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ARTICLE

Time-dependent decline of body-specific attention to the paretic limb in chronic stroke patients

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Abstract

Objective
To examine whether reduced body-specific attention to a paretic limb is found in chronic stroke patients in a time-dependent manner.

Methods
Twenty-one patients with chronic hemiparesis (10 left and 11 right hemiparesis) after subcortical stroke and 18 age-matched healthy controls were recruited in this study. Standard neuropsychological examinations showed no clear evidence of spatial neglect in any patient. In order to quantitatively measure spatial attention to the paretic hand, a visual detection task for detecting a target appearing on the surface of either a paretic or dummy hand was used. This task can measure the body facilitation effect, which makes faster detection of a target on the body compared with one far from the body.

Results
In stroke patients, there was no difference in the reaction time for a visual target between the paretic and the dummy hands, while the healthy participants showed faster detection for the visual target on the real hand than on the dummy one. The index of the body facilitation effect, subtracting the reaction time for the target-on-paretic hand from that for the target-on-dummy one, was correlated with the duration since onset and with finger function test on the Stroke Impairment Assessment Set.

Conclusions
The reduction of the body facilitation effect in the paretic limb suggests the decline of body-specific attention to the paretic one in patients with chronic hemiparesis. This decline of body-specific attention, leading to neglect for the paretic limb, will be one of the most serious problems for rehabilitation based on use-dependent plasticity.

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Glossary

ANOVA = analysis of variance; **CRPS** = complex regional pain syndrome; **RT** = reaction time; **SIAS** = Stroke Impairment Assessment Set.

Hemiparesis after stroke can markedly reduce quality of life.[1] Many patients with hemiparesis initially stop using their paretic limb to avoid failure and inconvenience. Over time, as patients become used to compensating for the paretic limb, attempts at use further decline, known clinically as learned nonuse.[2–4] Learned nonuse can worsen the motor impairment of the paretic limb due to use-dependent neuroplasticity.[5,6] Although learned nonuse is a serious factor preventing motor recovery in a paretic limb, we do not know how learned nonuse affects motor function of the paretic limb or decreases its use in daily lives.

In the complex regional pain syndrome (CRPS), pain evoked when moving the affected limb causes patients to stop attempting to use the affected limb and further ignore the limb despite having no brain damage and spatial-attention impairment, which is called neglect-like syndrome.[7,8] Similarly, in stroke patients, reduced attention directed specifically to the paretic limb, defined here as body-specific attention, would also coexist with learned nonuse of the limb.[9] However, the body-specific attention to the paretic limb cannot be measured quantitatively. Previous studies reported that a visual detection task can measure the spatial attention to body by the body facilitation effect, which is making faster detection for a target nearer the body.[10,11] Here we examined if reduced body-specific attention to a paretic limb is found in chronic stroke patients by using the visual detection task. Furthermore, we explored the major factors of the patient and clinical characteristics explaining the attentional declines.

Methods

Participants

We performed a cross-sectional study of prospectively collected data in Tohoku University Hospital, Japan. Twenty-one patients with chronic hemiparesis as the first stroke participated in this experiment (mean age ± SD, 60.6 ± 8.9 years; 15 male; 11 right hemiparesis; 20 right-handed, table). Patients with (1) cortical stroke, (2) global aphasia, (3) attentional bias to the left or right visual field, which can be found in unilateral spatial neglect, (4) hemianopia, or (5) serious uncontrolled medical conditions were excluded. To confirm the absence of the attentional bias to the visual field, all patients completed 2 conventional spatial neglect screening tests, horizontal line bisection,[12–14] and the computer version of the cancellation task.[15] From 2011 to 2014, 28 patients were recruited from Tohoku University Hospital and 7 patients were excluded by the criteria. The lesions of the patients were restricted to the subcortical areas including putamen, internal capsule, corona radiate, thalamus, pallidum, and caudate nucleus. We assessed motor, sensory, and visuospatial functions using the Stroke Impairment Assessment Set (SIAS).[12–14] The knee mouth test of the motor items in the SIAS set was used to evaluate proximal parts of the paretic upper limb, such as a shoulder and arm (score: 0 = worst to 5 = best), and the finger function test to evaluate the distal parts, such as fingers (scores: 0, 1A, 1B, 1C, 2, 3, 4, 5), where higher scores indicates milder severity of paresis.[12–14] Patients had not received intensive rehabilitation programs of their upper limb for at least 1 month when participating in this study.

