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Functional neuroanatomy underlying the clinical subcategorization of minimally conscious state patients

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Abstract Patients in a minimally conscious state (MCS) show restricted signs of awareness but are unable to communicate. We assessed cerebral glucose metabolism in MCS patients and tested the hypothesis that this entity can be subcategorized into MCS− (i.e., patients only showing nonreflex behavior such as visual pursuit, localization of noxious stimulation and/or contingent behavior) and MCS+ (i.e., patients showing command following).

Patterns of cerebral glucose metabolism were studied using [^{18}F]-fluorodeoxyglucose-PET in 39 healthy volunteers (aged 46 ± 18 years) and 27 MCS patients of whom 13 were MCS− (aged 49 ± 19 years; 4 traumatic; 21 ± 23 months post injury) and 14 MCS+ (aged 43 ± 19 years; 5 traumatic; 19 ± 26 months post injury). Results were thresholded for significance at false discovery rate corrected $p < 0.05$.

We observed a metabolic impairment in a bilateral subcortical (thalamus and caudate) and cortical (fronto-temporo-parietal) network in nontraumatic and traumatic MCS patients. Compared to MCS−, patients in MCS+ showed higher cerebral metabolism in left-sided cortical areas encompassing the language network, premotor, pre-supplementary motor, and sensorimotor cortices. A functional connectivity study showed that Broca's region was disconnected from the rest of the language network, mesiofrontal and cerebellar areas in MCS− as compared to MCS+ patients.

The proposed subcategorization of MCS based on the presence or absence of command following showed a different functional neuroanatomy. MCS− is characterized by preserved right hemispheric cortical metabolism

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interpreted as evidence of residual sensory consciousness. MCS+ patients showed preserved metabolism and functional connectivity in language networks arguably reflecting some additional higher order or extended consciousness albeit devoid of clinical verbal or nonverbal expression.

Introduction

The minimally conscious state (MCS) describes a condition of severely altered consciousness in which patients demonstrate minimal but definite behavioral evidence of awareness but are, by definition, unable to effectively communicate [1]. We recently propose to subcategorize MCS patients based on the complexity of their behavior into two entities: "MCS minus" (MCS−) and "MCS plus" (MCS+) [2]. MCS− describes patients with minimal level of behavioral interactions without command following (e.g., visual pursuit, localization of noxious stimulation and/or smiling/crying in contingent relationship to external stimuli). MCS+ patients show higher-level behavioral responses such as command following (Figure 1). Since the subcategorization of MCS is based on the complexity of behavior as previously proposed [2], the aim of this study was to characterize the integrity of residual cortical networks in MCS patients using [18F]-fluorodeoxyglucose-PET (FDG-PET) testing the hypothesis that this heterogeneous clinical entity can be subcategorized into MCS− and MCS+, each subcategory characterized by its own functional neuroanatomy.

Methods

Cerebral metabolic rates for glucose (CMRGlu) [3] were studied by means of FDG-PET in 27 subacute and chronic MCS patients (10 women; aged 45 ± 16 years) and 39 age-matched healthy controls (21 women; aged 46 ± 18 years). Inclusion criteria were the presence of acute brain damage, coma on admission, absence of sedation, and the presence of operational criteria for MCS (i.e., patients showing minimal but definite behavioral evidence of awareness). Exclusion criteria were patients with extremely vast structural damage encompassing more than two-thirds of one hemisphere in order to allow for reliable spatial normalization of brain images. Table 1 shows the patients' demographic and clinical data. Patients were diagnosed as being in a MCS according to the Aspen Neurobehavioral Conference Workgroup clinical criteria [1] and had repeated Coma Recovery Scale-Revised (CRS-R) [4] assessments (day of scanning, and in the week before and the week after) performed by an experienced multidisciplinary team (i.e., neurologists MB and SL and neuropsychologists MAB, AV, CS, OG, and AD). Given the known behavioral variability in this pathology, the diagnosis of MCS− was made if the patient repeatedly failed to show command following on all CRS-R assessments. Thirteen patients were classified as MCS− (6 women; aged 49 ± 19 years; 4 traumatic; 21 ± 23 months post injury) meaning they did not show command following but presented clearly discernible evidence of nonreflex "purposeful" behavior. Nonreflex behavior included (1) localization to noxious stimulation, (2) visual pursuit movements, (3) "automatic" motor responses (e.g., mouth opening to an approaching spoon, nose scratching, grasping the bedrail), (4) object manipulation (i.e., nongrasp reflex hand movements), (5) affective

