Original Article

Cerebral Glucose Metabolism in Patients with Chronic Disorders of Consciousness

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ABSTRACT: *Objective:* To measure regional cerebral metabolic rate of glucose (CMRGlu) in patients with chronic disorders of consciousness (DOCs) using ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET). *Methods:* This retrospective cohort study examined 50 patients (mean age: 40.9 ± 20.1 years) with traumatic brain injury (TBI)-induced chronic DOCs [minimally conscious state (MCS)+, $n = 20$; MCS−, $n = 15$ and vegetative state (VS), $n = 15$]. We measured FDG-PET-based CMRGlu values in 12 regions of both brain hemispheres and compared those among MCS+, MCS − and VS patients. *Results:* In both hemispheres, the regional CMRGlu reduced with consciousness deterioration in 11 of 12 regions (91.7%). In seven right hemisphere regions, CMRGlu values were markedly higher in MCS+ patients than in MCS− patients. Furthermore, CMRGlu was suggestive higher in the left occipital region in MCS− patients than in VS patients. *Conclusion:* Functional preservation in the left occipital region in patients with chronic DOCs might reflect an awareness of external environments, whereas extensive functional preservation in the right cerebral hemisphere might reflect communication motivation.

RÉSUMÉ : **Métabolisme cérébral du glucose chez des patients souffrant de troubles chroniques de la conscience.** *Objectif :* Mesurer le taux métabolique cérébral régional du glucose (TMCRGlu) chez des patients souffrant de troubles chroniques de la conscience (TCC) en utilisant la tomographie par émission de positons au 18F-fluorodéoxyglucose (^{18}F-FDG). *Méthodes :* Cette étude de cohorte rétrospective s'est penchée sur les cas de 50 patients (âge moyen : 40,9 ± 20,1 ans) ayant souffert d'un traumatisme cranio-cérébral et présentant un état de conscience minimale (ECM)+ ($n = 20$), un ECM- ($n = 15$) et un état végétatif (EV) ($n = 15$). Nous avons mesuré les valeurs de TMCRGlu basées sur la ^{18}F-FDG dans 12 régions des deux hémisphères cérébraux et les avons comparées ensuite chez les patients ECM+, ECM- et EV. *Résultats :* Dans les deux hémisphères, le TMCRGlu régional a diminué avec la détérioration de la conscience dans 11 des 12 régions du cerveau (91,7 %). Dans sept régions de l'hémisphère droit, les valeurs de TMCRGlu étaient nettement plus élevées chez les patients ECM+ que chez les patients ECM-. De plus, le TMCRGlu était de manière révélatrice plus élevé dans la région occipitale gauche chez les patients ECM- que chez les patients EV. *Conclusion :* La préservation fonctionnelle de la région occipitale gauche chez les patients atteints de TCC pourrait refléter une prise de conscience des environnements extérieurs alors que la préservation fonctionnelle étendue de l'hémisphère cérébral droit pourrait refléter une motivation de nature communicationnelle.

Introduction

Advancements in medical technologies and emergency medicine have done a marvellous job in saving human lives, remarkably decreasing the death rate attributed to neurological emergencies (neurotrauma and cerebrovascular diseases) over time.[1] Nevertheless, these advancements have increased the number of patients with chronic disorders of consciousness (DOCs), including patients in a vegetative state (VS) or a minimally conscious state (MCS). In Japan, a field assessment of

the Tohoku district by Sato et al.[2] reported the number of patients with chronic DOCs to be 3000 in 1978, whereas Fujiwara estimated the number to be 55,000 in 2010.[3] Thus, the number of patients with chronic DOCs increased 18-fold from 1978 to 2010. In the USA, about 14,000 patients with brain injuries were categorised as being in a VS every year.[4]

The treatment and care of patients with chronic DOCs result in both medical and social burdens. As no effective treatment exists

for patients with chronic DOCs, the prospect of consciousness recovery is low among those patients; however, for unknown reasons, a small number of patients emerge from chronic DOCs.[5–10] Per the Multi-Society Task Force on PVS, the recovery rate among patients with chronic DOCs within 12 months after traumatic brain injury (TBI) was 1.6%.[11] In patients with non-trauma-induced DOCs, Estraneo et al.[12] reported that 9 of 43 patients with prolonged anoxic VS had recovered responsiveness (although 2 of them died after regaining consciousness), whereas 12 patients remained in a VS and 22 died in the VS within 24 months after onset. Nonetheless, research on the cerebral metabolism of patients who recover from chronic DOCs is limited[13] and the details of this phenomenon remain unclear. In the last two decades, studies evaluating cerebral functions have increasingly focused on neuroradiological, neurophysiological and metabolic examinations designed to identify patients with the highest chance of improvement following aggressive rehabilitation.[14–23]

