Perception of pain in the minimally conscious state with PET activation: an observational study

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Summary

Background **Patients in a minimally conscious state (MCS) show restricted self or environment awareness but are unable to communicate consistently and reliably. Therefore, better understanding of cerebral noxious processing in these patients is of clinical, therapeutic, and ethical relevance.**

Methods **We studied brain activation induced by bilateral electrical stimulation of the median nerve in five patients in MCS (aged 18–74 years) compared with 15 controls (19–64 years) and 15 patients (19–75 years) in a persistent vegetative state (PVS) with ^{15}O-radiolabelled water PET. By way of psychophysiological interaction analysis, we also investigated the functional connectivity of the primary somatosensory cortex (S1) in patients and controls. Patients in MCS were scanned 57 (SD 33) days after admission, and patients in PVS 36 (9) days after admission. Stimulation intensities were 8·6 (SD 6·7) mA in patients in MCS, 7·4 (5·9) mA in controls, and 14·2 (8·7) mA in patients in PVS. Significant results were thresholded at p values of less than 0·05 and corrected for multiple comparisons.**

Findings **In patients in MCS and in controls, noxious stimulation activated the thalamus, S1, and the secondary somatosensory or insular, frontoparietal, and anterior cingulate cortices (known as the pain matrix). No area was less activated in the patients in MCS than in the controls. All areas of the cortical pain matrix showed greater activation in patients in MCS than in those in PVS. Finally, in contrast with patients in PVS, those in MCS had preserved functional connectivity between S1 and a widespread cortical network that includes the frontoparietal associative cortices.**

Interpretation **Cerebral correlates of pain processing are found in a similar network in controls and patients in MCS but are much more widespread than in patients in PVS. These findings might be objective evidence of a potential pain perception capacity in patients in MCS, which supports the idea that these patients need analgesic treatment.**

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Introduction

A persistent vegetative state (PVS) is defined by wakefulness without awareness of self or the environment,[1] whereas patients in a minimally conscious state (MCS) show some evidence of self and environmental awareness.[2] However, the carers of patients who are minimally conscious have difficulties in assessing the patients' level of conscious pain perception through their behaviour. Moreover, there are no guidelines on pain treatment in patients in MCS.[3] Noxious stimulation is a routine clinical procedure for the bedside assessment of consciousness in patients who are severely brain damaged. Noxious stimulation is also part of the commonly used coma scales, such as the Glasgow coma scale (GCS),[4] the reaction level scale,[5] the Innsbruck coma scale,[6] the Edinburgh 2 coma scale,[7] and the coma recovery scale.[8] The study of cerebral processing of noxious stimulation in these patients is also of clinical, therapeutic, and ethical relevance.[9] We have previously reported on the cortical responses of patients in PVS to similar noxious somatosensory stimuli by use of ^{15}O-radiolabelled water PET,[10] and found that the only areas that significantly responded to noxious stimulation in patients in PVS were the brainstem, contralateral thalamus, and primary somatosensory cortex (S1). Here, we used an identical set-up to study five patients who are in MCS and compared the results with those from patients in PVS and 15 healthy controls.

Methods

Participants

Five non-sedated patients in MCS (4 men; mean age 49 [SD 22] years, range 18–74 years), 15 non-sedated patients in PVS (12 men; mean age 48 [17] years, range 19–75 years), and 15 healthy volunteers (8 male; mean age 40 [9] years, range 19–64 years) were studied prospectively. Table 1 shows the demographic data of the patients in MCS. The aetiologies of the patients in PVS were: cardiorespiratory arrest (n=5), diffuse axonal injury (n=3), drugs overdose (n=2), prolonged respiratory insufficiency (n=2), encephalitis with diffuse white matter lesions (n=2), and carbon monoxide intoxication (n=1). Clinical diagnoses were made on the basis of repeated, standardised evaluation[11] and conformed to international criteria for PVS[12] and MCS.[13] Patients were assessed four times by trained and experienced assessors (SL and CS): 1 week and 1 day before scanning, the day of

the scan, and 1 week after the scan. None of the patients in MCS showed localisation in response to noxious stimuli and none of the patients in PVS showed normal flexion or withdrawal in response to noxious stimuli. Mean GCS[4] on admission were 6 (SD 5) points for the patients who were minimally conscious and 5 (3) points for the patients in PVS. All patients had preserved pupillary, corneal, and vestibulo-ocular reflexes. Assessment of median nerve sensory conduction velocity and somatosensory evoked potential excluded peripheral nerve, plexus, or spinal cord lesions. Short latency auditory evoked potentials showed preserved pontine and midbrain functions in all patients.