Fig. 1 Clinical criteria of disorders of consciousness illustrating the proposed difference between MCS− and MCS+. MCS− describes patients with minimal level of behavioral interactions such as visual pursuit, localization of noxious stimulation and/or appropriate smiling/crying. MCS+ is characterized by the presence of high-level behavioral responses as command following
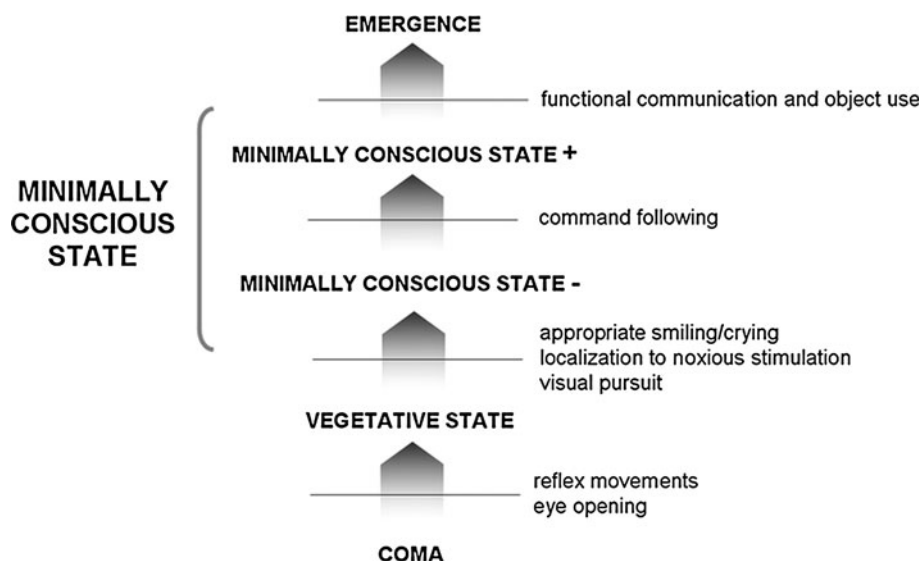
Table 1 Demographic and clinical data of patients in minimally conscious state

Clinical features	Age (years) (gender)	Cause	Time of PET-scan (months after insult)	Auditory function[a]	Visual function[a]	Motor function[a]	Oromotor/verbal function[a]	Communication[a]	Arousal[a]	Structural lesions on MRI/CT
MCS–1	66 (M)	Anoxia	3.2	Auditory startle	Visual pursuit	Flexion withdrawal	Vocalization/oral movement	None	Eyes open without stimulation	NA
MCS–2	56 (M)	CVA	2.4	Auditory startle	Visual pursuit	None	Oral reflexive movement	None	Eyes open without stimulation	Left frontal sub-cortical
MCS–3	72 (M)	Encephalitis	1.4	Localization to sound	Visual pursuit	Localization to noxious stimulation	Oral reflexive movement	None	Eyes open without stimulation	Cortico-sub-cortical cerebellum
MCS–4	33 (M)	Anoxia	38.2	Auditory startle	Visual pursuit	Abnormal posturing	Vocalization/oral movement	None	Eyes open without stimulation	Diffuse atrophy, bilateral fronto-parietal, periventricular, left temporal, brainstem
MCS–5	44 (F)	Hypoglycemia	2.5	Auditory startle	Visual pursuit	Flexion withdrawal	Vocalization/oral movement	None	Eyes open without stimulation	NA
MCS–6	46 (F)	Anoxia	62.6	Localization to sound	Visual pursuit	Abnormal posturing	Vocalization/oral movement	None	Eyes open without stimulation	Diffuse atrophy, periventricular, left fronto-parietal, mesencephalon
MCS–7	48 (F)	Hypoglycemia	1.2	Auditory startle	Visual pursuit	Localization to noxious stimulation	Oral reflexive movement	None	Eyes open without stimulation	Diffuse atrophy, bifrontal, periventricular, cerebellum, pontomesencephalic
MCS–8	88 (M)	Subarachnoid hemorrhage	1.2	Auditory startle	Visual pursuit	Flexion withdrawal	None	None	Eyes open with stimulation	Bilateral fronto-parieto-occipital, left temporal, pontomesencephalic
Mcs–9	31 (M)	Trauma	35.2	Auditory startle	Visual pursuit	Flexion withdrawal	Oral reflexive movement	None	Eyes open without stimulation	Left frontoparietal, periventricular, cerebellum
Mcs–10	44 (F)	Trauma	22.4	Auditory startle	Visual pursuit	Flexion withdrawal	Oral reflexive movement	None	Eyes open without stimulation	Bilateral temporal
Mcs–11	24 (F)	Trauma	61.8	Localization to sound	Visual pursuit	Automatic motor response	Vocalization/oral movement	None	Eyes open without stimulation	NA
Mcs–12	22 (F)	Trauma	29.3	None	Visual pursuit	Flexion withdrawal	Vocalization/oral movement	None	Eyes open without stimulation	Bifronto-temporal, diffuse axonal, cerebellum, right brainstem