Eighteen age-matched healthy adults (9 male; 16 right-handed; mean age 60.9 ± 11.3) were recruited as a control group.

Standard protocol approvals, registrations, and patient consents

The Tohoku University ethics committee approved this research (ID 2010-203, 2011-572), which was conducted with the ethical standards of the Declaration of Helsinki. Prior to our experiment, all participants agreed to participate in our experiment and provided written informed consent.

Experimental procedure

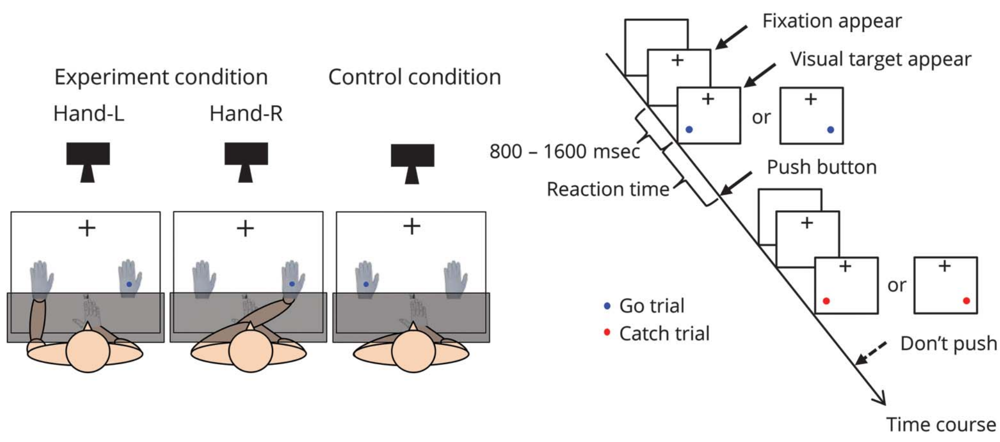
To measure body-specific attention to the paretic limb in stroke patients, we used a visual detection task designed for measuring the body facilitation effect for detecting a visual target near the body, previously tested on healthy adults.[10,11,16–18] Participants sat in front of a table in a quiet room and were required to respond to a visual target that appeared on either the patient's paretic hand or a dummy hand, both of which were placed on the table (figure 1A). To minimize differences in appearance between the real (paretic) and dummy hands, both hands were covered by white cotton gloves. We projected a visual target on the back of the patients' hands and a fixation point on the table from a projector attached to the ceiling. The response button was blinded under the desk and located at the same distance from each visual target on the table and at the center of a participant. The participants pushed a button with the nonparetic hand as soon as the visual target appeared. A blue-filled circle representing a "go" visual target appeared in the 80% of the trials, and in the rest of trials a red-filled circle representing a "no-go" target that required no response appeared. The visual target had a visual angle of 1.7° located 18 cm away from a midsagittal plane. The distance between the fixation and the projected visual target was 28 cm, and the distance from the projected visual target to the participants was 28 cm. The dummy hand was placed 36 cm away from a real hand on the table. At the beginning of each trial, participants were instructed to gaze at the fixation point. A visual target appeared randomly from 800 to 1,600 ms after the fixation point appeared on the table. Reaction time (RT) was defined as the time between the

