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ORIGINAL ARTICLE

Impact of Sensory Impairment on Improvement of Upper-limb Function in Patients under 75 Years of Age with Subacute Stroke: A Preliminary Study

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Objectives: The aim of this study was to investigate whether an interaction exists between sensory impairment and age with respect to the recovery of upper-limb function in patients with subacute stroke. **Methods:** This retrospective observational study included 83 patients recovering from subacute stroke in a rehabilitation hospital ward. The recovery of upper-limb function in four groups classified by age and sensory impairment were compared using analysis of covariance. Furthermore, multiple regression analysis was performed with recovery of upper-limb function as the dependent variable and with binarized sensory impairment and binarized age and their interaction term as the independent variables. **Results:** The estimated marginal means of upper-limb recovery were significantly higher in the non-late elderly (≤74 years) without sensory impairment group than in the other three groups. No significant differences were observed among the following three groups: the non-late elderly with sensory impairment, the late elderly (≥75 years) without sensory impairment, and the late elderly with sensory impairment. In multiple regression analysis, the interaction term between sensory impairment and age was significantly associated with improvement in upper-limb function (β=0.16, $P<0.05$). Age alone was significant, but sensory impairment alone was not significant. **Conclusions:** Sensory impairment in patients with subacute stroke affects the recovery of upper-limb function as a result of age interactions.

Key Words: interaction; rehabilitation; sensory impairment; stroke; upper limb function

INTRODUCTION

The recovery of upper-limb function is one of the major requirements of stroke patients[1] and constitutes the core element of stroke rehabilitation.[2] To predict the appropriate prognosis and to develop effective rehabilitation in stroke patients, it is important to clarify the factors related to the improvement of upper-limb function. Previous systematic reviews and meta-analyses reported that there was strong evidence that initial motor impairment, motor-evoked potentials, and somatosensory-evoked potentials were associated with improved upper-limb recovery.[3–5]

Previous studies have reported that sensory function has important implications for the prognosis of upper-limb function[6–9] and activities of daily living in patients with subacute stroke.[10–12] Furthermore, patients who need relearning and compensation for lost motor function may benefit from sensory therapies.[9,13] However, approaches to alleviate sensory impairment to improve the upper-limb function in patients with subacute stroke have not been adequately implemented in clinical rehabilitation.[11,12] One of the reasons why sensory impairment therapy is not widespread may be uncertainty

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regarding its benefits to patients. Bolognini et al.[9] pointed out that it was still unknown whether and how the clinical characteristics of the patients (e.g., stage of illness, severity of motor disorders, lesion location, hemorrhagic vs. ischemic stroke, and the presence of sensory or cognitive deficits) could be used to predict the efficacy of sensory therapy for motor recovery. This knowledge has implications on the optimization of sensory-based training, including the choice of sensory modality to be targeted, and the selection of patients who may benefit.[9] Considering this background, it would be meaningful to be able to identify patients with subacute stroke for whom sensory impairment therapy is appropriate to improve the upper-limb function; i.e., patients whose improvement in sensory impairment leads to a better prognosis for upper-limb function.

Both sensory impairment and age are considered to be factors associated with the recovery of upper-limb function (despite the evidence being inconclusive).[5] The authors considered that the effects of sensory impairment on upper-limb function improvement may vary with age. In other words, we believe that the interaction between sensory abilities and age is involved in improving upper-limb function. This hypothesis is based on the fact that in recent years it has become clear that the interactions among mental and physical functions are strongly associated with independent self-care and gait in patients with subacute stroke.[14,15] Previous studies[14,15] have reported that when both factors (e.g., knee extension strength and sensory function) were above or below the reference values, interactions occurred that promoted or diminished the independence of gait and self-care. Similarly, it cannot be denied that the combination of multiple factors can result in interactions, such as synergistic effects and offsetting effects in the recovery of upper-limb function. Consequently, factors such as sensory impairment and age, which are suggested to be independently associated with the recovery of upper-limb function (despite the evidence being inconclusive), may interact to affect the recovery of upper-limb function. However, no report has focused on the overlapping effects (interactions) of sensory impairment and other factors on upper-limb recovery.

