elicited pain in controls, resulted in increased neuronal activity in primary somatosensory cortex, even if resting brain metabolism was severely impaired. However, this activation of primary cortex seems to be isolated and dissociated

from higher-order associative cortices. © 2002 Elsevier Science (USA)

INTRODUCTION

Following severe brain injury, some patients progress from coma to a state of wakefulness without detectable awareness, called persistent vegetative state (PVS) (Multi-Society Task Force on PVS, 1994b). Positron emission tomography (PET) studies have shown a global depression of cerebral metabolism and blood flow in PVS patients (Levy *et al.*, 1987; De Volder *et al.*, 1990; Tommasino *et al.*, 1995; Rudolf *et al.*, 1999; Laureys *et al.*, 2001). In 1994, the position statement of the Multi-Society Task Force on PVS concluded: "Future PET studies should measure regional cerebral activity in response to visual, auditory, and somatosensory stimulation, to determine whether depressed cortical regions in patients in a PVS can be activated by peripheral sensory stimuli. A confirmation of the absence of evoked activity on the PET scan would help defend the assertion that these patients are completely unaware and insensate" (Multi-Society Task Force on PVS, 1994a). So far, PET activation studies are limited to isolated case reports. Using complex auditory (de Jong *et al.*, 1997) or visual (Menon *et al.*, 1998) stimuli, they have shown preserved higher cortical responses in PVS. We have previously reported that auditory clicks activated primary, but not associative, auditory cortices in five vegetative patients (Laureys *et al.*, 2000a). The present study investigates somatosensory processing in PVS patients, using high-intensity electrical stimulation of the median nerve at the wrist. As the stimuli were perceived as highly unpleasant to painful in the healthy control population, we consider the stimuli as "noxious." A better understanding of the cortical processing of noxious somatosensory stimuli in the

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PVS is of major clinical and ethical relevance (McQuillen, 1991). Using $H_2^{15}O$ -PET, we measured changes in regional cerebral blood flow (rCBF) during stimulation compared with rest in 15 patients in a PVS and in 15 healthy controls. Somatosensory evoked potentials (SEPs) were acquired simultaneously and cerebral metabolic rates for glucose were obtained in resting conditions using [^{18}F]fluorodeoxyglucose-PET.

MATERIAL AND METHODS

We prospectively studied 15 healthy volunteers (8 males, 7 females; aged 40 ± 9 years) and 15 nonsedated PVS patients (12 males, 3 females; aged 48 ± 17 years) diagnosed according to established criteria (ANA Committee on Ethical Affairs, 1993; Multi-Society Task Force on PVS, 1994a) and following repetitive neurological examinations and careful anamnesis of family members and medical caregivers. Patients with normal flexion or withdrawal to noxious stimuli; patients with disputable clinical signs (e.g., attempts to articulate or utter words, selective emotional responses, visual pursuit, visual fixation or response to visual threat); patients with uncertain diagnosis; and patients in a minimally conscious state (American Congress of Rehabilitation Medicine, 1995; Giacino *et al.*, 2002) were excluded from the present analysis. The etiologies of the PVS 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 ($n = 1$). Mean Glasgow coma scores (GCSs) (Teasdale and Jennett, 1974) were 4.9 ± 2.5 SD (range 3–13) on admission and 4.3 ± 1.2 (range 3–8) at Day 3 (maximum summed score is 15 points). The time spent in vegetative state prior to PET scanning was 36 ± 9 days. Median nerve sensory conduction velocity and SEP examinations excluded peripheral nerve, plexus, or spinal cord lesions. Short-latency auditory evoked potentials showed preserved pontine and midbrain function in all patients. All PVS patients had preserved pupillary, corneal, and vestibulo-ocular reflexes. Patients were scanned while in awake periods as demonstrated by simultaneous polygraphic recordings (electroencephalogram, electro-oculogram and chin-electromyogram). Due to the spontaneous head and trunk movements of PVS patients, scanning was performed during infusion of muscular blocking agents (rocuronium bromide). Throughout the procedure, patients were monitored by a senior anesthesiologist (M.E.F.) aided by a colleague anesthesiologist. Informed consent was obtained from all control subjects and from the persons having legal responsibility for the PVS patients. The study was approved by the Ethics Committee of the Faculty of Medicine of the University of Liège and conducted according to the

Declaration of Helsinki (World Medical Association, 1997) and to the International Association for the Study of Pain (IASP) Ethical Guidelines for Pain Research in Humans (Charlton, 1995).

Data Acquisition

SEPs were acquired on a Nicolet Viking System 4.0 (Nicolet Biomedical, Madison Wisconsin). Electrodes were positioned on Fz and 2 cm behind the 10–20 system C-3 and C-4 positions. Further leads explored the spinal potentials at the C-6 level (bipolar derivation) and the brachial plexus potentials on Erb's point. The ear lobe ipsilateral to the stimulated side served as reference for cephalic and brachial plexus electrodes (Tomberg *et al.*, 1991). Stimuli consisted of 0.2-ms electrical square-wave pulses delivered at 5.1 Hz to the median nerve at the wrist. Stimulation intensities were increased to the point where all SEP components showed maximal amplitude (Lesser *et al.*, 1979) and rated as highly unpleasant to painful in controls. Intensities tended to be higher, but were not significantly different, in patients compared with controls (mean \pm SD: 14.2 ± 8.7 mA vs 7.4 ± 5.9 mA). Automatic artifact rejection was used and filter bandpass was 0.5 to 3000 Hz. The time window was 100 ms. Latencies and amplitudes (baseline to peak) were measured on the screen with cursors.

PET data were obtained on a Siemens CTI 951 16/32 scanner. A transmission scan allowed for measured attenuation correction. Fifteen $H_2^{15}O$ PET scans were performed at 8-min intervals in three-dimensional mode following infusion of 6 mCi (222 MBq). Each scan consisted of a 30-s background frame and a 90-s frame. Scanning was performed during rest, (left then right), noxious stimulation, and (left then right) auditory stimulation (preliminary results from the latter are described elsewhere: Laureys *et al.*, 2000a). Each condition was repeated three times and the order of presentation was pseudorandomized. Stimulation started 10 s before the second frame and ended 60 s later. Controls kept their eyes closed and patients' eyes were taped. Patient's vital parameters (temperature, electrocardiogram, blood pressure, O_2 saturation, respiratory rate, tidal volume, airway pressures, inspired O_2 fraction and P_{CO_2} capnography) and SEPs were monitored throughout the procedure. Cerebral metabolic rates for glucose were measured after intravenous injection of 5–10 mCi (185–370 MBq) [^{18}F]fluorodeoxyglucose and arterial blood samples were performed for quantification (Laureys *et al.*, 2000a).

