

ORIGINAL REPORT

METABOLIC ACTIVITY IN EXTERNAL AND INTERNAL AWARENESS NETWORKS IN SEVERELY BRAIN-DAMAGED PATIENTS

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**Objective:** An extrinsic cerebral network (encompassing lateral frontoparietal cortices) related to external/sensory awareness and an intrinsic midline network related to internal/self-awareness have been identified recently. This study measured brain metabolism in both networks in patients with severe brain damage.

**Design:** Prospective [18F]-fluorodeoxyglucose-positron emission tomography and Coma Recovery Scale-Revised assessments in a university hospital setting.

**Subjects:** Healthy volunteers and patients in vegetative state/unresponsive wakefulness syndrome (VS/UWS), minimally conscious state (MCS), emergence from MCS (EMCS), and locked-in syndrome (LIS).

**Results:** A total of 70 patients were included in the study: 24 VS/UWS, 28 MCS, 10 EMCS, 8 LIS and 39 age-matched controls. VS/UWS showed metabolic dysfunction in extrinsic and intrinsic networks and thalami. MCS showed dysfunction mostly in intrinsic network and thalami. EMCS showed impairment in posterior cingulate/retrosplenial cortices. LIS showed dysfunction only in infratentorial regions. Coma Recovery Scale-Revised total scores correlated with metabolic activity in both extrinsic and part of the intrinsic network and thalami.

**Conclusion:** Progressive recovery of extrinsic and intrinsic awareness network activity was observed in severely brain-damaged patients, ranging from VS/UWS, MCS, EMCS to LIS. The predominance of intrinsic network impairment in MCS could reflect altered internal/self-awareness in these patients, which is difficult to quantify at the bedside.

**Key words:** vegetative state; minimally conscious state; positron emission tomography; consciousness; self-awareness; traumatic brain injury.

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INTRODUCTION

The assessment of consciousness in severely brain-damaged patients remains a major challenge (1). For clinicians, consciousness has two main components: arousal (i.e. wakefulness or vigilance) and awareness (i.e. comprising all subjective perceptions, feelings and thoughts) (2). Awareness has recently been subdivided into “external or sensory awareness” (i.e. perceptual awareness of the environment) and “internal or self awareness” (i.e. stimulus-independent thoughts, mental imagery, inner speech, daydreaming or mind wandering) (3). At the bedside, arousal is typically measured by examining eye opening. External awareness is assessed by showing the presence of reproducible command following or “non-reflex”/voluntary movements (4). After severe brain damage and the acute setting of coma, 4 different clinical entities can be disentangled: (i) patients who “awaken” but remain without reproducible signs of command following (i.e. vegetative state (VS), now also called “unresponsive wakefulness syndrome” (UWS) (5); (ii) minimally conscious state (MCS) patients showing reproducible, albeit fluctuating, signs of consciousness, but without functional communication (6); (iii) patients who emerge from MCS (EMCS) recovering functional communication or object use (6); and (iv) locked-in syndrome (LIS) patients who are fully aware yet completely paralysed with the exception of small eye-movements permitting an eye-coded communication (7).

The behavioural assessment of consciousness in non-communicative brain-damaged patients is difficult because movements can be very small, inconsistent and easily exhausted (8, 9). This issue is further complicated when patients have underlying deficits in the domain of verbal or non-verbal communication functions, such as aphasia, agnosia or apraxia (4, 10, 11). Quantifying internal or self-awareness is even more difficult than the assessment of external awareness in these patients. Most, if not all, of the employed consciousness scales mainly assess command-following or the presence of non-reflex movements (i.e. orientation to pain or visual pursuit) (12, 13). Regarding the latter behaviour, some scales,

such as the Coma Recovery Scale-Revised (CRS-R) (14) explicitly require the use of a mirror (15), hence possibly assessing some form of self-recognition/internal awareness. Similarly, presentation of the patient's own name, another auto-referential attention-grabbing stimulus, has been employed by some consciousness scales (e.g. the Wessex Head Injury Matrix (16)). Most behavioural scales, however, mainly, if not totally, assess external or sensory awareness and give little or no information about any possible form of internal or self-consciousness (17).

Recent studies have started to identify the neural correlates of internal and external awareness. An increasing body of evidence, mainly coming from functional neuroimaging (positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies) and electrophysiology point to the critical role of a widespread fronto-parietal network in the emergence of conscious awareness, also called "global neuronal workspace" (18–20). Within this widespread fronto-parietal network, two separate systems can be identified: (i) an *extrinsic/lateral* network encompassing lateral parietal and dorsolateral prefrontal cortices, mainly related to external awareness (i.e. stimulus-dependent or perceptual awareness of the environment) and (ii) an *intrinsic/midline* network encompassing midline precuneus/posterior cingulate and mesiofrontal/anterior cingulate cortices, mainly related to internal awareness (i.e. stimulus-independent thoughts and self-related thoughts) (3). Given our clinical limitation to objectively measure internal awareness, we here employed objective brain metabolism data obtained from PET in patients with disorders of consciousness (i.e. VS/UWS, MCS, EMCS) and conscious LIS and controls, aiming to measure differences in activity in extrinsic and intrinsic network activity.