The purpose of this study was to investigate whether interactions exist between sensory impairment and age with respect to the recovery of upper-limb function in patients with subacute stroke. The results of this study may help identify patients in whom improvement in sensory impairment would contribute to a good prognosis for upper-limb function. Therefore, this study should provide basic knowledge for selecting patients for whom the approach of improving sensory impairment to enhance upper-limb function can be used.

MATERIALS AND METHODS

The participants were 83 patients with subacute stroke who were admitted to and discharged from a convalescent rehabilitation ward of our hospital between April 2011 and December 2017. **Figure 1** shows the participant selection process. The inclusion criteria for this study were (1) diagnosis with initial cerebral hemorrhage or cerebral infarction, (2) diagnosis with unilateral supratentorial lesions, (3) ability to perform the Simple Test for Evaluating Hand Function (STEF), as described below,[16] at admission (i.e., STEF score ≥1), (4) grip strength of greater than 0.5 kg on the affected side, (5) STEF reassessment around 1 month (between 20 and 40 days) after the admission assessment, and (6) no missing analytical data. Exclusion criteria included (1) 100 points on STEF (the maximum score) at the time of admission or reassessment to prevent the ceiling effect, (2) STEF scores lower by six points or more at reassessment compared with scores at admission (because some events, such as shoulder pain, might have reduced upper-limb function), (3) difficulty in maintaining a sitting position at the time of admission, and (4) moderate or high pain levels. The institutional review boards of Kita-Fukushima Medical Center and Fukushima Medical University approved this study (No.72, 2020–081). Because the design of the study was retrospective and without intervention, the opt-out method was used instead of informed consent.

This study was a retrospective observational study, and information about demographics and stroke-related factors was collected from the medical records. Age, sex, affected side, type of stroke (cerebral hemorrhage or infarction), time from onset of stroke to admission evaluation, and time from admission evaluation to re-evaluation were collected as the background factors of the participants. The STEF score was used as an index of upper-limb function on the affected side. The STEF consists of 10 subtests that quantify the execution time required for the movement of objects of various sizes, shapes, and materials, to generate scores of upper-limb function between 0 and 100 points (higher scores indicated better functioning). The STEF is a reliable and validated assessment tool,[16] and it is sensitive to changes when used for patients with subacute stroke.[17] Sensory function of the affected upper-limb was assessed using the sensory items of the Stroke Impairment Assessment Set (SIAS).[18] The SIAS sensory items included the light touch and position sense