Table 1 continued

Clinical features	Age (years) (gender)	Cause	Time of PET-scan (months after insult)	Auditory function[a]	Visual function[a]	Motor function[a]	Oromotor/ verbal function[a]	Communication[a]	Arousal[a]	Structural lesions on MRI/CT
Mcs−13	64 (M)	Anoxia	1.2	Localization to sound	Visual pursuit	Automatic motor response	Vocalization/ oral movement	None	Eyes open without stimulation	No focal lesions
MCS+1	50 (F)	Anoxia	82	Reproducible movement to command	Object localization : reaching	Automatic motor response	None	Non-functional : Intentional	Eyes open with stimulation	No focal lesions
MCS+2	59 (M)	Anoxia	6.5	Reproducible movement to command	Object localization : reaching	Automatic motor response	Intelligible verbalization	Non-functional : Intentional	Eyes open without stimulation	Diffuse leucoencephalopathy and cortico-sub-cortical atrophy
MCS+3	64 (M)	Subarachnoid hemorrhage	5.6	Reproducible movement to command	Object recognition	Automatic motor response	Intelligible verbalization	Non-functional : Intentional	Eyes open with stimulation	Diffuse atrophy, left cerebellar, right frontal
MCS+4	76 (F)	CVA	1.4	Reproducible movement to command	Object localization : reaching	Automatic motor response	Vocalization/ oral movement	Non-functional : Intentional	Eyes open without stimulation	Right temporal
MCS+5	32 (M)	Anoxia	14.3	Reproducible movement to command	Visual pursuit	Abnormal posturing	Oral reflexive movement	None	Eyes open without stimulation	NA
MCS+6	38 (M)	Anoxia	3.6	Reproducible movement to command	Visual pursuit	Flexion withdrawal	Oral reflexive movement	None	Eyes open without stimulation	No focal lesion
MCS+7	71 (F)	Encephalitis	9	Reproducible movement to command	Object recognition	Flexion withdrawal	Vocalization/ oral movement	None	Eyes open with stimulation	Bifronto-temporal
MCS+8	46 (M)	Subarachnoid hemorrhage	18	Reproducible movement to command	Object recognition	Automatic motor response	Intelligible verbalization	Non-functional : Intentional	Attention	NA
MCS+9	17 (F)	Trauma	4	Reproducible movement to command	Visual fixation	Localization to noxious stimulation	Oral reflexive movement	None	Eyes open without stimulation	Diffuse edema, bifrontal
MCS+10	27 (M)	Trauma	41	Reproducible movement to command	Visual pursuit	Flexion withdrawal	Vocalization/ oral movement	None	Eyes open without stimulation	Diffuse atrophy
MCS+11	40 (M)	Trauma	2	Reproducible movement to command	Visual fixation	Localization to noxious stimulation	None	None	Eyes open without stimulation	Bitemporo-occipital

Table 1 continued

Clinical features	Age (years) (gender)	Cause	Time of PET-scan (months after insult)	Auditory function[a]	Visual function[a]	Motor function[a]	Oromotor/verbal function[a]	Communication[a]	Arousal[a]	Structural lesions on MRI/CT
MCS+12	23 (M)	Trauma	70	Reproducible movement to command	Object recognition	Automatic motor response	Intelligible verbalization	Non-functional : Intentional	Eyes open without stimulation	NA
MCS+13	37 (M)	Trauma	4	Reproducible movement to command	Visual pursuit	Flexion withdrawal	Oral reflexive movement	None	Eyes open without stimulation	Biparietal, right cerebellum, brainstem
MCS+14	27 (M)	Anoxia	4	Reproducible movement to command	Visual pursuit	Automatic motor response	Vocalization/oral movement	None	Eyes open with stimulation	Diffuse atrophy

NA not available

[a] As defined by Coma Recovery Scale-Revised criteria

behaviors occurring in contingent relation to relevant environmental stimuli and are not due to reflexive activity (e.g., smiling in response to a specific eliciting stimulus such as the patient's mother) as defined by CRS-R criteria [4]. Fourteen patients were classified as MCS+ (4 women; aged 43 ± 19 years; 5 traumatic; 19 ± 26 months post injury) meaning they showed reproducible command following (i.e., at least three correct responses out of four identical commands) as defined by CRS-R criteria. Commands were presented verbally and in written form. All patients were studied free of sedative drugs and following administration of a standardized arousal facilitation protocol [4]. MCS− and MCS+ groups were matched for age, etiology, and time since insult.

