ARTICLE IN PRESS

Journal of Clinical Neuroscience xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.journals.elsevier.com/journal-of-clinical-neuroscience

Original Research

Occupational therapy using a robotic-assisted glove ameliorates finger dexterity and modulates functional connectivity in amyotrophic lateral sclerosis

Isamu Yamakawa [a,*], Atsushi Yamada [b], Yuma Sonoda [c], Kiyoshi Wakita [d], Takashi Nishioka [d], Yoshinori Harada [d], Nobuhiro Ogawa [a], Akihiro Kitamura [a], Mitsuru Sanada [a], Tohru Tani [b], Shinji Imai [d,e], Makoto Urushitani [a]

[a] *From the Department of Neurology, Shiga University of Medical Science, Otsu, Shiga, Japan*
[b] *Department of Research and Development for Innovative Medical Devices and Systems, Shiga University of Medical Science, Otsu, Shiga, Japan*
[c] *Kobe University Graduate School of Health Sciences, Kobe, Hyogo, Japan*
[d] *Rehabilitaion Units, Shiga University of Medical Science Hospital, Otsu, Shiga, Japan*
[e] *Department of Orthopedic Surgery, Shiga University of Medical Science, Otsu, Shiga, Japan*

ARTICLE INFO

Keywords:
ALS
Robotic-assisted glove
rs-fMRI

ABSTRACT

Introduction: Although rehabilitation is recommended for amyotrophic lateral sclerosis (ALS), improvement of functional decline has hardly been achieved. We investigated the effect of occupational therapy that uses a robotic-assisted glove (RAG) on hand dexterity and the functional connectivities found in the brain of ALS patients.
Method: Ten patients diagnosed with ALS and admitted to the Shiga University of Medical Science (SUMS) Hospital from December 2018 to December 2021 participated in the study. These participants chose the hand side to wear RAG and exercised for two weeks. A sham movement was performed on the other side. We administered several functional assessments, including the Simple Test for Evaluating Hand Function (STEF), grip strength, pinch meter for grip strength, Canadian occupational performance measure (COPM), as well as nerve conduction study (NCS) before and after the exercise, and evaluated the results. We also analyzed six patients' resting-state functional magnetic resonance imaging (rs-fMRI).
Results: Two-week robotic rehabilitation improved the STEF, grip strength, and COPM scores when compared with those of the other side. However, no significant effect was observed in the pinch meter and the NCS results. The rs-fMRI data analysis revealed that the robotic rehabilitation augmented two functional connectivities between the left pallidum-right supplementary motor cortex and right insular cortex-right sensorimotor network among the patients, which had beneficial effects.
Conclusion: The occupational therapy using RAG displayed improved hand dexterity. The enhanced functional connectivities around the sensorimotor network might be associated with the improvement in hand dexterity because of the RAG.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a detrimental disease, characterized by progressive muscle wasting and weakness, leading to lethal respiratory failure. Despite intensive research, only a few drugs, including riluzole and edaravone, have demonstrated marginal effects in slowing ALS progression [1–2]. Rehabilitation is one of the most accessible therapies, and its role in preventing contracture and disuse conditions is warranted [3–4]. Moreover, exercise training is a potential approach to ameliorate ALS pathology [3]. However, its beneficial role remains controversial [5]. For instance, excessive exercise in ALS may exacerbate muscle weakness, increase fatigue, and accelerate disease progression [6]. A recent study has documented that high physical activity in the premorbid stage accelerates the development of ALS with C9orf72 mutations [7]. Until now, there has been no consensus on the kinds of exercise that can be effective in ALS. However, it is conceivable

* Corresponding author at: Department of Neurology, Shiga University of Medical Science, Tsukinowa, Seta, Otsu, Shiga, Japan.
E-mail address: isamu136@belle.shiga-med.ac.jp (I. Yamakawa).

https://doi.org/10.1016/j.jocn.2022.11.004
Received 7 July 2022; Accepted 8 November 2022
0967-5868/© 2022 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Please cite this article as: Isamu Yamakawa, *Journal of Clinical Neuroscience*, https://doi.org/10.1016/j.jocn.2022.11.004

that passive limb exercise along with physical support should be beneficial for ALS patients. Recently, robotic rehabilitation by Hybrid Assistive Limb (HAL) has improved cadences and may effectively ameliorate and preserve gait ability in patients with ALS [8]. Herein, we performed occupational therapy using a robotic-assisted glove (RAG), which aids the patients by lessening their burden. We also investigated the effect of the RAG therapy on the brain's functional connectivities using resting-state functional magnetic resonance imaging (rs-fMRI), which examines spontaneous fluctuations of blood oxygenation level-dependent (BOLD) signals without specific task demands.

