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Neuromuscular electrical stimulation-enhanced rehabilitation is associated with not only motor but also somatosensory cortical plasticity in chronic stroke patients: an interventional study

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Abstract

Background: Somatosensory function has been frequently overlooked in clinics and research in the field of chronic stroke. The effects of neurorehabilitation interventions on sensory processing have still to be investigated using electrophysiological means.
This study investigated the effect of hybrid assistive neuromuscular dynamic stimulation (HANDS) therapy utilizing closed-loop electromyography-controlled neuromuscular electrical stimulation (NMES), on sensory changes and cortical plasticity among patients with chronic stroke.

Methods: This study was a prespecified analysis of 23 participants involved in an ongoing large interventional study. Patients with severe upper limb hemiplegia dues to chronic stroke underwent 3 weeks of inpatient HANDS therapy, where daily treatment consisted of 8 h of NMES combined with wrist splinting, 90 min of comprehensive occupational therapy, and the practice of bimanual activities of daily living. Somatosensory evoked potentials (SEPs) and functional sensory assessments, including the Semmes–Weinstein monofilament test (SWMT) and thumb localizing test (TLT), were compared pre and post-treatment.

Results: While no significant recovery of tactile sensation was observed, significant improvements in proprioception and motor function were induced. The number of cortical peaks significantly increased in the median nerve, but not in the tibial nerve. A total of 9 out of 11 participants who initially lacked certain peaks responded to treatment. Further analysis revealed a significant improvement in latency and amplitude of SEP peaks.

Conclusions: Our results suggest that NMES-based neurorehabilitation induces certain plastic changes in the primary sensory cortex and in cortices associated with sensorimotor processing in people with chronic stroke sequelae, which may explain the observed improvements in proprioception.

Keywords: closed-loop, hemiplegia, neuromuscular electrical stimulation, plasticity, proprioception, sensorimotor integration, somatosensory evoked potentials, upper limb

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Introduction

Approximately half of all patients with stroke experience somatosensory impairments,[1] and the prevalence of tactile deficits, proprioceptive deficits, or both are reported in 28–33% of patients, even among those in the chronic phase.[2] Numerous studies have demonstrated that sensory functions are critical for motor performance and learning[3] *via* sensory feedback and central processing.[4,5] Therefore, it is likely that sensory impairments are closely related to outcome following rehabilitation in both the subacute[6] and chronic phases, when sensory dysfunction often leads to learned nonuse which, in turn, leads to further functional deterioration.[7,8] Rehabilitative research has indicated that sensory recovery may occur secondary to the specific rehabilitation of sensory discrimination[9] and thermal sensation,[10] and to sensory-oriented physiotherapies involving pneumatic compression[11] and electrical stimulation.[12] In addition, such recovery has been observed secondary to rehabilitative approaches targeting motor function.[13] Similarly, research has demonstrated that sensory-specific rehabilitation approaches facilitate the recovery of motor function.[10,14] Indeed, several studies have tried to combine sensory and motor rehabilitation,[15,16] or sensory training and cutaneous electrical stimulation, for the treatment of chronic stroke.[17]

However, the sensory function is frequently overlooked in clinical settings and in the majority of studies regarding stroke rehabilitation, especially in the chronic phase. Therefore, the mechanisms underlying sensory dysfunction and recovery in patients with stroke still need to be elucidated. One reason for this discrepancy is that the clinical demands of motor recovery are greater than those of sensory recovery. In addition, clinically available assessments for sensory dysfunction are less reliable and reproducible than those for motor dysfunction.[8,18] Systematic reviews have recommended that these assessments be combined with other objective modalities including somatosensory evoked potentials (SEPs) or neuroimaging methods (e.g. MRI and spectroscopy).[8,19] Compared with imaging methods, SEPs are advantageous because of their feasibility in a wide range of clinical settings. SEPs can be used to assess functioning in the dorsal column of the spinal cord and medial lemniscus, which are associated with tactile sensation and proprioception,[20] and to evaluate sensory and sensorimotor processing based on cortical peaks after the first negative cortical peak NI(N20).[21,22] In particular, bilateral recording of SEPs allows for minimization of inter and intra-individual variations associated with the state of awareness and cognition.[23,24] However, to the best of our knowledge, there are only a limited number of studies investigating the effect of rehabilitative approaches with SEPs for chronic stroke patients.[17,25]

Hybrid assistive neuromuscular dynamic stimulation (HANDS) therapy is a comprehensive neurorehabilitative treatment that utilizes integrated volitional control electrical stimulation (IVES),[26] which is a form of closed-loop electromyography (EMG)-controlled NMES.[27,28] NMES-based neurorehabilitation is recommended for severe upper extremity hemiparesis exerting minimal volitional muscle activation as class IIa therapy,[29] and has attracted wide attention in the field of stroke.[5,30] In particular, researchers have reported the combination of IVES and task-specific training induces significant functional recovery even in chronic stroke patients.[28,31] The HANDS therapy system is composed of an IVES device and a wrist–hand splint, which are used in conjunction with intensive occupational training and inpatient practice of the use of a paretic limb in their activities of daily living (ADLs). HANDS therapy is indicated when patients present with severe impairments, a small amount of detectable EMG activity in the wrist or finger extensor, and a lack of substantial voluntary movement. Because constraint-induced movement therapy cannot be applied in extreme cases,[27,28] HANDS therapy should theoretically occur in conjunction with brain machine interface-based rehabilitation for patients with the most severe forms of upper extremity paresis and with constraint-induced movement therapy for those with moderate to severe paresis.[32] Significant, long-lasting functional recovery of hand and wrist function and increases in daily practical use of the paretic limb have been reported in patients with subacute and chronic stroke.[33,34] Previous studies have suggested that long-lasting plastic changes in the motor cortex of the affected hemisphere underlie the recovery of motor function in such patients.[28]