Table Clinical characteristics of patients with chronic hemiparesis

ID	Age, y	Sex	Handedness	Paresis side	Cause	Lesion location	Duration, mo	Finger function test	Knee mouth test	SIAS total score	Tactile sensation	Sense of position	Index of body facilitation effect
S1	60	M	R	R	I	P, IC, CR	27	1A	2	57	Normal	Normal	−6.6
S2	67	F	R	R	H	P, T, CR	50	1B	3	47	Mild	Mild	12.3
S3	41	M	R	R	H	P, T, CR	32	1C	1	41	Moderate	Loss	31.0
S4	50	F	R	L	H	P, IC	24	4	2	54	Normal	Normal	40.5
S5	49	M	R	L	H	P, IC, CR	54	2	4	65	Normal	Normal	−1.1
S6	46	M	L	L	H	CR	7	4	4	71	Normal	Normal	16.9
S7	71	F	R	L	I	IC, CR	80	1B	4	56	Normal	Normal	4.3
S8	68	M	R	R	H	P, IC, T	153	1A	3	37	Loss	Moderate	−27.4
S9	66	M	R	L	H	P, IC, T	36	3	4	46	Mild	Moderate	11.2
S10	52	M	R	R	I	P, IC, CR, Pa, CN	58	3	4	67	Moderate	Moderate	10.6
S11	64	M	R	R	H	T	47	2	3	42	Mild	Mild	16.3
S12	64	M	R	R	H	CR	10	1C	3	43	Normal	Normal	10.3
S13	67	M	R	L	H	P, IC, CR, T	192	1A	2	47	Loss	Loss	−1.4
S14	60	F	R	L	I	P, CR	35	2	2	55	Normal	Normal	6.8
S15	71	F	R	L	I	P, IC, CR, Pa	51	1A	1	49	Normal	Normal	5.5
S16	68	M	R	R	I	P, CR	51	1A	3	51	Normal	Normal	−5.2
S17	61	M	R	R	I	P, Pa	59	1A	2	50	Normal	Mild	3.1
S18	50	F	R	L	H	P, CN	47	1A	2	41	Moderate	Moderate	−25.1
S19	68	M	R	R	H	T	116	4	5	66	Mild	Normal	−2.0
S20	65	M	R	L	I	P, CR	44	1A	1	45	Mild	Normal	−8.1
S21	65	M	R	R	H	P, IC, T	28	1A	3	47	Mild	Normal	19.9
Mean	60.6					Median	47	1B	3	49			5.5
SD	8.9					Range	7–192	1A–4	1–5	37–71			−27.4 to 40.5

Abbreviations: CN = caudate nucleus; CR = corona radiata; H = hemorrhage; I = infarction; IC = internal capsule; P = putamen; Pa = pallidum; SIAS = stroke impairment assessment set; T = thalamus.

Figure 1 Experimental setup and the visual detection task



(A) Experimental conditions and control condition. These schematic views show the hand-L, hand-R, and control conditions for patients with left hemiparesis. The patients placed their paretic hand either on the left side (hand-L) or right side (hand-R). In both conditions, the dummy hand was placed opposite to the paretic hand. In the control condition, the paretic hand was placed near the abdomen. For patients with right hemiparesis, in the hand-L condition, the right paretic hand was placed to the left of midline. (B) Visual detection task. After the fixation point appeared, the visual target randomly appeared from 800 to 1,600 ms, on 1 of 2 hands (paretic or dummy hand). Participants pushed the button only when a blue-filled circle appeared.

onset of the visual target and the reaction of the participants pushing the button (figure 1B).

Experimental design

At first, to examine the effects of hand position and target position on RT for detecting a target, we employed 2 (hand position) × 2 (visual target position) as within-subject factors, × 2 (group) as a between-subject factor in the experimental condition. For the hand position condition, the participants placed their paretic hand either on the left side (hand left condition: hand-L) or right side (hand right condition: hand-R) of the central fixation point and the visual target appeared either on the left side (target-L) or the right side (target-R) regardless of the side of hemiparesis. In other words, in hand-L, patients with left hemiparesis placed their left (paretic) hand on the left position, while the patients with right hemiparesis placed their right (paretic) hand on the left position. In the hand-L and hand-R conditions, the dummy hand was placed opposite to the paretic hand (figure 1A). In the control condition, we also measured RT using 2 dummy hands, placed in the left and right positions (the paretic hand was placed on the participant's abdomen) in order to measure the attentional bias between the left and right hemispaces. For comparison with the patients' data, we measured the RT for age-matched healthy controls using their nondominant hands, in the same way as for the stroke patients.

In the experiment, participants performed 160 trials of the experimental condition (hand-L: 80 trials, hand-R: 80 trials) and 80 trials of the control condition. Before the experiment, the participants performed 60 trials as a training session for the visual detection task. The order of hand positions (hand-L and hand-R), and the experimental and control conditions, were counterbalanced across participants. Patients and controls were separately exposed to tests in a counterbalanced way.