Procedures

Patients in MCS were scanned a mean of 57 (SD 33) days after admission and patients in PVS 36 (9) days after admission. Patients were scanned during awake periods, as shown by simultaneous polygraphic recordings (electroencephalogram and electro-oculogram). Throughout the procedure, patients were monitored by a senior anaesthetist (MEF), assisted by an intensive care physician. Written, informed consent was obtained from the people with legal responsibility for the patients and from all controls personally. Stimulation was kept at the minimum duration (6×70 s) and minimum intensity needed for PET. Stimulation intensities were increased to the point where all components of the somatosensory evoked potentials showed maximum amplitude;[14] the stimulation intensity was then kept constant throughout the experiment. Electrical stimulation of the median nerve at the intensity used was rated as highly unpleasant to painful by the controls.[10] Stimulation intensity was not significantly different for the patients in MCS than for patients in PVS or controls (MCS mean 8·6 [SD 6·7] mA; PVS mean 14·2 [8·7] mA; controls mean 7·4 [5·9] mA).

	Patient 1	Patient 2	Patient 3*	Patient 4	Patient 5*
Sex	Male	Female	Male	Male	Male
Age (years)	41	64	74	18	50
Cause	Cardiorespiratory arrest	Respiratory arrest and hypotension	Encephalitis	Traumatic posterior fossa haematoma	Diffuse axonal injury
Glasgow coma score on admission	3 points	3 points	14 points	6 points	6 points
Time from admission to PET	41 days	116 days	40 days	50 days	37 days
Outcome at 12 months	Distinctly dependent	Distinctly dependent	Died	Moderately dependent	Distinctly dependent
Clinical evaluation at time of PET					
Interactive communication	Absent	Absent	Absent	Absent	Absent
Functional use of ≥2 objects	Absent	Absent	Absent	Absent	Absent
Best verbal response	None	Incomprehensible sounds	None	None	Incomprehensible sounds
Best gestural response	Smiles in response to relevant visual stimuli	Inconsistent tongue protrusion to auditory command	Smiles in response to relevant verbal stimuli	Inconsistent movement of left foot to auditory command	Tongue protrusion
Best motor response to noxious stimuli	Flexion withdrawal	Stereotyped extension posturing	Stereotyped flexion posturing	Flexion withdrawal	Stereotyped extension posturing
Eye opening	Spontaneous	Spontaneous	Spontaneous	Spontaneous	Spontaneous
Sleep–wake cycles	Present	Present	Present	Present	Present
Arousal level	Fluctuates	Healthy	Healthy	Fluctuates	Fluctuates
Eye movements	Fixation on family members	Tracking	Tracking of family members	Tracking	Inconsistent tracking and fixation
Eye blinking to visual threat	Present	Present	Present	Present	Present
Breathing	Healthy	Healthy	Healthy	Healthy	Healthy
Gag reflex	Present	Present	Present	Present	Present
Deep tendon reflexes	Raised	Raised	Raised	Raised	Raised
Skeletal muscle tone	Spastic	Spastic	Spastic	Spastic	Spastic
Paralysis or paresis	Bilateral	Bilateral	Bilateral	Bilateral	Bilateral
Babinski's sign	Bilateral	Absent	Absent	Bilateral	Absent
EEG					
Background activity	Disorganised delta waves	Reactive and disorganised theta waves	Disorganised theta waves	Reactive and disorganised theta waves	Disorganised delta waves
MRI					
Increased intensity on T2-weighted MRI	Periventricular	Diffuse white matter and cortical atrophy	Diffuse white matter	Intracerebellar, left occipital, and bifrontal contusions	Diffuse white matter

*Previously reported.[1]

Table 1: **Clinical, electrophysiological, and structural imaging data of patients in MCS**

The stimulation intensities used in non-communicative patients were lower than those used routinely when somatosensory evoked potentials are recorded at an intensive care unit.[15]

The study was approved by the ethics committee of the Faculty of Medicine of the University of Liège and done in accordance with the Declaration of Helsinki[16] and the International Association for the Study of Pain (IASP) Ethical Guidelines for Pain Research in Humans.[17]

Changes in regional cerebral blood flow were measured with ^{15}O-radiolabelled water PET, as described elsewhere.[10] Data acquisition in patients in MCS started 24 months after the study in patients in PVS.[10] Scans were done during rest and electrical stimulation of the left-sided and right-sided median nerve (0·2 ms square-wave pulses at 5·1 Hz at the wrist). We chose bilateral median nerve stimulation because this meant that both hemispheres were recruited in patients with severe brain injury. The conditions of each test were repeated three times (except in one patient, in whom only two scans could be obtained for left-sided and two scans for right-sided noxious stimulation). The order or presentation was pseudorandomised for all patients. Haemodynamic parameters were monitored, and