FDG-PET data were acquired after intravenous injection of 300 MBq of FDG on a Philips Gemini TF PET-CT scanner [5]. Patients were monitored by two anesthesiologists throughout the procedure. PET data were spatially normalized, smoothed (14 mm full width at a half maximum) and analyzed using Statistical Parametric Mapping (SPM8; www.fil.ion.ucl.ac.uk/spm). The first analysis identified brain regions with significant decreased metabolism in the following: (1) MCS patients as compared to controls, (2) MCS− compared to control subjects, (3) MCS+ compared to control subjects, (4) MCS+ compared to MCS−. The design matrix included 13 MCS−, 14 MCS+, and 39 control subjects' scans and global normalization was performed by proportional scaling. A second analysis looked for differences in brain metabolism between MCS of traumatic ($n = 9$) and nontraumatic ($n = 18$) origin, taking into account age and duration since onset as confounding factors. A third analysis identified brain regions where residual metabolism correlated with the time spent since onset. We also identified areas showing a correlation with the CRS-R total scores. Next, a psychophysiological interaction analysis [3] tested the hypothesis on altered functional cortical connectivity in MCS− as compared to MCS+ and control subjects. This design matrix included the same scans as described above and took into account group differences in mean levels of glucose consumption. Now the analysis looked for brain regions that experienced a significant difference in reciprocal modulation with/from the cortical area that most differentiated MCS− from MCS+ (i.e., Broca's area; stereotaxic coordinates −44, 22, 4 mm). It assessed the difference in modulation of Broca's area depending on the condition MCS− versus MCS+ or control subjects. A conjunction analysis [6] identified areas showing functional connectivity (i.e., cross-correlation in metabolic activity) with the seed voxel (Broca's area) in healthy controls which also showed higher connectivity in MCS+ as compared to MCS−.

All results were corrected for multiple comparisons and considered significant at false discovery rate corrected

Table 2 Statistical results and localization of peak voxels where cerebral metabolism was impaired in patients in a minimally conscious state (MCS), MCS− (showing non-reflex behavior without command following) and MCS+ (showing command following)

Brain region (area)	Side	x (mm)	y (mm)	z (mm)	z-value	Corrected p-value
MCS						
Caudate	L	−8	12	10	6.15	<0.001
	R	14	14	8	7.6	<0.001
Bilateral thalamus		6	−16	8	7.24	<0.001
Posterior cingulate/precuneus (31/7)		0	−30	32	Inf	<0.001
Anterior cingulate (24/31)	R	4	12	24	5.83	<0.001
Premotor (6)	L	−30	6	52	5.26	<0.001
Middle frontal gyrus (9)	L	−44	12	34	4.66	<0.001
Superior frontal gyrus (10)	L	−32	54	14	3.73	0.001
Inferior frontal gyrus (47)	L	−40	20	−4	4.69	<0.001
Premotor cortex (6)	R	38	4	50	4.50	<0.001
Superior frontal gyrus (8)	R	2	18	50	4.64	<0.001
Superior temporal gyrus (38)	R	42	24	−22	4.5	<0.001
Inferior temporal gyrus (20)	L	−62	−26	−16	2.88	0.013
	R	64	−18	−18	2.95	0.011
Angular gyrus (39/40)	L	−44	−70	42	3.68	0.001
	R	54	−52	52	2.99	0.010
MCS−						
Caudate	L	−8	12	8	5.75	<0.001
	R	14	14	8	6.44	<0.001
Bilateral thalamus		0	−18	6	5.82	<0.001
Posterior cingulate/precuneus (31/7)		0	−26	32	6.93	<0.001
Anterior cingulate (33)	R	4	12	24	5.5	<0.001
Premotor (6)	L	−30	8	54	5.96	<0.001
Middle frontal gyrus (9/6)	L	−44	14	32	5.61	<0.001
	R	36	4	62	4.18	<0.001
Inferior frontal gyrus (47)	L	−40	20	−2	5.49	<0.001
Inferior temporal gyrus (20)	L	−60	−22	−16	3.96	0.001
	R	62	−20	−18	2.42	0.008
Angular gyrus (39/38)	L	−46	−68	40	4.58	<0.001
	R	42	24	−22	3.18	0.006
MCS+						
Caudate	L	−8	10	12	4.48	<0.001
	R	14	14	6	6.53	<0.001
Right thalamus	R	10	−16	10	6.86	<0.001
Posterior cingulate/precuneus (31/7)		0	−36	32	7.04	<0.001
Anterior cingulate (32)	R	8	12	38	4.21	<0.001
Middle frontal gyrus (9)	R	46	12	30	4.3	<0.001
Middle temporal gyrus (21)	R	68	−50	−2	2.67	0.033
Superior temporal gyrus (22)	R	52	12	−4	4.89	<0.001
Postcentral gyrus (7)	R	38	−70	52	2.69	0.031
Angular gyrus (39/40)	R	54	−50	52	3.08	0.012
Right premotor gyrus	R	48	10	48	3.85	<0.001
Preserved area in MCS+ as compared to MCS−						
Caudate	L	−8	8	−6	2.62	0.048
Sensory-motor area (4/3)	L	−60	−8	26	3.37	0.023
Premotor (6)	L	−30	8	56	3.76	0.023
Inferior frontal gyrus (45)	L	−44	22	4	3.99	0.023

