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BRAIN METABOLISM BUT NOT GRAY MATTER VOLUME UNDERLIES THE PRESENCE OF LANGUAGE FUNCTION IN THE MINIMALLY CONSCIOUS STATE (MCS): MCS+ VERSUS MCS- NEUROIMAGING DIFFERENCES

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KEYWORDS: minimally conscious state (MCS), language, brain metabolism, brain structure

ABSTRACT

Background. The minimally conscious state (MCS) is subcategorized into MCS- and MCS+, depending on the absence or presence, respectively, of high-level behavioral responses such as command-following. Objective. We aim to investigate the functional and structural neuroanatomy underlying the presence of these responses in MCS- and MCS+ patients. Methods. In this cross-sectional retrospective study, chronic MCS patients were diagnosed using repeated Coma Recovery Scale-Revised assessments. Fluorodeoxyglucose-positron emission tomography data were acquired on 57 patients (16 MCS-; 41 MCS+) and magnetic resonance imaging with voxel-

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based morphometry analysis was performed on 66 patients (17 MCS-; 49 MCS+). Brain glucose metabolism and gray matter integrity were compared between patient groups and control groups. A metabolic functional connectivity analysis testing the hypothesis of preserved language network in MCS+ compared with MCS- was also done. Results. Patients in MCS+ presented higher metabolism mainly in the left middle temporal cortex, known to be important for semantic processing, compared with the MCS- group. The left angular gyrus was also functionally disconnected from the left prefrontal cortex in MCS- compared with MCS+ group. No significant differences were found in gray matter volume between patient groups. Conclusions. The clinical subcategorization of MCS is supported by differences in brain metabolism but not in gray matter structure, suggesting that brain function in the language network is the main support for recovery of command-following, intelligible verbalization and/or intentional communication in the MCS. Better characterizing the neural correlates of residual cognitive abilities of MCS patients contributes to reduce their misdiagnosis and to adapt therapeutic approaches.

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Introduction

Following a severe brain injury and a period of coma, patients may progress into a minimally conscious state (MCS), recovering inconsistent but reproducible behavioral evidence of awareness.[1] This clinical entity is heterogeneous, with behaviors ranging from visual pursuit to the production of intelligible words. Consequently, a subcategorization has been suggested: the MCS- that mainly describes patients with visual pursuit and/or fixation, oriented movements, and localization to pain,[2 3 4] and the MCS + for patients who recover high-level behavioral responses, such as command-following, intelligible verbalization, and/ or intentional communication.[3,4] MCS patients may emerge from that state once they regain the ability to functionally communicate and/or use objects.[5]

Communication is one of the most important aspects in the recovery of postcomatose patients because it allows them to interact with their environment and to express their needs. Regaining command-following, intelligible verbalization, and/or intentional communication (ie, MCS +) appears to be the first step before implementing functional "yes/no" communication codes, and is therefore crucial.[5] Furthermore, the issue of aphasia is a major bias that all clinicians face when diagnosing patients' level of consciousness, in particular when assessing these "language- related abilities."[6] For instance, the presence of receptive language impairment could prevent conscious patients from responding to commands. Therefore, neuroimaging studies are capable of providing more accurate diagnoses, bypassing behavioral and language-dependent tests.[7]

Initially, the clinical sub-categorization of the MCS was supported by differences in brain metabolism as measured by fluorodeoxyglucose-positron emission tomography (FDG-PET) in 27 patients (13 MCS- and 14 MCS + according to the absence or presence of command-following criteria exclusively, and based on at least 1 behavioral assessment).[8] Compared with patients in the MCS- group, those in the MCS+ group showed a higher cerebral metabolism in left-sided cortical areas, including Broca and Wernicke areas, premotor, presupplementary motor, and sensorimotor cortices. Moreover, a disconnection of Broca's region from the rest of the language network, mesiofrontal, and cerebellar areas was observed in the MCS- group compared with the MCS+ group. Using resting functional magnetic resonance imaging (fMRI) in 19 MCS patients (9 MCS- and 10 MCS +), we also recently observed an impaired functional connectivity in the left frontoparietal network in the MCS- group compared with the MCS + group.[9] Specifically, this difference between patient groups was significant between the left dorsolateral prefrontal cortex and the left temporo-occipital fusiform cortex, which previously has been linked to semantic abilities.[10,11] Finally, a recent case series study showed that the reappearance of command-following in 3 chronic MCS patients (ie, > 10 months postinjury) was concomitant with the recovery of brain metabolism and gray matter preservation in brain regions that have been associated with self-consciousness (eg, precuneus and thalamus) and language processing (eg, left angular and temporal cortices).[12] However, these previous studies used small to very small sample sizes and

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mainly focused on brain function aspects (ie, glucose metabolism using FDG-PET, and functional connectivity based on blood oxygen level-dependent signal) rather than brain structure.

Here we aim to investigate the neural correlates of the language-related abilities in a specific population of patients with disorders of consciousness who had recovered these abilities (ie, MCS+) in comparison with another population of MCS patients who had not (ie, MCS-). To do so, we examined the regional and global brain metabolism and the metabolic functional connectivity differences in patients in MCS- versus MCS+ by means of FDG-PET, as well as structural differences between these subcategories by means of gray matter volume atrophy quantification (ie, voxel-based morphometry [VBM]). In line with previous studies, we expect that MCS + patients exhibit higher glucose metabolism and less gray matter atrophy compared with MCS- patients, in particular in consciousness and language-related areas.

