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Case Report Open Access

Multidisciplinary Rehabilitation in Combination with Repetitive Transcranial Magnetic Stimulation in a Patient with Apathy Following Traumatic Brain Injury: A Case Report

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Abstract

Currently, few reports are available on rehabilitation treatment combined with repetitive transcranial magnetic stimulation (rTMS) in patients with higher brain dysfunctions. Here, we report the case of a patient with apathy following traumatic brain injury, who underwent rehabilitation in combination with rTMS.

The patient is a 31-year-old woman who was diagnosed with higher brain dysfunction with symptoms of apathy and attentional deficit based on clinical symptoms and neuropsychological examinations. Single-photon emission computed tomography (SPECT) revealed decreased blood flow in the medial frontal lobe.

The patient was hospitalized for two weeks of inpatient treatment. Low-frequency rTMS was applied over the right dorsolateral prefrontal cortex (DLPFC) and administered at 90% of minimum motor threshold for the upper limb motor area, 1 Hz, for 40 minutes once daily (2,400 pulses per day) excluding Sunday, and a total of 12 rTMS treatments were implemented.

In addition, a physiotherapist and an occupational therapist provided rehabilitation treatment. The treatment outcomes were classified using the Apathy Evaluation Scale, Clinical Assessment of Attention Deficit (CAT), and SPECT. The easy Z-score Imaging System (eZIS), fine stereotactic regions of interest template (FineSRT), and three-dimensional stereotactic region of interest template (3DSRT) were used to analyze SPECT images.

The patient completed the two weeks of multidisciplinary rehabilitation treatment in combination with rTMS without the occurrence of adverse events, and achieved improvements in the Apathy Evaluation Scale, CAT score, and blood flow in the medial frontal lobe, angular gyrus, head of caudate nuclei, and posterior cingulate gyrus in SPECT images.

We successfully treated a patient with apathy following traumatic brain injury with multidisciplinary rehabilitation treatment combined with rTMS, and confirmed the safety and efficacy of this treatment approach. SPECT scans confirmed improvement in cerebral blood flow.

Keywords: Apathy; Repeated transcranial magnetic stimulation; Intensive physical therapy; Traumatic brain injury

Introduction

Our study group became aware at quite an early stage of the possibilities of repetitive transcranial magnetic stimulation (rTMS) as a treatment option to improve brain plasticity and promote functional reconstruction [1-3], and have implemented studies with applications in treatment. We have considerable experience especially in rehabilitation treatment in combination with rTMS for stroke or aftereffects of head injuries (paralysis of the upper or lower limbs, aphasia) [4-6]. Currently, treatment using rTMS is widely being studied not only for sequelae of stroke but also for neurological or psychiatric disorders such as depression, Parkinson's disease, and chronic pain [7]. The efficacy of rTMS, especially for drug-resistant depression, has been reported worldwide [8-10], and is also expected to be covered by health insurance in Japan. In treatments for depression, high-frequency (10 Hz) and high-intensity (100% to 130% of minimum motor threshold) rTMS over the left dorsolateral prefrontal cortex (DLPFC) [11] or low-frequency (1 Hz) and high-intensity (100% to 130% of minimum motor threshold) rTMS over the right DLPFC [12] is often selected.

There are some reports on rehabilitation treatment in combination with rTMS for higher brain dysfunction, including one that indicated the efficacy of high-frequency rTMS for apathy [13]. In that study, rTMS was selected at high-frequency (10 Hz) and low-intensity (90% of the minimum motor threshold) over the anterior cingulate gyrus.

Here, we present our experience with a patient with apathy following a head injury, whom we successfully treated with rehabilitation in combination with low-frequency and low-intensity rTMS, and confirmed improved parameters in neuropsychological examinations and cerebral blood flow scintigraphy.

Case Presentation

The patient is a 31-year-old woman. Nine months prior to visiting our hospital, the patient had a car accident that caused a concussion and traumatic cervical disc herniation. Although the head CT taken immediately after the accident did not reveal apparent structural lesions, the patient started to present symptoms of clouded consciousness and excessive somnolence with 12 hours or more of sleep in a day, immediately after the injury. The patient also showed other persistent symptoms including distractedness, hypobulia, aspontaneity, akinesia, and athymia. The patient was a speech therapist and suspected higher brain dysfunction based on her own symptoms. Because such diagnosis was not made at the acute or recovery care hospitals, the patient visited our outpatient clinic for higher brain dysfunction.