2. Methods

2.1. Patient enrolment and inclusion criteria

This study is prospective, and interventive; it was carried out at only one centre. Patients consecutively admitted to the SUMS Hospital and diagnosed with ALS from December 2018 to December 2021 provided written informed consent to be enrolled in the study. All of the patients fulfilled the diagnostic criteria of the Revised El Escorial or updated Awaji (definite or probable). The exclusion criteria included communication difficulties due to impaired consciousness and/or cognitive dysfunction. The clinical profiles of the participants, including sex, handedness, grip powers, tested or control side, disease duration, and Revised Amyotrophic Lateral Functional Rating Scale (ALSFRS-R) are shown in Table 1.

This study was approved by the Institutional Review Board of the SUMS (No. R2018-150).

2.2. Occupational therapy using robotic-assisted glove (RAG)

The participants were asked to exercise using a RAG (Carbonhand, Bioservo Technologies AB, Sweden). The RAG helps in gripping objects by using the tactile sensors installed on the tip of the thumb, middle finger, and ring finger [9–11]. The patients were asked to wear the RAG, hold and move the cone object to the place 30 cm away, and repeat this movement for 15 min (min.). They were asked to perform the same movement without wearing the RAG for 15 min, such as holding and moving the cone object to the place 30 cm away with repetition for 15 min. One example of a patient performing the RAG exercise is shown in the video (Supplementary information; video 1). The time of 15 min. was strictly measured by the examiner during the exercise.

The rehabilitation time, of 15 min., was determined based on a series of preliminary trials by occupational therapists. Notably, the RAG rehabilitation lets the patients have a passive movement of the fingers by helping the grip, which can avoid overexercising. The other control side mimicked the movement of the tested side, but whether there was gripping or not was determined by the therapist, depending on the muscle strength of the subjects. During the rehabilitation, the occupational therapist confirmed that the rehabilitation did not give patients excessive load by keeping the Borg scale reading at 11–13. If the gripping power was too low to hold the cone, the finger stretch exercise was performed by the examiner to minimize the demerits of sham movements. After the RAG rehabilitation, the patients were asked to take rest and avoid excessive finger movement.

We administered the Simple Test for Evaluating Hand Function (STEF), as well as assessed grip strength, three-point pinch strength, and the Canadian occupational performance measure (COPM). A nerve conduction study (NCS) was performed before and after the treatment. Since the RAG-wearing hand was not necessarily the dominant hand or the affected side, the effect was estimated by comparing these scores before and after rehabilitation in each patient, and the rate of improvement was analyzed. We also evaluated the change of functional connectivities in rs-fMRI of the six participants who accepted the protocol before the exercise and two weeks following the final day of the rehabilitation. The rs-fMRI was planned as a sub-study and was executed after separately obtaining the informed consent of the patients concerned. Six patients, # 1,5,6,7,8,9 in Table 1, agreed to participate in the rs-fMRI investigation. Two patients wore the RAG on the right hand, and four on the left.

The STEF assesses the upper extremity's accuracy, smoothness, and speed of voluntary movements. It assesses the time taken to move ten objects of different shapes and sizes to a predetermined location and, accordingly, assiging a score from 1 to 10, which is quantify based on the the time taken. In these, the items for turning over the cloth, moving the coin, and moving the light ball do not require much strength, and even those with grip strength as 0 kg can perform (Supplementary Table). The time scores summed to provide a total test score [12]. The STEF has a high correlation with the action research arm test, which is used to assess upper limb function [13]. The COPM quantifies performance and satisfaction in self-care, productivity, and leisure from the client's perspective. Since 1991, the COPM has been translated into more than 20 languages in over 35 countries [14].

2.3. Electrophysiological studies

A NCS was performed using standard electrodiagnostic equipment (Neuropack X. Nihon Kohden, Tokyo, Japan). The median and ulnar nerves were stimulated electrically at the wrist, and the resultant baseline-to-peak compound muscle action potential (CMAP) amplitude (mV) was recorded at the abductor pollicis brevis (APB), first dorsal interossei (FDI), and abductor digiti minimi (ADM) muscles by employing disc electrodes positioned in a belly tendon arrangement. The split-hand index (SHI), using the amplitude of the CMAP, was calculated by multiplying the CMAP parameters recorded over the APB and FDI muscles divided by the CMAP parameters recorded over the ADM

Table 1
Demographic characteristics of participants.

Patient. #	Age	Gender	BMI	Duration (months)	ALSFRS-R H/T	Region of onset	Dominant hand	Treated hand	MRC	Grip treated hand (kg)	Grip another hand (kg)
1	39	F	18	25	6/33	L/E	R	R	51	7	6.5
2	66	M	20	19	8/44	U/E	R	L	50	9.2	20.1
3	62	F	19.5	20	8/39	B	R	L	47	0	10.5
4	60	M	19.2	12	5/30	U/E	R	R	38	18	23.5
5	68	M	19.1	27	8/44	U/E	R	R	47	26	23
6	76	F	21.4	21	8/35	L/E	R	L	38	16.5	17.5
7	56	M	30.3	25	12/48	U/E	R	L	58	18	25
8	66	F	23.5	19	11/47	U/E	R	L	54	0	15.9
9	66	M	26.6	29	12/46	B	R	L	59	36.1	44.6
10	60	M	19.3	18	6/39	U/E	R	L	47	18	0

BMI: Body mass index; ALSFRS-R: Revised Amyotrophic Lateral Functional Rating Scale; H/T: Hand associated ALSFRS-R score/Total ALSFRS-R score, MRC: Medical Research Council score; F: Female; M: Male, U/E: Upper extremity, L/E Lower extremity, B: Bulbar, R: Right; L: Left.

muscle: SHI CMAP = APB CMAP × FDI CMAP/ADM CMAP [15].