Methods

PARTICIPANTS

Behavioral and neuroimaging data were collected during a 1-week hospitalization of patients with disorders of consciousness for diagnostic and prognostic purposes. The PET and MRI acquisitions were performed within 4 days and patients were assessed by a team of experienced clinician-researchers using the Coma Recovery Scale-Revised (CRS-R).[4,13]

At least 5 CRS-R assessments were performed for each patient (ie, including on the days of neuroimaging assessments) and the best diagnosis of MCS was retained.[14] Patients were categorized as being MCS- (criteria: presence of object localization, visual pursuit and fixation, automatic motor reaction, object manipulation and/or localization to noxious stimulation) or MCS+ (criteria: presence of consistent/reproducible movement to command, including object recognition, intelligible verbalization, and/or intentional communication).[1,3,5]

Exclusion criteria were (a) premorbid neurological conditions, (b) time postinjury less than 28 days, (c) age lower than 18 years, (d) diabetes, and (e) MRI contraindication (eg, pacemaker), and masking/segmentation issues (eg, structural brain damage exceeding 25% of the whole brain volume disabling reliable spatial normalization to the standardized stereotaxic brain template) (Figure 1). None of the patients who participated in the previous FDG-PET study of Bruno et al[7] was included in the present research. Nevertheless, 1 patient from our case series[12] and 9 patients who participated in our previous MRI study[9] were included in our VBM analyses (10 out of 66 patients).

Healthy control subjects (HCS) were recruited using advertisements posted at the university and none had a history of psychiatric or neurological disease. The control groups were composed of 34 participants (age range 19-70 years, 15 women) for PET imaging and 36 participants (age range 20-75 years, 13 women) for VBM imaging.

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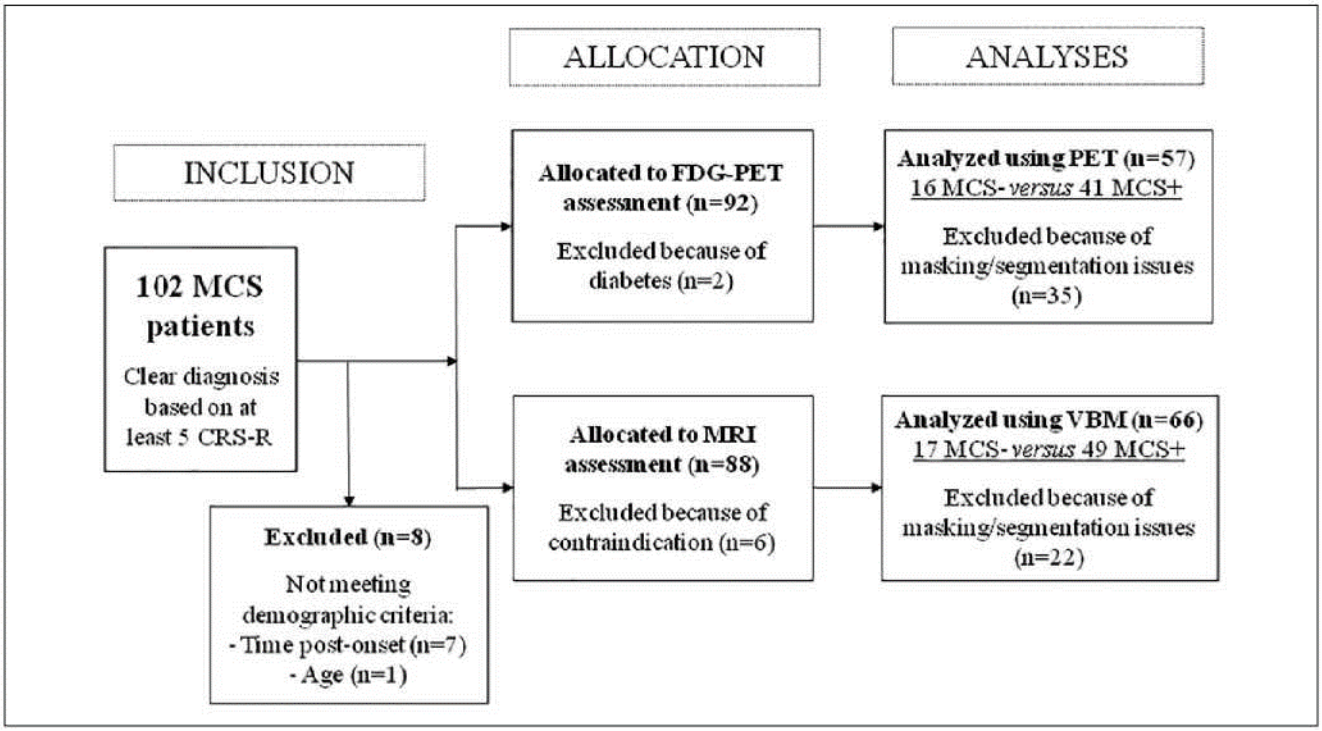
The study was approved by the Ethics Committee of the Faculty of Medicine at the University of Liège (No. 2009241). Written informed consent to participate in the study was obtained from all HCS and from the legal surrogates of the MCS patients.

Figure I. *Selection of patients according to exclusion criteria. MCS, minimally conscious state; PET, positron emission tomography; MRI, magnetic resonance imaging.*



FDG-PET

We acquired FDG-PET data with a Gemini TF CT scanner (Philips Medical Systems). Following intravenous injection of 150 to 300 MBq FDG, we recorded a single PET frame for 12 minutes, after circulation of the tracer for at least 30 minutes. We kept the patients awake during the uptake period. The images were corrected for attenuation using X-ray computed tomography, as well as for random scatter and physical decay. All data were preprocessed as described elsewhere,[15] smoothed with an isotropic 14 mm full-width at half-maximum (FWHM) Gaussian kernel and analyzed using Statistical Parametric Mapping 12 (SPM12; Wellcome Department of Cognitive Neurology, London, UK). To partially overcome the issue of brain lesions, the normalization was performed using a customized FDG template as described in a previous study.[16] A global normalization was performed by proportional scaling. We used the FDG-PET standardized uptake values (SUV) to estimate the global cerebral metabolic rate of glucose consumption:

$$SUV = \frac{\left(Decay\,corrected\,Voxel\,Intensity\right)}{\frac{Injected\,Dose}{Body\,Weight}}$$