Table 2 continued

Brain region (area)	Side	x (mm)	y (mm)	z (mm)	z-value	Corrected p-value
Middle frontal gyrus (9)	L	−42	14	30	3.87	0.023
Superior temporal gyrus (39)	L	−58	−56	26	3.19	0.024
Middle temporal gyrus (21)	L	−54	−8	−14	3.77	0.023

Coordinates are in standardized stereotaxic Montreal Neurological Institute space

Fig. 2 Areas with impaired metabolism (*shown in blue*) in patients in a minimally conscious state (MCS), MCS− (showing nonreflex behavior) and MCS+ (showing command following). The lowest panel shows areas with higher metabolism in MCS+ as compared to MCS− (*shown in orange*). All results are shown on a 3D MRI template and thresholded at false discovery rate corrected $p < 0.05$
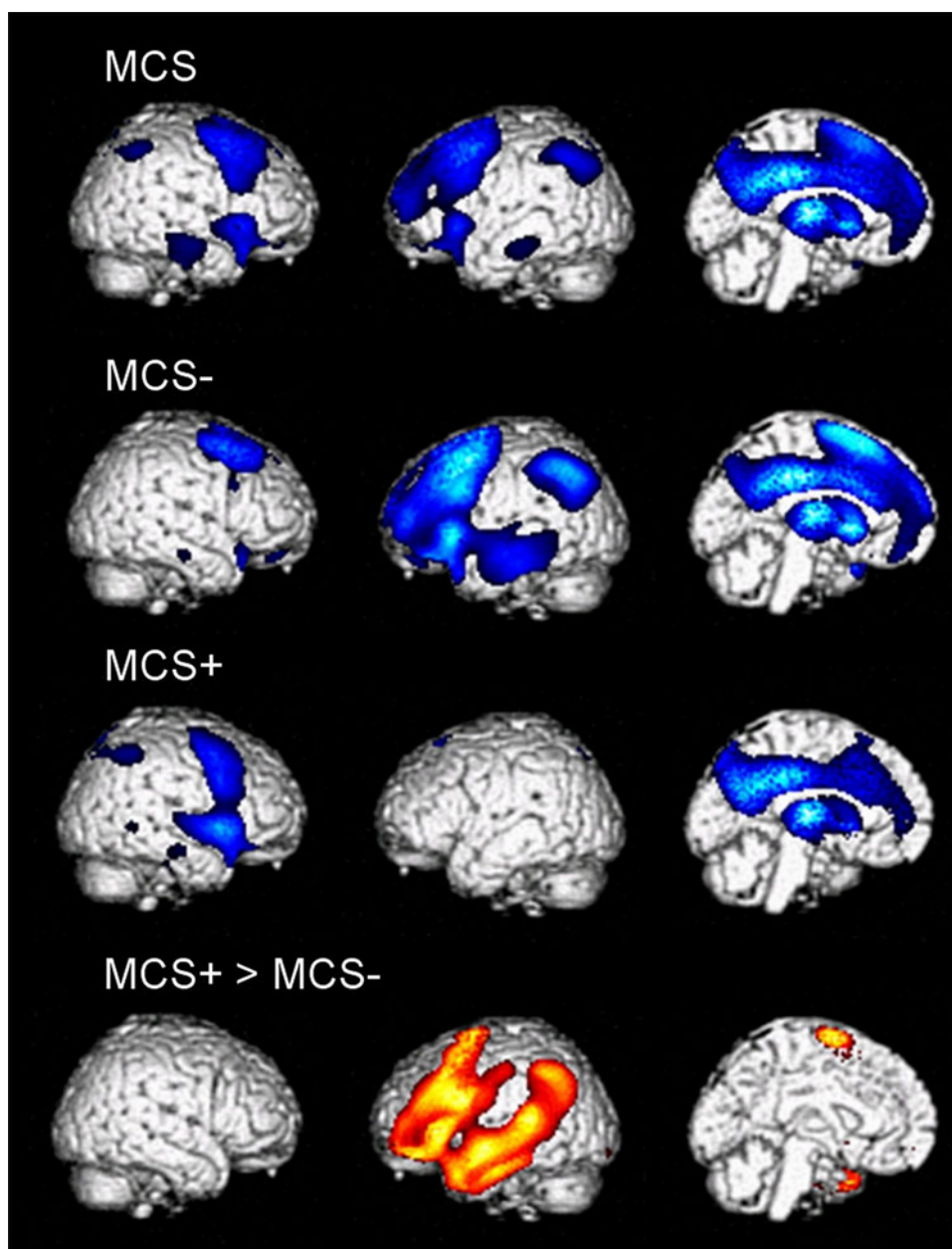
$p < 0.05$ [7]. The study was approved by the Ethics Committee of the Faculty of Medicine of the University of Liege and written informed consent was obtained from all healthy controls and the patients' legal representatives.