	Region (Brodmann area)	Side	*x*	*y*	*z*	*z* value	Corrected p value
Controls							
Activations	Thalamus	Contralateral	−10	−10	8	4·50	0·0001
		Ipsilateral	6	−6	8	3·85	0·001
	Primary somatosensory cortex	Contralateral	−48	−28	58	5·42	<0·0001
	Secondary sensory cortex/insula	Contralateral	−38	−22	12	7·42	<0·0001
	Inferior parietal lobule (39/40)	Contralateral	−64	−34	36	4·70	<0·0001
		Ipsilateral	66	−42	34	3·34	0·007
	Inferior parietal lobule (7/40)	Contralateral	−50	−66	44	2·82	0·023
		Ipsilateral	48	−66	46	2·90	0·020
	Superior temporal gyrus (22/42)	Contralateral	−62	−34	20	5·97	<0·0001
		Ipsilateral	66	−34	24	4·19	0·0004
	Striatum	Contralateral	−26	−10	0	5·04	<0·0001
		Ipsilateral	22	16	2	4·28	0·0003
	Anterior cingulate cortex (24/32)	Medial	2	20	36	5·10	<0·0001
	Posterior cingulate cortex (23)	Medial	−4	−20	32	4·76	<0·0001
	DLPFC (9/10)	Contralateral	−32	52	26	3·16	0·010
		Ipsilateral	44	50	−6	2·60	0·039
Deactivations	Posterior cingulate or precuneus	Medial	10	−54	62	3·58	0·002
	Medial prefrontal cortex	Medial	−2	52	26	2·77	0·019
	Parietal cortex	Ipsilateral	24	−36	54	4·61	<0·0001
	Occipital cortex	Ipsilateral	6	−76	8	6·17	<0·0001
Patients in MCS							
Activations	Thalamus	Contralateral	−14	−10	14	3·27	0·019*
	Primary somatosensory cortex	Contralateral	−46	−26	54	4·40	0·008
	Secondary sensory cortex or insula	Contralateral	−34	−24	26	4·93	0·007
	Inferior parietal lobule (39/40)	Contralateral	−64	−38	28	3·14	0·016*
	Inferior parietal lobule (7/40)	Contralateral	−36	−32	44	4·75	0·007
	Superior temporal gyrus (22/42)	Contralateral	−66	−42	20	3·16	0·016*
	Anterior cingulate cortex (24/32)	Medial	12	10	36	3·21	0·038*
	DLPFC (9/10)	Contralateral	−38	48	30	3·48	0·045*
Deactivations	Posterior cingulate or precuneus	Medial	−6	−56	20	3·07	0·001†
	Medial prefrontal cortex	Medial	0	50	−18	2·67	0·004*
Differences in stimulation-induced regional cerebral blood flow changes							
Activations	No areas identified						
Deactivations	Posterior cingulate or precuneus	Medial	2	−54	62	4·21	0·009
	Occipital cortex	Contralateral	−18	−78	18	4·42	0·009

*Results are thresholded at p values <0·05 corrected for multiple comparisons with FDR at the whole brain level or in a 10 mm radius sphere around predetermined coordinates from healthy controls. †Uncorrected p values (these areas did not reach significance when corrected for multiple comparisons). DLPFC=dorsolateral prefrontal cortex.