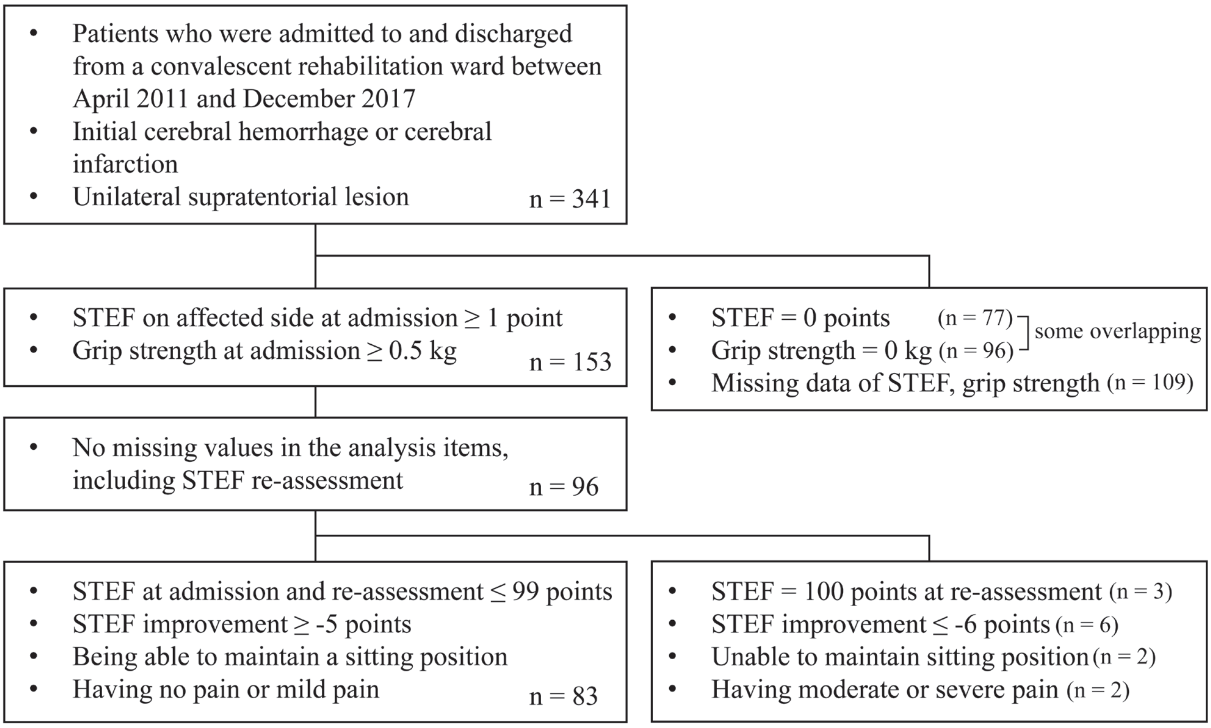

Fig. 1. Flowchart of the selection criteria for the study participants. STEF, the Simple Test for Evaluating Hand Function.

test. The SIAS light touch test was performed on the palm of the hand using a brush. A score of 3 was normal, 2 indicated mild hypoesthesia or dysesthesia, 1 indicated moderate or severe hypoesthesia, and 0 indicated anesthesia. The SIAS position sense test assessed the presence or absence of movement and its direction when the thumb was passively moved. A score of 3 indicated that the patient could correctly identify the direction, even if the movement was less than 10% of the range of motion. If the patient could correctly perceive the direction of a moderate excursion (10% or more of the range of motion), the score was 2. A score of 1 meant that the patient recognized movement of the digits but not the correct direction, even at maximal excursion; and a score of 0 was assigned if the patient could not detect the maximum possible motion.[18)]

Additional mental and physical functions, such as the gross motor function of the upper-limb, the range of motion of the upper-limb joints on the affected side, pain levels, trunk function, and visuospatial perception were assessed using the respective SIAS items. Cognitive function was assessed using the revised Hasegawa Simple Intelligence Scale (HDS-R).[19)] STEF was used to collect data at two time points, i.e., at admission and 1 month later, to assess the degree of recovery in upper-limb function and other indicators recorded at the time of admission.

In this study, sensory impairment was binarized to its absence (3 points in both SIAS sensory items) or presence (2 points or less in one or both items), and age was binarized to late elderly (75 years or older) or non-late elderly (74 years or younger). Participants were classified into four groups according to the combination of binarized sensory impairment and age. Except for sensory impairment and age, comparisons between groups were performed for background factors and mental and physical functions at admission. Comparisons among groups were done using one-way analysis of variance, the Kruskal–Wallis test, the chi-square test, or Fisher's exact test. Next, analysis of covariance was performed to compare the degree of improvement in upper-limb function among the four groups after adjusting for confounding variables. The improvement in the STEF score was set as the dependent variable, and variables that showed significant differences in comparisons between the groups (by one-way analysis of variance, Kruskal-Wallis test, or chi-square test) were set as the moderator variables. If the correlation between the independent and moderator variables was 0.4 or higher, one variable was excluded to avoid multicollinearity.[20)] Bonferroni's correction was used for multiple comparisons after analysis of covariance.