^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) facilitates the quantitative measurement of cerebral glucose metabolism in specific brain regions considered vital for consciousness. Stender et al.[24] reported that the median cortical glucose metabolic rates averaged 42% of normal cortical activity in patients with VS and 55% of normal cortical activity in patients with MCS. A meta-analysis by Bender et al.[25] demonstrated that FDG-PET is the most sensitive clinical examination for differentiating MCS from VS compared with functional magnetic resonance imaging, event-related cognitive potentials, quantitative electroencephalography (EEG), combined transcranial magnetic stimulation and EEG, electromyography and eye-tracking. Indeed, several studies have established correlations between metabolically reduced brain regions shown by qualitative analyses and consciousness levels in patients with chronic DOCs. For example, Nakayama et al.[26] demonstrated that in patients with diffuse brain injury, bilateral hypometabolism in the medial prefrontal regions, medial frontobasal regions, cingulate gyrus and thalamus might reflect clinical deterioration and that hypometabolism in these regions was more prevalent and prominent in those with severe consciousness impairment. In addition, Thibaut et al.[27] reported that patients with VS due to various diseases demonstrated metabolic dysfunction in both the thalamus and an extensive cortical network, whereas MCS patients displayed metabolic dysfunction in both the thalamus and the intrinsic/internal awareness system. To the best of our knowledge, no study has clarified brain region-specific differences in quantitatively analysed brain glucose metabolism among patients with different levels of chronic DOCs. Perhaps, the quantitative approach might contribute to the understanding of the mechanisms of prolonged disturbance of consciousness.

Hence, this retrospective cohort study aims to quantitatively measure the regional cerebral metabolic rate of glucose (CMRGlu) using FDG-PET in patients with TBI-induced chronic DOCs and assess differences noted in each brain region based on the chronic DOC classification.[28]

Patients and Methods

Patients

Among 60 consecutive patients with TBI-induced chronic DOCs due to traffic accidents admitted to the Chubu Medical Centre for Prolonged Traumatic Brain Dysfunction, between 1 April 2014 and 31 March 2019, we enrolled 50 patients (mean age: 40.9 ± 20.1 years; 39 men; mean injury-to-admission interval: 285.4 ± 145.3 days) who fulfilled the inclusion criteria. The inclusion criteria were as follows: patients without massive focal morphological brain damage (detectable lesions were <10 cm^3, such as contusions, haematomas or infarctions on the high spatial resolution T1-weighted MRI image collected at the time of the study); patients aged ≥16 years and patients without consciousness level changes within 2 weeks before/after FDG-PET examination. Meanwhile, the exclusion criteria, based on which we excluded 10 patients, were as follows: massive focal morphological brain damage more than 10 cm^3 ($n = 2$); missing data ($n = 6$); aged <16 years ($n = 1$) and insufficient neuroradiological examination owing to the physical ability ($n = 1$).

We divided the 50 patients into 3 groups (MCS+, MCS− and VS) based on their JFK Coma Recovery Scale-Revised score.[29,30] MCS is used when patients with chronic DOCs show minimal signs of consciousness but cannot communicate reliably.[29,30] MCS patients were further subcategorised according to the complexity of their behaviours: MCS+ describes high-level behavioural responses, such as command following, intelligible verbalisations or non-functional communication; MCS− describes low-level behavioural responses, including visual pursuit, localisation of noxious stimulation or contingent behaviour, such as appropriate smiling, or crying in response to emotional stimuli.[30]

Of note, the consciousness level of each patient was examined during the admission process, which was determined by three neurosurgeons, three specialist nurses and three rehabilitation therapists. Accordingly, we assigned 20 patients to the MCS+ group (mean age: 40.9 ± 19.3 years; 17 men; 2 left-handed patients; mean injury-to-admission interval: 293.5 ± 142.1 days), 15 to the MCS− group (mean age: 40.0 ± 19.5 years; 12 men; 1 left-handed patient; mean injury-to-admission interval: 270.3 ± 88.3 days) and 15 to the VS group (mean age: 41.6 ± 23.1 years; 10 men; 1 left-handed patient; mean injury-to-admission interval: 322.5 ± 203.0 days; Table 1). No significant differences were noted in age ($P = 0.984$), sex ($P = 0.429$), the proportion of left-handed patients ($P = 0.915$) or the injury to study ($P = 0.973$) among the three groups.

Magnetic Resonance Imaging

MRI was conducted using a 3-T system (Achieva 3.0T TX QD MRI System; Philips) to obtain transaxial T1-weighted inversion recovery images [repetition time (TR), 2200 ms; echo time (TE), 9.5 ms; number of excitations, 1; inversion recovery delay, 950 ms; field of view (FOV), 23 cm × 23 cm; matrix size, 512 × 510; slice thickness, 5 mm with a 1-mm slice gap].

F-fluorodeoxyglucose Positron Emission Tomography

FDG-PET was performed within 2 weeks (either before or after) of consciousness level assessment. The PET scanner used was an Eminence STARGATE instrument (Shimadzu Corporation, Kyoto, Japan), which provides 99 transaxial images at 2.65-mm intervals. The in-plane spatial resolution (full-width at half-maximum) was 3.5 mm and the scan mode was the standard three-dimensional (3D) mode. All participants were placed in a PET scanner such that slices were parallel to the canthomeatal line. Notably, the participants fasted for at least 4 h before FDG injections. Each patient received a 3.5 MBq/kg dose of FDG administered intravenously through the cubital vein over 1 min. Then, the arterial blood radioactivity concentration was measured over time and the time curve of plasma tracer radioactivity was obtained using an FDG autoradiographic Eminence STARGATE scanner, as reported by Phelps et al.[31] Furthermore, we generated