High-resolution T_1 -weighted MRI (voxel size: $0.96 \times 0.96 \times 1.35$ mm) was performed on a 1.5-T Magnetom imager (Siemens, Erlangen, Germany) within 5 days of the PET study and used for coregistration to the PET data in each patient.

Data Analysis

PET data were analyzed using statistical parametric mapping (SPM99; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). Scans obtained during left-sided stimulation were flipped. Hence, results should be interpreted as contra- and ipsilateral to the side of stimulation and not as left- or right-sided. Data from each subject were realigned, normalized into standard stereotactic space using a symmetrical template, and smoothed using a 16-mm full-width at half-maximum isotropic kernel (Friston, 1997). The random-effect analyses used a two-step procedure (Holmes and Friston, 1998; Peigneux *et al.*, 2000). A first-level analysis modeled within-subject variances related to the experimental conditions, estimated according to the general linear model at each voxel. Proportional scaling performed global flow normalization. Primary contrasts estimated the effect of noxious stimulation versus rest in each subject (Friston, 1997). The resulting set of voxel values for each contrast constituted a map of the t statistic, $SPM(T)$, thresholded at $P \leq 0.001$ ($T \geq 3.1$). The “contrast images” obtained were then entered into a second-level simple one-sample t test which took into account between-subject variances and identified generic activations common to all healthy controls. A similar second-level analysis independently identified significant activations in PVS patients. We then looked for brain areas that would be significantly less activated by noxious stimulation in each patient compared with controls using a first-level group interaction analysis followed by a second-level random-effect analysis. Finally, a psychophysiological interaction analysis (Friston *et al.*, 1997) looked for differences in modulation between S1 (the peak cortical voxel activating in patients: $x = -54$, $y = -26$, $z = 58$) and the rest of the brain in patients compared with controls, using a fixed-effect approach (Laureys *et al.*, 1999, 2000b). The results obtained in controls were considered significant at voxel level $P < 0.05$ corrected for multiple comparisons. In patients, as we had an a priori hypothesis concerning the brain areas of interest, results were considered significant at small-volume-corrected $P < 0.05$, using a 10-mm radius spherical volume of interest on our predetermined regions (i.e., coordinates of brain regions previously identified in our control population: brain stem, thalami, S1, S2, insula, posterior parietal, anterior cingulate and midcingulate cortices). In contrast to the functional segregation maps, we had not any firm a priori hypothesis for the functional integration maps. Hence, results obtained from psychophysiological interaction analyses were considered significant at voxel level $P < 0.05$ corrected for whole-volume multiple comparisons.

TABLE 1

 Heart Rate and Blood Pressure in PVS Patients^a

	Rest	Stimulation
Heart rate	96.3 ± 24.2	98.7 ± 23.2
Systolic blood pressure	140.2 ± 18.0	142.7 ± 17.4
Diastolic blood pressure	76.6 ± 14.6	79.0 ± 16.1

^a Values are means ± SD.

Differences between patients and controls for cerebral metabolic rates for glucose and SEPs and differences in patients' vital parameters during rest and stimulation were assessed using a two-tailed Student t test. Results were considered significant at $P < 0.05$.

RESULTS

In PVS patients, mean metabolic rates for glucose in overall gray matter were less than 40% of normal values (2.5 ± 0.7 vs 7.1 ± 1.3 mg/100 g per minute, $P < 0.001$). Patients' vital parameters did not show significant changes during somatosensory stimulation compared with rest (Table 1 shows heart rate and blood pressure values). SEPs showed preserved peripheral nerve, cervical, and brainstem responses in all patients. Primary cortical responses (N20) were present bilaterally in 11 and unilaterally in 1, and absent in 3 patients. None showed late cortical potentials (Fig. 1). Latencies, amplitudes, and central conduction time (P14–N20) were lower in PVS patients than in controls (Table 2) but remained within internationally accepted normal limits (Guérit *et al.*, 1999).

In controls, stimulation resulted in the subjective experience of pain and increased rCBF in midbrain, contralateral thalamus, and contralateral primary somatosensory (S1), contralateral secondary somatosensory (S2), bilateral insular, posterior parietal, and anterior cingulate cortices ($P < 0.05$ corrected for multiple comparisons) (Table 3, Fig. 2). In patients, stimulation increased regional neural activity in brain stem and contralateral thalamus and S1 (small-volume-corrected $P < 0.05$) (Table 4, Fig. 2). No other cerebral areas showed stimulus-related activation, even at lower thresholds. Conversely, brain regions that showed significantly less activation in patients compared with controls were identified in hierarchically higher-order cortices: contralateral S2, bilateral insula, caudal, and rostral anterior cingulate and bilateral posterior parietal cortices (small-volume-corrected $P < 0.05$) (Table 5, Fig. 2). In order to better understand the meaning of the preserved cortical activation during noxious stimulation in PVS we studied its functional connectivity. In patients, the activity measured in S1 did not correlate with that measured in