2.4. Magnetic resonance imaging (MRI) acquisition

MR images were acquired on a 3 Tesla (T) MRI scanner (Discovery MR750w 3.0 T, General Electric Healthcare, Milwaukee, Wisconsin). We obtained T1-weighted, magnetization-prepared, inversion-prepared (IR-prep), fast spoiled gradient echo (SPGR) sequence (brain volume [BRAVO]) images with the following parameters: repetition time (TR)/echo time (TE) = 13.74/5.836 ms, flip angle = 15°, acquisition matrix = 512 × 512; field of view (FOV) = 240 × 240 mm^2, slice thickness = 2 mm, number of slices = 164, voxel size = 0.47 × 0.47 × 2 mm^3. The rs-fMRI scans were obtained, using gradient echo-planar imaging (*EPI*): TR/TE = 20000/30 ms, flip angle = 90°, acquisition matrix = 64 × 64; FOV = 220 × 220 mm^2, slice thickness = 3.6 mm, number of slices = 150, voxel size = 3.4 × 3.4 × 3.6 mm^3.

During the functional scan, the study participants were asked to keep their eyes closed and stay motionless, awake, and relaxed. No visual or auditory stimuli were presented at any time during the functional scanning. The total duration of each scan was about 35 min.

2.5. Functional magnetic resonance imaging (fMRI) data analysis

Preprocessing. Preprocessing of the structural MRI data included the removal of non-brain tissue and cerebrospinal fluid using the segmentation function of a brain imaging analysis software (SPM13, Wellcome Trust Centre for Neuroimaging, University College London). The rs-fMRI data were preprocessed in the functional connectivity toolbox (CONN toolbox version 20b) [16]. The preprocessing included the following steps: a) functional realignment and unwarping; b) functional slice-timing correction, structural segmentation, and normalization; c) functional normalization; d) functional outlier detection; and e) functional smoothing with a Gaussian kernel of 8 mm full width at half maximum. We further applied denoising to the first-level analysis by employing a linear regression followed by a band-pass filter (0.01–0.1 Hz) to remove unwanted motions, physiological effects, and other artifacts from the BOLD signal before calculating connectivity measures.

Resting-state functional magnetic resonance imaging (rs-fMRI) analyses. To assess differences in resting-state functional connectivity across the brain regions traditionally associated with sensory-discriminative, affective-motivational, and cognitive-evaluative aspects of pain processing [17–19], we divided the brain volume into 91 cortical and 15 subcortical regions of interests (ROIs) based on FSL Harvard-Oxford Atlas maximum likelihood cortical atlas. We further performed ROI-to-ROI analyses by utilizing these ROIs. The seeds used for the analysis comprised the sensory-motor network, cerebellar network, and supplementary motor cortices, as the number was small. This set of particular brain areas has been related to exercise. An ROI-to-ROI analysis was performed using the CONN software. The connectivity between all ROIs was compared before and after rehabilitation, and the threshold was defined as p-false discovery rate (FDR) < 0.05.

2.6. Outcome

The primary endpoint of our study is safety and efficacy for the dexterity of the hand movement by subjective and objective evaluations. The secondary outcome contains findings of the NCS, the connectivity in the rs-fMRI, and the relationship between the connectivity and hand motor function. The rs-fMRI was a sub-study, involving those who agreed to being a part of the experiment.

2.7. Statistics

The Wilcoxon signed-rank test was used to assess the pre-post STEF, COPM, grip strength, three-pinch strength, and SHI-related capacity. The Mann-Whitney's *U* test was employed to evaluate the group differences. A non-parametric test using a statistical software package (Statistical Package for the Social Science [SPSS] version 26, IBM, USA) was also conducted, and the significance level was set at a two-tailed $p < 0.05$.

The paired t-tests were performed to examine the differences in brain functional connectivity before and after rehabilitation. The statistical results were used to determine the brain regions that demonstrated significant differences in the BOLD signal time series synchronization between the seed regions. The group-level results were corrected for multiple comparisons (FDR) at seed-level ($p < 0.05$) within the CONN toolbox. Seed-level correction is a parametric correction method offered in CONN that carries out corrections for multiple comparisons, arising from the testing of the significance of functional connectivity between multiple target ROIs. The significance of ROI-to-ROI connection by intensity was determined via the FDR-corrected $p < 0.05$ with seed-level correction. Furthermore, Spearman's correlation was also found, using SPSS, which helped in the evaluation of the associations between the change of the connection and the STEF.