Table 1: Summary of patient characteristics

CRS-R	Gender	Age	Interval from injury to study (days)	Structural lesions on MRI/CT	Auditory function	Visual function	Motor function	Oromotor/verbal function	Communication	Arousal
Patients with MCS+										
MCS + 9	M	45.5	118	Frontal lobe on both sides	Reproducible movement to command	Visual pursuit	Flexion withdrawal	None	None	Eye - opening without stimulation
MCS + 12	F	70.3	232	Left temporal lobe	Reproducible movement to command	Object localisation: recognition	Localisation to noxious stimulation	None	None	Eye - opening without stimulation
MCS + 11	M	20.9	283	Right parietal lobe and basal nucleus	Reproducible movement to command	Visual pursuit	Flexion withdrawal	Oral reflexive Movements	None	Eye - opening without stimulation
MCS + 10	M	26.2	148	Left temporal lobe	Reproducible movement to command	Visual pursuit	Flexion withdrawal	None	None	Eye - opening without stimulation
MCS + 19	M	37.9	156	Left temporal lobe	Reproducible movement to command	Object recognition	Object manipulation	Intelligible verbalisation	Non-functional: intentional	Eye - opening without stimulation
MCS + 10	M	56.8	358	Left frontal lobe–temporal lobe	Reproducible movement to command	Visual pursuit	Flexion withdrawal	None	None	Eye - opening without stimulation
MCS + 16	M	19.1	447	Left frontal lobe–temporal lobe	Reproducible movement to command	Object localisation: reach	Localisation to noxious stimulation	Intelligible verbalisation	Non-functional: intentional	Eye - opening without stimulation
MCS + 10	M	18.1	326	Left temporal lobe	Reproducible movement to command	Visual pursuit	Flexion withdrawal	None	None	Eye - opening without stimulation
MCS + 14	M	18.9	223	Left temporal lobe	Reproducible movement to command	Object recognition	Localisation to noxious stimulation	Oral reflexive Movements	None	Eye - opening without stimulation
MCS + 12	M	65.6	783	No focal lesions	Reproducible movement to command	Object recognition	Flexion withdrawal	None	None	Eye - opening without stimulation
MCS + 11	F	67.5	230	Both sides frontal lobe –parietal lobe	Reproducible movement to command	Object recognition	Flexion withdrawal	None	None	Eye - opening without stimulation
MCS + 12	M	36.6	220	Left temporal lobe	Reproducible movement to command	Object recognition	Flexion withdrawal	None	None	Eye - opening without stimulation
MCS + 10	M	58.4	235	Left temporal lobe	Reproducible movement to command	Visual pursuit	Flexion withdrawal	None	None	Eye - opening without stimulation

Table 1: (*Continued*)

CRS-R	Gender	Age	Interval from injury to study (days)	Structural lesions on MRI/CT	Auditory function	Visual function	Motor function	Oromotor/ver-bal function	Communication	Arousal
MCS + 10	M	22.2	216	Left-thalamus–brainstem	Reproducible movement to command	Visual pursuit	Flexion withdrawal	None	None	Eye - opening without stimulation
MCS + 10	M	67	360	Left frontal lobe	Reproducible movement to command	Visual pursuit	Flexion withdrawal	None	None	Eye - opening without stimulation
MCS + 10	M	36.5	358	Both sides frontal lobe –parietal lobe	Reproducible movement to command	Visual pursuit	Flexion withdrawal	None	None	Eye - opening without stimulation
MCS + 10	F	59.8	295	Left frontal lobe, Bilateral lobes	Reproducible movement to command	Visual pursuit	Flexion withdrawal	None	None	Eye - opening without stimulation
MCS + 10	M	20.5	333	watershed area/border zone	Reproducible movement to command	Visual pursuit	Flexion withdrawal	None	None	Eye - opening without stimulation
MCS + 10	M	22.9	328	Left temporal lobe	Reproducible movement to command	Visual pursuit	Flexion withdrawal	None	None	Eye - opening without stimulation
MCS + 10	M	47.8	220	Left brainstem	Reproducible movement to command	Visual pursuit	Flexion withdrawal	None	None	Eye - opening without stimulation

Patients with MCS−

CRS-R	Gender	Age	Interval from injury to study (days)	Structural lesions on MRI/CT	Auditory function	Visual function	Motor function	Oromotor/verbal function	Communication	Arousal
MCS-8	M	25.6	265	Left frontal lobe –temporal lobe	Auditory startle	Fixation	Localisation to noxious stimulation	None	None	Eye opening without stimulation
MCS-12	M	21	146	Right temporal lobe	Localisation to sound	Visual pursuit	Localisation to noxious stimulation	Vocalisation/oral movement	None	Eye opening without stimulation
MCS-10	M	42.7	172	corpus callosum	Localisation to sound	Visual pursuit	Localisation to noxious stimulation	None	None	Eye opening without stimulation
MCS-10	F	71.5	273	Right frontal lobe, corpus callosum	Localisation to sound	Visual pursuit	Localisation to noxious stimulation	None	None	Eye opening without stimulation
MCS-7	M	46.3	329	Left frontal lobe –temporal lobe	Auditory startle	Fixation	Flexion withdrawal	None	None	Eye opening without stimulation
MCS-11	M	27.1	255	Both sides frontal lobe –parietal lobe	Localisation to sound	Visual pursuit	Localisation to noxious stimulation	Oral reflexive Movements	None	Eye opening without stimulation