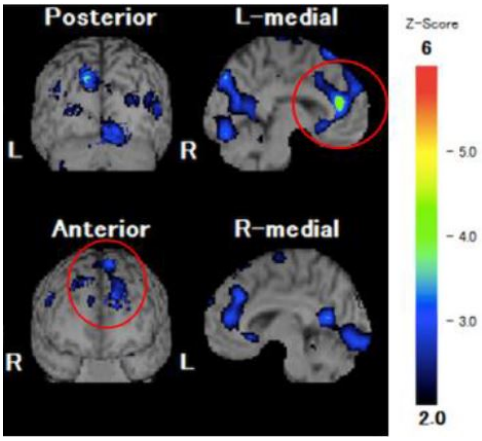

Figure 1a: SPECT before treatment (analyzed by e-ZIS).

Although no abnormal findings were obtained in the head MRI test upon a visit at our clinic, decreased blood flow in the frontal lobe was found in a single photon emission computer tomography (SPECT) examination, when analysed using the Easy Z-score Imaging System (eZIS) (Figure 1a).

Decrease in cerebral blood flow of about 3 to 4 Z - Score is observed in the area surrounded by red circles.

Neuropsychological examinations, including the Apathy Evaluation Scale and Clinical Assessment of Attention Deficit (CAT) scoring, revealed the presence of apathy and attention deficit (Table 1).

Digit Span (digit)	Forward	9	9
	Backward	9	9
Tapping Span (digit)	Forward	9	8
	Backward	8	7
Visual Cancellation (%)	3: Correct answer rate	99.1	100
	LP : Correct answer rate	100	100
Visual Cancellation (sec)	3: Time required	67	60
	Time required	88	73
Auditory Detection (%)	Correct answer rate	82	100
	Correct answer rate	57	100
SDMT (%)	Achievement rate	59	76.4
3 span:			
Memory Updating (%)	Correct answer rate	93	100
4 span:			
	Correct answer rate	81	100
PASAT (%)	2 seconds condition:	91	98
	Correct answer rate		
	1 seconds condition:		
	Correct answer rate	63	76
Position Stroop (%)	Correct answer rate	99.1	100
Position Stroop (sec)	Time required	68	51
CPT (msec) SRT	Average reaction time	304.7	326.9
X	Average reaction time	486.1	476.5
AX	Average reaction time	491.6	475.6

Table 1: Results of apathy scale and CAT before and after treatment.

Based on these findings, the patient was diagnosed with higher brain dysfunction (apathy and attention deficit) due to diffuse brain injury.

Treatment for the patient was approved by the ethical committee of this hospital and implemented after obtaining written informed consent from the patient.

Methods

MagVenture MagPro R30 magnetic stimulator and a MagVenture butterfly coil were used for the treatment. The patient was hospitalized to receive two weeks of inpatient treatment. For rTMS therapy, low-frequency magnetic stimulation was applied over the right dorsolateral prefrontal cortex (DLPFC) and administered at 90% of minimum motor threshold for the right upper limb motor area, 1 Hz, for 40 minutes once daily (2,400 pulses per day) excluding Sunday, and a total of 12 rTMS treatments were implemented (Table 2).

	Monday	**Tuesday - Saturday**	**Sunday**	**Monday - Friday**	**Saturday**
A.M.	Hospitalization	rTMS	None	rTMS	rTMS
	Evaluation at hospitalization	Individual OT		Individual OT	Individual OT
	Lunch break			Lunch break	
P.M.	rTMS	Individual PT,OT		Individual PT,OT	Evaluation and guidance at discharge

	Individual 0T	Voluntary training	Voluntar y training	Discharge	
The duration of hospitalization was 2 weeks, and daily rTMS and individual exercises were conducted except Sunday; OT: Occupational Therapists; PT: Physical Therapists					

Table 2: rTMS combined rehabilitation treatment protocol.

The daily rehabilitation treatment included 40-minute aerobic or muscle-strengthening exercise instructed by a physiotherapist and 80-minute self-instruction or problem-solving training with an occupational therapist, which were implemented every day excluding Sunday. In addition, outing training on Sunday was voluntarily implemented.

The treatment outcome was classified using the Apathy Evaluation Scale, Clinical Assessment of Attention Deficit (CAT), and SPECT. The software used for SPECT analysis included the easy Z-score Imaging System (eZIS) for qualitative analysis [14], and the fine stereotactic regions of interest template (FineSRT) and three-dimensional stereotactic regions of interest template (3DSRT) for quantitative analysis [15-17].