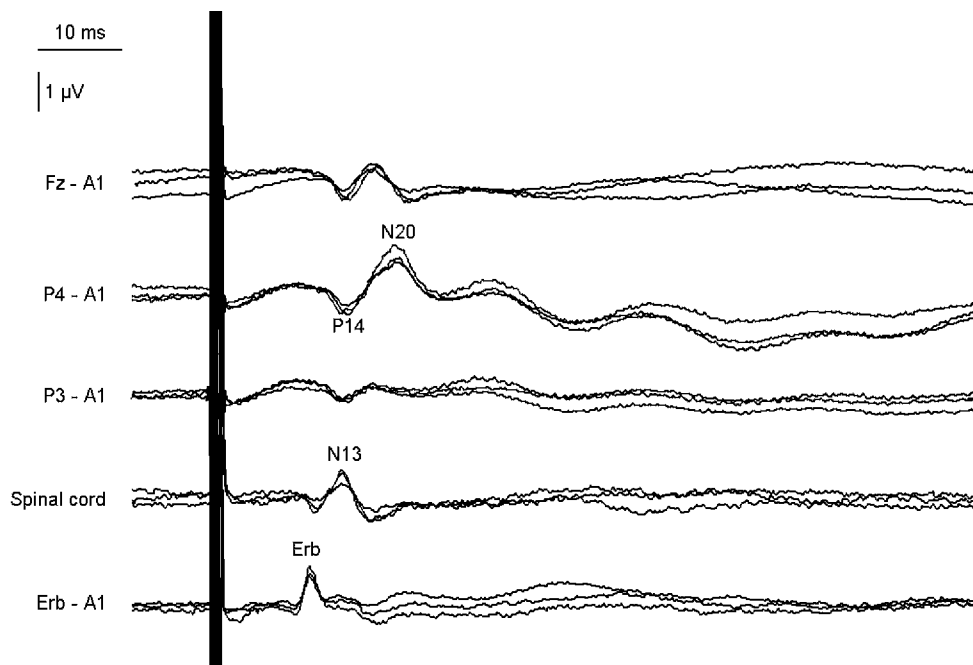


FIG. 1. Example of SEPs to left median nerve stimulation obtained in a patient in PVS with preserved peripheral and primary cortical responses.

any other cortical region ($P < 0.001$ uncorrected). Using a psychophysiological interaction analysis (Friston *et al.*, 1997), we identified differences in modulatory interactions from and to S1 in patients compared with controls. S1 did no longer experience direct or indirect functional relationships with S2, premotor, posterior parietal, superior temporal, and prefrontal cortices ($P < 0.05$ corrected for multiple comparisons) (Table 6, Fig. 3A). Moreover, at a less stringent threshold ($P <$

0.001 uncorrected), these regions spatially extended to include broad parts of frontal, parietal, and parieto-temporal associative cortices and included precuneus, cingulate, and mesiofrontal areas (Fig. 3B).

DISCUSSION

Functional imaging studies of “noxious” processing in vegetative patients raise ethical and methodological concerns. Patients were immobilized by neuromuscular blockade (to avoid movement artifacts) without sedation or analgesia (to avoid suppression of cerebral function). In severely brain-injured patients, the exploration of behavioral responses to nociceptive stimuli (e.g., applying pressure to the fingernail bed with a pencil, applying pressure to the supraorbital ridge or jaw angle, pinching the trapezium, or rubbing the sternum) is a routine clinical procedure that is used to evaluate the state of consciousness. Reactivity to pain is part of widely used “consciousness scales” such as the Glasgow Coma Scale (Teasdale and Jennett, 1974), the Reaction Level Scale (Starmark *et al.*, 1988), the Innsbruck Coma Scale (Benzer *et al.*, 1991), and the Edinburgh-2 Coma Scale (Sugiura *et al.*, 1983). Prior to the PET study, repeated neurological examinations and heteroanamnesis gave no indication that the patients showed any voluntary interaction with their environment. Our PVS patients never withdrew from noxious stimuli but showed only reflexive decortication

TABLE 2

Somatosensory Evoked Potentials^a

Peak	Controls	Patients
Latency (ms)		
Erb's point	10.2 ± 0.8	11.3 ± 0.9*
N13	13.5 ± 1.2	14.8 ± 1.0*
P14	14.3 ± 1.0	15.9 ± 1.4*
N20	19.3 ± 1.3	21.7 ± 2.0*
P14–N20	5.0 ± 0.6	5.6 ± 0.9**
Amplitude (μV)		
Erb's point	3.7 ± 1.0	2.3 ± 1.4*
N13	1.2 ± 0.4	0.9 ± 0.6**
P14	1.0 ± 0.4	0.7 ± 0.2*
N20	1.6 ± 0.5	1.0 ± 0.6*

^a Erb, brachial plexus; N13, cervical cord; P14, brainstem; N20, primary somatosensory cortex; P14–N20, brainstem and subcortical transmission time. Values are means ± SD.

* $P < 0.001$.

** $P < 0.05$.

TABLE 3

Cerebral Areas That Showed Significant Activation during Noxious Somatosensory Stimulation Compared with Rest in Normal Controls^a

Side	Region	x	y	z	T value
	Midbrain	-8	-26	-4	4.70
Contralateral	Thalamus	-15	-24	2	4.72
Contralateral	Primary somatosensory cortex	-44	-26	60	7.04
Contralateral	Secondary somatosensory cortex	-46	-22	20	10.51
Contralateral	Insula	-40	-16	10	13.78
Ipsilateral	Insula	32	-10	-2	5.98
Contralateral	Posterior parietal cortex (area 40)	-52	-30	22	9.05
Ipsilateral	Posterior parietal cortex (area 40)	70	-36	22	5.88
	Anterior cingulate cortex (area 24/32)	2	16	38	6.17
	Midcingulate cortex (area 23/24')	-6	-18	32	7.14

^a All results are significant at $P < 0.05$ corrected for multiple comparisons.

or decerebration postures. Hence, neuromuscular blockade did not change their capability to withdraw from the stimuli. Patients with ambiguous behavioral responses to auditory, visual, or somatosensory stimulation were excluded. Neuromuscular blockade did not imply tracheal intubation as all patients were already tracheotomized prior to the study for clinical reasons. No sign of autonomic distress was observed in PVS

patients in response to neuromuscular blockade. It is unlikely that the administration of rocuronium bromide (a muscle relaxant that undergoes no detectable metabolism and does not pass the blood-brain barrier) (Khuenl-Brady and Sparr, 1996) could account for the observed differences in neural activation with healthy volunteers. The stimulation intensities used were below those commonly employed when SEPs are recorded