CRS-R	Gender	Age	Interval from injury to study (days)	Structural lesions on MRI/CT	Auditory function	Visual function	Motor function	Oromotor/ verbal function	Communication	Arousal
MCS-11	M	18.1	204	Left frontal lobe	Localisation to sound	Visual pursuit	Localisation to noxious stimulation	Oral reflexive Movements	None	Eye opening without stimulation
MCS-8	M	26.6	396	Right frontal lobe –temporal lobe	Auditory startle	Fixation	Localisation to noxious stimulation	None	None	Eye opening without stimulation
MCS-7	F	49.6	233	Both sides temporal lobe	Auditory startle	Fixation	Flexion withdrawal	None	None	Eye opening without stimulation
MCS-10	M	80.7	319	Both sides temporal lobe, parietal lobe	Localisation to sound	Visual pursuit	Localisation to noxious stimulation	None	None	Eye opening without stimulation
MCS-10	M	31.4	229	Both sides of the frontal lobe	Localisation to sound	Visual pursuit	Localisation to noxious stimulation	None	None	Eye opening without stimulation
MCS-7	M	59.4	177	Both sides frontal lobe –parietal lobe	Auditory startle	Fixation	Flexion withdrawal	None	None	Eye opening without stimulation
MCS-7	M	25.2	299	Right frontal lobe –temporal lobe	Auditory startle	Fixation	Flexion withdrawal	None	None	Eye opening without stimulation
MCS-10	M	52.4	274	Both sides temporal lobe, parietal lobe	Localisation to sound	Visual pursuit	Localisation to noxious stimulation	None	None	Eye opening without stimulation
MCS-8	F	22.7	483	Right frontal lobe –temporal lobe	Auditory startle	Visual pursuit	Flexion withdrawal	None	None	Eye opening without stimulation
Patients with VS										
CRS-R	Gender	Age	Interval from injury to study (days)	Structural lesions on MRI/CT	Auditory function	Visual function	Motor function	Oromotor/ verbal function	Communication	Arousal
VS-6	M	48.6	231	Brainstem	Auditory startle	Visual startle	Flexion withdrawal	None	None	Eye opening without stimulation
VS-6	M	21.6	218	Both sides of the frontal lobe	Auditory startle	Visual startle	Flexion withdrawal	None	None	Eye opening without stimulation
VS-1	F	28.4	580	Both sides frontal lobe –temporal lobe	None	None	None/Flaccid	None	None	Eye opening with stimulation
VS-6	F	75.1	219	Both sides frontal lobe, brainstem	Auditory startle	Visual startle	Flexion withdrawal	None	None	Eye opening without stimulation
VS-1	F	23.6	228	Right frontal lobe –temporal lobe	None	None	None/Flaccid	None	None	Eye opening with stimulation

(Continued)

Table 1: (*Continued*)

CRS-R	Gender	Age	Interval from injury to study (days)	Structural lesions on MRI/CT	Auditory function	Visual function	Motor function	Oromotor/verbal function	Communication	Arousal
VS-2	F	76.7	105	No focal lesions	Auditory startle	None	None/Flaccid	None	None	Eye opening with stimulation
VS-2	M	16.2	831	The left cerebellum and frontal lobe, both sides of the parietal lobe	None	None	Abnormal posturing	None	None	Eye opening with stimulation
VS-2	M	30.6	220	No focal lesions	None	None	Abnormal posturing	None	None	Eye opening with stimulation
VS-2	M	55.7	368	Both sides occipital lobe and midbrain, left cerebellum	Auditory startle	None	Abnormal posturing	None	None	Eye opening with stimulation
VS-2	M	32.4	296	Left frontal lobe –temporal lobe	None	None	Abnormal posturing	None	None	Eye opening with stimulation
VS-3	M	18.4	271	Left frontal lobe –temporal lobe	Auditory startle	None	Abnormal posturing	None	None	Eye opening with stimulation
VS-4	M	27.5	391	Left frontal lobe –temporal lobe	Auditory startle	Visual startle	Abnormal posturing	None	None	Eye opening without stimulation
VS-3	F	87.6	156	Left frontal lobe –temporal lobe, medulla oblongata, right Parietal lobe	Auditory startle	None	Abnormal posturing	None	None	Eye opening with stimulation
VS-5	M	29.8	123	Left temporal lobe, pons, both sides frontal lobe	Auditory startle	Visual startle	Abnormal posturing	None	None	Eye opening without stimulation
VS-3	M	52.5	601	Both sides frontal lobe –temporal lobe	Auditory startle	None	Abnormal posturing	None	None	Eye opening with stimulation