***Table 2*: Peak voxels for significant changes in regional cerebral blood flow in response to noxious stimulation**

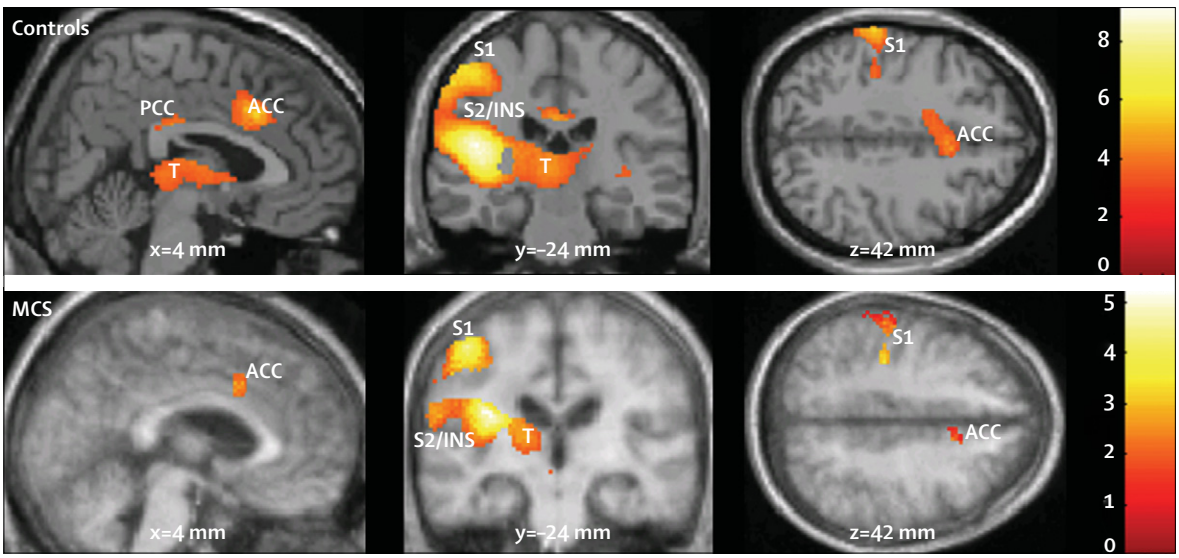

Figure: **Brain activation to pain in controls and patients in MCS**
(Top) Regions of the brain that were activated during noxious stimulation in controls (stimulation–rest). (Bottom) Brain regions commonly activated during stimulation in patients in MCS and in controls. Significant results were thresholded for display at uncorrected p value <0·001 and projected on sagittal (*x*=4 mm), coronal (*y*=–24 mm), and transverse (*z*=42 mm) sections of a normalised brain MRI template in controls and on the mean MRI of the patients (distances are relative to the bicommisural plane). T=thalamus. PCC=posterior cingulate cortex. ACC=anterior cingulate cortex. S2/INS=secondary somatosensory cortex or insula. S1=primary somatosensory cortex.

electroencephalogram, electromyogram, ocular movements, and somatosensory evoked potentials were recorded throughout the procedure. A high-resolution, T1-weighted brain MRI was obtained for coregistration to the functional data.

Statistical analysis

For more on **statistical parametric mapping (SPM)** see www.fil.ion.ucl.ac.uk/spm

PET data were realigned, spatially normalised, smoothed, and analysed with statistical parametric mapping. Because SPM is a more powerful voxel-based statistical method with more precise anatomical validity, it was preferred over the region-of-interest approach. A smoothing kernel of full width at a half maximum of 16 mm was chosen owing to the severely damaged brains of the patients in MCS or PVS. The smoothing was identical to that used in our previous study.[10] Data obtained during left-sided noxious stimulation and at rest were flipped, as reported previously.[10] A random effects analysis[18] identified the areas of the brain that were activated during noxious stimulation. We calculated one contrast between stimulation and rest per patient, which accounts for the within-patient component of the variance. We used these contrast images in a second design matrix that took into account the between-patient component of the variance and separated the data into three groups (controls, patients in PVS, and patients in MCS). The first two contrasts searched for brain activation in response to noxious stimulation in controls and patients in an MCS. We also looked for the group interaction ([controls–patients in MCS] × condition [stimulation–rest]) to search for areas that were less activated in patients in MCS than in healthy controls.[19] A second group interaction was done ([patients in MCS–patients in VS]×condition [stimulation–rest]) to search for the areas that were more activated in patients in MCS than patients in PVS. By use of reversed T contrasts we also looked for and compared deactivations during noxious processing with baseline in controls and patients in MCS. The results from the patients were masked inclusively by the results from the controls (uncorrected $p<0·05$). The results from controls and comparisons between patient populations were thresholded at a whole-brain false discovery rate (FDR)-corrected p value of less than 0·05.[20,21] Results from patients in MCS were thresholded at p values less than 0·05 and corrected for multiple comparisons with FDR at the whole-brain level or in a small volume (spheres with 10 mm radii) centred on the peak voxels of interest that were identified in controls.

Finally, we did a psychophysiological analysis, as previously described.[10] Our previous analysis was of the modulation between S1 and the rest of the brain in controls and patients. The first analysis looked for preserved modulation between S1 and the rest of the brain in patients in MCS compared with controls, by way of a conjunction approach—a conjunction analysis requires that all tested comparisons are individually significant.[22] Here, we looked for brain regions that were significantly modulated by S1 in patients in MCS and controls. A second analysis looked for differences between patients in MCS and controls. Finally, we searched for differences of S1 functional connectivity between patients in MCS or patients in PVS. Results were masked inclusively by controls results (uncorrected

p<0·05). All results from psycho-physiological interactions were thresholded at a whole-brain FDR-corrected p value of less than 0·05.

Role of the funding source

The funding sources had no role in the study design, data collection, data analysis, data interpretation, or writing of this report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

In the controls, noxious stimulation resulted in the subjective experience of pain and increased regional cerebral blood flow in several areas, including the thalamus, striatum, contralateral S1, secondary somatosensory or insular cortices, superior temporal, posterior, parietal, posterior cingulate, prefrontal, and anterior cingulate cortices (table 2 and figure). Compared with baseline, deactivations could also be found in the posterior cingulate and precuneus and medial prefrontal cortices (table 2).