Results

Patients in MCS (as compared to healthy controls) showed hypometabolism in bilateral thalamus, caudate, posterior

Table 3 Peak voxels showing linear correlation between regional metabolism and Coma Recovery Scale-Revised total scores

Brain region (area)	Side	x (mm)	y (mm)	z (mm)	z-value	Corrected p-value
Left caudate	L	−10	12	8	6.60	<0.001
	R	14	14	8	6.63	<0.001
Left thalamus	L	−2	−18	6	6.76	<0.001
Insula	L	−38	20	−4	5.59	<0.001
	R	38	24	−2	3.33	<0.001
Posterior cingulate (31)		0	−28	34	7.71	<0.001
Precuneus (7)	L	−2	−70	38	4.27	<0.001
Anterior cingulate (33)	R	4	12	24	5.82	<0.001
Mesiofrontal (10)		0	52	0	3.46	0.002
Premotor (6)	L	−30	8	52	6.21	<0.001
	R	34	6	64	4.09	<0.001
Superior frontal gyrus (8)	L	−4	48	42	4.31	<0.001
	R	26	28	54	3.76	0.001
Middle frontal gyrus (9/10)	L	−44	14	30	5.92	<0.001
	L	−36	52	12	4.70	<0.001
Inferior parietal gyrus (39)	L	−46	−68	42	5.01	<0.001
Middle temporal gyrus (21)/ Primary auditory area	L	−62	−26	−14	3.68	0.001

cingulate and precuneal, anterior cingulate and mesiofrontal, posterior parietal, temporal, and dorsolateral prefrontal cortices. Patients in MCS− showed metabolic dysfunction in bilateral thalami, caudate, posterior cingulate and precuneal, anterior cingulate and mesiofrontal, angular gyrus, left posterior parietal and bilateral temporal and dorsolateral prefrontal cortices. Patients in MCS+ showed hypometabolism in right thalamus, bilateral caudate, posterior cingulate and precuneal, anterior cingulate and mesiofrontal, right posterior parietal, temporal, and premotor cortices. Finally, MCS+ patients showed significant higher metabolism as compared to MCS− in Broca's and Wernicke's regions, left premotor, left caudate, and post- and precentral cortices (Table 2; Fig. 2). No differences were observed between traumatic and nontraumatic etiology.

This analysis as a function of lesion type was also performed for each MCS group separately (MCS− traumatic versus MCS− nontraumatic; MCS+ traumatic versus MCS+ nontraumatic). No differences were found between traumatic and nontraumatic groups within each subcategory. Time since onset showed no negative correlation with brain metabolism (similar results were observed when acute (<3 months) and subacute/chronic patients were compared). Conversely, a positive correlation was observed with precuneus—albeit at a less conservative threshold (coordinates $x = 10$ $y = −58$ $z = 48$ mm, z value = 3.72; small volume corrected $p < 0.05$).

CRS-R total scores showed a linear correlation with metabolism in the left thalamus, precuneus, posterior parietal, left primary and associative auditory cortices, bilateral premotor cortex, frontal eye field, insula, dorsolateral prefrontal and anterior cingulate cortices (Table 3; Fig. 3).

The connectivity study showed that Broca's area was functionally connected with the language network, mesiofrontal and cerebellar areas in controls and that this connectivity was significantly higher in MCS+ as compared to MCS− patients (Table 4; Fig. 4).