CT=computed tomography; MCS=minimally conscious state; MRI=magnetic resonance imaging; VS=vegetative state.
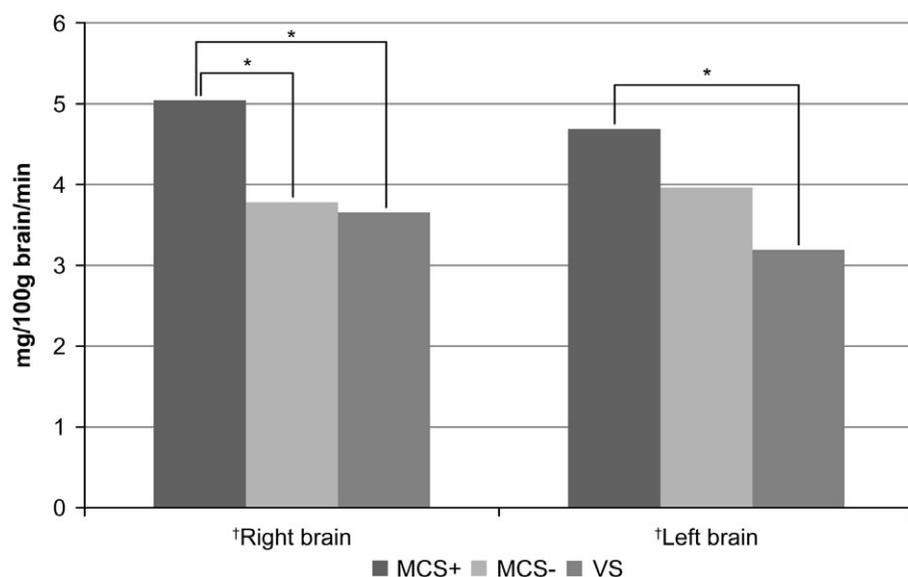
Figure 1: The regional cerebral metabolic rate of glucose (CMRGlu) values in the right and left hemispheres. The regional CMRGlu values were markedly lower in both brain hemispheres in patients with more deteriorated consciousness levels, as assessed using analysis of variance (ANOVA; †). The regional CMRGlu value in the right hemisphere was markedly higher in MCS+ patients than in MCS− patients, as assessed by multiple comparisons using the Tukey method. Conversely, the regional CMRGlu values were similar between both patient groups in the left hemisphere. We observed no significant differences in regional CMRGlu values between MCS patients and VS patients in either the right or left hemispheres after multiple comparisons. *$P < 0.01$.

a quantitative image representing the regional glucose metabolic from the frame and the time-activity curve of the local tracer PET measurements.

To analyse regions of interest (ROIs), FDG images were atlas-based parcellated into ROIs through a 3D stereotactic ROI template (3D-SRT; Fujifilm RI Pharma, Tokyo Japan). The embedded 3D-SRT software normalised the FDG images for the ROI analysis per SPM2 algorithm. Next, we acquired regional CMRGlu measurements in the following 12 brain regions of each hemisphere: the corpus callosum, precentral region, central region, parietal region, angular gyrus, temporal region, occipital region, pericallosal region, lenticular nucleus, thalamus, hippocampus and cerebellum.

Statistical Analysis

First, we determined the presence or absence of homogeneity of variance using Levene's test and then analysed differences in the regional CMRGlu values between the right and left hemispheres and in the 12 brain regions for each hemisphere among the three patient groups (MCS+, MCS− and VS) using analysis of variance (ANOVA) or Welch's test. Second, significant between-group regional CMRGlu differences identified by ANOVA were further analysed by multiple comparisons using the Tukey method and significant differences highlighted by Welch's test were further analysed by multiple comparisons using the Games–Howell method. In this study, all *P* values were two-sided and $P < 0.05$ was considered statistically significant. Furthermore, all statistical analyses were performed using SPSS ver. 26 (IBM).

Ethics

The Institutional Research Ethics Committee of Kizawa Memorial Hospital approved this study (Approval number 30-039. 12/6/2018), which was performed in accordance with the Declaration of Helsinki. We obtained written informed consent regarding participation in this study and the publication of study results from a family member of each participant.

Results

Comparison of CMRGlu Values among the MCS+, MCS− and VS Groups

Regional CMRGlu values in both the right and left hemispheres decreased with deteriorating levels of consciousness among patients ($P = 0.002$, ANOVA; Figure 1; Table 2). In the right hemisphere, regional CMRGlu values decreased with deteriorating levels of consciousness in 11 of 12 regions examined, including the corpus callosum ($P = 0.015$, ANOVA), central region ($P = 0.007$, ANOVA), parietal region ($P = 0.001$, ANOVA), angular gyrus ($P = 0.001$, ANOVA), temporal region ($P = 0.007$, ANOVA), occipital region ($P < 0.001$, ANOVA), pericallosal region ($P = 0.001$, ANOVA), lenticular nucleus ($P = 0.029$, Welch's test), thalamus ($P = 0.003$, ANOVA), hippocampus ($P = 0.047$, ANOVA) and cerebellar hemisphere ($P = 0.037$, ANOVA; Figure 2). We observed no statistically significant differences in regional CMRGlu values in the precentral region ($P = 0.068$, ANOVA).

In the left hemisphere, the regional CMRGlu values reduced with increasing deterioration of consciousness in 11 of 12 regions examined, including the corpus callosum ($P = 0.024$, ANOVA), central region ($P = 0.037$, ANOVA), parietal region ($P = 0.002$, ANOVA), angular gyrus ($P = 0.040$, ANOVA), temporal region ($P = 0.012$, ANOVA), occipital region ($P < 0.001$, ANOVA), pericallosal region ($P = 0.001$, Welch's test), lenticular nucleus ($P = 0.008$, ANOVA), thalamus ($P = 0.001$, ANOVA), hippocampus ($P = 0.008$, ANOVA) and cerebellar hemisphere ($P = 0.005$, ANOVA; Figure 3). We observed no significant differences in regional CMRGlu values in the precentral region ($P = 0.098$, ANOVA).