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at the single subject level. For regional brain metabolism, the design matrices included the scans of both patient groups and the scans of the HCS. In a first analysis, brain regions with significantly decreased metabolism were identified in MCS- and MCS+ patients compared to HCS (ie, MCS- vs HCS and MCS+ vs HCS). We also investigated the direct comparison between patient groups (ie, MCS- vs MCS +). In the second analysis, we used a seed-based approach to explore which brain regions' metabolism correlates with the areas that most differentiate MCS- from MCS +. In this metabolic connectivity analysis, the design matrix included the same data as in the first analysis and tested the group differences in mean levels of glucose consumption. We looked for cortical regions that presented a significant difference in reciprocal modulation with areas found to be more preserved in MCS+ compared with patients in MCS- (ie, MCS- vs MCS+ in the first analysis). Two supplementary analyses were also performed. First, the initial MCS+ sample was reduced to 20 MCS + patients (ie, randomly chosen and matched to the MCS- group for gender, age, etiology, and time postinjury) to ensure that the FDG-PET results were not driven by the larger sample size of the MCS +. Moreover, the 7 MCS- patients who had both PET and MRI data were compared with 7 MCS+ patients matched for gender, age, etiology, and time postinjury, using both FDG-PET and VBM analyses.

VBM

Structural MRI data were obtained with T1 -weighted 3D gradient echo sequence (120 slices, repetition time 2.3 seconds, echo time 2.47 ms, voxel size 1 X 1 X 1.2 mm^3, flip angle 9°, field of view 256 X 256 mm^2). A T1 VBM analysis[17] was carried out with VBM8 toolbox (http://www. neuro.uni-jena.de/vbm/), with nonlinear warping and modulation of the gray matter to ensure the preservation of the volumes after the normalization step, and a DARTEL[18] template as previously described.[19] Normalized modulated gray matter data were smoothed with an isotropic Gaussian kernel of 12 mm FWHM. A full factorial design matrix was constructed, including the scans of both patient groups and the scans of the MRI-specific HCS, with the age of subjects centered to the mean as a regressed covariate. Indeed, gray matter structure was shown to be particularly dependent on age.[20]

STATISTICAL ANALYSES

We first checked the potential equivalence between patient groups regarding the time postinjury, age and CRS-R total score using Wilcoxon tests, and the gender and etiology (traumatic vs nontraumatic) using chi-square tests. The same statistical analyses were performed to investigate the equivalence of age and gender between the patient groups and their corresponding control group.

Regarding global brain metabolism, Wilcoxon tests were performed to check for SUV differences between patient groups. FDG-PET analyses for regional brain metabolism were based on t tests and identified (a) brain areas showing hypometabolism in patient groups as compared with HCS, (b) brain areas showing significant differences in the direct comparison of both patient groups (MCS- < MCS +), and (c) brain areas whose glucose consumption significantly correlates with that

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of regions emerging in the previous analysis. VBM analyses, also based on t tests, intended to identify (a) brain areas showing gray matter impairment in patient groups as compared with HCS and (b) brain areas showing significant differences by directly comparing both patient groups (MCS- < MCS +). All FDG-PET and VBM results were thresholded at P < .05 with family-wise error (FWE) correction for whole brain multiple comparisons. Furthermore, to compare with previous studies that used a false discovery rate (FDR) correction,[8] results are also given at P < .05 FDR corrected. FWE correction is more conservative but less sensible (ie, avoid false-positives), whereas FDR correction is more sensible but less specific (ie, avoid false-negatives).[21]

Results

PARTICIPANTS

Between January 2011 and June 2018, 102 severely brain- injured patients stayed for 1 week in our hospital and were diagnosed MCS as assessed by repeated CRS-R. Following the exclusion criteria (Figure 1), PET analyses focused on 16 MCS- (4 women, age 42 ± 18 years) and 41 MCS+ (19 women, age 39 ± 16 years) patients. VBM analyses were conducted on 17 MCS- (9 women, age 38 ± 14 years) and 49 MCS+ (18 women, age 43 ± 17 years) patients.

As shown in Table 1, 36 patients (7 MCS- and 29 MCS +) were included in both FDG-PET and VBM analyses. Individual demographic data of patients and their diagnosis criteria of MCS- or MCS+ are also reported in this table. All MCS+ patients exhibited reproducible responses to command in the present research.

Age and time postinjury did not differ between patient groups (Table 2), neither did gender, etiology, and handedness. As expected, CRS-R total scores differed between groups with higher scores for MCS+ patients. Regarding FDG-PET data, there was no significant difference between patients and HCS for age (W = 1069; P = .284) and gender (X^2 = 0.037; P = .847). There was also no significant difference between patients and HCS for the VBM analyses (age: W = 1405; P = .13; gender: x^2 = 0.225; P = .635).

FDG-PET ANALYSES

Regarding global brain metabolism, MCS+ patients showed a significantly higher SUV mean (median = 4.51) as compared with MCS- patients (median = 3.47; W = 161, P = .014; see individual data in Supplementary Table 2). Regional brain metabolism results are presented in Figure 2 and Supplementary Table 1.

COMPARISON BETWEEN PATIENT GROUPS AND HEALTHY CONTROL SUBJECTS.

The results are shown in Figure 2A. Individual hypometabolism data are reported in Supplementary Table 2. Compared with HCS, the group of MCS- patients presented an extended hypometabolism in bilateral frontal and temporoparietal areas, including the left angular gyrus

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(BA39) and middle temporal gyrus (BA21), as well as left caudate and left thalamus. Compared with HCS, the group of MCS+ patients showed hypometabolism in bilateral frontal lobules including middle frontal gyri (BA10), left anterior cingulate cortex (BA32), and left thalamus.

COMPARISON BETWEEN PATIENT GROUPS.