Subsequently, multiple regression analysis (forced injection) was performed to investigate whether there is an interaction between sensory impairment and age for improvement in upper-limb function. The dependent variable was the improvement in the STEF score, and the independent variables were as follows: the binarized sensory impairment, the binarized age, and the interaction term created by these two variables. To avoid multicollinearity, mean centering was performed when creating the interaction terms. In addition, as was done in the analysis of covariance, background factors and mental and physical function items at admission that were significantly different in comparisons between groups were input as adjustment variables. SPSS Statistics version 25.0 software was used for the statistical analysis, and the level of significance was set at $P < 0.05$.

RESULTS

Table 1 shows the background factors and mental and physical functions of the 83 participants in this study. Participants were 73.3 ± 12.2 (mean ± SD) years old, and 49% were late elderly (≥75 years), 58% were male, and 63% were right-side affected. The types of strokes were cerebral hemorrhage in 22% and cerebral infarction in 78% of participants. The STEF at admission was 57.0 ± 29.8 points, and 49% of participants had sensory impairment. As a result of comparisons between the four groups categorized according to sensory impairment and age, significant differences were found in stroke type, upper-limb gross motor function (SIAS knee–mouth and finger function tests), upper-limb range of motion, upper-limb function (STEF) at admission and reassessment, and cognitive function (HDS-R).

Among the variables that were significantly different in the comparisons between groups, the correlation coefficient between SIAS knee–mouth test, finger function tests, and STEF at admission was 0.4 or more. The STEF score at admission was chosen for further analysis because of its clinical significance, and SIAS knee–mouth and finger function tests were excluded as moderator variables. As a result of analysis of covariance using these four variables as moderator variables (stroke type, upper-limb range of motion, STEF at admission, and cognitive function), the estimated marginal mean STEF improvement values were 26.9 ± 2.9 (mean ± SE) points in the non-late elderly without sensory impairment, 15.1 ± 2.7 points in the late elderly without sensory impairment, 15.1 ± 2.7 points in the non-late elderly with sensory impairment, and 14.9 ± 3.0 points in the late elderly with sensory impairment. The estimated marginal mean STEF improvement values were significantly higher in the non-late elderly without sensory impairment group than in the other groups (**Fig. 2**). Moreover, no significant difference was observed among the non-late elderly with sensory impairment, the late elderly without sensory impairment, and the late elderly with sensory impairment groups. Investigation of the interaction between sensory impairment and age by multiple regression analysis showed that the interaction term between sensory impairment and age was significantly associated with improvement in upper-limb function ($\beta=0.16$, $P < 0.05$, **Table 2**). Age alone was also significant ($\beta=0.17$, $P < 0.01$), but sensory impairment alone was not significant ($\beta=0.16$, $P=0.06$). The adjusted R^2 value was 0.58.

DISCUSSION

In this study, we analyzed interaction effects with a focus on sensory impairment and age, both of which were unclear factors with respect to recovery of upper-limb function in patients with subacute stroke. As a result, it was shown here for the first time that sensory impairment in patients with subacute stroke may affect the recovery of upper-limb function because of its interaction with age. Specifically, the present study suggested that the absence or presence of sensory impairment was associated with the recovery of upper-limb function in the non-late elderly (≤74 years).

A previous systematic review and meta-analysis reported that the evidence was inconclusive for an association between sensory impairment and upper-limb recovery.[5] Van der Lee et al.[21] reported that the effects of forced-use therapy on upper-limb function were greater in patients with sensory impairment than in patients without sensory impairment. Consequently, the association between sensory impairment and improvement of upper-limb function were still undefined. The relationships between age and upper-limb function improvement are not also well understood. A systematic review and meta-analysis[5] suggested that younger people were more likely to have better upper-limb recovery, but the evidence was inconclusive. Another systematic review[22] concluded that there was conflicting evidence regarding the impact of age on functional outcomes, length of stay, discharge destination, and mortality after stroke. In the multiple regression analysis carried out in the current study, age was significantly associated with upper-limb function recovery, but the presence or absence of sensory impairment was not significant. Conversely, we found that the age–sensory impairment interaction term was associated with improved upper-limb function. In this multiple regression analysis, we