Regarding eZIS, Z-score is calculated based on the following formula: Z-score=([control mean voxel value]-[individual voxel value])/(control standard deviation [SD]). For example, "Z-score=3" indicates that the voxel value for the subject is lowered by 3SDs compared to the control mean value. In eZIS images, Colors corresponding to the Z-score are added to virtual brain images without displaying numerical values. Therefore, values need to be read according to the color scale.

On the other hand, FineSRT and 3DSRT can calculate cerebral blood flow numerically for regions of interest (ROIs) in quantitative analysis. In this case, the difference in regional cerebral blood flow (rCBF) between the left and right ROI was calculated using the asymmetry index (AI) [18,19]. Because decreased blood flow in the left hemisphere was confirmed with eZIS, we set the left side as having decreased blood flow (rCBF of corresponding ROIs in ipsilesional hemispheres [rCBFI]) and the right side as the opposite side (rCBF of corresponding ROI in contralesional hemisphere [rCBFC]). AI is calculated based on the following formula: AI (%)=[(rCBFC-rCBFI)/{(rCBFC+rCBFI) × 0.5}] × 100. The rCBFC and rCBFI were set as the median rCBF (mL/100 g/min) for each ROI. An AI value of 0 to 5 is normal, and an AI value larger than 5 indicates significantly decreased blood flow. A negative AI value indicates decreased blood flow on the right side, and its absolute value was used for evaluation according to the criteria mentioned above. A bigger absolute value of AI is considered to be an indication of further decrease in blood flow. The amount of change in AI value is described as ΔAI, which is calculated based on the following formula: ΔAI=|pre-change AI|−|post-change AI|. A negative ΔAI value indicates improved blood flow, while a positive ΔAI value indicates worsened blood flow.

Results

The patient completed the two weeks of multidisciplinary rehabilitation treatment in combination with rTMS without the occurrence of adverse events. The results of neuropsychological examinations for pre- and post-treatment are shown in Table 1. The Apathy Evaluation Scale improved from 33 points to 26 points, and the CAT evaluation presented shortened task performance time and an increased percentage of correct answers. Improvements in auditory attention parameters were particularly significant.

Regarding subjective symptoms, improvements were seen in motivation and spontaneity, such as improved outing motivation and more smoothly start daily tasks. Improvements were also seen in attentional functions including sustained and divided attention, with longer concentration on a task and reduced frequency of error in dual tasks.

The SPECT results (eZIS analysis) prior to and 4 months after treatment are shown in Figures 1b and 1c.

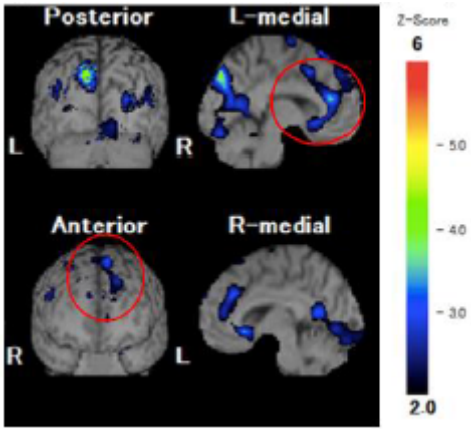

Figure 1b: SPECT after treatment (analyzed by e-ZIS) Improvement of blood flow reduction and reduction of range in the area surrounded by red circles is allowed.

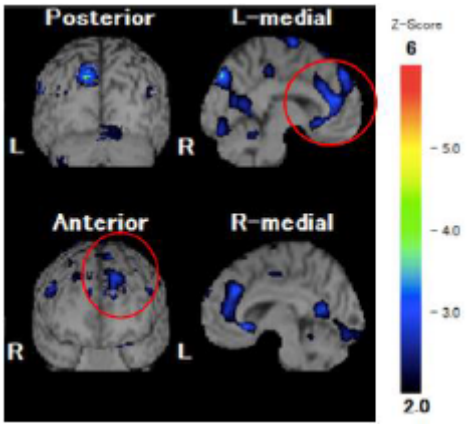

Figure 1c: SPECT after 4 months of treatment (analyzed by e-ZIS) Improvement in blood flow is maintained in the area surrounded by red circles.