Compared with the group of MCS- patients, MCS+ patients exhibited higher metabolism in the left middle temporal cortex (BA21). The FDR-corrected results also showed higher metabolism in MCS+ patients in the left angular gyrus (BA39), left middle frontal gyrus (BA9), left inferior frontal gyrus (pars opercularis; BA44), bilateral prefrontal cortex/supplementary motor area (BA8), and premotor cortex (BA6), compared with MCS- patients. These results are shown in Figure 2B and Table 3.

The supplementary analysis performed with a smaller sample of MCS+ patients (ie, 16 MCS- vs 20 MCS +) showed that these patients had higher metabolisms than MCS- patients in the left middle temporal cortex (BA21), left fusiform cortex (BA37), left inferior and middle frontal gyrus (BA44 and BA9), left prefrontal cortex/supplementary motor area (BA8), as well as left inferior frontal gyrus (BA47) (FWE correction). Similar results (notably concerning the left middle temporal cortex) were obtained when comparing 7 MCS- and 7 MCS+ patients, with uncorrected $P < .001$ (but not using FDR or FWE corrections). These data are presented in the Supplementary Material (see Supplementary Analyses 1 and 2). As the differences between patient groups regarding time postinjury and handedness were close to significant, we also performed supplementary FDG-PET analyses: (a) including time postinjury as covariate (Supplementary Analysis 3) and (b) excluding patients with left-handedness, ambidexterity, or missing handedness data (Supplementary Analysis 4). Both analyses also led to similar results.

***Table I**. Individual Demographic Data of Patients.*

Patient	Group	Age (Years)	Gender	Etiology	Time Postinjury (Days)	MCS Criteria	Best CRS-R Total Score	Analyses	Handed-ness
1	MCS-	24	Male	TBI	167	VP-VF	8	PET	R
2	MCS-	57	Male	NTBI	247	VF	7	PET	R
3	MCS-	74	Male	NTBI	46	OL-VP-VF	10	PET	R
4	MCS-	64	Male	NTBI	400	VP-VF-OM	12	PET	R
5	MCS-	22	Male	TBI	1016	VF-VP	8	PET	R
6	MCS-	49	Male	TBI	224	OM	12	PET	R
7	MCS-	31	Male	NTBI	100	OL-VP-OM	13	PET	R
8	MCS-	60	Male	TBI	2147	OL-VP-VF-OM	13	PET	MD
9	MCS-	21	Female	NTBI	1102	VP-OM	12	PET	R
10	MCS-	25	Male	TBI	322	OM	12	PET-VBM	MD

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11	MCS-	28	Male	TBI	517	VP-VF	10	PET-VBM	R
12	MCS-	49	Female	NTBI	467	VF	9	PET-VBM	R
13	MCS-	42	Female	NTBI	222	VP-VF	8	PET-VBM	R
14	MCS-	19	Male	TBI	1306	VP-VF	7	PET-VBM	R
15	MCS-	46	Female	TBI	238	VP-VF	10	PET-VBM	R
16	MCS-	54	Male	NTBI	159	VP-VF-OM	13	PET-VBM	R
17	MCS-	40	Female	TBI	1290	VP-VF	11	VBM	R
18	MCS-	30	Female	TBI	565	VF	12	VBM	L
19	MCS-	53	Female	NTBI	49	VP	7	VBM	R
20	MCS-	30	Male	TBI	39	OM	6	VBM	R
21	MCS-	26	Female	TBI	36	VP-VF-OM	13	VBM	MD
22	MCS-	29	Female	NTBI	745	VF	5	VBM	R
23	MCS-	29	Male	TBI	68	VP-VF	5	VBM	MD
24	MCS-	52	Male	NTBI	1459	OL-VP-VF-OM	13	VBM	R
25	MCS-	68	Female	NTBI	1379	PL	8	VBM	R
26	MCS-	25	Male	TBI	333	VP-VF	10	VBM	R
27	MCS +	19	Female	TBI	485	CF-IC	13	PET	R
28	MCS +	62	Female	NTBI	714	CF	17	PET	R
29	MCS+	30	Female	TBI	565	CF	12	PET	L
30	MCS+	47	Male	TBI	529	CF-IC	13	PET	R
31	MCS+	35	Male	NTBI	532	CF-IC	20	PET	R
32	MCS+	78	Female	TBI	2070	CF-IC	20	PET	R
33	MCS+	50	Female	NTBI	273	CF-IC	13	PET	R
34	MCS+	61	Male	TBI	131	CF	12	PET	L
35	MCS+	27	Male	TBI	220	CF	12	PET	A
36	MCS+	48	Female	TBI	287	CF-IC	11	PET	MD
37	MCS+	67	Male	NTBI	39	CF-IC-IV	15	PET	MD
38	MCS+	49	Female	TBI	477	CF	8	PET	R
39	MCS+	19	Male	TBI	428	CF-IC	11	PET-VBM	R
40	MCS+	27	Male	TBI	1544	CF	12	PET-VBM	R
41	MCS+	32	Female	TBI	557	CF	11	PET-VBM	R
42	MCS+	30	Female	NTBI	2407	CF	10	PET-VBM	MD
43	MCS+	27	Female	TBI	1013	CF	11	PET-VBM	R