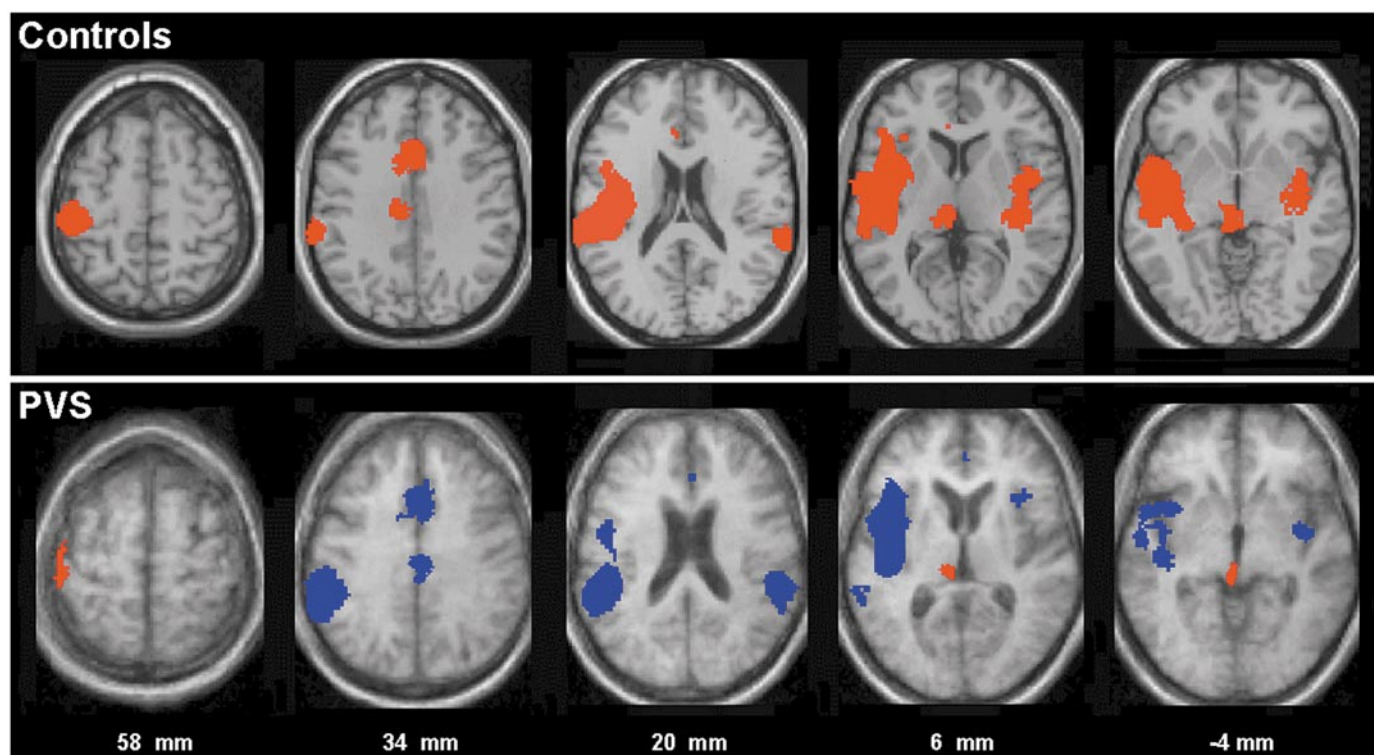


FIG. 2. (A) Brain regions, shown in red, that activated during noxious stimulation in controls [subtraction stimulation - rest]. (B) Brain regions that activated during stimulation in PVS patients, shown in red [subtraction stimulation - rest] and regions that activated less in patients than in controls [interaction (stimulation vs rest) \times (patient vs control)], shown in blue. Projected on transverse sections of a normalized brain MRI template in controls and on the mean MRI of the patients (distances are relative to the bicommissural plane).