Table 1. Demographic and stroke-related factors of the subjects

	Overall (n=83)	No sensory deficit		Sensory deficit		P-value
		≤74 years (n=20)	≥75 years (n=22)	≤74 years (n=22)	≥75 years (n=19)	
Age						
Years, mean (SD)	73.3 (12.2)	63.5 (9.3)	84.0 (5.1)	63.3 (7.7)	83.1 (4.4)	
Late elderly (≥75 years), %	49					
Sensory function						
SIAS U/L light touch, points, median (IQR)	3.0 (2.0–3.0)	3.0 (3.0–3.0)	3.0 (3.0–3.0)	2.0 (1.8–2.0)	2.0 (1.0–2.0)	
SIAS U/L position sense, points, median (IQR)	3.0 (2.0–3.0)	3.0 (3.0–3.0)	3.0 (3.0–3.0)	2.0 (2.0–3.0)	2.0 (1.0–3.0)	
Sensory impairment, %	49					
Sex, male, %	58	65	55	59	53	0.86
Affected side, right, %	63	55	68	59	68	0.76
Stroke type, hemorrhage, %	22	5	14	41	26	<0.05†
Time from stroke onset to assessment at admission, days, mean (SD)	32.2 (11.8)	32.0 (7.2)	29.8 (9.5)	34.1 (16.5)	34.4 (12.8)	0.34
Time from assessment at admission to reassessment, days, mean (SD)	28.6 (3.9)	28.8 (5.0)	28.3 (3.5)	27.7 (4.1)	29.0 (3.4)	0.70
Grip strength	14.3 (8.8)	14.9 (8.4)	13.8 (8.9)	15.9 (9.8)	12.3 (8.2)	0.61
Motor function of upper limb						
SIAS knee–mouth test	4.0 (4.0–5.0)	4.0 (3.3–5.0)	5.0 (5.0–5.0)	4.0 (3.0–5.0)	4.0 (3.0–5.0)	<0.01
SIAS finger function test	4.0 (4.0–5.0)	4.0 (3.0–4.8)	5.0 (4.0–5.0)	4.0 (3.0–5.0)	4.0 (4.0–5.0)	<0.05
Trunk function						
SIAS verticality test	3.0 (3.0–3.0)	3.0 (3.0–3.0)	3.0 (3.0–3.0)	3.0 (3.0–3.0)	3.0 (3.0–3.0)	0.11
SIAS abdominal muscle strength	2.0 (2.0–3.0)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	0.90
SIAS U/L range of motion	3.0 (2.0–3.0)	3.0 (2.3–3.0)	3.0 (2.8–3.0)	3.0 (2.0–3.0)	2.0 (2.0–3.0)	<0.05
SIAS pain	3.0 (3.0–3.0)	3.0 (3.0–3.0)	3.0 (3.0–3.0)	3.0 (3.0–3.0)	3.0 (3.0–3.0)	0.69
SIAS visuospatial perception	3.0 (3.0–3.0)	3.0 (3.0–3.0)	3.0 (3.0–3.0)	3.0 (3.0–3.0)	3.0 (3.0–3.0)	0.16
Revised Hasegawa's dementia scale, points, median (IQR)	23.0 (16.0–27.0)	27.0 (23.3–28.8)	23.0 (16.3–25.0)	21.5 (14.0–25.8)	19.0 (7.0–26.0)	<0.01
STEF at admission, points, mean (SD)	57.0 (29.8)	65.0 (26.2)	67.2 (25.9)	53.0 (32.3)	41.6 (29.2)	<0.05
STEF at reassessment, points, mean (SD)	74.9 (22.8)	86.6 (12.0)	77.6 (16.1)	73.6 (28.7)	61.2 (24.3)	<0.05
STEF improvement, points, mean (SD)	17.9 (18.6)	21.6 (20.9)	10.4 (13.9)	20.5 (21.3)	19.6 (16.2)	0.17

SD, standard deviation; SIAS, Stroke Impairment Assessment Set; U/L, upper limb; IQR, interquartile range; STEF, Simple Test for Evaluating Hand Function.
†Fisher's exact test.