Statistical analyses

For elucidating the body facilitation effect of the paretic hand, we performed a 3-way mixed analysis of variance (ANOVA) (hand position, visual target position, and group). If there was an interaction effect among the 3 factors (hand position, visual target position, and the group), we contrasted the RT of the paretic hand (nondominant hand in the healthy group) to that of a dummy hand using a 2-way ANOVA with repeated measures and multiple comparisons, as a post hoc test with the Bonferroni correction. In the control condition, we used paired *t* tests to compare the RTs of both sides. Furthermore, to examine what patient-specific factors affected attention to the paretic hand, we analyzed the correlation between the index of body facilitation effect, calculated from subtracting the RT with a real hand from that of a dummy hand, and patients' characteristics such as age, duration since onset, finger function test, knee mouth test, tactile sensation, position sense, and SIAS total score with Pearson product-moment correlation coefficients. In addition, we classified the patients into high and low groups based on scores of the body facilitation effect. In the comparison between the 2 groups, patients' clinical characteristics and imaging data were compared by using the Mann-Whitney *U* test and the χ^2 test, respectively. Statistical significance was set at $p < 0.05$.

Data availability statement

The data that support the findings of this study are openly available from Dryad (reaction times and characteristics in both healthy controls and patients, doi.org/10.5061/dryad.hs3q65d).