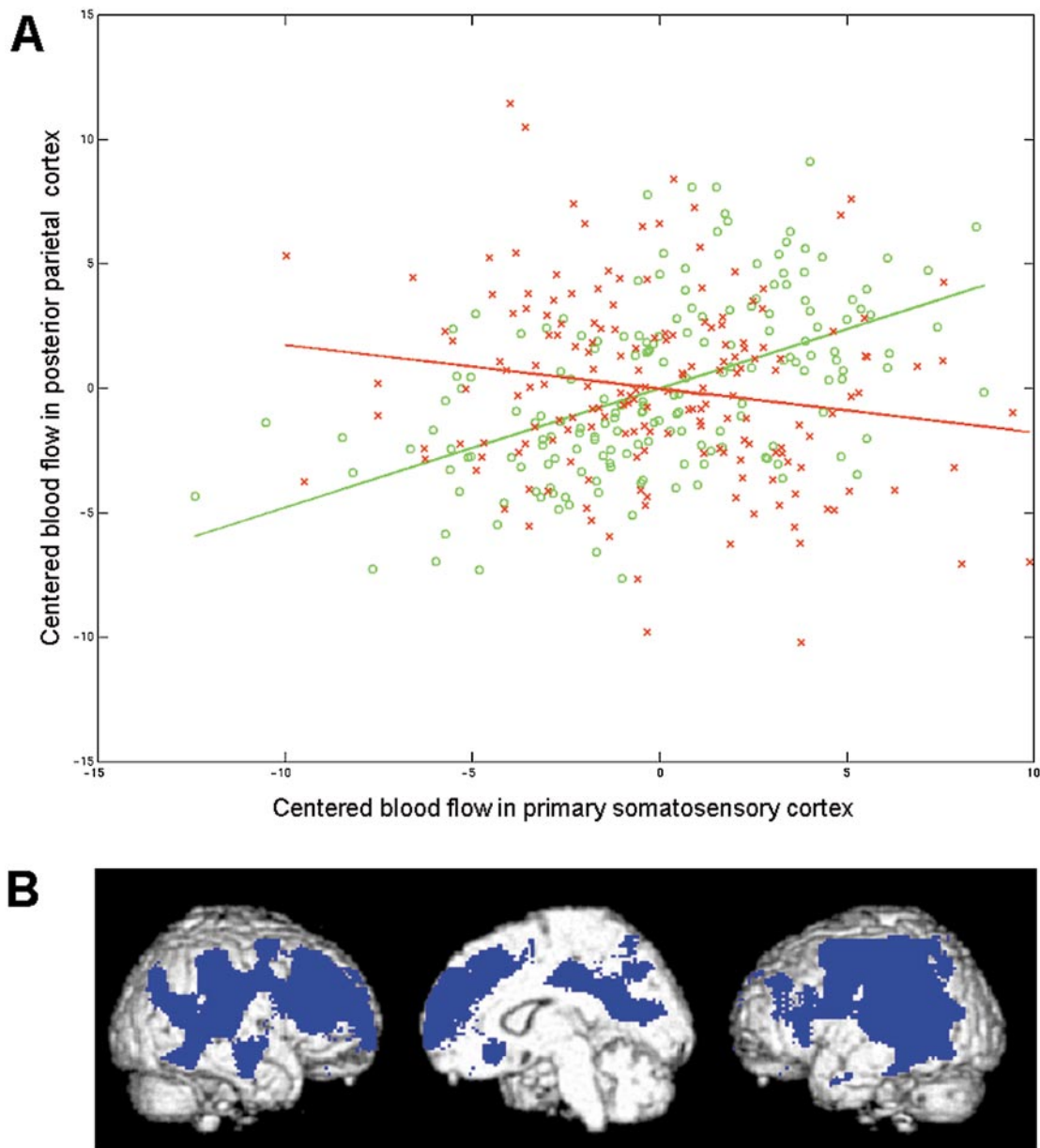


FIG. 3. (A) Plot of the regression of neural activity in primary somatosensory cortex and posterior parietal cortex in controls (green circles) and in PVS (red crosses). (B) Regions that showed a deficient functional connectivity with primary somatosensory cortex in patients relative to controls (blue), projected on 3D MRI. (Display thresholded at uncorrected $P < 0.001$.)

in unconscious patients at the intensive care unit (e.g., Madl *et al.*, 2000). PVS represents such an immense affective, social, and economic problem (Beresford, 1997) that it warrants further research to better understand its underlying cerebral dysfunction. We hope that the present study contributes to this aim, and, although fully aware of the ethical problems, we believe that the scope of the problem justified our efforts.

Pain is an unpleasant experience that involves the conscious awareness of noxious sensations (Ingvar, 1999). We used high-intensity electrical stimulation of

the median nerve, instead of thermal or chemical noxious stimuli, as this provided the possibility of easily and reliably measuring SEPs during the acquisition of rCBF data. The simultaneously recorded SEPs offered independent information on the integrity of peripheral nerves, spinal cord, and ascending central sensory pathways and ensured that patients were properly stimulated. In healthy volunteers, the electric shocks were perceived as highly unpleasant to painful and significantly activated brain areas previously described in brain imaging studies of pain using electrical

TABLE 4

Cerebral Areas That Showed Significant Activation during Noxious Somatosensory Stimulation Compared with Rest in PVS Patients

Side	Region	x	y	z	T value
	Midbrain	-6	-18	-10	4.09
Contralateral	Thalamus	-22	-26	2	3.40
Contralateral	Primary somatosensory cortex	-54	-26	58	4.41

^a All results are significant at small-volume-corrected $P < 0.05$.

(Davis *et al.*, 1997; Disbrow *et al.*, 1998; Oshiro *et al.*, 1998) or other (for review see Treede *et al.*, 1999; Chen, 2001) stimuli.

Based on clinical, electrophysiological, PET, and neuropathological findings, PVS patients are thought to lack the cerebral capacity to consciously experience the inner and external world (Multi-Society Task Force on PVS, 1994b). At the patient's bedside, however, assessment of cognitive function in severely brain-injured patients is difficult because voluntary movements may be very small, easily exhausted, and inconsistent (Zeman, 1997; Wade and Johnston, 1999). In accordance with previous reports (Levy *et al.*, 1987; De Volder *et al.*, 1990; Tommasino *et al.*, 1995; Rudolf *et al.*, 1999; Laureys *et al.*, 2001), our PVS patients showed a profound reduction of cerebral glucose metabolism. Nevertheless, external stimulation still resulted in significant increases in rCBF (taken as a marker of local neural activity) compared with the resting state. This neural activation, however, was limited to midbrain, contralateral thalamus, and S1. The observed subcortical activation could reflect a nonspecific arousal response (involving thalamoreticular structures) to acute pain (Peyron *et al.*, 1999). This response is preserved in patients in a PVS but can also be observed in infants with anencephaly (Medical Task Force on Anencephaly, 1990). Given our limited spatial resolution (16-mm FWHM smoothing of the

PET data) we cannot reliably differentiate between activation foci in lateral or medial thalamic nuclei. The only cortical area that activated during stimulation in PVS patients was S1, even in patients lacking cortical SEPs (N20). As evoked potentials depend on time-locked averages, a temporal desynchronization of the electrophysiological response will alter SEPs but leave rCBF increases unaffected. It is important to stress that our statistical analyses used a random-effect model and can hence be considered as characteristic of the population from which we sampled (Holmes and Friston, 1998; Peigneux *et al.*, 2000).

The role of different brain areas in pain processing remains controversial. Of the cerebral areas commonly identified by human neuroimaging studies, only the anterior cingulate shows a consistent response during the experience of pain (Derbyshire *et al.*, 1997). Traditionally, S1 is considered to be involved in the sensory-discriminative component of pain processing (Bushnell *et al.*, 1999) and single neurons in monkey S1 code for stimulus intensity, location, and duration (Kaas, 1993; Kenshalo *et al.*, 2000). In neurological patients, somatosensory stimuli below threshold for conscious sensation elicited activation of S1 but not of downstream areas (Libet *et al.*, 1967) and isolated electrical stimulation of S1 did not evoke the sensation of pain (Penfield and Jasper, 1954). The affective-motivational and cognitive evaluative components of pain are only partly understood but have been proposed to depend on insular, anterior cingulate, and posterior parietal cortices (Ingvar, 1999; Treede *et al.*, 1999). All these regions failed to activate in PVS patients. However, it is important to stress that the absence of stimulation-related neural activation (i.e., rCBF changes) can never formally exclude conscious perception of the stimulation. It can also not be excluded that PVS patients would experience continuous pain and that our subtraction ("acute pain" - "rest") would fail to provide sufficient stimulation to result in a significant difference. Previous neuroimaging studies have indeed suggested that pain-related activation in patients with

TABLE 5

Cerebral Areas That Showed Significantly Less Stimulation-Related Activation in PVS Patients than in Normal Controls (Interaction Analysis)^a

Side	Region	x	y	z	T value
Contralateral	Secondary somatosensory cortex	-46	-28	18	9.21
Contralateral	Insula	-44	-2	0	10.08
Ipsilateral	Insula	42	2	-2	5.74
Contralateral	Posterior parietal cortex (area 40)	-56	-30	24	6.56
Ipsilateral	Posterior parietal cortex (area 40)	64	-36	30	6.73
	Anterior cingulate cortex (area 24/32)	0	20	36	4.90
	Midcingulate cortex (area 23/24')	6	-20	30	5.08

^a All results are significant at small-volume-corrected $P < 0.05$.