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44	MCS+	50	Male	TBI	253	CF	21	PET-VBM	R
45	MCS+	32	Female	TBI	573	CF-IC	16	PET-VBM	R
46	MCS+	21	Female	NTBI	620	CF-IC	13	PET-VBM	R
47	MCS+	38	Male	NTBI	202	CF	11	PET-VBM	R
48	MCS+	26	Female	TBI	310	CF	10	PET-VBM	R
49	MCS+	23	Male	TBI	1231	CF	13	PET-VBM	MD
50	MCS+	60	Male	NTBI	711	CF	13	PET-VBM	R
51	MCS+	30	Female	TBI	2729	CF	9	PET-VBM	R
52	MCS +	45	Male	TBI	4786	CF	11	PET-VBM	R
53	MCS+	21	Female	TBI	510	CF	7	PET-VBM	L
54	MCS+	29	Male	NTBI	405	CF	17	PET-VBM	L
55	MCS+	25	Male	TBI	1153	CF	16	PET-VBM	R
56	MCS+	46	Male	NTBI	1379	CF	11	PET-VBM	L
57	MCS+	55	Female	TBI	198	CF	18	PET-VBM	R
58	MCS+	35	Male	TBI	1327	CF	9	PET-VBM	R
59	MCS+	24	Male	TBI	2036	CF-IC	18	PET-VBM	R
60	MCS+	23	Male	TBI	641	CF	12	PET-VBM	MD
61	MCS+	42	Female	NTBI	266	CF	10	PET-VBM	R
62	MCS+	40	Male	TBI	329	CF	16	PET-VBM	R
63	MCS +	43	Female	NTBI	100	CF	6	PET-VBM	R
64	MCS +	22	Male	TBI	425	CF	12	PET-VBM	L
65	MCS +	69	Male	NTBI	312	CF-IC	17	PET-VBM	R
66	MCS +	46	Male	TBI	648	CF	16	PET-VBM	R
67	MCS +	65	Female	NTBI	421	CF	12	PET-VBM	R
68	MCS+	67	Female	NTBI	284	CF	7	VBM	R
69	MCS+	49	Male	TBI	54	CF	14	VBM	MD
70	MCS+	20	Male	TBI	389	CF	15	VBM	R
71	MCS+	54	Male	TBI	2082	CF	15	VBM	R
72	MCS+	43	Female	NTBI	3237	CF	8	VBM	R
73	MCS+	46	Male	NTBI	227	CF	9	VBM	R
74	MCS+	57	Male	NTBI	254	CF	6	VBM	R
75	MCS+	48	Female	NTBI	205	CF	7	VBM	L
76	MCS+	45	Female	NTBI	34	CF-IC-IV	19	VBM	R
77	MCS+	74	Female	NTBI	46	CF	13	VBM	R

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78	MCS+	24	Male	TBI	2686	CF	9	VBM	R
79	MCS+	72	Male	NTBI	3063	CF	9	VBM	R
80	MCS+	25	Male	TBI	529	CF	12	VBM	R
81	MCS+	57	Male	NTBI	392	CF	7	VBM	R
82	MCS+	62	Male	NTBI	38	CF	16	VBM	MD
83	MCS+	66	Male	NTBI	318	CF	15	VBM	A
84	MCS+	74	Male	NTBI	98	CF	9	VBM	R
85	MCS+	67	Male	TBI	28	CF	14	VBM	R
86	MCS+	39	Male	NTBI	254	CF-IC	17	VBM	R
87	MCS+	54	Female	NTBI	389	CF	11	VBM	R

Abbreviations: MCS, minimally conscious state; TBI, traumatic brain injury; NTBI, nontraumatic brain injury; VP, visual pursuit; VF, visual fixation; OL, object localization; OM, oriented movements; CF, command-following; IV, intelligible verbalization; PL, pain localization; IC, intentional communication; PET, positron emission tomography; VBM, voxel-based morphometry; R, right; L, left; MD, missing data; A, ambidextrous.

Table 2. *Comparison of Patient Groups According to Demographic Data.*

PET	MCS- (n = 16)	MCS+ (n = 41)		
Age (years)	41.57 ± 17.57[a]	39.48 ± 15.77	W[b] = 345	P = .772
Time postinjury (days)	542.5 ± 570.64	825.27 ± 901.39	W = 227.5	P = .076
CRS-R total score	10.25 ± 2.21	13.05 ± 3.55	W = 183	P = .01*
Gender	4 females	19 females	X^{2c} = 2.178	P = .14
Etiology	8 TBI	27 TBI	X^2 =1.22	P = .27
Handedness	0 L/14 R (2 MD)	6 L/29 R (6 MD)	X^2 =2.735	P = .098
VBM	**MCS- (n = 17)**	**MCS+ (n = 49)**		
Age (years)	37.9 ± 13.65	42.66 ± 16.81	W = 361	P = .424
Time postinjury (days)	540.76 ± 508.76	859.61 ± 1024.91	W = 356.5	P = .383
CRS-R total score	9.41 ± 2.72	12.22 ± 3.69	W = 242.5	P = .011*
Gender	9 females	18 females	X^2 = 1.371	P = .242
Etiology	10 TBI	25 TBI	X^2 = 0.309	P = .579
Handedness	1 L/13 R (3 MD)	5 L/38 R (6 MD)	X^2 = 0.226+	P = .635

Abbrevitions: MCS, minimally conscious state; PET, positron emission tomography; VBM, voxel-based morphometry; TBI, traumatic brain injury; NTBI, nontraumatic brain injury; L, left-handed; R, right-handed; MD, missing data.
[a]Expressed as mean ± standard deviation.
[b]Wilcoxon rank-sum test.
[c]Chi-square test.
*P < .05.

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FUNCTIONAL CONNECTIVITY ANALYSIS.

We then focused on the regions that most differentiated MCS+ from MCS- (ie, clusters emerging from the previous first [whole sample] comparison between patient groups), and examined their connectivity in the group of MCS+ patients compared with MCS- patients. Among these seeds, the left angular gyrus (BA39; MNI coordinates: x = -46, y = -60, z = 33) was the only one to show significant results. This region presented higher metabolic functional connectivity in MCS + compared with MCS- with the left prefrontal cortex/supplementary motor area (BA8) using FWE correction (see Figure 2C and Table 3).

INDIVIDUAL RESULTS.

As described in Supplementary Table 2, left frontoparietal hypometabolism was reported in 69% of the MCS- patients (ie, 11/16), while only 24% of the MCS+ patients had such brain metabolism impairment (ie, 10/41).

VBM ANALYSES

The results are presented in Figure 3 and Supplementary Table 3.