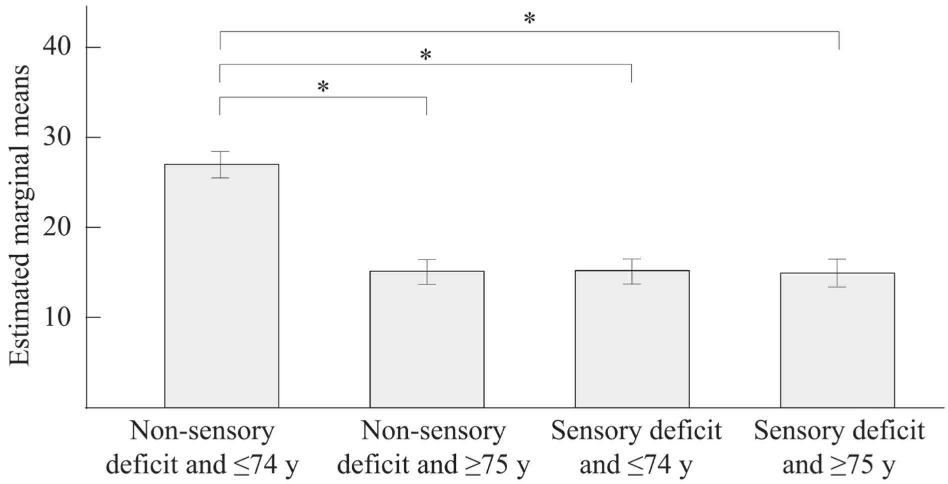

Fig. 2. Comparison of estimated marginal means of upper-limb improvement in the four groups. *P <0.05 (post-hoc test: Bonferroni correction). Error bars: ±1 SE.

used sensory impairment, age, and confounders in addition to the interaction term as independent variables. Therefore, our results showed that the interaction (synergic effect) between age (≤74 years) and the absence of sensory impairment influenced the improvement of upper-limb recovery, even after adjustment for the effects of sensory impairment, age, and confounders.

The mechanism by which this synergistic effect on upper-limb function improvement occurs (attributed to the combination of being ≤74 years old and the absence of sensory impairment) is unclear at this stage. Consequently, further research is needed, but cerebral cortex reorganization and motor learning may be involved. Functional recovery after the acute stage of stroke is largely attributed to the use-dependent plasticity of the brain resulting from use of the affected limbs, but it has been pointed out that both sensory impairment and age may affect brain plasticity. If the motor cortex is injured, the brain attempts to maintain motor control by remapping sensorimotor interactions through the recruitment of secondary motor areas, primary sensory cortices, and higher-order association areas involved in sensorimotor transformations.[9,23] Therefore, in patients with stroke with less extensive damage in the primary somatosensory cortex and less prominent effects on sensory function, cortical remodeling that compensates for damage to the primary motor cortex is likely to occur. Moreover, in recent years, it has been reported that the motor-related cortex can be activated by inputting sensory stimuli from the periphery.[24] This fact may also favor the likelihood of cortical remodeling in patients without sensory impairment. Conversely, based on experiments in rehabilitation training in mice with an injured primary motor cortex, Tennant et al.[25] reported that aging may limit the reorganization of the motor cortex of the brain. Therefore, it cannot be denied that aging may suppress cortical reorganization after stroke, even in humans. In terms of motor learning, it has been reported that both aging and sensory impairment can be factors that reduce the ability to acquire new tasks.[25,26] Motor learning is required for both true recovery and compensation.[27] For example, cortical changes may occur only with the learning of new skills and not just with repetitive use.[28] Furthermore, a study in adult rats with focal cortical ischemia suggested that motor improvement was principally mediated by compensatory mechanisms, such as changes in movement patterns, rather than true recovery.[29] In summary, the absence of sensory impairment and age (i.e., classification into the non-late elderly group) may be factors that favor cortical reorganization and motor learning in patients with subacute stroke, and the combination of these factors may contribute to cortical reorganization. As a result, the recovery of upper-limb function may be promoted.