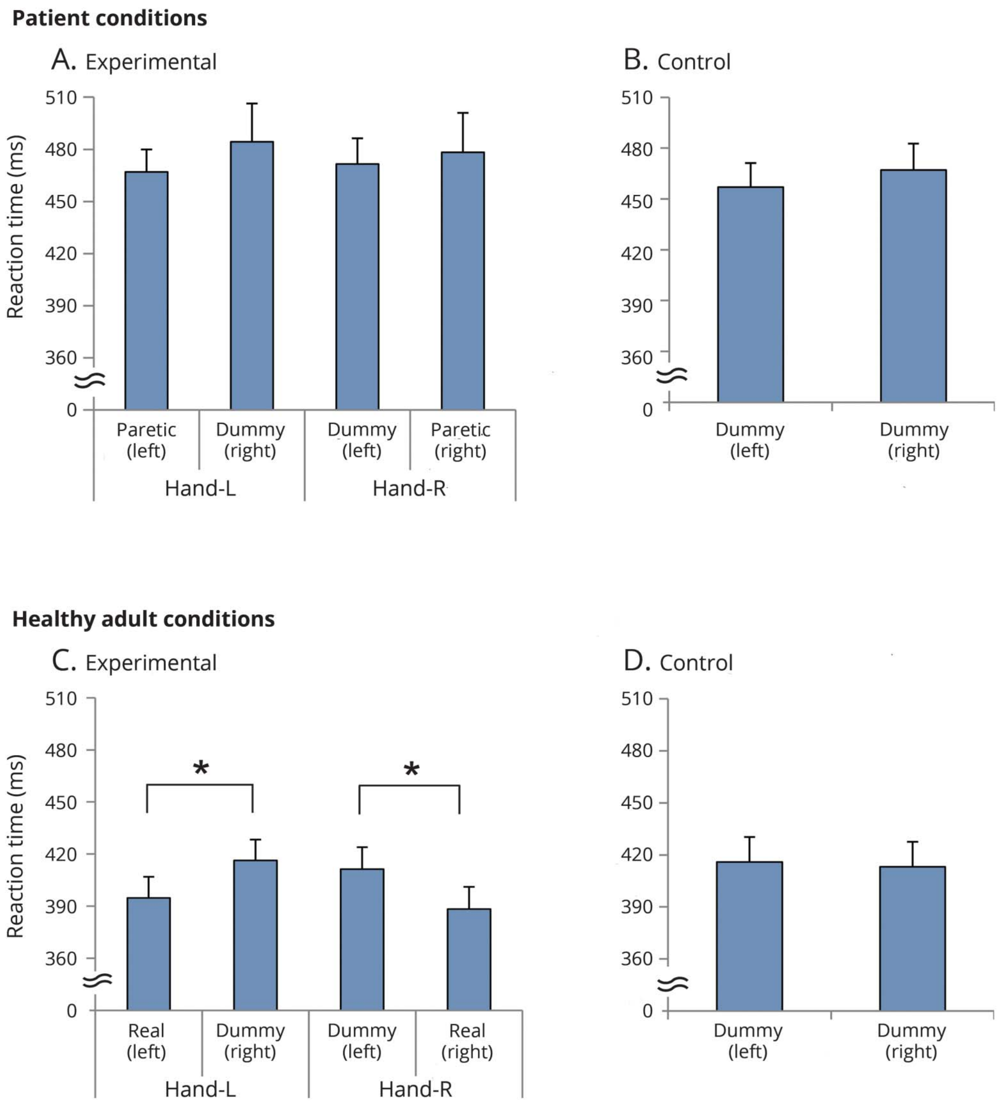
Results

Three-way mixed ANOVA showed a statistically significant interaction term (3 factors: hand position, visual target position, and the group, $F_{1,37} = 13.24$, $p < 0.01$) and main effect (group, $F_{1,37} = 11.78$, $p < 0.01$). Thus, we performed 2-way ANOVA with repeated measures for each group (patients and healthy controls). ANOVA (figure 2, A and C) of patients and healthy adults showed that there was no main effect for the factors (patients: hand position $F_{1,20} = 0.017$, $p = 0.899$, visual target position $F_{1,20} = 0.601$, $p = 0.447$; healthy adults: hand position $F_{1,17} = 1.676$, $p = 0.213$, visual target position $F_{1,17} = 0.037$, $p = 0.851$). Only in healthy adults was there an interaction between hand position and visual target position (healthy adults: $F_{1,17} = 57.185$, $p < 0.001$; patients: $F_{1,20} = 2.347$, $p = 0.141$). In multiple comparisons with the Bonferroni correction, the RT of the real hand was shorter than that of the dummy hand in the hand-L ($p < 0.001$) and hand-R conditions ($p < 0.001$) in healthy adults. In the control condition, there was no difference in RT between the dummy hand in patients and healthy controls (figure 2, B and D).

The average incorrect response in the patient group was 0.95 times in the "no-go" target (16 trials) and 0.69 in the healthy control group, showing no difference in the incorrect response times between the patients and healthy controls. The horizontal line-bisection task and the cancellation task showed no attentional bias in any patient.

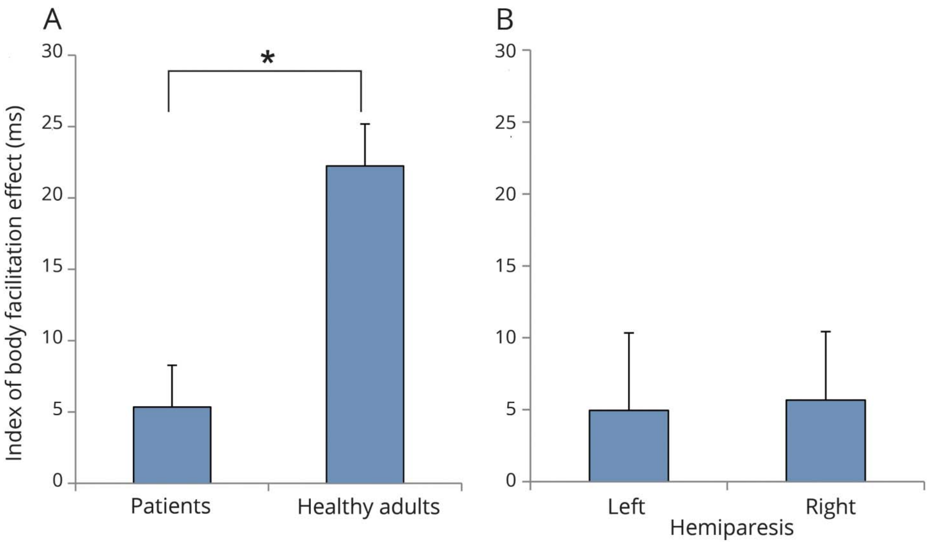
For clarity of the analysis, we used the difference in RTs between real and dummy hands (referred to as index of the body

Figure 2 The reaction time of patients with hemiparesis and healthy controls



Result of the visual detection task in patients with hemiparesis (A, B) and healthy controls (C, D) are shown. Reaction time of real hand was shorter than that of dummy hand in hand-L ($p < 0.001$) and hand-R conditions ($p < 0.001$) in healthy controls (C), but this facilitated effect was not found in the paretic hand of patients (A). In the control condition, there was not a significant difference in reaction time between the dummy hands in patients and healthy controls. Asterisks depict significant post hoc tests at $p < 0.001$ and the error bar represents standard error.