Compared with HCS, the group of MCS- patients exhibited atrophy mainly in the bilateral thalami and angular gyri (BA39), left caudate and insula, left primary sensory area, right orbitofrontal cortex (BA11), right fusiform (BA37), and occipital cortex (BA18). Compared with HCS, the group of MCS+ patients showed atrophy in the bilateral thalami, left caudate, right orbitofrontal cortex (BA11), left insula, left prefrontal cortex (BA8), right orbitofrontal cortex (BA11), right fusiform (BA37), and occipital cortex (BA18). There was no significant difference in gray matter volume between the groups of patients in MCS- and MCS +.

The supplementary analysis of 7 MCS- and 7 matched MCS+ patients did not lead to significant differences in gray matter volume, neither at a threshold for the P value of .001 uncorrected, as it was in the whole sample.

Discussion

In this study, we aimed to investigate brain function and structure underpinning the recovery of language-related abilities in MCS patients using FDG-PET and VBM techniques by comparing patients with (ie, MCS +) and without (ie, MCS-) such behaviors. To our knowledge, this is the first study that examines brain metabolism and gray matter atrophy in the 2 groups of MCS patients (MCS- and MCS +). Our main findings show metabolic differences in the left-sided language network sustaining the clinical subcategorization of the MCS, while no gray matter volume differences were found.

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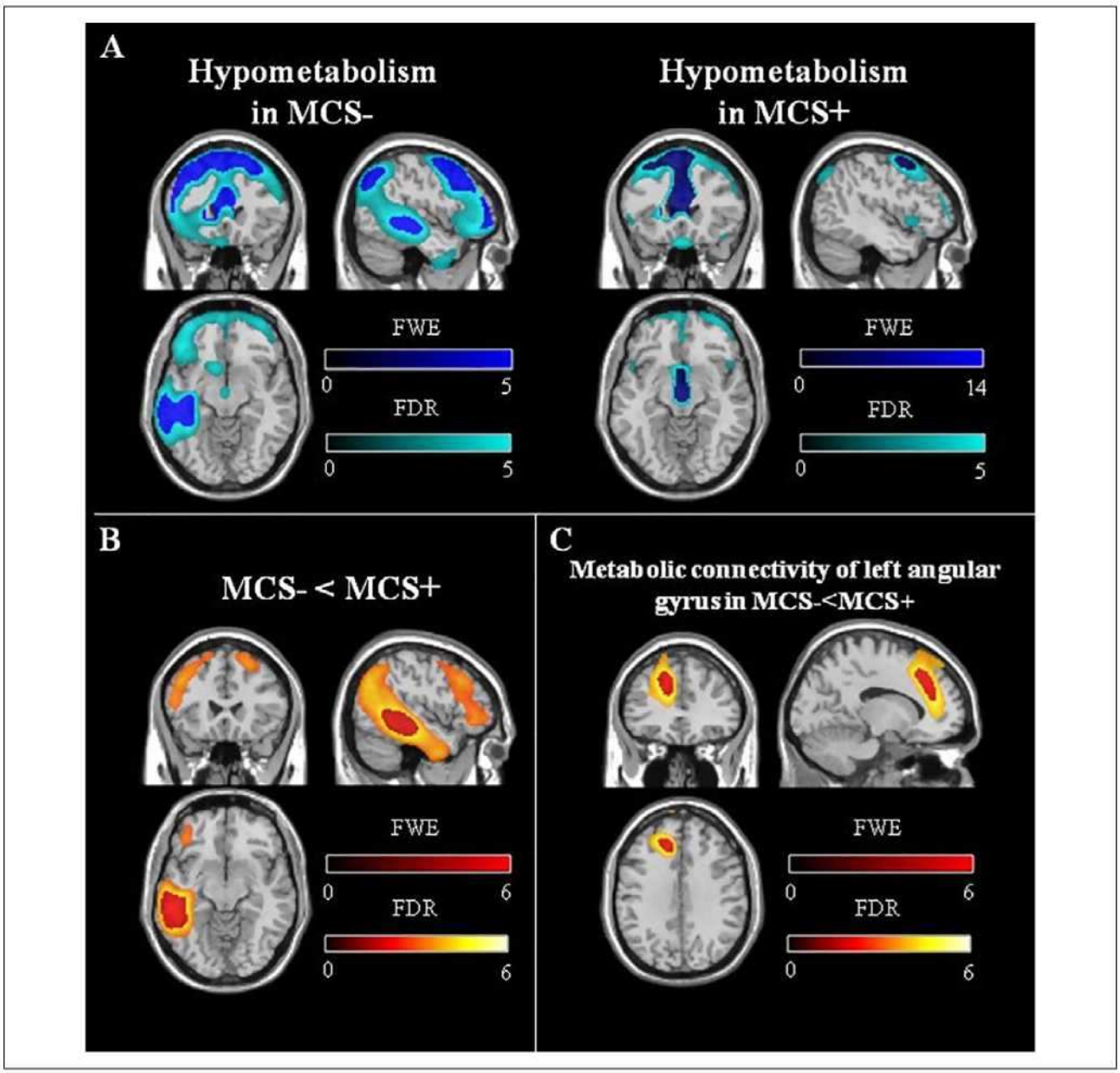
Figure 2. *Brain metabolism results using positron emission tomography. (A) Comparison of glucose uptake between patients in MCS- and healthy subjects, and between patients in MCS+ and healthy subjects. (B) Comparison of glucose uptake between patients in MCS- and MCS + groups. (C) Comparison of metabolic connectivity of the left angular gyrus between patients in MCS- and MCS+ groups. All color scales correspond to the t-test value. MCS, minimally conscious state; FWE, family-wise error; FDR, false discovery rate.*