Patients who were minimally conscious also showed significant activation in all the areas activated in the controls (table 2, webfigure), although the pattern of activation was lateralised and with less spatial extent. The total extent of stimulus-induced cerebral activation (at an uncorrected p value of <0·001) in controls and patients in MCS was 4395 and 1471 voxels, respectively, taking into account the differences in the numbers of patients. However, the interaction analysis did not identify any voxel that was significantly less activated in the patients in MCS compared with controls. During noxious stimulation, the posterior cingulate or precuneus and medial prefrontal cortices also showed deactivation in patients in MCS, but there was no difference in deactivation after correction for multiple comparisons. However, deactivations in patients in MCS were significantly less pronounced than in controls (table 2).

Compared with patients in PVS, patients who were minimally conscious showed significantly greater activation in the S1, secondary somatosensory cortex or insula, anterior cingulate cortex, and posterior parietal and dorsolateral prefrontal cortices (table 3). No voxels were significantly less activated in patients in MCS compared with patients in PVS.

Finally, psychophysiological interaction analysis revealed preserved modulation between S1 and a large set of associative areas, including the high order frontoparietal cortices, in patients in MCS (table 4). Compared with controls, patients in MCS had impaired connectivity in the posterior cingulate or precuneus and in the medial prefrontal cortices. When patients in MCS were compared with patients in PVS, functional connectivity between the S1 and the lateral and medial frontoparietal areas was significantly higher in patients in MCS than those in PVS.

	Side	x	y	z	z value	Corrected p value
Primary somatosensory cortex	Contralateral	–36	–28	34	4·18	0·019
Secondary sensory cortex/insula	Contralateral	–38	–22	22	4·14	0·019
Inferior parietal lobule (39/40)	Contralateral	–44	–32	32	4·00	0·023
Inferior parietal lobule (7/40)	Contralateral	–36	–34	42	5·07	0·013
Superior temporal gyrus (41)	Contralateral	–42	–30	6	3·10	0·046
Anterior cingulate cortex (24)	Medial	12	8	40	3·02	0·050
DLPFC (9/10)	Contralateral	–38	46	32	3·66	0·030

All results are thresholded at a whole-brain FDR-corrected p value <0·05. Figures in brackets are Brodmann areas. DLPFC=dorsolateral prefrontal cortex. Data from patients in PVS has been published previously.[10]

***Table 3*: Peak areas that show greater activation in response to noxious stimulation in patients in MCS compared with patients in PVS**

	Side	x	y	z	z value	Corrected p value
Patients in MCS and controls						
Secondary sensory cortex/insula	Contralateral	–38	–34	22	4.36	0·0001
Posterior parietal cortex (40)	Contralateral	–62	–16	22	6·07	<0·0001
Premotor cortex (6)	Contralateral	–56	2	34	4·98	<0·0001
DLPFC (9/10)	Contralateral	–40	52	20	3·34	0·004
Superior temporal cortex (22)	Contralateral	–50	–38	0	6·80	<0·0001
Patients in MCS<controls						
Posterior cingulate or precuneus	Medial	6	–68	50	3·81	0·0003
Medial prefrontal cortex	Medial	6	66	20	3·74	0·0003
Occipital cortex	Ipsilateral	26	–72	8	Inf	<0·0001

All results are thresholded at whole-brain FDR-corrected p value <0·05. Areas are significantly more connected to S1 during noxious processing in patients in MCS compared with patients in PVS. Figures in brackets are Brodmann area. DLPFC=dorsolateral prefrontal cortex.

***Table 4*: Areas that show preserved functional connectivity in patients in MCS and controls and in patients in MCS compared with patients in PVS**

Discussion

Pain is a subjective experience.[23] By definition, patients in MCS are unable to consistently and reliably communicate their experiences, and their behavioural responses to noxious stimulation are often difficult to interpret. Even if some patients in MCS can correctly answer yes or no questions at a level above chance, a question such as, "Are you in pain?" might not elicit a reliable response. The behavioural assessment of motor or autonomic signs (ie, respiratory frequency, heart rate, blood pressure, pupillary diameter, and skin conductance) are not reliable markers of the conscious perception of pain, as shown in studies done in general anaesthesia.[24] The evaluation and treatment of pain is therefore an important clinical and ethical problem in patients in MCS. In this context, functional neuroimaging can objectively measure changes in brain function during noxious stimulation in these patients. Indeed, several authors have stressed the need for brain imaging studies of pain processing in patients who are in altered states of consciousness.[12,25–27] The study of cerebral responses to painful stimuli in patients with altered states of consciousness can also help to understand pain processing in healthy patients.[28]