Figure 3 Comparison of the indexes of body facilitation effect



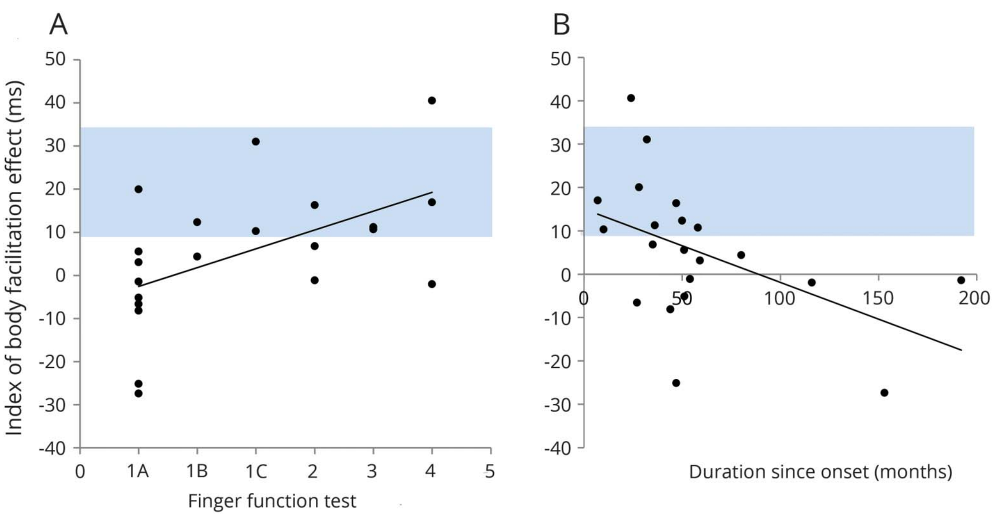
The patients' indexes were lower than those of healthy controls ($p < 0.001$, A). No difference was found in the indexes of body facilitation effect between patients with left and right hemiparesis (B). Asterisks depict significant *t* tests at $p < 0.001$; the error bar represents standard error.

facilitation effect). Comparing the indexes of body facilitation effect, the patients (5.3 ± 3.9 ms, mean ± SE) scored lower than the healthy adults (22.2 ± 2.9 ms) ($t = 3.709$, $df = 37$, $p < 0.001$, figure 3A). No difference was found in the indexes of body facilitation effect, lesion location, age, duration since onset, finger function test, knee mouth test, tactile sensation, position sense in subscale, and total sore in SIAS between left and right hemiparesis groups (figure 3B).

The correlation analysis showed the correlations between the index of body facilitation effect and the finger function test ($r = 0.489$, $p = 0.025$, figure 4A), and the duration since onset ($r = -0.481$, $p = 0.027$, figure 4B). No correlation was found between these 2 factors.

By the score of the body facilitation effect, we classified the patients into the high and low groups, resulting in 2 almost equal-size groups, 11 patients in the low group and 10 in the high one. There was a statistically significant difference in the duration since onset (low group; median = 54 months, high group; median = 33.5 months, $p = 0.012$) and finger function test (low group; median = 1A, high group; median = 4, $p = 0.024$). The other characteristics did not reach a statistical difference between the 2 groups.

Figure 4 Correlation analysis of the index of body facilitation effect



The index of body facilitation effect was positively correlated with the finger function test ($r = 0.489$, $p = 0.025$, A) and was negatively correlated with the duration since onset ($r = -0.481$, $p = 0.027$, B). The black dots represent individual patients. The gray area represents the mean ± SD of the index of body facilitation effect in healthy controls.

Discussion

We quantitatively evaluated the decline of body-specific attention to the paretic hand in 21 stroke patients with chronic hemiparesis using a visual detection task. The relationship between the body facilitation effect of the paretic hand and clinical characteristics of the patients was examined. Our result did not show a facilitative effect of the RT to the visual target on the paretic hand compared to the dummy one in the stroke patients, while the effect was found in healthy controls. Our study also showed that patients with low body-specific attention to the paretic hand had more severe finger function and longer time since onset. Thus, it is suggested that body-specific attention to the paretic limb declined in a time-dependent manner, according to the severity of the motor impairment.

Indeed, there is a possibility that stroke-induced brain damage caused the decline of the body-specific attention to the paretic limb in our study, but this possibility could be low, because (1) we found no difference in the body facilitation effect between the left- and right-hemisphere-damaged patients. Specifically, no dominant effect of the right hemisphere in attentional function was found. (2) Lesion locations in the patients had no influence on the index of the body facilitation effect. (3) Neuropsychological tests for spatial neglect, the line-bisection test,[12–14] and the canceling task[15] found no attentional deficits in the participants. Taken together, these results showed that brain damage was not the direct factor for the decline of body-specific attention.