When pre- and post-treatment findings were compared, shrinkage of area with decreased blood flow and improved Z-score were mainly seen in the front lobes, and the blood flow especially improved in the medial left frontal lobe (Figures 1a-1c). No aggravation of blood flow was identified in the right frontal lobe, to which rTMS was applied. In addition, improvement in the areas where decreased blood flow had been detected was maintained when evaluated 4 months after

treatment, which indicates long-term efficacy of this treatment. Results of FineSRT and 3DSRT analyses are shown in Tables 3 and 4. In pre-treatment FineSRT, the regions of interest (ROIs) in the cerebral area with AI value larger than 5 included gyrus angularis, head of caudate nucleus, and posterior cingulate gyrus (Table 3).

Segments	**pre**		**post**		**4M**		**AI**			**AAI**		
	R	L	R	L	R	L	pre	Post	4M	post-pre	4M-post	4M-pre
Superior frontal	52.64	50.99	43.71	43.14	51.13	51.48	3.18	1.31	-0.68	-1.87	-0.63	-2.5
Medial frontal	60.35	62.06	47.66	48.85	56.91	57.5	-2.79	-2.47	-1.03	-0.33	-1.43	-1.76
Paracentral lobule	61.43	62.84	52.83	52.87	62.23	62.67	-2.27	-0.08	-0.7	-2.19	0.63	-1.56
Anterior cingulate	54.8	53.83	43.67	42.62	48.89	49.88	1.79	2.43	-2	0.65	-0.43	0.22
Subcallosal	65.15	64.9	48.36	49.79	58.48	60.62	0.38	-2.91	-3.59	2.53	0.68	3.21
Orbital	53.8	52.53	47.17	48.78	55.62	57.99	2.39	-3.36	-4.17	0.97	0.82	1.78
Rectal	55.73	55.85	47.3	47.59	58.53	58.03	-0.22	-0.61	0.86	0.4	0.25	0.64
Middle frontal	60.33	61.89	47.36	48.84	55.79	55.91	-2.55	-3.08	-0.21	0.52	-2.86	-2.34
Inferior frontal	60.56	61.04	49.63	51.02	56.97	58.09	-0.79	-2.76	-1.95	1.97	-0.82	1.16
Precentral	52.59	53.85	45.33	44.92	52.09	54.13	-2.37	0.91	-3.84	-1.46	2.93	1.47
Postcentral	54.84	55	44.42	45.18	51.95	52.7	-0.29	-1.7	-1.43	1.41	-0.26	1.14
Insula	71.32	70.59	54.8	53.64	62.24	63.24	1.03	2.14	-1.59	1.11	-0.55	0.57
Superior parietal	45.34	44.93	41.27	41.21	49.85	48.35	0.91	0.15	3.05	-0.76	2.91	2.15
Inferior parietal	53.77	54.64	44.95	47.13	52.52	53.57	-1.61	-4.74	-1.98	3.13	-2.76	0.37
Supramarginal	61.01	62.22	46.63	47.69	51.98	50.85	-1.96	-2.25	2.2	0.28	-0.05	0.23
Angular	65.21	61.27	45.74	43.46	54.01	52.36	6.23	5.11	3.1	-1.12	-2.01	-3.13
Superior temporal	59.26	61.04	46.87	49.34	53.55	55.75	-2.96	-5.13	-4.03	2.18	-1.11	1.07
Middle temporal	59.87	58.9	47.64	46.65	53.54	53.16	1.63	2.1	0.71	0.47	-1.39	-0.92
Inferior temporal	56.86	55.31	42.93	41.3	48.65	48.49	2.76	3.87	0.33	1.11	-3.54	-2.43
Transverse temporal	79.82	81.2	62.21	59.95	74.94	71.12	-1.71	3.7	5.23	1.99	1.53	3.52
Superior occipital	59.73	57.54	40.92	42.18	52.66	51.11	3.73	-3.03	2.99	-0.7	-0.05	-0.75
Middle occipital	54.95	54.66	41.47	42.18	49.39	51	0.53	-1.7	-3.21	1.17	1.51	2.68
Inferior occipital	55.63	56.52	41.2	42.44	50.59	52.33	-1.59	-2.97	-3.38	1.38	0.42	1.79
Precuneus (lower)	70.73	69.72	58.92	54.77	70.31	67.49	1.44	7.3	4.09	5.86	-3.21	2.65
Cuneus	67	64.84	51.12	51.98	63.4	62.94	3.28	-1.67	0.73	-1.61	-0.94	-2.55
Hippocampus	48.27	47.93	40.54	41.49	46.79	47.39	0.71	-2.32	-1.27	1.61	-1.04	0.57
Fusiform	59.93	61.08	49.18	50.6	58.42	58.6	-1.9	-2.85	-0.31	0.95	-2.54	-1.59
Lingual	64.38	68.34	51.45	53.49	61.96	64.73	-5.97	-3.89	-4.37	-2.08	0.48	-1.59
Parahippocampal	52.85	51.4	41.57	42.77	50.27	49.66	2.78	-2.85	1.22	0.06	-1.62	-1.56
A mygdaloid body	51.56	49.78	35.78	37.34	39.89	39.71	3.51	-4.27	0.45	0.75	-3.81	-3.06
Thalamus	62.82	61.58	53.58	52.68	61.26	61.33	1.99	1.69	-0.11	-0.3	-1.58	-1.88
Putamen	69.06	71.32	55.93	55.95	63.72	64.83	-3.22	-0.04	-1.73	-3.18	1.69	-1.49