See Online for webfigure

The role of different areas of the brain in pain processing is only partially understood, and the neural representation of the brain is thought to be both specific and integrated. In summary, the sensory-discriminative component of pain is thought to depend on primary and secondary somatosensory cortices, and the affective-motivational on the anterior cingulate cortex and prefrontal areas—the insular cortex has an intermediate role.[29–32]

In healthy volunteers, electrical stimulation of the median nerve was perceived as highly unpleasant to painful and activated areas of the brain that were previously described in pain imaging studies—the pain matrix.[30,31,33] A similar set of cortical and subcortical areas was activated during noxious stimulation in patients in MCS and in healthy controls. The only areas that were not significantly activated in patients in MCS were the posterior cingulate cortex and the striatum, but direct comparison of the activation of these areas between controls and patients in MCS did not show a significant difference. We cannot exclude the possibility that there is a difference in the cerebral processing of painful stimuli between patients in MCS and controls because the activation volumes were greater and more bilateral in controls than in patients in MCS; however, this might also be because of the few patients in MCS who were scanned. Finally, when patients in MCS were compared with controls no area was significantly less activated, whereas the activation of a large number of associative areas during noxious stimulation was not seen in any of the patients in PVS.[10] Indeed, the patients in MCS not only had activation in the contralateral thalamus and S1, as did the patients in PVS, but also in high-order associative areas, including contralateral secondary somatosensory and posterior insular cortices, posterior parietal and dorsolateral prefrontal cortices, and anterior cingulate cortex. The whole cortical pain matrix was significantly more activated in patients in MCS than in patients in PVS when both populations were compared directly. In patients in MCS, functional connectivity between the primary somatosensory cortices and lateral frontoparietal cortices was similar to the functional connectivity in the controls. This frontoparietal network connectivity was significantly stronger in patients in MCS than in patients in PVS. These findings indicate that patients in MCS might show an elaborate and integrated level of noxious processing, which contrasts with previous findings in patients in PVS.[10] The time lapse between the study in patients in PVS and the current study in patients in MCS makes unbiased comparisons difficult. However, the infrastructure (scanner, scanning protocol, and painful stimulation methodology) was matched for both studies.

Peak pain-related activation was found in the secondary somatosensory or posterior insular cortex in patients in MCS and in controls. The insular cortex is thought to be important for pain perception because it was activated in brain imaging studies on pain,[31,34] and direct electrical stimulation of the insular cortex induces the sensation of pain in human beings.[35] However, a recent PET study showed activation of the insular cortex during general anaesthesia in healthy volunteers;[36] the authors interpreted these results as brain autonomic responses evoked by the noxious stimulation. In patients in MCS, however, activation of the insular cortex in response to noxious stimulation was associated with brain activity and functional connectivity in several brain areas that are involved in both the sensory and limbic aspects of pain processing.[29–31] More specifically, the activation of high-order frontoparietal cortices has been repeatedly associated with the conscious perception of external stimuli in visual[37,38] and somatosensory[28,39] modalities. Even if the neural correlates of conscious perception and pain processing need to be fully elucidated,[40] the coactivation of specialised sensory cortices and frontoparietal areas seems both necessary and sufficient to generate conscious perception.[41] Although brain imaging is not a shortcut to subjectivity, we interpret the brain activation and functional connectivity patterns seen in patients in MCS as likely to show conscious perception of noxious stimuli.

Among the commonly identified cerebral areas in human neuroimaging studies, the anterior cingulate and insular cortices show particularly consistent responses during the pain.[42] Moreover, the level of activation in the anterior cingulate cortex correlates with pain intensity scores.[30,42] In brain imaging studies, activation of the anterior cingulate cortex was associated with the affective-motivational components of pain perception,[43] and in the processing of stimulus intensity[44] and stimulus awareness.[28,44] The activation of the anterior cingulate cortex in response to noxious stimuli in patients in MCS is important because it suggests that they might also have pain affect. The impaired deactivation and functional connectivity seen in areas of the default network (ie, the posterior cingulate or precuneus and medial prefrontal cortices),[45] which are thought to be involved in self-related processes,[46] could show preserved but different-from-normal perception of pain in patients in MCS.[3]

We believe that these results should prompt the use of analgesics in patients in MCS, particularly when invasive surgery or other clinical procedures are necessary. Although pain is a first-person experience and the neural substrates of the conscious perception of pain are unknown, the extent of brain activation induced in patients in MCS in response to noxious stimulation, which was not different from that in controls, suggests that there is at least some level of pain sensory and affective perception. In our study, patients in MCS did not have significantly less activation than did the controls. However, this negative finding might be biased by reduced statistical power due to the small number of patients studied. This concern does not apply when comparing patients in MCS with those in PVS, in whom