As expected, both patient groups showed decreased cerebral metabolism and structural damage compared to healthy subjects. As in previous studies, we observed an alteration of brain function, in particular in the frontoparietal network (eg, Crone et al[22] and Aubinet et al[23]). Moreover, our structural analyses show a significant atrophy for both patient groups in subcortical structures such as the thalamus, which was also previously found to be damaged in MCS patients.[24,25]

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In comparison with the group of MCS- patients, MCS + patients presented higher metabolism preservation in different language-related areas. Using a more conservative correction (ie, FWE), higher metabolism was identified in MCS+ compared with MCS- in the left middle temporal cortex, which has been associated to selective processing of speech,[26,27] semantic processing,[28,29] and word generation.[30] The FDR correction analysis also highlighted other language-related brain regions: the left angular gyrus,[31-33] the left middle frontal gyrus,[34-38] the left inferior frontal gyrus (pars opercularis),[39-41] the prefrontal and premotor cortex as well as supplementary motor area,[42] which are also involved in various motor functions.[43] These results are in line with previous research showing that the left middle temporal cortex and left angular gyrus could differentiate MCS subcategories at the subject level,[12] and that a preserved metabolism in these regions was associated with residual language comprehension in 3 postcoma patients.[23] The involvement of motor regions is also not surprising since command-following, the most frequent MCS+ criteria to be observed (see Table 1), requires both language comprehension and motor execution. Note that the difference in sample size cannot be considered as a confounding factor since we obtained similar results using smaller samples of MCS+ patients (Supplementary Analyses 1 and 2).

Altogether, these findings corroborate previous results reported in the study of Bruno et al[8] on a larger sample size (n = 57). In addition, more stringent diagnostic criteria were used following the recent recommendation (ie, minimum of 5 CRS-R assessments needed before any diagnosis)[14] and therefore are likely to be more accurate than in the Bruno et al study. Finally, in the present study PET analyses were performed using the computed tomography (CT) of each individual patient, which allows a more precise image reconstruction than when the standard ellipse is used.[16]

Moreover, the functional connectivity analysis showed a disconnection between the left angular gyrus and the left prefrontal cortex/supplementary motor area in MCS- as compared with MCS+ (FWE correction), which could reflect a deficit in language integration in MCS- patients. Indeed, several studies have shown a reduced functional connectivity of the left frontoparietal network in aphasic poststroke patients, which subsequently increased when patients recovered language comprehension.[44,45] Additionally, when looking at patients' individual FDG-PET reports, left frontoparietal hypometabolism was reported in 69% of the MCS- patients against 24% of the MCS+ patients, showing the overall difference between the 2 subgroups. However, it also means that our results are not systematically observable at the subject level.

The main novelty of this study is to combine functional and structural analyses in MCS- and MCS+ patients at group level in a representative sample. While functional measurements provide an accurate picture of the functioning brain areas and networks, structural data give information on the location of tissue's damage.[46] We did not find any gray matter volume difference between MCS- and MCS +. These results suggest that brain function (rather than gray matter structure) is determinant for the presence of clinical signs of language processes in the MCS. The extent and severity of structural lesions are also not predictive of a good outcome as was shown recently.[47] Gray matter structure as measured with T1, however, was found to discriminate levels of consciousness (ie, unresponsive wakefulness syndrome vs MCS) with a sensitivity of 0.92.[25]

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Our results are clinically relevant as they contribute to the diagnosis of postcomatose patients by better characterizing their residual brain function. In line with previous multimodal studies,[7] brain metabolism seems to be the most accurate marker for the differential diagnosis of MCS- and MCS +. A preservation of glucose metabolism in the left frontoparietal network may consequently suggest the presence of a cognitive-motor dissociation[48,49] in patients who do not follow command at bedside. The efforts to seek voluntary responses should consequently be intensified in these patients by repeating the behavioral assessments or using brain-computer interfaces.[50] Similarly, speech therapists should endeavor to obtain any sign of residual language in those patients, by using various language assessments (eg, Coleman et al[51] and Owen and Coleman[52]). Noninvasive brain stimulation further represents an emerging approach for patients with disorders of consciousness.[53,54] Techniques such as transcranial direct current stimulation could be applied on top of the cortical representation of the left angular gyrus in MCS- patients. Indeed, applying such stimulation over a functionally impaired area could potentially induce an increase in brain metabolism and lead to an improvement of language-related behaviors. However, this hypothesis should be tested prospectively, including neuroimaging evaluations of patients' individual structural and metabolic impairment. PET data could thus guide clinicians to target specific brain regions for non-invasive brain stimulation technique. Overall, the present study could be of great help to identify patients with cognitive abilities missed at the bedside, which should improve their rehabilitation care by choosing the most suitable therapeutic strategies.

One may ask if MCS- and MCS+ subcategories represent different states of consciousness per se or rather distinct cognitive profiles. The first hypothesis would be sustained by global brain metabolism results, which are significantly lower in MCS- patients compared with MCS+ patients. Such global glucose metabolism was previously shown to correlate with patients' level of consciousness.[46] Nevertheless, the second hypothesis is supported by other data. Indeed, whereas the language network distinguishes both MCS subcategories, we found no differences in regional brain function regarding specific areas considered to be associated with various aspects of consciousness (eg, default mode network including thalamus and precuneus),[15,55] in line with our previous research using functional MRI.[9]

It has been proposed that MCS- patients show a preservation of neural networks associated with a feeling of pain[56,57] or with internal self-awareness.[8,9] However, these patients fail to understand commands, establish a communication code or intelligibly verbalize due to a severe impairment of language function. Analogously, MCS+ patients should not be considered as "more conscious" than MCS- patients. These hypotheses raise theoretical questions about the categorization of disorders of consciousness, which could be considered as global brain dysfunctions or as a sum of focal dysfunctions (ie, including language impairment).[58] Further studies are needed to address these concerns and develop new strategies allowing disentanglement of language and consciousness impairments in this population. For example, new bedside behavioral assessments of residual language abilities could be developed. Research looking at the difference in prognosis between these 2 categories of patients could also unveil whether language function recovery is a marker of good outcome. In this regard, we hypothesize that MCS+ patients may have a better outcome than MCS- patients given their abilities to interact with their environment and because of

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smaller neurophysiological impairment as exposed in the present study. Note that it has recently been shown that MCS- patients have a higher degree of disability at discharged from rehabilitation compared with MCS+ patients. However, longterm outcome differences between these 2 subcategories of patients need to be investigated, which could have a significant clinical impact.