## METHODS

Brain metabolism was studied by means of [18F]-fluorodeoxyglucose-PET (FDG-PET). The clinical diagnosis was based on the best response obtained by repeated CRS-R (14) assessments the day of the PET study and the two days before and after the PET acquisition. We applied the diagnostic criteria, as published by the Multi Society Task Force on PVS (21), the Aspen Neurobehavioral Conference Workgroup (22) and the American Congress of Rehabilitation Medicine (7). Exclusion criteria for the present study were: (i) the presence of pre-morbid neurological disease; (ii) the presence of ambiguous behavioural signs not permitting reliable clinical diagnosis; (iii) the presence of large structural brain damage exceeding 25% of the whole brain volume not permitting reliable spatial normalization to the standardized stereotaxic brain template; and (iv) the absence of good quality PET data not permitting reliable image reconstruction or correction for attenuation. The control population consisted of age-matched healthy volunteers ( $n=39$ ; mean age 45 years (median 45) (range 18–80); 18 men).

FDG-PET data were acquired after intravenous injection of 5–10 mCi of FDG on a Siemens CTI 951 R16/31 scanner (as described in 23) at the University Hospital of Liège, Belgium. Data were pre-processed and analysed using Statistical Parametric Mapping (SPM8; <http://www.fil.ion.ucl.ac.uk/spm>) as described elsewhere

(24–26). In brief, FDG-PET data from each subject were normalized to a standard stereotaxic space (using a spatial template adapted to severe brain damage, as previously described in 27) and smoothed with a 14-mm full-width half-maximum isotropic kernel. The design matrix included the VS/UWS, MCS, EMCS and LIS patients' and control subjects' scans. Global normalization was performed by applying proportional scaling. The analyses identified brain regions where glucose metabolism was lower in each patient population compared with the control group. The resulting set of voxels values for each contrast, constituting a map of the  $t$  statistics (SPMt), was transformed to the unit normal distribution (SPMZ) and thresholded at  $p < 0.001$ . Results were considered significant at  $p < 0.01$  family-wise correction for multiple comparisons. Next, we identified brain areas showing a linear correlation with CRS-R total scores. Here, results were thresholded for significance at  $p < 0.001$  with small volume correction (8 mm radius) for multiple comparisons around the previously identified areas (24–26).

Informed consent was obtained from all control subjects and for LIS and EMCS patients, and from the legal representative of all non-communicative patients. The study was approved by the ethics committee of the University and University Hospital of Liège, Belgium.

## RESULTS

A total of 132 patients were prospectively enrolled, of whom 62 were excluded because of: (i) pre-morbid neurological disease (8 patients); (ii) ambiguous behavioural signs not permitting reliable clinical diagnosis (12 patients); (iii) large structural brain damage (19 patients) and (iv) technical problems related to the FDG-PET acquisition (23 patients). Hence, 70 patients of the initial cohort were included for further analysis: 24 VS/UWS (mean age 51 years (median 50.5) (range 20–78); 10 men, 2 traumatic), 28 MCS (mean age 41 years (median 36.5) (range 17–81); 19 men, 16 traumatic), 10 EMCS (mean age 41 years (median 41) (range 14–76); 8 men, 4 traumatic) and 8 LIS (mean age 40 years (median 43) (range 22–53); 2 men, 1 traumatic). Patients were studied after a median of 26 months (interquartile range 24 months). Demographic and clinical data are summarized in Table I.

VS/UWS patients showed metabolic dysfunction in both thalami and in a widespread cortical network encompassing the extrinsic/lateral network (i.e. bilateral posterior parietal and prefrontal areas) and the intrinsic/medial network (i.e. the precuneus and adjacent posterior cingulate cortex and mesiofrontal and adjacent anterior cingulate cortex), compared with controls (Fig. 1). MCS patients showed metabolic dysfunction in both thalami and in the intrinsic/medial network. EMCS patients showed metabolic dysfunction in the posterior cingulate cortex and adjacent retrosplenial cortex. LIS patients showed metabolic dysfunction only in infratentorial regions (i.e. the cerebellum) (Table II).

At the group level, CRS-R total scores showed a positive correlation with a widespread cortical network encompassing both extrinsic/lateral network (i.e. bilateral posterior parietal and prefrontal areas) and part of the intrinsic/medial network (i.e. the precuneus and adjacent posterior cingulate cortex) (see Table III).