The findings of this study will be useful when deciding whether to treat sensory impairment for improving upper-limb function in patients with subacute stroke. To date, the clinical characteristics of patients who can expect sensory therapy to be effective for motor recovery remain unknown.[9] The results of the current study suggest that good sensory function is associated with subsequent improvement in upper-limb function in patients younger than 75 years of age. In other words, for rehabilitation aimed at improving

Table 2. Multiple linear regression with interaction terms of sensory deficit and age

	Regression coefficient	Standardized coefficient	P-value	VIF
No sensory deficit (mean centered)	5.76	0.16	0.06	1.30
≤74 years (mean centered)	6.12	0.17	<0.05	1.11
Interaction term of above	11.56	0.16	<0.05	1.13
Stroke type (0: hemorrhage, 1: infarction)	–15.00	–0.34	<0.01	1.13
Range of motion	8.08	0.23	<0.01	1.18
STEF on admission	–0.45	–0.72	<0.01	1.18
Revised Hasegawa’s dementia scale	0.11	0.05	0.56	1.20

Adjusted R^2=0.58, P<0.01.
VIF, variance inflation factor.

upper-limb function, an approach that improves sensory impairment is one option for patients under the age of 75 with subacute stroke, but other approaches should be recommended for patients over 75 years of age. However, this study did not actually implement an approach to improve sensory impairment and compare the results by age. Therefore, clinical trials are needed to obtain more direct evidence in the future.

The results of this study provide a different perspective on the relationship between sensory impairment and the improvement of upper-limb function. A systematic review and meta-analysis by Couper et al.[5] suggested that sensory impairment was associated with upper-limb recovery, but the evidence was inconclusive. Methodological factors, such as differences in study populations, upper-limb motor outcome scales, the timing of baseline data, and outcome assessments and predictor selection, were thought to be involved in the lack of consensus. However, the results of the current study allow a different interpretation, i.e., that the effect of sensory impairment on the recovery of upper-limb function changes with age.

One of the major limitations of this study is that SIAS alone was used to assess sensory impairment. SIAS may be not the gold standard for sensory testing, and multiple assessments would be preferable. Furthermore, the cut-off points for age and sensory impairment (i.e., ≤74 years and ≥75 years and 3 points on SIAS sensory items) are not absolute. However, there is still room to re-examine this. Regarding activities of daily living, several studies have reported that improvement in these activities in patients aged 75 years or older with subacute stroke is significantly less than that in patients aged 74 years or younger.[30–33] However, it is unclear whether this age cutoff is the most relevant issue for upper-limb function improvement and interaction. Similarly, for sensory impairment, the degree of impairment and the type of sensation (e.g., tactile, proprioception, or both) may be associated with upper-limb function improvement and interaction in a complex manner. Another limitation is that the sample size in this study was not sufficient. One hundred seventy-nine participants are required when f, α, and the power are set at 0.25, 0.05, and 0.8, respectively, during the analysis of covariance; moreover, 103 participants are required when f^2, α, and the power are set at 0.15, 0.05, and 0.8, respectively, during multiple regression analysis. Therefore, this study should be considered a preliminary study, and further research is needed to address these issues.

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CONFLICTS OF INTEREST

There are no conflicts of interest to declare.

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