3. Results

3.1. Patients profiles

The clinical profiles of ten participants (aged 61.9 ± 23 years) are listed in Table 1. Almost all of the patients chose the weaker side for wearing the RAG. In that, three of them chose the right side, whereas seven chose the left side. The difference in dispersion between the robotic and control sides was insignificant for all of the parameters, including those of the STEF, grip strength, three-pinch meter, and SHI. However, a non-significant trend was established, demonstrating that the more affected side was preferred, as shown in the grip and SHI (Table 1, Figs. 1 and 2). The participants had various clinical courses, including initial symptoms and progression. No patient dropped out during the protocols, and no adverse event occurred during the observations.

3.2. RAG hand exercise improved occupational performance and satisfaction scores

The RAG exercise, i.e. gripping the plastic cup and moving it to the other side immediately improved hand dexterity, as shown in the video (supplementary information). We thus evaluated the effects of occupational therapy, using the RAG for 14 days on various clinical and electrophysiological scores. Compared to the initial assessment, the two-week RAG exercise significantly improved the STEF scores, which are often used to evaluate hand dexterity. The scores for the control group remained unchanged during the sham exercise. However, one patient (# 10 in Table 1) underwent the finger stretch exercise instead of the actual gripping movement on the control side because he completely lost the gripping power to perform the control exercise. A significant elevation of COPM scores was also found for both performance and satisfaction, as well as grip strength (Fig. 1). On the other hand, the RAG exercise did not sig nificantly improve the three-pinch strength (Fig. 2). Moreover, the nerve conduction assessed by the SHI remain unchanged (Fig. 2).

3.3. RAG exercise modulated functional connectivities

The following two pathways showing altered functional connectivities were observed: left pallidum and right supplementary motor cortex and right lateral sensory-motor network and right insular cortex. The sidedness did not significantly affect the results of the rs-f MRI analysis. The change in the functional connectivity of the left pallidum and right supplementary motor cortex was unrelated to the STEF-related changes before and after rehabilitation (Fig. 3A-C). However, the difference in the right lateral sensory-motor network and right insular cortex was moderately associated with the STEF-related change (Fig. 3D, E). As two

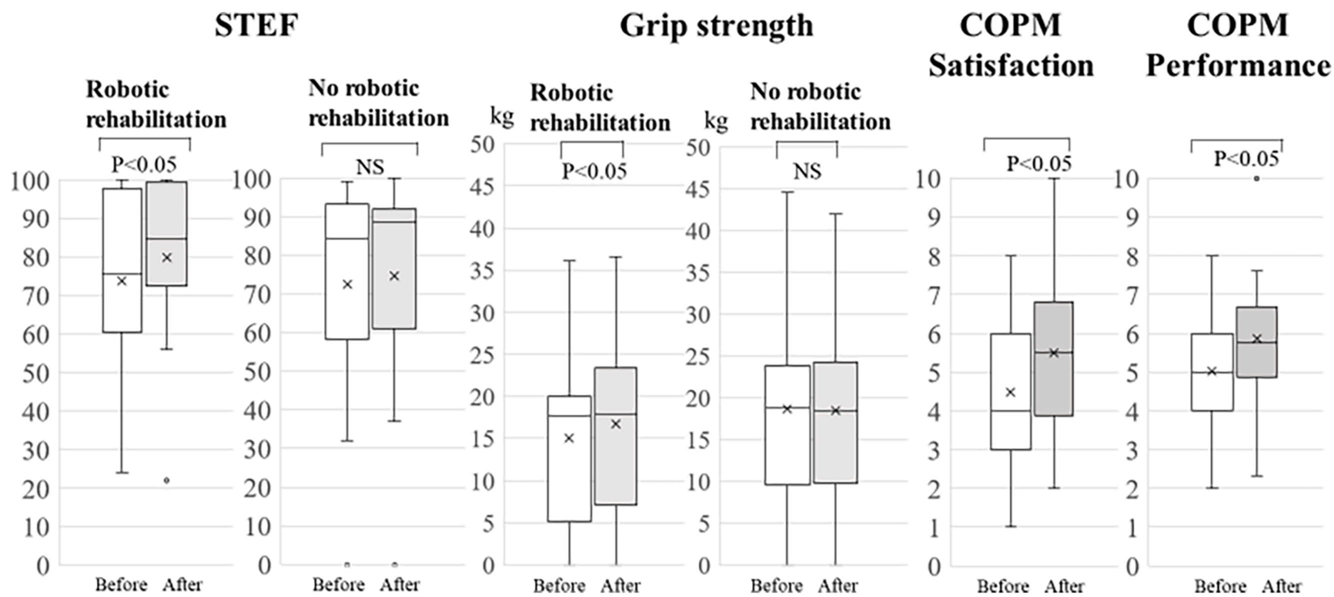

Fig. 1. Robotic rehabilitation improved STEF, grip strength-related, and COPM scores. Comparison of the STEF score and grip strength between, before, and after rehabilitation. Wilcoxon signed-rank test showed that the hand of robotic rehabilitation improved the STEF score ($P = 0.01$) and grip strength ($P = 0.01$); however, the hand of no robotic rehabilitation did not change. Comparison of the COPM scores between, before, and after rehabilitation. Wilcoxon signed-rank test showed that robotic rehabilitation improved the COPM satisfaction ($P = 0.01$) and performance scores ($P = 0.01$). Before: Before rehabilitation. After: Two weeks after rehabilitation.