Table I. Patient demographic, clinical and Coma Recovery Scale-Revised subscore data

State	Age, sex	Aetiology	Time of PET	Audition	Visual	Motor	Verbal	Comm	Arousal
VS/UWS 1	30, M	ARCA	25 months	Startle reflex	None	Flexion to pain	Oral reflexes	None	Without stimulation
VS/UWS 2	44, M	ARCA	11 days	None	None	Abnormal posturing to pain	None	None	With stimulation
VS/UWS 3	69, M	ARCA	24 days	None	None	Abnormal posturing to pain	Oral reflexes	None	With stimulation
VS/UWS 4	62, M	Anoxia	9 months	Startle reflex	None	Flexion to pain	Oral reflexes	None	Without stimulation
VS/UWS 5	53, M	Basilar stroke	16 days	None	None	Flexion to pain	None	None	With stimulation
VS/UWS 6	34, F	ARCA	18 months	Startle reflex	Blink to threat	Flexion to pain	Oral reflexes	None	Without stimulation
VS/UWS 7	47, M	ARCA	55 days	Startle reflex	None	None	Oral reflexes	None	With stimulation
VS/UWS 8	63, F	ARCA	40 months	Startle reflex	None	Abnormal posturing to pain	Oral reflexes	None	Without stimulation
VS/UWS 9	65, F	Anoxia	12 months	Startle reflex	Blink to threat	Flexion to pain	Oral reflexes	None	With stimulation
VS/UWS 10	54, M	ARCA	6 months	Startle reflex	None	Abnormal posturing to pain	Oral reflexes	None	With stimulation
VS/UWS 11	42, M	Anoxia	20 days	Startle reflex	None	Abnormal posturing to pain	Vocalization	None	Without stimulation
VS/UWS 12	43, M	ARCA	29 days	Startle reflex	None	Abnormal posturing to pain	None	None	Without stimulation
VS/UWS 13	73, F	Stroke	45 days	Startle reflex	None	Flexion to pain	Oral reflexes	None	With stimulation
VS/UWS 14	41, M	ARCA	6 months	Startle reflex	Visual fixation	Abnormal posturing to pain	Oral reflexes	None	Without stimulation
VS/UWS 15	56, F	ARCA	43 days	Startle reflex	None	Abnormal posturing to pain	Oral reflexes	None	Without stimulation
VS/UWS 16	70, F	Anoxia	52 days	Startle reflex	None	Flexion to pain	Oral reflexes	None	With stimulation
VS/UWS 17	49, F	ARCA	4 months	Startle reflex	None	None	Oral reflexes	None	Without stimulation
VS/UWS 18	52, M	Anoxia	10.5 months	Startle reflex	Blink to threat	Abnormal posturing to pain	Oral reflexes	None	Without stimulation
VS/UWS 19	78, F	Aneurysm	32 days	None	None	Flexion to pain	Oral reflexes	None	None
VS/UWS 20	48, M	Anoxia	30 months	Startle reflex	Blink to threat	Flexion to pain	Oral reflexes	None	With stimulation
VS/UWS 21	53, M	Stroke	66 days	Startle reflex	Blink to threat	Flexion to pain	None	None	Without stimulation
VS/UWS 22	46, F	Traumatism	37 days	Startle reflex	None	None	Oral reflexes	None	With stimulation
VS/UWS 23	34, F	Anoxia	260 months	Startle reflex	Blink to threat	Flexion to pain	Oral reflexes	None	Without stimulation
VS/UWS 24	20, M	Traumatism	15 days	None	None	Flexion to pain	Oral reflexes	None	None
MCS 1	35, F	Traumatism	101 months	Reproducible movement to command	Visual pursuit	Flexion to pain	Vocalization	None	Without stimulation
MCS 2	28, F	Traumatism	80 months	Localization to sound	Visual pursuit	Automatic motor reaction	Vocalization	None	Without stimulation
MCS 3	81, F	Stroke	44 days	Reproducible movement to command	Object localization	Automatic motor reaction	Vocalization	Intentional	Without stimulation
MCS 4	37, M	Traumatism	87 months	Reproducible movement to command	Visual pursuit	Flexion to pain	Oral reflexes	Intentional	Without stimulation