significant differences could be shown. We only did analyses at the group level; hence, our results do not imply that none of the patients in PVS could activate a large number of brain areas in response to noxious stimulation or that all patients in MCS do so—even if the random effects analyses we used took within-patient and between-patient variability into account. Unfortunately, the ^{15}O-radiolabelled water PET technique does not enable us to identify reliably activation maps in individual patients. Functional MRI can tackle this problem because many more scans can be acquired per patient; these studies are currently ongoing. Our findings are relevant for the understanding of pain processing and to ethical discussions but do not provide sufficient evidence to guide the clinical management of individual patients. Variability in pain processing is expected between individuals in heterogeneous populations of patients. Although our study also stresses the need to distinguish at the bedside patients in MCS from patients in PVS, several studies have shown that misdiagnosis is common between these populations of patients.[27] The evidence is not sufficient to choose not to treat potentially painful conditions in patients in PVS. Analgesic intervention in these patients is also desirable to prevent potentially damaging defensive hormonal reactions (eg, adrenal stress hormones), despite the possible absence of pain. Controlled trials that report objective outcomes, such as the absence of negative complications and survival, would enable assessment of the clinical appropriateness of analgesia in patients in PVS or MCS.

Contributors

SL, PM, AL, ML, and GM participated in the conception and design of this study. SL, MEF, CS, BL, and PL acquired the data. SL, MB, PP, CP, and PM analysed and interpreted the data. MB and SL drafted the manuscript. MEF, CS, PP, BL, CP, PL, AL, ML, GM, and PM revised the manuscript for intellectual content. SL, MB, PP, CP, and PM provided statistical expertise. SL, AL, PM, ML, and GM obtained funding. MEF, CS, BL, and PL provided administrative, technical, or material support, and SL, MEF, ML, GM, and PM supervised the study.

Conflicts of interest

We have no conflicts of interest.

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References

1 Bernat JL. Chronic disorders of consciousness. *Lancet* 2006; **367:** 1181–92.
2 Giacino JT, Ashwal S, Childs N, et al. The minimally conscious state: definition and diagnostic criteria. *Neurology* 2002; **58:** 349–53.
3 Laureys S, Boly M. What is it like to be vegetative or minimally conscious? *Curr Opin Neurol* 2007; **20:** 609–13.
4 Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet* 1974; **2:** 81–84.
5 Starmark JE, Stalhammar D, Holmgren E, Rosander B. A comparison of the Glasgow coma scale and the reaction level scale (RLS85). *J Neurosurg* 1988; **69:** 699–706.
6 Benzer A, Mitterschiffthaler G, Marosi M, et al. Prediction of non-survival after trauma: Innsbruck Coma Scale. *Lancet* 1991; **338:** 977–78.
7 Sugiura K, Muraoka K, Chishiki T, Baba M. The Edinburgh-2 coma scale: a new scale for assessing impaired consciousness. *Neurosurgery* 1983; **12:** 411–15.
8 Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. *Arch Phys Med Rehabil* 2004; **85:** 2020–29.
9 Fins JJ, Illes J, Bernat JL, Hirsch J, Laureys S, Murphy E. Neuroimaging and disorders of consciousness: envisioning an ethical research agenda. *Am J Bioeth* 2008; **8:** 37–46.
10 Laureys S, Faymonville ME, Peigneux P, et al. Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. *Neuroimage* 2002; **17:** 732–41.
11 Giacino JT, Kezmarsky MA, DeLuca J, Cicerone KD. Monitoring rate of recovery to predict outcome in minimally responsive patients. *Arch Phys Med Rehabil* 1991; **72:** 897–901.
12 The Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state. *N Engl J Med* 1994; **330:** 1499–508.
13 Giacino JT, Ashwal S, Childs N, et al. The minimally conscious state: definition and diagnostic criteria. *Neurology* 2002; **58:** 349–53.
14 Lesser RP, Koehle R, Lueders H. Effect of stimulus intensity on short latency somatosensory evoked potentials. *Electroencephalogr Clin Neurophysiol* 1979; **47:** 377–82.
15 Madl C, Kramer L, Domanovits H, et al. Improved outcome prediction in unconscious cardiac arrest survivors with sensory evoked potentials compared with clinical assessment. *Crit Care Med* 2000; **28:** 721–26.
16 World Medical Association. World Medical Association declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. *JAMA* 1997; **277:** 925–26.
17 Charlton E. Ethical guidelines for pain research in humans. Committee on Ethical Issues of the International Association for the Study of Pain. *Pain* 1995; **63:** 277–78.
18 Peigneux P, Maquet P, Meulemans T, et al. Striatum forever, despite sequence learning variability: a random effect analysis of PET data. *Hum Brain Mapp* 2000; **10:** 179–94.
19 Boly M, Faymonville ME, Peigneux P, et al. Auditory processing in severely brain injured patients: differences between the minimally conscious state and the persistent vegetative state. *Arch Neurol* 2004; **61:** 233–38.
20 Genovese CR, Lazar NA, Nichols T. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage* 2002; **15:** 870–78.
21 Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard JD. Detecting awareness in the vegetative state. *Science* 2006; **313:** 1402.
22 Nichols T, Brett M, Andersson J, Wager T, Poline JB. Valid conjunction inference with the minimum statistic. *Neuroimage* 2005; **25:** 653–60.
23 IASP. Classification of Chronic Pain: descriptions of chronic pain syndromes and definitions of pain terms. Task force on taxonomy. Seatle: IASP Press; 1994.
24 Halliburton JR. Awareness during general anesthesia: new technology for an old problem. *CRNA* 1998; **9:** 39–43.
25 Klein M. Perception of pain in the persistent vegetative state? *Eur J Pain* 1997; **1:** 165–67.
26 Zeman A. Persistent vegetative state. *Lancet* 1997; **350:** 795–99.
27 Schnakers C, Zasler ND. Pain assessment and management in disorders of consciousness. *Curr Opin Neurol* 2007; **20:** 620–26.
28 Boly M, Balteau E, Schnakers C, et al. Baseline brain activity fluctuations predict somatosensory perception in humans. *Proc Natl Acad Sci USA* 2007; **104:** 12187–92.
29 Craig AD. A new view of pain as a homeostatic emotion. *Trends Neurosci* 2003; **26:** 303–07.
30 Coghill RC, Eisenach J. Individual differences in pain sensitivity: implications for treatment decisions. *Anesthesiology* 2003; **98:** 1312–14.
31 Treede RD, Kenshalo DR, Gracely RH, Jones AK. The cortical representation of pain. *Pain* 1999; **79:** 105–11.
32 Peyron R, Laurent B, Garcia-Larrea L. Functional imaging of brain responses to pain. A review and meta- analysis (2000). *Neurophysiol Clin* 2000; **30:** 263–88.
33 Singer T, Seymour B, O'Doherty J, Kaube H, Dolan RJ, Frith CD. Empathy for pain involves the affective but not sensory components of pain. *Science* 2004; **303:** 1157–62.