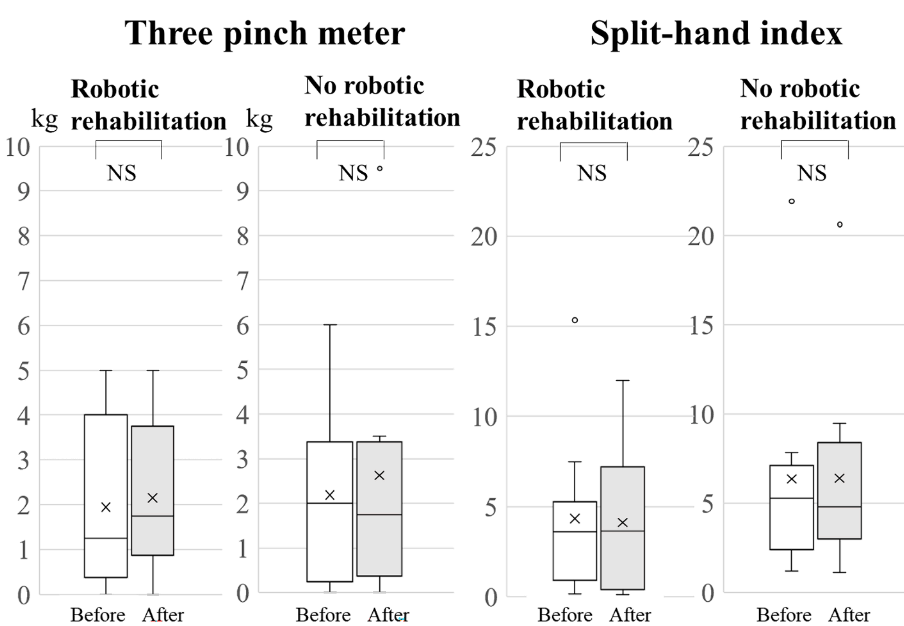

Fig. 2. Robotic rehabilitation did not improve scores on three-pinch meter and split hand index. Comparison of the three-pinch meter, split-hand index between before and after rehabilitation. Both hands of robotic and no robotic rehabilitation did not change the three-pinch meter and split-hand index according to the findings of the Mann–Whitney U test. Before: Before rehabilitation. After: Two weeks after rehabilitation.: APB CMAP(mV) × FDI CMAP(mV) /ADM CMAP(mV) Split-hand index: SHI, Abductor Pollicis Brevis: APB, First Dorsal Interossei: FDI, and Abductor Digiti Minimi: ADM.

patients showed the STEF scores of 99 and 100, reaching the maximum (100), the effect of the RAG exercise could be underestimated. The subanalysis without the two patients illustrated that the functional connectivity change in the right lateral sensory-motor network and right insular cortex strongly correlated with the change in the STEF scores (Fig. 3F).

4. Discussion

In this study, passive occupational therapy using the RAG for 14 days improved hand dexterity in ALS patients. Ten patients showed a significant difference in their scores on the STEF, COPM, and grip strength measurement. Although hand clumsiness is a burden for daily activities, there is currently no effective cure. Therefore, our study shows that the RAG exercise is advantageous for ALS patients, even though the effect is transient. The improvement of motor function was accompanied by enhanced functional connectivities in several sensorimotor pathways. Although precise roles remain unclear, further research with a larger number of participants may uncover the mechanism.

The effect of the rehabilitation on the clinical course and whether physical activity promotes or prevents the progression of motor neuron degeneration in ALS remains unclear. Excessive exercise exacerbates the disease progression in ALS animal models [6]. A recent Cochrane analysis, evaluating the studies focused on the therapeutic effect of