Table I. *Contd.*

State	Age, sex	Etiology	Time of PET	Audition	Visual	Motor	Verbal	Comm	Arousal
MCS 5	33, M	ARCA	39.5 months	Startle reflex	Visual pursuit	Automatic motor reaction	Vocalization	None	Without stimulation
MCS 6	64, M	Aneurysm	6 months	Consistent movement to command	Object recognition	Automatic motor reaction	Intelligible verbalization	Intentional	With stimulation
MCS 7	50, F	Aneurysm	28 days	Startle reflex	Visual pursuit	Flexion to pain	Oral reflexes	None	Without stimulation
MCS 8	38, M	Anoxia	4 months	Reproducible movement to command	Visual pursuit	Flexion to pain	Oral reflexes	None	Without stimulation
MCS 9	81, M	meningitis encephalopathy	46 days	Localization ton sound	Visual pursuit	Localization to pain	Oral reflexes	None	Without stimulation
MCS 10	19, F	Traumatism	30 months	Startle reflex	Visual pursuit	Flexion to pain	Vocalization	None	Without stimulation
MCS 11	46, M	Traumatism	17 months	Startle reflex	Visual pursuit	Flexion to pain	None	None	Without stimulation
MCS 12	36, M	Traumatism	270 months	Reproducible movement to command	Visual pursuit	Automatic motor reaction	None	None	Without stimulation
MCS 13	29, M	Traumatism	46 days	Startle reflex	Visual pursuit	Flexion to pain	Oral reflexes	None	Without stimulation
MCS 14	50, F	ARCA	65 days	Reproducible movement to command	Blink to threat	Flexion to pain	Vocalization	None	With stimulation
MCS 15	40, M	Traumatism	70 days	Reproducible movement to command	Visual fixation	Localization to pain	None	None	Without stimulation
MCS 16	50, M	ARCA	7 months	Reproducible movement to command	Object localization	Automatic motor reaction	Intelligible vocalization	Intentional	Without stimulation
MCS 17	56, F	Hydrocephaly	75 days	Startle reflex	Visual pursuit	None	Oral reflexes	None	Without stimulation
MCS 18	63, F	Stroke	17 days	Consistent movement to command	Visual fixation	None	None	None	With stimulation
MCS 19	17, M	Traumatism	4 months	Reproducible movement to command	Visual fixation	Localization to pain	Oral reflexes	None	Without stimulation
MCS 20	32, F	Anoxia	15 months	Startle reflex	Visual pursuit	Abnormal posturing to pain	Oral reflexes	None	With stimulation
MCS 21	50, M	Anoxia	85 months	Reproducible movement to command	Object localization	Automatic motor reaction	None	Intentional	With stimulation
MCS 22	23, M	Traumatism	11 months	Reproducible movement to command	Visual pursuit	Flexion to pain	Oral reflexes	None	Without stimulation
MCS 23	22, M	Traumatism	99 months	Startle reflex	Visual fixation	Automatic motor reaction	None	None	Without stimulation
MCS 24	27, M	Traumatism	4 months	Reproducible movement to command	Visual pursuit	Flexion to pain	Oral reflexes	None	Without stimulation
MCS 25	30, M	Traumatism	131 months	Reproducible movement to command	Visual pursuit	Flexion to pain	Oral reflexes	None	With stimulation
MCS 26	36, M	Traumatism	4 months	Reproducible movement to command	Visual pursuit	Flexion to pain	Oral reflexes	None	Without stimulation
MCS 27	65, M	Traumatism	21 months	Reproducible movement to command	None	Abnormal posturing to pain	Vocalization	None	With stimulation

Table I. *Contd.*

State	Age, sex	Etiology	Time of PET	Audition	Visual	Motor	Verbal	Comm	Arousal
MCS 28	23, M	Traumatism	73 months	Consistent movement to command	Object recognition	Automatic motor reaction	Intelligible vocalization	Intentional	Attention
EMCS 1	38, M	ARCA	45 months	Consistent movement to command	Object recognition	Automatic motor reaction	Intelligible vocalization	Functional	Attention
EMCS 2	45, F	Traumatism	6 months	Consistent movement to command	Object recognition	Automatic motor reaction	Intelligible vocalization	Functional	Attention
EMCS 3	32, M	Traumatism	26 months	Consistent movement to command	Object recognition	Functional use of object	Intelligible vocalization	Functional	Attention
EMCS 4	37, M	ARCA	9 months	Consistent movement to command	Object recognition	Functional use of object	Intelligible vocalization	Functional	Attention
EMCS 5	14, M	Traumatism	14 months	Consistent movement to command	Object recognition	Functional use of object	Intelligible vocalization	Functional	Attention
EMCS 6	56, M	Stroke	64 days	Consistent movement to command	Object localization	Functional use of object	Intelligible vocalization	Intentional	Attention
EMCS 7	25, M	Traumatism	9 months	Consistent movement to command	Object recognition	Functional use of object	Intelligible vocalization	Functional	Attention
EMCS 8	44, M	Stroke	7.5 months	Consistent movement to command	Object recognition	Functional use of object	Intelligible vocalization	Functional	Attention
EMCS 9	44, M	ARCA	88 days	Consistent movement to command	Object recognition	Automatic motor reaction	Intelligible vocalization	Functional	Attention
EMCS 10	76, F	Intoxication	81 days	Reproducible movement to command	Object recognition	Automatic motor reaction	Intelligible vocalization	Functional	Attention
LIS 1	53, M	Basilar stroke	81 days	Reproducible movement to command	Visual pursuit	Abnormal posturing to pain	Vocalization	Intentional	None
LIS 2	47, F	Basilar stroke	20 days	Reproducible movement to command	Object recognition	Flexion to pain	Oral reflexes	Intentional	Without stimulation
LIS 3	39, M	Traumatism	51 months	Reproducible movement to command	Object recognition	Flexion to pain	Oral reflexes	Intentional	Attention
LIS 4	44, F	Basilar stroke	52 months	Consistent movement to command	Object recognition	Functional use of object	None	Functional	Attention
LIS 5	44, F	Basilar stroke	19 days	Consistent movement to command	Object recognition	Flexion to pain	Oral reflexes	Functional	Attention
LIS 6	22, F	Basilar stroke	14 days	None	None	Flexion to pain	Oral reflexes	None	None
LIS 7	27, F	Basilar stroke	71 months	Consistent movement to command	Object recognition	Functional use of object	Intelligible vocalization	Functional	Attention
LIS 8	42, F	Brain stem haemorrhage	56 days	Reproducible movement to command	Visual pursuit	Flexion to pain	None	Intentional	With stimulation

PET: positron emission tomography; VS/UWS: vegetative state/unresponsive wakefulness syndrome; MCS: minimally conscious state; EMCS: emergence from MCS; LIS: locked-in syndrome; M: male; F: female; Comm: communication; ARCA: cardiac arrest.