Globus pallidus	63.25	67.83	47.58	52.3	58.03	57.63	-6.99	-9.45	0.69	2.46	-8.76	-6.3
Caudate head	53.94	49.61	41.81	40.68	46.95	48.35	8.36	2.74	-2.94	-5.62	0.2	-5.43
Caudate tail	31.91	36.75	31.67	31.95	36.29	40.24	-14.1	-0.88	-10.32	-13.22	9.44	-3.78
Precuneus (upper)	58.68	60.55	49.19	47.88	58.34	57.36	-3.14	2.7	1.69	-0.44	-1.01	-1.44
Cingulate	61.79	63.43	47.46	47.41	54.23	55.31	-2.62	0.11	-1.97	-2.51	1.87	-0.65
Posterior cingulate	68.63	60.27	51.01	46.47	60.21	56.13	12.97	9.31	7.01	-3.66	-2.3	-5.96
Vermis	74.43	75.83	55	55.63	64.25	66.32	-1.86	-1.14	-3.17	-0.72	2.03	1.31
Anterior lobe	67.94	68.76	48.24	49.87	55.02	56.33	-1.2	-3.32	-2.35	2.12	-0.97	1.15
Posterior lobe	76.28	77.55	56.89	57.38	67.57	68.18	-1.65	-0.86	-0.9	-0.79	0.04	-0.75
Hypothalamus	48.78	53.21	38.33	38.15	43.76	46.87	-8.69	0.47	-6.86	-8.22	6.39	-1.82
Quadrigemini	47.61	41.07	40.67	36.36	48.75	44.92	14.75	11.19	8.18	-3.56	-3.01	-6.57
Substantia nigra	67.88	57.74	39.25	39.51	45.33	46.07	16.14	-0.66	-1.62	-15.48	0.96	-14.52
Nucleus ruber	64.75	58.49	38.37	42.27	45.75	48.51	10.16	-9.67	-5.86	-0.49	-3.82	-4.3
Pons	50.83	53.61	37.14	37.85	39.03	40.17	-5.32	-1.89	-2.88	-3.43	0.99	-2.44
Brota	62.15	62.31	49.18	51.93	56.96	58.47	-0.26	-5.44	-2.62	5.18	-2.82	2.36
Wernicke	62.72	63.8	49.89	52.07	56.21	58.86	-1.71	-4.28	-4.61	2.57	0.33	2.9
Primary visual	64.45	68.56	45.39	50.41	55.24	61.35	-6.18	-10.48	-10.48	4.3	0	4.3
Primary auditory	72.72	73.54	59.72	59.29	70.1	68.35	-1.12	0.72	2.53	-0.4	1.81	1.41
Premotor	54.01	54.46	44.1	44.97	52.85	52.8	-0.83	-1.95	0.09	1.12	-1.86	-0.74
Supplementary motor	56.63	58.2	46.59	47.54	56.43	55.55	-2.73	-2.02	1.57	-0.72	-0.45	-1.16
Improvement of A I is recognized mainly in Angular, Caudate head, and Posterior cingulate; pre: before treatment, post: after treatment, 4M : 4 months after treatment.												

Table 3: Results of FineSRT.

In the comparison of AI between pre- and post-treatment, ΔAI was smaller than 0 for both ROIs mentioned above, which indicated the efficacy of this treatment. The result of ΔAI less than 0 remained the same in comparison to AI between pre-treatment vs. 4 months after treatment. This indicates that the treatment contributed to the sustained and maintained improvement in blood flow, in other words, a long-term improving effect of the treatment. The findings in 3DSRT were similar to that in FineSRT, which confirmed that AI and ΔAI in gyrus angularis had improved and that the improvements had remained (Table 4).