Comparison of CMRGlu Values between the MCS+ and MCS− Groups

The CMRGlu value in the right hemisphere was significantly higher in the MCS+ group than in the MCS− group ($P = 0.009$); however, no significant difference was observed in the regional CMRGlu value in the left hemisphere between MCS+ patients

Table 2: Regional cerebral glucose metabolic rates in each brain hemisphere

CMRGlu	Levels of consciousness		
	MCS+	MCS−	VS
Right hemisphere (mg/100 g hemisphere/min)*	5.04 ± 0.81	3.78 ± 0.71	3.66 ± 0.59
Left hemisphere (mg/100 g hemisphere/min)*	4.64 ± 0.72	3.96 ± 0.74	3.19 ± 0.68

CMRGlu=cerebral metabolic rate of glucose; MCS=minimally conscious state; VS=vegetative state.

*$P = 0.002$ (ANOVA).

and MCS− patients (Figure 1). In the right hemisphere, the regional CMRGlu values were significantly higher in the MCS+ group than in the MCS− group in the corpus callosum ($P = 0.028$), parietal region ($P = 0.008$), angular gyrus ($P = 0.004$), temporal region ($P = 0.014$), occipital region ($P = 0.044$), pericallosal region ($P = 0.005$) and thalamus ($P = 0.007$; Figure 2). We observed no regions with significantly different regional CMRGlu values in the left hemisphere between the MCS+ and MCS− groups (Figure 3).

Comparison of CMRGlu Between the MCS− and VS Groups

We found no significant differences in regional CMRGlu values between the MCS− and VS groups in either the right or left hemispheres (Figure 1). In the right hemisphere, no significant regional differences were observed in CMRGlu values between the MCS− and VS groups (Figure 2). In the left hemisphere, the regional CMRGlu value in the occipital region was significantly higher in the MCS− group than in the VS group ($P = 0.013$; Figure 3).

Discussion

CMRGlu in Patients with Chronic DOCs

Regional CMRGlu measurements obtained by FDG-PET have been used as indirect neuronal activity indices. In patients with chronic DOCs, CMRGlu values declined with increasing deterioration in the level of consciousness compared with those in healthy individuals. In a separate FDG-PET study, Thibaut et al.[27] demonstrated that VS patients exhibited metabolic dysfunctions in both the thalamus and the wide cortical network that encompasses the extrinsic/lateral (the bilateral posterior parietal and prefrontal areas) and the intrinsic/medial (the precuneus area and adjacent posterior cingulate cortex and the mesiofrontal area and adjacent anterior cingulate cortex) networks compared with the functions noted in healthy controls. Nevertheless, metabolic dysfunction in MCS patients was limited to both the thalamus and the intrinsic/medial network compared with the metabolic function observed in healthy controls.[27] In our study, CMRGlu values in VS patients displayed larger reductions than those in MCS patients relative to standard values. Nakayama et al.[26] reported that FDG-PET imaging of patients with diffuse brain injury-induced chronic DOCs presented marked bilateral hypometabolism in the medial prefrontal region and medial frontobasal region, as well as in the anterior and posterior regions of the cingulate gyrus and thalamus. Moreover, VS patients demonstrated more extensive hypometabolism than MCS patients, especially in the medial prefrontal and medial frontobasal regions.[26]

In an FDG-PET study, Stender et al.[32] reported that VS patients, MCS patients and patients emerging from MCS presented mean CMRGlu values that were 38%, 56% and 63% that of the mean

CMRGlu values observed in healthy individuals. In other studies, the overall cortical metabolism rate in VS patients was 30%–50% of the standard range for healthy individuals.[33–38] These metabolic levels were comparable with those observed in healthy subjects undergoing deep anaesthesia and those detected during stages II–IV of non-REM sleep.[39,40]

In an FDG-PET study by Hatazawa et al.,[41] the mean CMRGlu values in the cortical grey matter, basal ganglia and centrum semi-ovale of healthy individuals were 5.17, 4.92 and 2.67 mg/100 g brain/min, respectively. In this study, the mean regional CMRGlu values in the right and left hemispheres were 5.04 and 4.64 mg/100 g brain/min in the MCS+ group, 3.78 and 3.96 mg/100 g brain/min in the MCS− group and 3.66 and 3.19 mg/100 g brain/min in the VS group, respectively. These values corresponded to 89.7%–97.5%, 73.1%–76.6% and 61.7%–70.8, respectively, of the regional CMRGlu values reported in the cortical grey matter of healthy individuals.[41] In our study, the CMRGlu values decreased with increased deterioration in the levels of consciousness, corroborating Stender et al.[32] In addition, we observed significant differences in regional CMRGlu values among the three levels of consciousness in both the right and left hemispheres and in 11 of 12 (91.7%) anatomical regions examined in each hemisphere (as revealed by ANOVA or Welch's test), thereby supporting the validity of the classifications used (MCS+, MCS− and VS) to assess consciousness levels in patients with chronic DOCs.