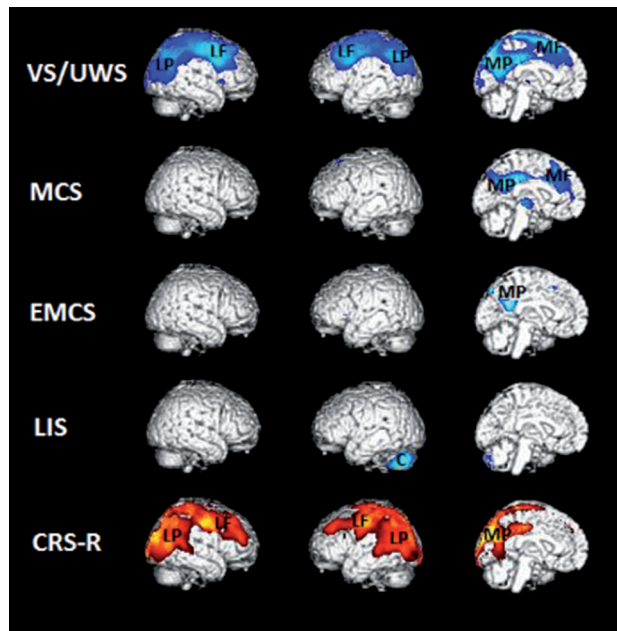


Fig. 1. Areas with significant metabolic impairment (blue) in vegetative state/unresponsive wakefulness syndrome (VS/UWS,  $n=24$ ), minimally conscious state (MCS,  $n=28$ ), emergence from MCS (EMCS,  $n=10$ ) and locked-in syndrome (LIS,  $n=8$ ) compared with age-matched controls ( $n=39$ ) (thresholded at  $p < 0.01$  family-wise correction for multiple comparisons). The lower panel shows the areas where metabolic activity correlated with Coma Recovery Scale-Revised (CRS-R) scores (thresholded at uncorrected  $p < 0.001$ ; red). Note that in VS/UWS there is a metabolic dysfunction in the thalamus (T) external network encompassing left and right lateral parietal (LP) and lateral prefrontal (LF) cortices and in the internal network encompassing midline precuneus/posterior cingulate (MP) and mesiofrontal/anterior cingulate (MF) cortices. In MCS the thalamus (T) and intrinsic network is impaired (MP, MF). EMCS shows partly impaired intrinsic network activity (MP) and LIS fully preserved awareness networks, with only impairment in the cerebellum (C). The behavioural assessment scores correlate with activity in the extrinsic network (LP, LF) and part of the intrinsic network (MP).

DISCUSSION

Our results in VS/UWS of different aetiologies show a widespread fronto-parietal cortical dysfunction, in agreement with previous studies (9, 28–30). We observed a hypometabolism in the external network encompassing left and right lateral parietal and lateral prefrontal cortices and in the internal network encompassing midline precuneus/posterior cingulate and mesiofrontal/anterior cingulate cortices. In MCS patients it seems that the extrinsic/lateral network is less impaired than is the intrinsic/medial network. This result is consistent with the clinical finding that these patients show evidence of external/sensory awareness, known to depend upon the functional integrity of the extrinsic/lateral fronto-parietal system (3, 31–35). The predominance of intrinsic/midline network impairment in MCS could reflect an impaired internal/self-awareness in these patients, which is very difficult to quantify at the bedside. Indeed, CRS-R assessments only have one item possibly assessing some

Table II. Coordinates of peak voxels of hypometabolic areas in vegetative state/unresponsive wakefulness syndrome (VS/UWS), minimally conscious state (MCS), emergence from MCS (EMCS) and locked-in syndrome (LIS)

Areas	x (mm)	y (mm)	z (mm)	Z	p
VS/UWS					
Right thalamus	8	-18	4	5.21	<0.0001
Left thalamus	-2	16	2	4.94	<0.0001
Right lateral parietal	50	18	0	4.5	<0.0001
Left lateral parietal	-38	-72	42	7.29	<0.0001
Right lateral prefrontal	52	-4	52	Inf	<0.0001
Left lateral prefrontal	-34	4	54	7.56	<0.0001
Precuneus/posterior cingulate	2	-36	34	Inf	<0.0001
Mesiofrontal/anterior cingulate	2	-36	34	Inf	<0.0001
MCS					
Right thalamus	4	-18	2	7.37	<0.0001
Left thalamus	-4	-20	2	4.2	<0.0001
Precuneus/posterior cingulate	0	-36	32	Inf	<0.0001
Mesiofrontal/anterior cingulate	6	18	30	6.22	<0.0001
EMCS					
Posterior cingulate/restrospenial	-2	-48	22	5.49	<0.0001
LIS					
Cerebellum	-38	-68	-38	3.88	<0.0001

Inf: inferior than 0.0001.