Segments	pre		post		4M		AI			ΔAI		
	R	L	R	L	R	L	Pre	Post	4M	Post-pre	4M-Post	4M-Pre
Callosomarginal	56.29	55.87	45.78	45.78	53.99	54.37	0.75	0	-0.7	-0.75	0.7	-0.05
Precentral	60.45	61.78	48.33	49.9	56.3	56.98	-2.18	-3.2	-1.2	1.02	-2	-0.98
Central	53.76	54.44	44.86	45.04	52.03	53.36	-1.26	-0.4	-2.52	-0.86	2.12	1.27
Parietal	51.36	51.74	43.73	44.89	51.41	51.22	-0.74	-2.62	0.37	1.88	-2.25	-0.37
Angular	65.06	61.4	45.6	43.52	53.83	52.44	5.79	4.67	2.62	-1.12	-2.05	-3.17
Temporal	59.49	59.46	46.68	46.74	52.99	53.52	0.05	-0.13	-1	0.08	0.87	0.94
Posterior cerebral	61.77	61.62	48.2	48.74	58.46	58.72	0.24	-1.11	-0.44	0.87	-0.67	0.2
Pericallosal	61.88	62.07	48.99	47.76	56.86	56.39	-0.31	2.54	0.83	2.24	-1.71	0.52

Lenticular nucleus	66.75	69.22	52.61	54	61.41	61.37	-3.63	-2.61	0.07	-1.03	-2.54	-3.57
Thalamus	62.69	61.58	53.46	52.66	61.11	61.34	1.79	1.51	-0.38	-0.28	-1.13	-1.41
Hippocampus	48.65	48.55	40.96	42.56	47.64	48.51	0.21	-3.83	-1.81	3.63	-2.02	1.6
Cerebellum	74.48	75.6	55.07	55.75	64.93	65.59	-1.49	-1.23	-1.01	-0.27	-0.22	-0.48
Improvement of AI is recognized in Angular. pre: before treatment, post: after treatment, 4M: 4 months after treatment												

Table 4: 3DSRT results.

Discussion

In rTMS therapy for refractory depression, high-intensity stimulations (100 to 130% of the minimum resting motor threshold) are often selected [10]. Because the patient had higher brain dysfunction, with consideration for structural brain injuries and side effects such as epilepsy or headache [20,21], we implemented rTMS at a low-intensity. No adverse events such as headaches or epilepsy developed during the treatment. Patients tend to complain about headaches when treated with high-frequency or high-intensity stimulations [14]. If low-frequency and low-intensity treatments can be replaced with high-frequency and high-intensity treatments, it is likely to avoid the occurrence of headaches, which may lead to the expansion of patients indicated for rTMS treatment.

Improvement in cerebral blood flow was confirmed by comparing pre- and post-treatment SPECT images, and the improved cerebral blood flow was confirmed to have been maintained at the examination 4 months after treatment. Regarding the long-term improvement effect on cerebral blood flow, further follow-ups are needed to assess sustained improvement year after year.

In this case, we performed qualitative and quantitative analysis, taking advantage of each software characteristics. In the eZIS qualitative analysis, improved blood flow in the medial left frontal lobe was confirmed. In the FineSRT and 3DSRT quantitative evaluations, improved blood flow was confirmed in the gyrus angularis, head of caudate nuclei, and posterior cingulate gyrus. The fact that FineSRT and 3DSRT did not show improvement in frontal lobe blood flow may be explained by decreased blood flow in both frontal lobes and that the areas of ROI for the frontal lobes were relatively wide, therefore the results may have been influenced by areas with normal blood flow. Although decreased blood flow was detected in some parts of the occipital lobe, we considered this phenomenon to be a physiological response.

Regarding the targeting area and stimulation frequency in patients with declined frontal lobe blood flow, 1) high-frequency stimulation of the anterior cingulate gyrus, 2) low-frequency stimulation of the right DLPFC, 3) high-frequency stimulation of the left DLPFC, and 4) a combination of 2) and 3) are considered as an option. Although we selected the 2) approach in this case, the efficacy on cerebral blood flow regarding other treatment approaches also needs to be assessed. Further studies are required to determine the best target area and frequency for rTMS in patients with apathy, and we will continue our research.

Conclusion

In this case, we successfully treated a patient with apathy following traumatic brain injury using multidisciplinary rehabilitation in combination with low-frequency and low-intensity rTMS, and confirmed its safety and efficacy. Improved blood flow was confirmed with SPECT in the area where decreased blood flow had been detected.

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