Differences in CMRGlu Between the MCS+ and MCS− Groups

The clinical discrimination between MCS+ and MCS− depends on the patients' ability to communicate using linguistic/paralinguistic methods. In MCS+ patients, motivation to engage in communication is paramount and precedes the execution of verbal and motor functions during communication, which involves the left hemisphere. The potential of the right hemisphere to promote communication has been recognised in recent decades, including the motivation to engage in communication, recognition of proverbs, humour and metaphors and recognition of paralinguistic methods of communication, such as body language, gestures, facial expressions, tone and pitch.[42–44]

In this study, regional CMRGlu values were markedly higher in the MCS+ group than in the MCS− group in both the whole brain and 7 of 11 regions in the right hemisphere, supporting the idea that the preserved right hemispheric function, rather than the left hemispheric function, could be essential to initiate attention to verbal stimulation and stimulate communication. Bruno et al.[45] reported that MCS+ patients demonstrated markedly higher metabolism than MCS− patients in Broca's and Wernicke's regions and the left premotor, left caudate and post- and precentral cortices. In contrast, we observed no significant differences in CMRGlu values between the MCS+ and MCS− groups in any left hemisphere regions examined. These discordant results are attributable to differences in the statistical and quantitative analyses performed between studies. During communication, regional CMRGlu values in the left hemisphere, which encompasses verbally dominant functions, could be higher than those in the right hemisphere among MCS+ patients, although we did not perform such a functional analysis in this study.

Differences in CMRGlu Between the MCS− and VS Groups

The clinical discrimination between MCS and VS is based on patients' awareness of the external environment. MCS− patients
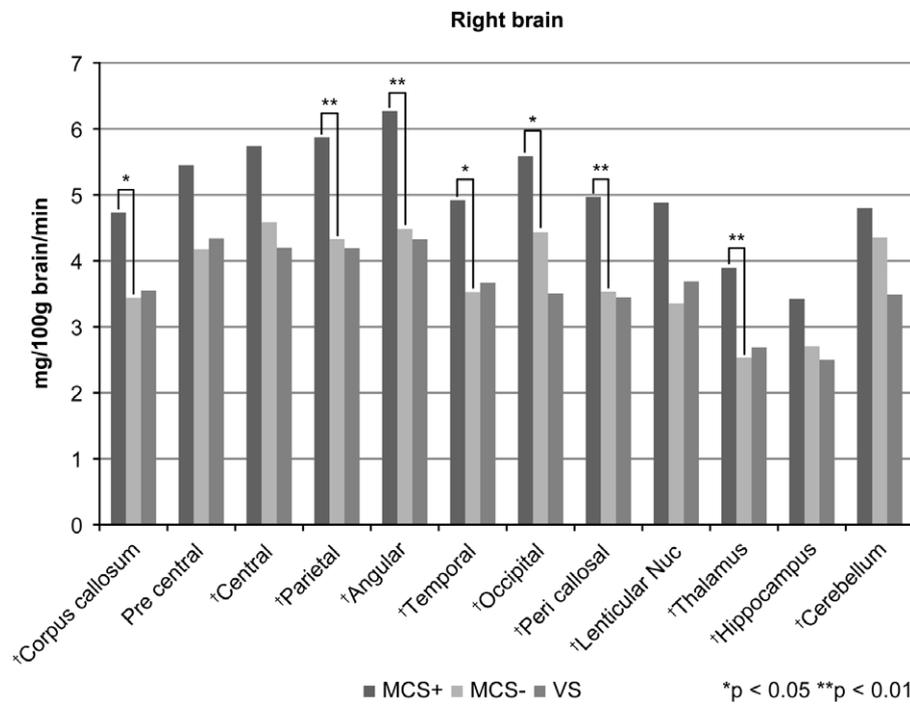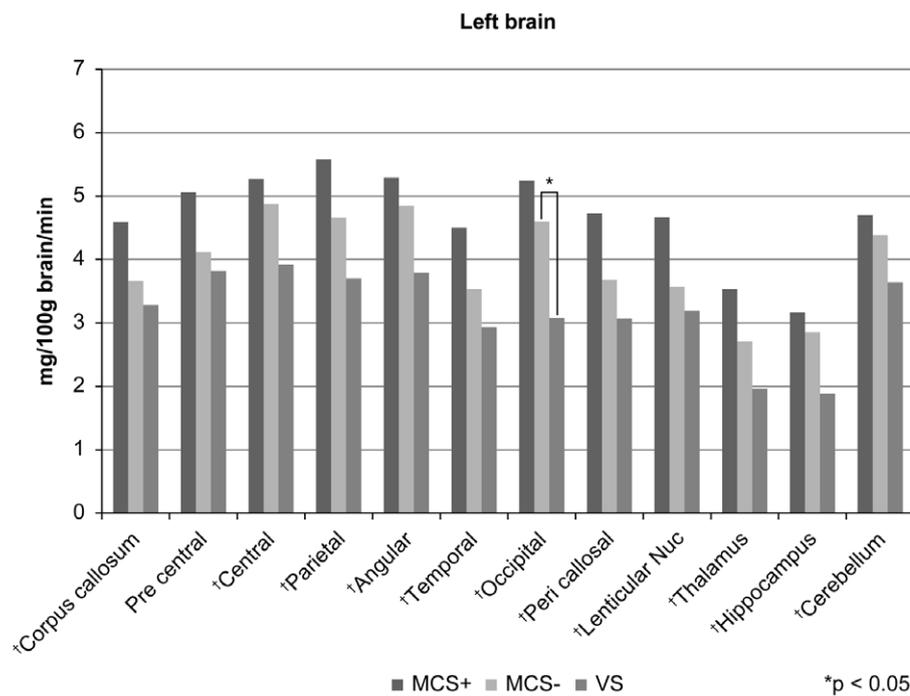
Figure 2: Table regional cerebral metabolic rate of glucose (CMRGlu) values in 12 regions in the right hemisphere. Regional CMRGlu values declined with increased consciousness deterioration in 11 of 12 (91.7%) regions examined, as assessed by analysis of variance (ANOVA)/Welch's test (†). Multiple comparisons revealed that the regional CMRGlu values were markedly higher in MCS+ patients than in MCS− patients for 7 of 11 regions that exhibited significant differences in the initial analysis. We found no regions with significant differences in regional CMRGlu values between MCS patients and VS patients. Using the Games–Howell method, multiple comparisons were performed in the right lenticular nucleus and left pericallosal region and the Tukey method for multiple comparisons of the remaining 20 regions. $*P < 0.05$, $**P < 0.01$.