Table III. Coordinates of peak voxels from areas showing a linear positive correlation with Coma Recovery Scale-Revised total scores

Regions	x (mm)	y (mm)	z (mm)	Z	p
Right lateral parietal	50	18	0	4.5	<0.0001
Left lateral parietal	-58	-50	38	4.85	<0.0001
Right lateral prefrontal	52	-4	52	Inf	<0.0001
Left lateral prefrontal	-34	4	54	7.56	<0.0001
Precuneus/posterior cingulate	2	-36	34	Inf	<0.0001

Inf: inferior than 0.0001.

form of internal/self-awareness: visual pursuit in response to a moving mirror (36).

In our view, the current data could shed some light on impaired internal/self-awareness in MCS via the study of patients' residual brain function. An increasing body of evidence points to the critical role of the intrinsic network in the emergence of internal/self-awareness including stimulus-independent cognitive processes, such as daydreaming, mental imagery, inner speech and self-oriented thoughts (37–40). In fMRI studies, the latter network, recorded during the so-called "resting state" condition has also been coined "default mode network" (41–43). In both VS/UWS and MCS patients a significant thalamic metabolic impairment was identified, in line with previous PET (29, 30, 44) and diffusion tensor imaging (45) MRI studies, and post-mortem neuropathology (46). This finding can also be related to the clinical observation that both patient groups have fluctuating arousal levels. Indeed, in our cohort 10 out of 24 (42%) VS/UWS and 7 out of 28 (25%) MCS showed CRS-R

arousal subscores of 1, meaning that patients needed tactile or noxious stimulation at least once during the examination in order to obtain sustained eye opening (47).

EMCS patients showed a near-normal brain metabolism with preserved extrinsic network activity and only dysfunction of posterior cingulate cortex and adjacent retrosplenial cortex. This area, part of the intrinsic network, is known to be involved in autobiographical memory and self-reflexion (48, 49). Clinically, EMCS patients indeed classically experience confusion and amnesia syndromes (50, 51). Finally, our studied LIS patients failed to show metabolic dysfunction in any supratentorial brain area. Both the extrinsic and intrinsic network activity was preserved in LIS and only the cerebellum was shown to be impaired, in line with previous studies (52, 53). Previous neuropsychological studies have indeed shown that classical LIS patients have no deficit in cognitive functioning (54). Despite the fact that 6/8 LIS patients experienced basilar artery stroke and showed structural lesions on MRI in the ventral pontine region (encompassing the corticospinal and adjacent corticobulbar pathways) the resulting metabolic impairment was localized not in the brainstem, but in the cerebellum. This can be explained by the fact that PET-FDG functional imaging, in contrast to MRI structural imaging, does not show white matter structural damage (i.e. in brainstem), but rather the cortical metabolic consequences (i.e. in cerebellar hemispheres), reflecting de-afferentation.

The observed progressive recovery of intrinsic network metabolic activity, as measured by FDG-PET in severely brain-damaged patients, ranging from VS/UWS, MCS, EMCS to LIS, corroborates previous fMRI “resting state” studies showing a progressive recovery of functional connectivity in the “default mode network” in these patients (55). The latter study also identified a linear correlation between CRS-R total scores and functional connectivity in the default mode network. We expand these findings here, showing an additional correlation with the extrinsic/lateral network metabolic activity and CRS-R total scores.

In conclusion, the objective measurement of extrinsic/lateral and intrinsic/midline metabolic activity in severely brain-injured patients following coma, permits us to better understand the residual external/sensory and internal/self-awareness in disorders of consciousness. Our data show, for the first time, that patients with MCS, in contrast to those with VS/UWS, show cortical dysfunction of the intrinsic/internal awareness system more than of the extrinsic/external awareness networks. If confirmed, these findings indicate an impairment of a clinically barely measurable dysfunction of internal or self-awareness in MCS.