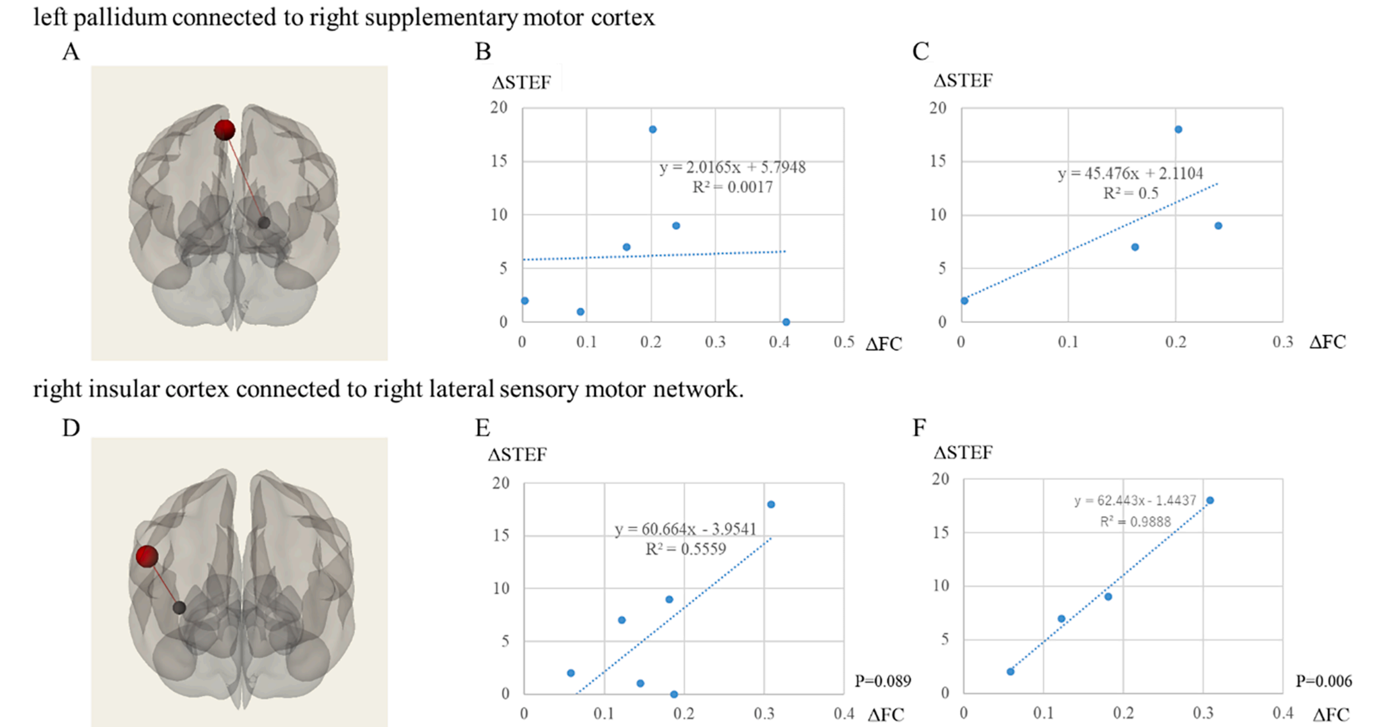

Fig. 3. Connection results A, B, C: Left pallidum connected to the right supplementary motor cortex D, E, F: Right insular cortex connected to right lateral sensory-motor network A, D: Location of ROI (Region of Interest) B, E: Scatter plots display the association between the change of the STEF score and the change of functional connectivity during our robotic rehabilitation. C, F: Scatter plots without the two patients whose STEF scores before rehabilitation were almost perfect (99–100 scores) display the association between the change of the STEF score and the change of functional connectivity during our robotic rehabilitation. ΔSTEF: The score difference between before and after rehabilitation. ΔFC: The difference in functional connectivity between, before, and after rehabilitation.

exercise in people with ALS identified only two randomized controlled trials. One study investigated 25 participants, 11 subjects undertaking rehabilitation and 14 without, and another examined 27 participants, 13 subjects undertaking the resistance exercise three times a week and 14 without the training [4]. Both studies depicted a reduction of motor deterioration as evaluated by ALSFRS-R when compared with usual activities. However, further study is required to conclude whether exercise is beneficial or harmful for ALS patients [20–21]. Recently, strictly monitored exercise programs were observed by ALSFRS-R to be more effective than the usual exercise [22]. Notably, the enrolled patients in this study were at the early and mild stages. Moreover, a relatively small number of reports describe the effect of rehabilitation of the upper extremity in ALS. One case report, using a device (Armeo Power) reported the efficacy of the robotic rehabilitation for an ALS patient of frail arm type [23]. Several reports describe the effect of orthoses and rehabilitation on hand motor function in ALS [24–26]. However, our study is the first one to show the benefit of using robotics for hand dexterity. The grip strengths of the participants varied; patients with severe weakness significantly improved their COPM score (Fig. 1). As our rehabilitation protocol is passive movement with robotic support, it would be safe and effective regardless of the progression of muscle weakness.

Several reports describe the therapeutic benefit of the RAG in neurological diseases. Rehabilitation with the RAG improved performance on the Toronto rehabilitation institute hand function test and three-pinch strength in chronic spinal cord injury [9]. The RAG exercise of 30 patients with hand weakness, caused by stroke and cervical spondylosis also improved the pinch strength [11]. To date, there are no reports that describe the effect of the RAG on ALS patients. Almost all patients in our study responded positively to the RAG exercise as shown in the COPM score for satisfaction. For example, one participant told us that she could write more efficiently, whereas another participant found less difficulty in buttoning their shirt following the two-week RAG exercise. Occupational therapy for ALS is usually conservative, aiming to preserve joint movement range, avoid contracture, or lessen pain. Therefore, the subjective recognition of the efficacy of limb function represents a considerable impact on the patients.