Discussion

Metabolic impairment in a bilateral subcortical (thalamus and caudate) and cortical (fronto-temporo-parietal) network in nontraumatic and traumatic MCS patients, comparable but less widespread than previously shown in the vegetative state [3], was shown with this research. These results are in line and extend a previous FDG-PET study in 13 MCS patients of traumatic origin [8]. We observed no differences in residual brain function depending on etiology of MCS. In the vegetative state, a progressive loss of cortical metabolic function was reported as a function of the duration of the condition. The absence of such decreased brain metabolism with time in our MCS cohort might illustrate the absence of progressive Wallerian and transsynaptic degeneration characterizing the chronic vegetative state [9]. In contrast, an increase in metabolism seemed present in some areas such as the precuneus in our subacute and chronic MCS patients. This can be interpreted as a sign of residual cortical plasticity in areas previously identified by means of diffusion tensor
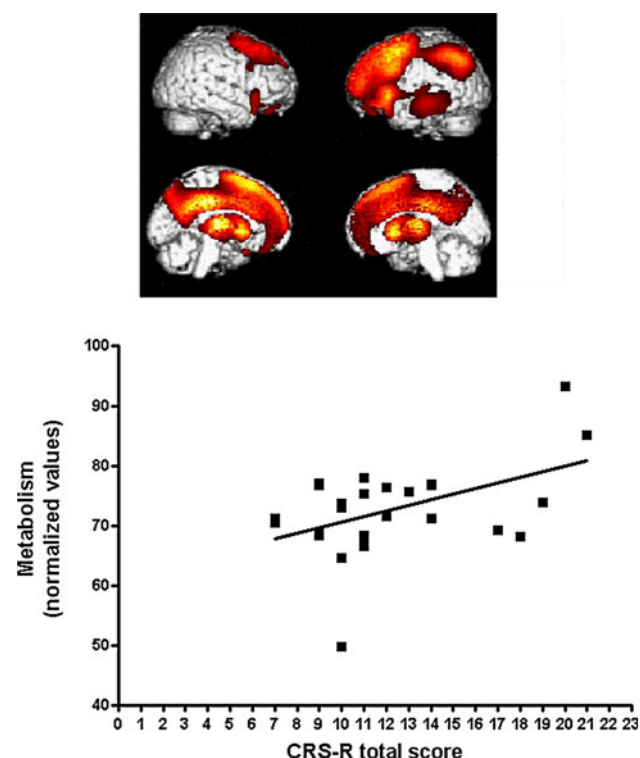
Fig. 3 Areas showing linear correlation of metabolism with Coma Recovery Scale-Revised (CRS-R) total scores (*shown in red*) shown on a 3D MRI template and thresholded at false discovery rate corrected $p < 0.05$. The lower panel graphically illustrates that CRS-R scores increase as metabolic activity becomes more robust

MRI techniques in exceptional cases of recovery from longstanding MCS [10].

We found a positive linear correlation between metabolism in frontoparietal cortices and the CRS-R total scores, in line with our previous study showing a correlation between this behavioral score and spontaneous "default network" brain activity as measured by functional MRI in "resting state" conditions [11]. The identified polymodal frontoparietal network is considered critical for the emergence of conscious awareness [12]. These results corroborate previous findings on pain [13, 14], auditory [15, 16],
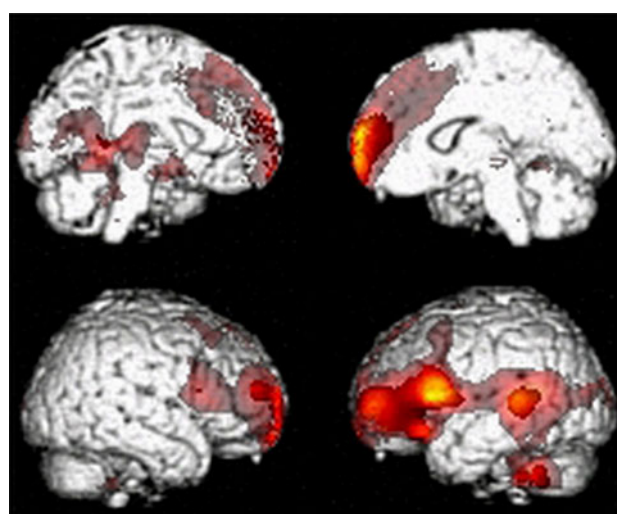
Fig. 4 Functional disconnections with Broca's area in MCS− as compared to MCS+ showing the language network, mesiofrontal and cerebellar areas (thresholded at false discovery rate corrected $p < 0.05$; transparency denotes uncorrected $p < 0.05$)

and emotional [17, 18] processing showing that MCS patients demonstrate a more elaborated and integrated level of noxious, auditory, and emotional processing than vegetative state patients who only showed activation of primary "lower level" sensory cortices which are disconnected from "higher order" associative cortical networks [5, 14].

Clinically, the MCS entity regroups patients with different degrees of cognitive dysfunction or disability. We here propose to subcategorize MCS in patients showing only minimal levels of nonreflex behavioral responses (coined MCS−) and patients showing higher levels of behavioral interactions such as command following (MCS+). Our FDG-PET results showed a different functional neuroanatomy for both groups. MCS− seems characterized by a partially preserved functioning brainstem and right hemisphere with impaired left cortical networks encompassing Broca's and Wernicke's regions, posterior

Table 4 Peak voxels of functional connectivity assessment with Broca's area (peak voxel identified in MCS+ > MCS− comparison) identifying areas with higher connectivity in MCS+ as compared to MCS− patients