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#### REFERENCES

1. Schnakers C, Vanhaudenhuyse A, Giacino J, Ventura M, Boly M, Majerus S, et al. Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment. *BMC Neurol* 2009; 9: 35.
2. Zeman A. Consciousness. *Brain* 2001; 124: 1263–1289.
3. Vanhaudenhuyse A, Demertzi A, Schabus M, Noirhomme Q, Bredart S, Boly M, et al. Two distinct neuronal networks mediate the awareness of environment and of self. *J Cogn Neurosci* 2011; 23: 570–578.
4. Majerus S, Gill-Thwaites H, Andrews K, Laureys S. Behavioral evaluation of consciousness in severe brain damage. *Prog Brain Res* 2005; 150: 397–413.
5. Laureys S, Celesia GG, Cohadon F, Lavrijns J, Leon-Carrion J, Sannita WG, et al. Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. *BMC Med* 2010; 8: 68.
6. Giacino J, Ashwal S, Childs N, Cranford R, Jennett B, Katz D, et al. The minimally conscious state: definition and diagnostic criteria. *Neurology* 2002; 58: 349–353.
7. American Congress of Rehabilitation Medicine Recommendations for use of uniform nomenclature pertinent to patients with severe alterations of consciousness *Arch Phys Med Rehabil* 1995; 76: 205–209.
8. Gosseries O, Bruno M, Chatelle C, Vanhaudenhuyse A, Schnakers C, Soddu A, et al. Disorders of consciousness: what’s in a name? *NeuroRehabilitation* 2011; 28: 3–14.
9. Bruno M, Gosseries O, Ledoux D, Hustinx R, Laureys S. Assessment of consciousness with electrophysiological and neurological and neurological imaging techniques. *Curr Opin Crit Care* 2011; 17: 146–151.
10. Majerus S, Bruno MA, Schnakers C, Giacino JT, Laureys S. The problem of aphasia in the assessment of consciousness in brain-damaged patients. *Prog Brain Res* 2009; 177: 49–61.
11. Bruno M-A, Fernández-Espejo D, Lehenbre R, Tshibanda L, Vanhaudenhuyse A, Gosseries O, et al. Multimodal neuroimaging in patients with disorders of consciousness showing “functional hemispherectomy”. *Prog Brain Res* 2011; 193: 323–333.
12. Bruno M, Ledoux D, Lambermont B, Damas F, Laureys S. Comparison of the Full Outline of Responsiveness (FOUR), the Glasgow Coma Scale (GCS) and the Glasgow Liège Scale (GLS) in an intensive care unit population. *Neurocrit Care* 2011; 15: 447–453.
13. Schnakers C, Giacino J, Kalmar K, Piret S, Lopez E, Boly M, et al. Does the FOUR score correctly diagnose the vegetative and minimally conscious states? *Ann Neurol* 2006; 60: 744–745.
14. Giacino J, Kalmar K, Whyte J. The JFK Coma Recovery Scale-revised. *Arch Phys Med Rehabil* 2004; 85: 2020–2029.
15. Vanhaudenhuyse A, Schnakers C, Bredart S, Laureys S. Assessment of visual pursuit in post-comatose states: use a mirror. *J Neurol Neurosurg Psychiatry* 2008; 79: 223.
16. Shiel A, Horn S, Wilson B, Watson M, Campbell M, McLellan D. The Wessex Head Injury Matrix (WHIM) main scale: a preliminary report on a scale to assess monitor patient recovery after severe head injury. *Clin Rehabil* 2000; 14: 408–416.
17. Laureys S, Perrin F, Brédart S. Self-consciousness in non-communicative patients. *Conscious Cogn* 2007; 16: 722–741.
18. Baars B, Ramsoy T, Laureys S. Brain, conscious experience and the observing self. *Trends Neurosci* 2003; 26: 671–675.
19. Dehaene S, Naccache L. Towards a cognitive neuroscience of consciousness: basic evidence and a workspace framework. *Cognition* 2001; 79: 1–37.
20. Laureys S. The neural correlate of (un)awareness: lessons from the vegetative state. *Trends Cogn Sci* 2005; 9: 556–559.
21. The Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state. *N Engl J Med* 1994; 330: 1499–1508.
22. Giacino JT. Disorders of consciousness: differential diagnosis and neuropathologic features. *Semin Neurol* 1997; 17: 105–111.