TABLE 6

Brain Regions Where Functional Modulation with Primary Somatosensory Cortex was Impaired in PVS Compared with Controls^a

Side	Region	x	y	z	T value
Contralateral	Secondary somatosensory cortex	-48	-20	20	4.64
Contralateral	Posterior parietal cortex (area 40)	-52	-30	26	6.19
Ipsilateral	Posterior parietal cortex (area 40)	56	-24	30	4.86
Contralateral	Premotor cortex (area 6)	-22	-2	50	4.71
Contralateral	Dorsolateral prefrontal cortex (area 9)	32	48	32	5.44
Contralateral	Superior temporal cortex (area 22)	-52	-44	18	4.65

^a All results are significant at $P < 0.05$ corrected for multiple comparisons.

persistent pain may differ from that observed in healthy subjects (Di Piero *et al.*, 1991; Apkarian *et al.*, 1992; Hsieh *et al.*, 1995; Iadarola *et al.*, 1995; Jones and Derbyshire, 1997). To better understand the meaning of the preserved activation of S1 during noxious stimulation in PVS patients, we studied its functional connectivity (assessing stimulus-related functional integration) in addition to the classically used subtraction analyses (assessing stimulus-related functional segregation).

Using a psychophysiological interaction analysis (Friston *et al.*, 1997) we have shown that the preserved activation of S1 was isolated from downstream areas. Indeed, S1 was directly or indirectly "functionally disconnected" from S2, polysensory superior temporal, posterior parietal, prefrontal, and premotor cortices. In primates, S1 projects mainly to S2, which in turn innervates the insular cortices from where the somatosensory information reaches the limbic system. S2 and posterior parietal cortices are considered as important stations for the higher-order analysis and relay of somatosensory inputs to areas of affective, motivational, attentional, and motor control (Kaas, 1993). The prefrontal cortex is considered a critical component in conscious perception, working memory, behavioral control, affective attachment, directed and sustained attention, planning, and motor programming (Courtney *et al.*, 1998). Its disconnection from somatosensory cortices in PVS patients can be interpreted as further evidence of their deficient processing of noxious external stimuli. The lack of involvement of premotor areas could reflect the absence of the normal voluntary urge to move away from the painful stimulus (Ingvar, 1999). Our findings are also in agreement with lesion studies that suggested a necessary role of secondary and association cortices in the conscious processing of somatosensory stimuli (Caselli, 1993). In the same line, previous PET activation studies have shown that general anesthesia abolishes cortical, but not subcortical, responses to noxious electric shocks (Antognini *et al.*, 1997). Similarly, rCBF increases in associative cortices, but not thalami, have been shown to differentiate

silent from painful angina (Rosen *et al.*, 1996). Finally, a recent magnetoencephalographic study reported activation in S1, but not in secondary somatosensory or association cortices, in two patients with a tumor near the central sulcus that showed a unilateral complete lack of tactile sensation (both painful and nonpainful) (Preissl *et al.*, 2001).

In the absence of a generally accepted neural correlate of pain and consciousness, it is difficult to make definite judgements about awareness in PVS patients. Pain and suffering are first-person subjective experiences. Although no single study can claim to prove the absence or presence of conscious perception in another being, the present data make an important contribution to our understanding of the cerebral processing of noxious stimuli in PVS. We found no evidence of stimulation-related downstream activation beyond S1. More importantly, functional connectivity assessment showed that the observed activation of primary sensory cortex seems to subsist as an island, dissociated from higher-order cortices that would be necessary to produce awareness (Schiff *et al.*, 2002). It is, however, of major importance to stress that our results are representative of the population from which we sampled (i.e., PVS without normal flexion or withdrawal to noxious stimuli; absence of sustained visual pursuit, visual fixation, or response to visual threat; absence of selective emotional responses; and absence of attempts to articulate or utter words) and should be used with appropriate caution regarding clinical or ethical decisions in individual persons in a vegetative state. Future studies, using more powerful techniques such as functional MRI, are needed to confirm these findings in individual PVS cases. Future studies also need to assess the cortical processing of different sensory modalities of varying complexity in individual patients studied over time. Apart from their clinical interest, our data complement the current debate among neuroscientists concerning the relationship between neuronal activity in the nervous system (especially in primary cortex) and human consciousness (Crick and Koch, 1995; Tononi and Edelman, 1998).