The RAG exercise improved the STEF and grip strength; however, it did not change the three-pinch strength and SHI in the NCS. The RAG exercise made the hand move smoothly and ameliorated hand clumsiness. The improvement of grip strength might be explained by the acquisition of effective co-flexion of all fingers by the RAG; the direct effect of increasing muscle strength during the 14-day study is unlikely. In agreement with this view, we found no change in three-pinch strength, which is also supported by the SHI.

To rationalize the effect of the RAG on motor function, especially the higher motor control, we investigated the cortical functional connectivity in MRI. Unexpectedly, the RAG significantly changed several functional connectivities regarding sensorimotor networks. Therefore, the improvement of motor functions may be associated with altered functional connectivities in the brain. Our results depicted that the RAG exercise enhanced two connectivities in the brain. However, the increased functional connectivity of the left pallidum and right supplementary motor cortex did not correlate with the change in the STEF. In recent times, repetitive transcranial magnetic stimulation on the supplemental motor area improved the motor performance of the hands [27]. The pallidum plays a critical role in the processing and execution of motivated behaviors [28]. The increased functional connectivity of the left pallidum and the right supplementary motor cortex might be more relevant to the motivational effect than motor function. The insula subserves various functions in humans ranging from sensory and affective processing to high-level cognition [29]. The change in the connection between the right lateral sensory-motor network and the right insular cortex might be related to the motor function since the changes in the connection were correlated with the change of the STEF.

This study has several limitations. First, the number of participants was small. Second, the patients' profiles were variable, including clinical course, initial symptoms, or upper or lower motor neuron impairment predominance. We were unable to investigate the effect of each type and then compare one another. Third, this study does not include healthy or other disease controls, which may yield an expectation bias and argue against the ALS-specific effect of the RAG exercise. Another limitation of this study is the single-arm design which lacks control groups with classical rehabilitation therapy or placebo. Further, the follow-up duration is too short. Further, the follow-up duration is too short. Nevertheless, the temporal profiling and the consistent and significant effect of the RAG in ten patients warrant reporting.

In conclusion, occupational therapy using the RAG was effective in ALS in ameliorating STEF, COPM, and grip strength scores. Our study has documented that the RAG is a potential option to fit the unmet needs of ALS with hand weakness. Future improvement of devices, modification of the therapeutic protocols, and clarification of mechanisms are required to further improve this novel therapy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We express our special gratitude towards Ryota Tamura, Hideki Wada, Hiroyuki Yabata, Takahito Tsukamoto, and Shuhei Kobashi of the Department of Neurology and Youhei Higashide, Keika Sekiguchi, Akane Kumazaki, and Shinichiro Sawano of the Rehabilitation Units, SUMS Hospital, for their unconditional efforts towards this study. We acknowledge the helpful comments offered by Kim Hyoh of the Department of Neurology, National Hospital Organization Shigaraki Hospital and Hiromichi Kawai of the Department of Neurology, Japan Community Healthcare Organization Shiga Hospital. Moreover, we are immensely grateful to all of the members of the Department of Neurology and Rehabilitation Units at the SUMS Hospital. This study is supported by Intramural research grant from Shiga University of Medical Science.

Contributorship

I.Y. contributed to the conception and design of the study, interpretation of data, and drafting of the manuscript. A.Y. contributed to the collection and analysis of data, revision of the manuscript for intellectual content.

Y.S., K.W., T.N., Y.H., N.O., A.K., M.S., T.T., and S.I. contributed to the collection and analysis of data. M.U. contributed to the conception and design of the study, critical revision of the manuscript, drafting of the manuscript, and final approval of the published version.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2022.11.004.

References

[1] Thakore NJ, Lapin BR, Pioro EP. Stage-specific riluzole effect in amyotrophic lateral sclerosis: a retrospective study. Amyotroph Lateral Scler Frontotemporal Degener 2020;21(1–2):140–3.

[2] Shefner J, Heiman-Patterson T, Pioro EP, Wiedau-Pazos M, Liu S, Zhang J, et al. Long-term edaravone efficacy in amyotrophic lateral sclerosis: Post-hoc analyses of Study 19 (MCI186-19). Muscle Nerve 2020;61(2):218–21.

[3] Angelini C, Siciliano G. An updated review on the role of prescribed exercise in the management of Amyotrophic lateral sclerosis. Expert Rev Neurother 2021;21(8):871–9.

[4] Dal Bello-Haas V, Florence JM. Therapeutic exercise for people with amyotrophic lateral sclerosis or motor neuron disease. Cochrane Database Syst Rev. 2013(5):CD005229.

[5] Tsitkanou S, Della Gatta P, Foletta V, Russell A. The role of exercise as a non-pharmacological therapeutic approach for amyotrophic lateral sclerosis: beneficial or detrimental? Front Neurol 2019;10:783.

[6] Mahoney DJ, Rodriguez C, Devries M, Yasuda N, Tarnopolsky MA. Effects of high-intensity endurance exercise training in the G93A mouse model of amyotrophic lateral sclerosis. Muscle Nerve 2004;29(5):656–62.