23. Laureys S, Faymonville M, Moonen G, Luxen A, Maquet P. PET scanning and neuronal loss in acute vegetative state. *Lancet* 2000; 355: 1825–1826.
24. Laureys S. Functional neuroimaging in the vegetative state. *Neuro-Rehabilitation* 2004; 19: 335–341.
25. Laureys S, Lemaire C, Maquet P, Phillips C, Franck G. Cerebral metabolism during vegetative state and after recovery to consciousness. *J Neurol Neurosurg Psychiatry* 1999; 67: 121.
26. Bruno M, Vanhauzenhuyse A, Schnakers C, Boly M, Gosseries O, Demertzi A, et al. Visual fixation in the vegetative state: an observational case series PET study. *BMC Neurol* 2010; 10: 35.
27. Phillips C, Bruno M, Maquet P, Boly M, Noirhomme Q, Schnakers C, et al. “Relevance vector machine” consciousness classifier applied to cerebral metabolism of vegetative and locked-in patients. *Neuroimage* 2011; 56: 797–808.
28. Laureys S, Goldman S, Phillips C, Van Bogaert P, Aert J, Luxen A, et al. Impaired effective cortical connectivity in vegetative state: preliminary investigation using PET. *Neuroimage* 1999; 9: 377–382.
29. Nakayama N, Okumura A, Shinoda J, Nakashima T, Iwama T. Relationship between regional cerebral metabolism and consciousness disturbance in traumatic diffuse brain injury without large focal lesions: an FDG-PET study with statistical parametric mapping analysis. *JNNP* 2006; 77: 856–862.
30. Juengling F, Kassubek J, Huppertz H, Krause T, Els T. Separating functional and structural damage in persistent vegetative state using combined voxel-based analysis of 3-D MRI and FDG-PET. *J Neurol Sci* 2005; 228: 179–184.
31. Boly M, Balteau E, Schnakers C, Degueldre C, Moonen G, Luxen A, et al. Baseline brain activity fluctuations predict somatosensory perception in humans. *Proc Natl Acad Sci* 2007; 104: 12187–12192.
32. 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: 1326–1336.
33. Fuhrmann A, Hein G, Tsai N, Naumer M, Knight R. Temporal characteristic of audiovisual information processing. *J Neurosci* 2008; 28: 5344–5349.
34. Rees G. Neural correlates of the contents of visual awareness in humans. *Philos Trans R Soc Lond Biol Sci* 2007; 362:877–886.
35. Sergent C, Dehaene S. Neural process underlying conscious perception: experimental findings and global neuronal workspace framework. *J Physiol Paris* 2004; 98: 374–384.
36. Vanhauzenhuyse A, Giacino J, Schnakers C, Kalmar K, Smart C, Bruno M, et al. Blink to visual threat does not herald consciousness in the vegetative state. *Neurology* 2008; 71: 1374–1375.
37. Mason M, Norton M, Van Horn J, Wegner D, Grafton S, Marcrac C. Wandering minds: the default network and stimulus-independent thought. *Science* 2007; 315: 393–395.
38. Knauff M, Fangmeier T, Ruff C, Johnson-Laird P. Reasoning, models, and images: behavioral measures and cortical activity. *J Cogn Neurosci* 2003; 15: 559–573.
39. Lou H, Lubner B, Crupain M, Keenan J, Nowak M, Kjaer T, et al. Parietal cortex and representation of mental self. *Proc Natl Acad Sci* 2004; 101: 6827–6832.
40. Goldberg I, Harel M, Malach R. When the brain loses its self: prefrontal inactivation during sensorimotor processing. *Neuron* 2006; 50: 329–339.
41. Raichle M, MacLeod A, Snyder A, Powers W, Gusnard D, Shulman G. A default mode of brain function. *Proc Natl Acad Sci* 2001; 98: 676–682.
42. Boly M, Phillips C, Tshibanda J, Vanhauzenhuyse A, Schabus M, Dang-Vu T, et al. Intrinsic brain activity in altered states of consciousness: how consciousness is the default mode of brain function? *Ann N Y Acad Sci* 2008; 1129: 119–129.
43. Soddu A, Vanhauzenhuyse A, Bahri M, Bruno M, Boly M, Demertzi A, et al. Identifying the default-mode component in spatial IC analyses of patients with disorders of consciousness. *Hum Brain Mapp* 2011 Apr 11 doi: 10.1002/hbm.21249. [Epub ahead of print].
44. Lull N, Noé E, Lull J, Garcia-Panach J, Chirivella J, Ferri J, et al. Voxel-based statistical analysis of thalamic glucose metabolism in traumatic brain injury: relationship with consciousness and cognition. *Brain Inj* 2010; 24:1098–1107.
45. Fernandez-Espejo D, Bekinschtein T, Monti M, Pickard J, Junque C, Coleman M, et al. Diffusion weighted imaging distinguishes the vegetative state from the minimally conscious state. *Neuroimage* 2010; 54: 103–112.
46. Graham D, Adams J, Murrays L, Jennet B. Neuropathology of vegetative state after head injury. *Neuropsychol Rehabil* 2005; 15: 198–213.
47. Cologan V, Schabus M, Ledoux D, Moonen G, Maquet P, Laureys S. Sleep in disorders of consciousness. *Sleep Med Rev* 2010; 14: 97–105.
48. Vogt B, Vogt L, Laureys S. Cytology and functionally correlated circuits of human posterior cingulate areas. *Neuroimage* 2006; 29: 452–466.
49. Vogt B, Laureys S. Posterior cingulate, precuneal and retrosplenial cortices: cytology and components of the neural network correlates of consciousness. *Prog Brain Res* 2005; 150: 205–217.
50. Machado C, Perez-Nellar J, Rodriguez R, Scherle C, Korein J. Emergence from minimally conscious state: insights from evaluation of posttraumatic confusion. *Neurology* 2009; 74: 1156.
51. Katz D, Polyak M, Coughlan D, Nichols M, Roche A. Natural history of recovery from brain injury after prolonged disorders of consciousness: outcome of patients admitted to inpatient rehabilitation with 1–4 year follow-up. *Prog Brain Res* 2009; 177: 73–88.
52. Laureys S, Owen A, Schiff N. Brain function in coma, vegetative state, and related disorders. *Lancet Neurol*. 2004; 3: 537–546.
53. Laureys S, Pellas F, Van Eeckhout P, Ghorbel S, Schnakers C, Perrin F, et al. The locked-in syndrome: what is it like to be conscious but paralysed and voiceless? *Prog Brain Res* 2005; 150: 495–511.
54. Schnakers C, Majerus S, Goldman S, Boly M, Van Eeckhout P, Gay S, et al. Cognitive function in the locked-in syndrome. *J Neurol* 2008; 255: 323–330.
55. Vanhauzenhuyse A, Noirhomme Q, Tshibanda J, Bruno M, Ledoux D, Brichant J, et al. Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients. *Brain* 2010; 133: 161–171.