Brain region (area)	Side	x (mm)	y (mm)	z (mm)	z-value	Corrected p-value
Posterior cingulate (30)	L	−14	−46	6	3.37	0.029
Middle frontal gyrus (10)	L	−42	52	6	4.46	0.003
Mesiofrontal (10)	R	8	64	0	4.77	0.001
Superior frontal gyrus (10)	R	30	54	16	3.49	0.023
Inferior frontal gyrus (44)	R	64	14	16	3.09	0.048
Middle temporal gyrus (22)	L	−60	−40	6	3.56	0.020
Cerebellum	L	−52	−54	−46	4.15	0.005

parietal, presupplementary motor, sensorimotor and pre-motor cortices. Phylogenetically, the midbrain is capable of driving the eyes to track objects [19, 20], and the human phenomenon of blindsight in the absence of occipital lobe function suggests that tracking could be coordinated in the optic tectum [21]. Command following requires a series of cognitive and motor skills, including language compre-hension, memory, volition, and motor execution, each depending on the functional integrity of multiple neuronal networks. Given that the vast majority of the patients sample had nonlateralizing injury etiologies, our observa-tion that the syndrome lateralizes points to the critical role of the dominant hemisphere and language functions. These results are in line with a recent fMRI study in disorders of consciousness and locked-in patients suggesting that activity of the language network may serve as an indicator of high-level cognition and possibly volitional processes that cannot be discerned through conventional behavioral assessment alone [22]. Understanding spoken language requires a complex series of processing stages to translate speech sounds into meaning encompassing left-lateralized frontal and temporal cortical regions [23–25] shown to be dysfunctional in MCS−. Moreover, our functional con-nectivity analysis identified corticocortical disconnections within these networks and with speech motor production networks also involving the cerebellum [26, 27]. This functional connectivity analysis was also performed on patients without left focal lesions and showed the same results. Previous work suggested that complementary analyses should be used in studies comprising of traumatic patients. Some of these patients may exhibit extreme focal lesions and, as a result, any statistical inference could be driven by such outliers [28]. Previous studies have located various subprocesses of verbal working memory in struc-tures of the left inferior frontal gyrus [29]. The capacity for voluntary action is thought to depend on the functional integrity of presupplementary motor area, anterior pre-frontal, and parietal cortices [30]. Finally, limb praxis control and motor sequencing are considered to depend mainly upon left frontoparietal circuits [31]. All the aforementioned areas were observed to be highly dys-functional in MCS− but showed near-normal metabolism in MCS+ patients characterized by the clinical demon-stration of reproducible but inconsistent command following.

Our findings on MCS− suggest that the metabolically functionally preserved but isolated right hemisphere function might permit these patients to show nonreflex behaviors such as visual pursuit, localization to pain, "automatic" movements such as scratching or affective behaviors contingent upon emotionally relevant stimuli [32], while remaining unable to show command following as an unambiguous clinical proof of consciousness [31,

33]. Split-brain research has previously identified different cognitive processing styles for each cerebral hemisphere [34]. The right hemisphere appears to process what it perceives and no more, while the left hemisphere is considered to make elaborations above the level of min-imal sensory consciousness [35]. It should be noted that MCS− patients also showed more frequently left-sided damage on structural MRI scans (5 out of 10 patients), while MCS+ patients had most frequently right hemi-spheric lesions (3 out of 10 patients). Structural and metabolic functions are obviously linked. These findings can also be seen in light of Damasio's [36] prelinguistic core consciousness seemingly present in both MCS− and MCS+ patients. Core consciousness corresponds to the transient process that is incessantly generated relative to any external stimulation without requiring language. Similarly, Edelman has differentiated "primary" from "higher order" consciousness, the latter considered to require language for its most developed expression [37]. Damasio's extended consciousness is a more complex process depending on an autobiographical self and is enhanced by language, possibly partially preserved in MCS+. However, both MCS− and MCS+ patients showed a functional impairment in midline cortices (me-siofrontal and precuneus) considered critical for the emergence of self consciousness [38]. Our limited understanding of the dynamical neural complexity underlying consciousness and its resistance to quantifica-tion in the absence of communication [39] makes it dif-ficult to establish strong claims about the self-consciousness in MCS patients. In our view, even MCS patients lacking clinical proof of consciousness in terms of command following (here coined MCS−) show a functional neuroanatomy reflecting the presence of pre-served sensory, core, or primary consciousness. An alternative explanation might be that MCS− patients have a comparable level of consciousness as MCS+ patients but that they fail to understand verbal or written com-mands due to a selective impairment of language function [40]. This may also explain why some MCS patients fail to show activations during fMRI active paradigms [22, 41]. As discussed elsewhere since language function may impact CRS-R scores, detecting impaired language net-works may represent an important factor to consider for the clinical evaluation of patients with disorders of con-sciousness. This result emphasizes the importance of language independent assessment [42].

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