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REFERENCES

- American Congress of Rehabilitation Medicine 1995. Recommendations for use of uniform nomenclature pertinent to patients with severe alterations of consciousness. *Arch. Phys. Med. Rehabil.* **76**: 205–209.
- ANA Committee on Ethical Affairs 1993. Persistent vegetative state: Report of the American Neurological Association Committee on Ethical Affairs. *Ann. Neurol.* **33**: 386–390.
- Antognini, J. F., Buonocore, M. H., Disbrow, E. A., and Carstens, E. 1997. Isoflurane anesthesia blunts cerebral responses to noxious and innocuous stimuli: A fMRI study. *Life Sci.* **61**: 349–354.
- Apkarian, A. V., Stea, R. A., Manglos, S. H., Szeverenyi, N. M., King, R. B., and Thomas, F. D. 1992. Persistent pain inhibits contralateral somatosensory cortical activity in humans. *Neurosci. Lett.* **140**: 141–147.
- Benzer, A., Mitterschiffthaler, G., Marosi, M., Luef, G., Puhlinger, F., De La Renotiere, K., Lehner, H., and Schmutzhard, E. 1991. Prediction of non-survival after trauma: Innsbruck Coma Scale. *Lancet* **338**: 977–978.
- Beresford, H. R. 1997. The persistent vegetative state: A view across the legal divide. *Ann. NY Acad. Sci.* **835**: 386–394.
- Bushnell, M. C., Duncan, G. H., Hofbauer, R. K., Ha, B., Chen, J., and Carrier, B. 1999. Pain perception: Is there a role for primary somatosensory cortex? *Proc. Natl. Acad. Sci. USA* **96**: 7705–7709.
- Caselli, R. J. 1993. Ventrolateral and dorsomedial somatosensory association cortex damage produces distinct somesthetic syndromes in humans. *Neurology* **43**: 762–771.
- Charlton, E. 1995. Ethical guidelines for pain research in humans: Committee on Ethical Issues of the International Association for the Study of Pain. *Pain* **63**: 277–278.
- Chen, A. C. 2001. New perspectives in EEG/MEG brain mapping and PET/fMRI neuroimaging of human pain. *Int. J. Psychophysiol.* **42**: 147–159.
- Courtney, S. M., Petit, L., Haxby, J. V., and Ungerleider, L. G. 1998. The role of prefrontal cortex in working memory: Examining the contents of consciousness. *Philos. Trans. R. Soc. London B* **353**: 1819–1828.
- Crick, F., and Koch, C. 1995. Are we aware of neural activity in primary visual cortex? *Nature* **375**: 121–123.
- Davis, K. D., Taylor, S. J., Crawley, A. P., Wood, M. L., and Mikulis, D. J. 1997. Functional MRI of pain- and attention-related activations in the human cingulate cortex. *J. Neurophysiol.* **77**: 3370–3380.
- de Jong, B., Willemsen, A. T., and Paans, A. M. 1997. Regional cerebral blood flow changes related to affective speech presentation in persistent vegetative state. *Clin. Neurol. Neurosurg.* **99**: 213–216.
- De Volder, A. G., Goffinet, A. M., Bol, A., Michel, C., de B. T., and Laterre, C. 1990. Brain glucose metabolism in postanoxic syndrome: Positron emission tomographic study. *Arch. Neurol.* **47**: 197–204.
- Derbyshire, S. W., Jones, A. K., Gyulai, F., Clark, S., Townsend, D., and Firestone, L. L. 1997. Pain processing during three levels of noxious stimulation produces differential patterns of central activity. *Pain* **73**: 431–445.
- Di Piero, V., Jones, A. K., Iannotti, F., Powell, M., Perani, D., Lenzi, G. L., and Frackowiak, R. S. 1991. Chronic pain: A PET study of the central effects of percutaneous high cervical cordotomy. *Pain* **46**: 9–12.
- Disbrow, E., Buonocore, M., Antognini, J., Carstens, E., and Rowley, H. A. 1998. Somatosensory cortex: A comparison of the response to noxious thermal, mechanical, and electrical stimuli using functional magnetic resonance imaging. *Hum. Brain Mapp.* **6**: 150–159.
- Friston, K. J. 1997. Analysing brain images: Principles and overview. In *Human Brain Function* (R. S. J. Frackowiak, K. J. Friston, C. D. Frith, R. J. Dolan, and J. C. Mazziotta, Eds.), pp. 25–41. Academic Press, San Diego.
- Friston, K. J., Buechel, C., Fink, G. R., Morris, J., Rolls, E., and Dolan, R. J. 1997. Psychophysiological and modulatory interactions in neuroimaging. *NeuroImage* **6**: 218–229.
- Giacino, J. T., Ashwal, S., Childs, N., Cranford, R., Jennett, B., Katz, D. I., Kelly, J. P., Rosenberg, J. H., Whyte, J., Zafonte, R. D., and Zasler, N. D. 2002. The minimally conscious state: Definition and diagnostic criteria. *Neurology* **58**: 349–353.
- Guérit, J. M., Fischer, C., Facco, E., Tinuper, P., and Murri, L. 1999. Standards of clinical practice of EEG and EPs in comatose and other unresponsive states. In *Recommendations for the Practice of Clinical Neurophysiology: Guidelines of the International Federation of Clinical Neurophysiology* (G. Deuschl, and A. Eisen, Eds.), pp. 117–131. Elsevier, Amsterdam.
- Holmes, A., and Friston, K. 1998. Generalisability, random effects and population inference. *NeuroImage* **7**: 754.
- Hsieh, J. C., Belfrage, M., Stone-Elander, S., Hansson, P., and Ingvar, M. 1995. Central representation of chronic ongoing neuropathic pain studied by positron emission tomography. *Pain* **63**: 225–236.
- Iadarola, M. J., Max, M. B., Berman, K. F., Byas-Smith, M. G., Coghill, R. C., Gracely, R. H., and Bennett, G. J. 1995. Unilateral decrease in thalamic activity observed with positron emission tomography in patients with chronic neuropathic pain. *Pain* **63**: 55–64.
- Ingvar, M. 1999. Pain and functional imaging. *Philos. Trans. R. Soc. London B* **354**: 1347–1358.
- Jones, A. K., and Derbyshire, S. W. 1997. Reduced cortical responses to noxious heat in patients with rheumatoid arthritis. *Ann. Rheum. Dis.* **56**: 601–607.
- Kaas, J. H. 1993. The functional organization of somatosensory cortex in primates. *Anat. Anz.* **175**: 509–518.
- Kenshalo, D. R., Iwata, K., Sholas, M., and Thomas, D. A. 2000. Response properties and organization of nociceptive neurons in area 1 of monkey primary somatosensory cortex. *J. Neurophysiol.* **84**: 719–729.
- Khuenl-Brady, K. S., and Sparr, H. 1996. Clinical pharmacokinetics of rocuronium bromide. *Clin. Pharmacokinet.* **31**: 174–183.
- Laureys, S., Berré, J., and Goldman, S. 2001. Cerebral function in coma, vegetative state, minimally conscious state, locked-in syndrome and brain death. In *2001 Yearbook of Intensive Care and Emergency Medicine* (J. L. Vincent, Ed.), pp. 386–396. Springer-Verlag, Berlin.
- Laureys, S., Faymonville, M. E., Degueldre, C., Fiore, G. D., Damas, P., Lambermont, B., Janssens, N., Aerts, J., Franck, G., Luxen, A., Moonen, G., Lamy, M., and Maquet, P. 2000a. Auditory processing in the vegetative state. *Brain* **123**: 1589–1601.
- Laureys, S., Faymonville, M. E., Luxen, A., Lamy, M., Franck, G., and Maquet, P. 2000b. Restoration of thalamo-cortical connectivity