34 Oshiro Y, Fuijita N, Tanaka H, Hirabuki N, Nakamura H, Yoshiya I. Functional mapping of pain-related activation with echo-planar MRI: significance of the SII-insular region. *Neuroreport* 1998; **9:** 2285–89.

35 Ostrowsky K, Magnin M, Ryvlin P, Isnard J, Guenot M, Mauguiere F. Representation of pain and somatic sensation in the human insula: a study of responses to direct electrical cortical stimulation. *Cereb Cortex* 2002; **12:** 376–85.

36 Hofbauer RK, Fiset P, Plourde G, Backman SB, Bushnell MC. Dose-dependent effects of propofol on the central processing of thermal pain. *Anesthesiology* 2004; **100:** 386–94.

37 Rees G, Kreiman G, Koch C. Neural correlates of consciousness in humans. *Nat Rev Neurosci* 2002; **3:** 261–70.

38 Dehaene S, Changeux JP, Naccache L, Sackur J, Sergent C. Conscious, preconscious, and subliminal processing: a testable taxonomy. *Trends Cogn Sci* 2006; **10:** 204–11.

39 Bornhovd K, Quante M, Glauche V, Bromm B, Weiller C, Buchel C. Painful stimuli evoke different stimulus-response functions in the amygdala, prefrontal, insula and somatosensory cortex: a single-trial fMRI study. *Brain* 2002; **125:** 1326–36.

40 Zeman A. Consciousness. *Brain* 2001; **124:** 1263–89.

41 Rees G. Neural correlates of the contents of visual awareness in humans. *Philos Trans R Soc Lond B Biol Sci* 2007; **362:** 877–86.

42 Derbyshire SW, Jones AK, Gyulai F, Clark S, Townsend D, Firestone LL. Pain processing during three levels of noxious stimulation produces differential patterns of central activity. *Pain* 1997; **73:** 431–45.

43 Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC. Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science* 1997; **277:** 968–71.

44 Buchel C, Bornhovd K, Quante M, Glauche V, Bromm B, Weiller C. Dissociable neural responses related to pain intensity, stimulus intensity, and stimulus awareness within the anterior cingulate cortex: a parametric single-trial laser functional magnetic resonance imaging study. *J Neurosci* 2002; **22:** 970–76.

45 Boly M, Phillips C, Tshibanda L, et al. Intrinsic brain activity in altered states of consciousness: how conscious is the default mode of brain function? *Ann N Y Acad Sci* 2008; **1129:** 119–29.

46 Boly M, Phillips C, Balteau E, et al. Consciousness and cerebral baseline activity fluctuations. *Hum Brain Mapp* 2008; **29:** 868–74.