The correlation analysis showed that decline of body-specific attention was related to duration since onset and severity of the paresis, which was confirmed by direct comparison between the 2 groups (high and low body facilitation groups). These results suggest that this attentional decline occurred as a result of learned nonuse, which is learning to avoid using the paretic limb by treating the paretic limb as useless for daily tasks.[3,4] The strong correlation between attentional decline and the duration since onset demonstrated a time-dependent decline of body-specific attention since onset. This is because the longer time since onset has passed, the more failures and mistakes the patients experience when using the paretic hand in their daily lives, leading to disuse of the paretic limb.[4,19] Even though moving the paretic limb to some extent, the patients will use not the paretic limb but the intact limb to perform an action by actively inhibiting the use of the paretic limb, resulting in decreasing attention to, or neglecting, the paretic limb.

We found a statistically significant correlation between the severity of paresis and the attentional decline, showing that patients with more severe motor impairments have larger attentional declines to the paretic hand. Patients with severe impairment will quickly learn to consider the paralyzed limb as useless due to the greater restriction on their movement in daily life.[4] Previous animal studies[20,21] reported that sensory deafferentation after damage to the afferent pathway gradually causes disuse and motor impairment of the affected limb without damaging the motor network. This is because the animals with sensory deafferentation learned that they could not control their deafferented limb due to the absence of sensory feedback, leading to disuse of the deafferented limb.[3] In addition, it has been reported that patients with CRPS, which caused pain in the affected limb on movement, exhibited limb nonuse and neglect-like symptoms.[7,8] The patients learned not to move their affected limb because of repeated experiences of strong pain in the limb during movement.[9] In our study, the 2 patients with more severe motor impairments (1A in the SIAS score) had significantly delayed RT to the target on the paretic hand, compared to the dummy one. This significant delayed RT might be caused by preventing the patients from redirecting attention to the paretic limb, which is consistent with the neglect-like syndrome in CRPS. These findings showed that motor impairment by brain damage led to learning that the paretic limb was no longer useful for daily activities.

Previous studies reported that there was strong relationship between motor deficits and lesion volume only in the acute phase,[22–24] and not in the chronic one,[25] because motor function following stroke changed gradually from that observed in the acute phase. In many cases, motor function could be worsened by learned nonuse. Our correlation analysis and previous studies suggest that declines of body-specific attention to the paretic hand were caused by the learned nonuse, which was responsible for the disuse of the paretic limb.

As for the sensory input, tactile and positional sense of the paretic limb were not correlated with the decline of the index of body facilitation effect to the paretic hand. However, previous studies on monkeys reported that after deafferentation, the monkeys tended not to use the deafferented limb due to learned nonuse.[3,4] This deafferentation-induced disuse of the paretic limb might have been derived not from sensory loss per se, but from a motor deficit of the paretic limb caused by sensory loss. Other animal studies[3,26] reported that bilateral deafferentation in a monkey was less likely to cause disuse of the deafferented limbs than unilateral deafferentation. This suggests that forced use of the deafferented arm in bilateral deafferentation prevented disuse of the arm due to use-dependent plasticity. From these findings, it is assumed that limb nonuse in patients with sensory deficit is mainly caused by associating failure or clumsiness with the paretic limb brought about by inaccurate motor control with inadequate sensory feedback. Thus, our finding of no correlation between sensory function and the index of body facilitation effect of the paretic hand indicates the tight connection between the body-specific attention to the paretic limb and motor function of the paretic limb.

This study showed that time-dependent decline of body-specific attention to the paretic limb was found in chronic stroke patients. This decline is a serious problem for rehabilitation because reductions in body-specific attention to the paretic limb potentially cause patients to neglect the paretic limb. Further studies are needed to discover ways to prevent the decline of this body-specific attention to the paretic limb in order to facilitate rehabilitation of motor symptoms in patients following stroke.

Author contributions

Naoki Aizu: study concept and design, acquisition of data, analysis and interpretation of data. Yutaka Oouchida: study concept and design, analysis and interpretation of data. Shinichi Izumi: study supervision.

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Disclosure

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