- after recovery from persistent vegetative state. *Lancet* **355**: 1790–1791.
- Laureys, S., Goldman, S., Phillips, C., Van Bogaert, P., Aerts, J., Luxen, A., Franck, G., and Maquet, P. 1999. Impaired effective cortical connectivity in vegetative state: Preliminary investigation using PET. *NeuroImage* **9**: 377–382.
- Lesser, R. P., Koehle, R., and Lueders, H. 1979. Effect of stimulus intensity on short latency somatosensory evoked potentials. *Electroencephalogr. Clin. Neurophysiol.* **47**: 377–382.
- Levy, D. E., Sidtis, J. J., Rottenberg, D. A., Jarden, J. O., Strother, S. C., Dhawan, V., Ginos, J. Z., Tramo, M. J., Evans, A. C., and Plum, F. 1987. Differences in cerebral blood flow and glucose utilization in vegetative versus locked-in patients. *Ann. Neurol.* **22**: 673–682.
- Libet, B., Alberts, W. W., Wright, E. W., Jr., and Feinstein, B. 1967. Responses of human somatosensory cortex to stimuli below threshold for conscious sensation. *Science* **158**: 1597–1600.
- Madl, C., Kramer, L., Domanovits, H., Woolard, R. H., Gervais, H., Gendo, A., Eisenhuber, E., Grimm, G., and Sterz, F. 2000. Improved outcome prediction in unconscious cardiac arrest survivors with sensory evoked potentials compared with clinical assessment. *Crit. Care Med.* **28**: 721–726.
- McQuillen, M. P. 1991. Can people who are unconscious or in the “vegetative state” perceive pain? *Issues Law Med.* **6**: 373–383.
- Medical Task Force on Anencephaly 1990. The infant with anencephaly. *N. Engl. J. Med.* **322**: 669–674.
- Multi-Society Task Force on PVS 1994a. Medical aspects of the persistent vegetative state (1). *N. Engl. J. Med.* **330**: 1499–1508.
- Multi-Society Task Force on PVS 1994b. Medical aspects of the persistent vegetative state (2). *N. Engl. J. Med.* **330**: 1572–1579.
- Menon, D. K., Owen, A. M., Williams, E. J., Minhas, P. S., Allen, C. M., Boniface, S. J., and Pickard, J. D. 1998. Cortical processing in persistent vegetative state. *Lancet* **352**: 200.
- Oshiro, Y., Fujita, N., Tanaka, H., Hirabuki, N., Nakamura, H., and Yoshiya, I. 1998. Functional mapping of pain-related activation with echo-planar MRI: Significance of the SII-insular region. *NeuroReport* **9**: 2285–2289.
- Peigneux, P., Maquet, P., Meulemans, T., Destrebecqz, A., Laureys, S., Degueldre, C., Delfiore, G., Aerts, J., Luxen, A., Franck, G., Van der Linden, M., and Cleeremans, A. 2000. Striatum forever, despite sequence learning variability: A random effect analysis of PET data. *Hum. Brain Mapp.* **10**: 179–194.
- Penfield, W., and Jasper, H. 1954. *Epilepsy and the Functional Anatomy of the Human Brain*, p. 895. Little, Brown, Boston.
- Peyron, R., Garcia-Larrea, L., Gregoire, M. C., Costes, N., Convers, P., Lavenne, F., Mauguiere, F., Michel, D., and Laurent, B. 1999. Haemodynamic brain responses to acute pain in humans: Sensory and attentional networks. *Brain* **122**: 1765–1780.
- Preissl, H., Flor, H., Lutzenberger, W., Duffner, F., Freudenstein, D., Grote, E., and Birbaumer, N. 2001. Early activation of the primary somatosensory cortex without conscious awareness of somatosensory stimuli in tumor patients. *Neurosci. Lett.* **308**: 193–196.
- Rosen, S. D., Paulesu, E., Nihoyannopoulos, P., Tousoulis, D., Frackowiak, R. S., Frith, C. D., Jones, T., and Camici, P. G. 1996. Silent ischemia as a central problem: Regional brain activation compared in silent and painful myocardial ischemia. *Ann. Intern. Med.* **124**: 939–949.
- Rudolf, J., Ghaemi, M., Haupt, W. F., Szeli, B., and Heiss, W. D. 1999. Cerebral glucose metabolism in acute and persistent vegetative state. *J. Neurosurg. Anesthesiol.* **11**: 17–24.
- Schiff, N., Ribary, U., Moreno, D. R., Beattie, B., Kronberg, E., Blasberg, R., Giacino, J., McCagg, C., Fins, J. J., Llinas, R., and Plum, F. 2002. Residual cerebral activity and behavioural fragments can remain in the persistently vegetative brain. *Brain* **125**: 1210–1234.
- Starmark, J. E., Stalhammar, D., Holmgren, E., and Rosander, B. 1988. A comparison of the Glasgow Coma Scale and the Reaction Level Scale (RLS85). *J. Neurosurg.* **69**: 699–706.
- Sugiura, K., Muraoka, K., Chishiki, T., and Baba, M. 1983. The Edinburgh-2 coma scale: A new scale for assessing impaired consciousness. *Neurosurgery* **12**: 411–415.
- Teasdale, G., and Jennett, B. 1974. Assessment of coma and impaired consciousness: A practical scale. *Lancet* **2**: 81–84.
- Tomberg, C., Desmedt, J. E., and Ozaki, I. 1991. Right or left ear reference changes the voltage of frontal and parietal somatosensory evoked potentials. *Electroencephalogr. Clin. Neurophysiol.* **80**: 504–512.
- Tommasino, C., Grana, C., Lucignani, G., Torri, G., and Fazio, F. 1995. Regional cerebral metabolism of glucose in comatose and vegetative state patients. *J. Neurosurg. Anesthesiol.* **7**: 109–116.
- Tononi, G., and Edelman, G. M. 1998. Consciousness and complexity. *Science* **282**: 1846–1851.
- Treede, R. D., Kenshalo, D. R., Gracely, R. H., and Jones, A. K. 1999. The cortical representation of pain. *Pain* **79**: 105–111.
- Wade, D. T., and Johnston, C. 1999. The permanent vegetative state: practical guidance on diagnosis and management. *Br. Med. J.* **319**: 841–844.
- World Medical Association 1997. World Medical Association declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. *JAMA* **277**: 925–926.
- Zeman, A. 1997. Persistent vegetative state. *Lancet* **350**: 795–799.