[7] Julian TH, Glascow N, Barry ADF, Moll T, Harvey C, Klimentidis YC, et al. Physical exercise is a risk factor for amyotrophic lateral sclerosis: Convergent evidence from Mendelian randomisation, transcriptomics and risk genotypes. EBioMedicine 2021;68:103397.

[8] Morioka H, Hirayama T, Sugisawa T, Murata K, Shibukawa M, Ebina J, et al. Robot-assisted training using hybrid assistive limb ameliorates gait ability in patients with amyotrophic lateral sclerosis. J Clin Neurosci 2022;99:158–63.

[9] Osuagwu BAC, Timms S, Peachment R, Dowie S, Thrussell H, Cross S, et al. Home-based rehabilitation using a soft robotic hand glove device leads to improvement in hand function in people with chronic spinal cord injury:a pilot study. J NeuroEng Rehabil 2020;17(1).

[10] Radder B, Prange-Lasonder GB, Kottink AI, Gaasbeek L, Holmberg J, Meyer T, et al. A wearable soft-robotic glove enables hand support in ADL and rehabilitation: A feasibility study on the assistive functionality. J Rehabil Assist Technol Eng. 2016;3:2055668316670553.

[11] Hashida R, Matsuse H, Bekki M, Omoto M, Morimoto S, Hino T, et al. Evaluation of motor-assisted gloves (SEM Glove) for patients with functional finger disorders: A clinical pilot study. Kurume Med J 2019;65(2):63–70.

[12] Irie K, Iseki H, Okamoto S, Okamoto K, Nishimura S, Kagechika K. Development of the modified simple test for evaluating hand function (modified STEF): Construct, reliability, validity, and responsiveness. J Hand Ther 2019;32(3):388–94.

[13] Shindo K, Oba H, Hara J, Ito M, Hotta F, Liu M. Psychometric properties of the simple test for evaluating hand function in patients with stroke. Brain Inj 2015;29(6):772–6.

[14] Yang SY, Lin CY, Lee YC, Chang JH. The Canadian occupational performance measure for patients with stroke: a systematic review. J Phys Ther Sci 2017;29(3):548–55.

[15] Seok HY, Park J, Kim YH, Oh KW, Kim SH, Kim BJ. Split hand muscle echo intensity index as a reliable imaging marker for differential diagnosis of amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 2018;89(9):943–8.

[16] Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect 2012;2(3):125–41.

[17] Spisak T, Kincses B, Schlitt F, Zunhammer M, Schmidt-Wilcke T, Kincses ZT, et al. Pain-free resting-state functional brain connectivity predicts individual pain sensitivity. Nat Commun 2020;11(1):187.

[18] Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain 2005;9(4):463–84.

[19] Woo CW, Schmidt L, Krishnan A, Jepma M, Roy M, Lindquist MA, et al. Quantifying cerebral contributions to pain beyond nociception. Nat Commun 2017;8:14211.

[20] Drory VE, Goltsman E, Reznik JG, Mosek A, Korczyn AD. The value of muscle exercise in patients with amyotrophic lateral sclerosis. J Neurol Sci 2001;191(1–2):133–7.

[21] Bello-Haas VD, Florence JM, Kloos AD, Scheirbecker J, Lopate G, Hayes SM, et al. A randomized controlled trial of resistance exercise in individuals with ALS. Neurology 2007;68(23):2003–7.

[22] Lunetta C, Lizio A, Sansone VA, Cellotto NM, Maestri E, Bettinelli M, et al. Strictly monitored exercise programs reduce motor deterioration in ALS: preliminary results of a randomized controlled trial. J Neurol 2016;263(1):52–60.

[23] Lazovic M, Nikolic D, Boyer FC, Borg K, Ceravolo MG, Zampolini M, et al. Evidence based position paper on Physical and Rehabilitation Medicine (PRM) practice for people with amyotrophic lateral sclerosis (ALS). Eur J Phys Rehabil Med 2021.

[24] Ivy CC, Smith SM, Materi MM. Upper extremity orthoses use in amyotrophic lateral sclerosis/motor neuron disease: three case reports. Hand (N Y) 2014;9(4):543–50.

[25] Dal Bello-Haas V, Kloos AD, Mitsumoto H. Physical therapy for a patient through six stages of amyotrophic lateral sclerosis. Phys Ther 1998;78(12):1312–24.

[26] Ivy CC, Smith SM, Materi MM. Upper extremity orthoses use in amyotrophic lateral sclerosis/motor neuron disease: a systematic review. Int J Phys Med Rehabil 2015;3(2):264.

[27] Kim YK, Shin SH. Comparison of effects of transcranial magnetic stimulation on primary motor cortex and supplementary motor area in motor skill learning (randomized, cross over study). Front Hum Neurosci 2014;8:937.

[28] Root DH, Melendez RI, Zaborszky L, Napier TC. The ventral pallidum: Subregion-specific functional anatomy and roles in motivated behaviors. Prog Neurobiol 2015;130:29–70.

[29] Uddin LQ, Nomi JS, Hébert-Seropian B, Ghaziri J, Boucher O. Structure and function of the human insula. J Clin Neurophysiol 2017;34(4):300–6.