Our work is not without limitations since it is a cross-sectional retrospective study. The use of neuroimaging also requires technical settings and expertise, and consequently could be difficult to implement in current rehabilitation processes. Moreover, the fact that we did not find gray matter volume differences between both patient groups does not mean that such differences do not exist. Still a recent study using diffusion tensor imaging demonstrated a reduced connectivity of premotor and left temporal cortices with the thalamus in MCS- compared with MCS+ patients.[58] White matter differences between groups of MCS- and MCS + should further be investigated. As stated above, outcome measurements were also not included. Finally, we found a metabolic disconnection within the left frontoparietal network in MCS- compared with MCS + , and further studies should bring evidence on the causality of this disconnection (ie, missing top-down/bottom-up and feedforward/feed- back connections).

Table 3. *Brain Glucose Metabolism Results.*

	Brain Region	x	y	z	Z Value	P Value[a]
MCS- < MCS+	Left middle temporal gyrus (BA21)[b]	-54	-38	-8	5.323	<.001
	Left angular gyrus (BA39)	-46	-70	28	3.699	<.001
	Left middle frontal gyrus (BA9)	-44	26	36	3.318	<.001
	Left prefrontal cortex/supplementary motor area (BA8)	-36	22	46	3.218	.001
	Left inferior frontal gyrus (pars opercularis; BA44)	-52	20	18	3.195	.001
	Right premotor cortex (BA6)	20	8	68	3.273	.001
	Right prefrontal cortex/supplementary motor area (BA8)	24	24	54	3.135	.001
	Left premotor cortex (BA6)	-18	10	68	3.027	.001
Connectivity of left angular	Left prefrontal cortex/supplementary motor area (BA8)[b]	-12	30	40	5.125	<.001
gyrus in MCS- < MCS+	Left inferior occipital gyrus (BA19)	-18	-78	32	3.250	.001

Abbreviations: MCS, minimally conscious state; BA, Brodmann area.
[a]False discovery rate corrected.
[b]Areas emerging using the family-wise error correction.

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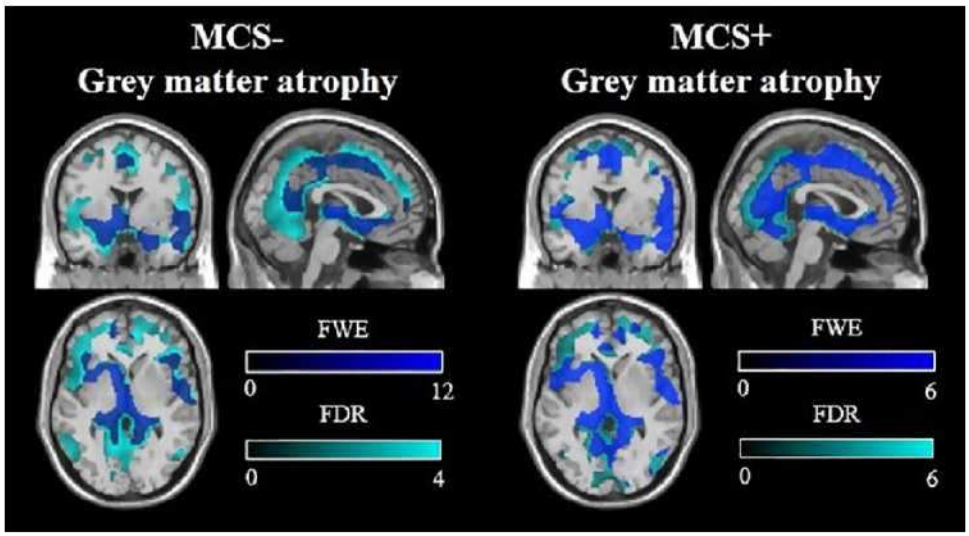
Figure 3. *Brain structure results using voxel-based morphometry. Comparison of gray matter structure volume between patients in MCS- and healthy subjects and between patients in MCS+ and healthy subjects. The color scales correspond to the t-test value. MCS, minimally conscious state; FWE, family-wise error; FDR, false discovery rate.*



Conclusions

In the present study, we aimed to investigate the metabolic activity and functional connectivity needed for residual language abilities in postcomatose patients by means of FDG-PET, as well as possible structural differences between MCS- and MCS+ using VBM. We found metabolic differences sustaining the clinical subcategorization of MCS. Indeed, MCS+ patients showed preserved glucose metabolism in left-sided language-related areas such as the left middle temporal gyrus, compared with MCS- patients, as well as preserved connectivity in the left frontoparietal network. No gray matter volume differences were identified between MCS- patients and MCS + patients, suggesting that brain metabolism, more than structural damage, is determinant for the recovery of language-related abilities in the MCS. Our results are of clinical relevance since they contribute to reduce the misdiagnosis of MCS patients and consequently establish better therapeutic strategies.

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AUTHOR CONTRIBUTIONS

C.A., S.L., and A.T. conceived and planned the presented research. C.A., A.T., H.C., C.C., C.M., G.M., O.G., and M.C. contributed to clinical and neuroimaging data acquirement. C.A., A.T., H.C.,

S.K.L., M.A.B., S.M., O.G., C.C., and S.L. worked on data analyses and interpretation. C.A. drafted the manuscript under A.T.'s supervision and all authors provided critical feedback and helped shape the manuscript.

DECLARATION OF CONFLICTING INTERESTS

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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