Figure 3: Regional cerebral metabolic rate of glucose (CMRGlu) values in 12 regions in the left hemisphere. Regional CMRGlu values declined as consciousness levels deteriorated in 11 of 12 (91.7%) regions examined, as assessed using analysis of variance (ANOVA)/Welch's test (†). After multiple comparisons, we found no regions in the left hemisphere with significant differences in regional CMRGlu values between MCS+ patients and MCS− patients. Nevertheless, the regional CMRGlu value was significantly higher in MCS patients than in VS patients in the left occipital region. Multiple comparisons were performed using the Games–Howell method in the right lenticular nucleus and left pericallosal region and the Tukey method in the other 20 regions. $*P < 0.05$.

can recognise the environment using all five senses, and visual function is the most commonly used in this context. The complexity of neural representations increases as visual information passes through the visual hierarchy. Visual information is received and processed into a visual image by the primary visual cortex, located in the occipital lobe. Then, visual images are analysed and recognised, as particular objects or human faces, by neurons in the visual association cortex. Hildebrandt et al.[46] reported that patients who recovered from hypoxia-induced VS demonstrated higher perfusion in the visual cortex and precuneus than those with permanent VS using technetium-99 m ethyl cysteinate dimer single-photon emission computed tomography ($^{99\,m}$Tc-ECD-SPECT), concluding that occipital and parietal lobe perfusion might represent critical characteristics for distinguishing between VS patients and patients emerging from VS. In this study, the regional CMRGlu value was markedly higher in the left occipital region in MCS− patients than in VS patients. These findings indicate that patients who exhibit preserved visual function in the occipital region are more likely to be aware of their external environments.

Behavioural assessment of each patient is generally performed on the day of admission to our hospital. Because it is a specific examination that requires booking, it was difficult to perform FDG-PET on the same day as admission. The behavioural condition of patients is assumed to be stable within 2 weeks before/after the FDG-PET examination because the patients were in the chronic phase.

Limitations

First, our study sample lacked massive focal brain damage, as assessed by MRI, implying that their principal pathology was severe diffuse brain injury, in which axonal injury is highly likely, occurring at the cerebellar peduncle, brainstem and deep structures of the cerebral hemispheres. The brainstem comprises the reticular activating system, which dominates consciousness. As we did not measure the regional CMRGlu values in the brainstem, further studies should address this limitation.

Second, of the 50 patients enrolled in this study, 4 (8% of the total population) were left-handed. Around 95% of normal, right-handed people and nearly 80% of left-handed people have left hemispheric language dominance.[47] As 8% is a small proportion of the enrolled patients, we do not believe that the enrolment of these individuals affected the laterality of language dominance in our results. Nevertheless, the possibility that a similar study on left-handed patients exclusively might provide different results cannot be excluded. Hence, further studies with larger cohorts are essential to validate the correlation between the level of consciousness and regional CMRGlu values in patients with chronic DOCs.

Conclusions

In this study, regional CMRGlu values were lower in patients with chronic DOCs than in healthy individuals, corroborating the related literature. In addition, metabolism decreased with increased deterioration in the level of consciousness for most bilateral brain regions examined. Thus, this study suggests that the awareness of the external environment correlates with the preservation of the left occipital function and that the motivation to communicate correlates with the preservation of function in extensive areas of the right cerebral hemisphere among patients with TBI-induced chronic DOCs.

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Noriko Usami, the corresponding author of the work, certifies that all authors have participated sufficiently in the conception and design of the work and were involved in the acquisition of data. All authors have also participated in the analysis and interpretation of the data, as well as the drafting of the work. All authors also revised the work and contributed to the final approval of the version for publication. Each author also agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part are appropriately investigated and resolved.

Conflicts of Interest. The authors have no conflicts of interest to declare.

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