To the best of our knowledge to date, no NMES studies assessing its sensory aspect by electrophysiological means have been carried out, while a functional MRI study demonstrated functional improvement induced by EMG-triggered NMES in chronic stroke patients.[35] There is a lack of SEP studies in other rehabilitative treatments for

chronic stroke. An uncontrolled study demonstrated that antispastic botulinum toxin A treatment combined with a home based exercise program induced a restoration in the amplitude of an SEP peak corresponding to primary sensory cortex,[25] and a relatively large controlled study demonstrated that 3 weeks of inpatient cutaneous electrical stimulation (cES) treatment induced an improvement in the SEP qualitative pattern despite no changes in the control.[17]

Based on previous findings regarding treatment effects and electrophysiological data indicative of plasticity in the sensorimotor cortex, this study investigated the effect of a closed-loop NMES treatment on somatosensory changes among patients with chronic stroke using SEPs and behavioral assessments. We hypothesized that a closed-loop NEMS treatment targeting sensorimotor system would induce plastic changes in motor function and in somatosensory function in chronic stroke patients which could be detected by electrophysiological means.

Materials and methods

Study approval and samples

This study was a prespecified analysis of participants involved in an ongoing large interventional study, which is registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) public database (Tokyo; No. UMIN000021912). All of the protocols were performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Keio University School of Medicine in advance (Tokyo; No. 20150466).

The sample size was calculated as 21–22 in two different ways, based on our pilot investigation of SEPs in a population of patients with nearly identical impairments (Fuseya and colleagues, in preparation) and according to a previous study regarding SEP changes after botulinum toxin injections for chronic stroke patients.[25] Therefore, 25 participants with chronic stroke sequelae were registered with the expectancy of exclusions or drop-outs.

Participants

Participants were recruited from the outpatient clinic of the Department of Rehabilitation at Keio University Hospital in Tokyo, Japan. Advertisements for the study were included on the departmental website and the UMIN-CTR, and all participants provided written informed consent. Inclusion criteria were as follows: hemiparesis due to stroke; at least 6 months since stroke; stroke impairment assessment set (SIAS)[36,37] knee–mouth test score $\geqslant 2$ (the paretic hand can be voluntarily elevated to the level of the nipple); SIAS finger test score <3 (each digit cannot be voluntarily flexed and extended fully); passive range of finger extension >0 degree; muscle contraction detectable from the extensor digitorum communis or extensor pollicis longus; independent ambulatory ability with or without walking aids; independent ADLs with or without functional aids, and age ranging from 14 to 80 years. Exclusion criteria were people with: a history of major psychiatric or previous neurological disease; severe pain in the paretic upper extremity; a pacemaker or other implanted stimulator; a score of Mini-Mental Examination Scale <25; and visuospatial neglect or apraxia.[27,33] Any medications, including ones affecting the central nervous system or for antispastic treatment, were not listed for the exclusion criteria. No patient's oral medication was modified during the period from 3 months before the intervention until the end of it, while toxin A botulinum injections were performed in four patients during the intervention (12.5 ± 4.5 days after the initiation). The spasticity and motor function were assessed 1 week after the injection or at the final examination.

HANDS therapy was performed for 25 patients with chronic stroke exhibiting severe upper extremity paresis from 22 August 2016 to 31 March 2017 on their admission dates. Only two patients were excluded due to missing SEP data after the intervention. Data from 23 patients were used for the exploratory analysis. No significant functional difference was observed between patients included or not.

Intervention

All participants underwent comprehensive, inpatient rehabilitation using the HANDS therapy system, which was applied for 8 h each day for 21 days, in accordance with a previously described protocol.[33] This system was composed of a closed-loop EMG-controlled NMES device to apply IVES (MURO solutions, Pacific Supply Co., Osaka, Japan) and a wrist–hand splint (Pacific Supply Co.). A hybrid electrode (10 mm diameter) for EMG detection and stimulation

was placed on the belly of the affected extensor digitorum communis (EDC), and an electrode (10 mm) for stimulation was positioned on the affected extensor indicis propris. The reference electrode was placed on the tendon of the EDC. This device applied preset electrical stimulation when EMG activity reached a target threshold and changed the stimulation intensity in proportion to the changes in EMG amplitude. Therefore, voluntary contraction of the affected EDC was always combined with electrical stimulation for 8 h during the daytime (from 07:00 to 15:00). Stimulation parameters, that is, the range of stimulus intensity, the sensitivity of the EMG, the threshold of EMG amplitude which triggers stimulation, and gradient of stimulus intensity change to the change of EMG amplitude were set once a week using an external adjustment device.[27,28,33] Each participant underwent 90 min of occupational therapy involving gentle passive stretching 5 days per week. During these sessions, participants were instructed to concentrate on the proprioceptive sensation, muscular contraction, or both. In addition, occupational therapy sessions included active reeducation of the paretic upper extremities (i.e. shaping tasks). Participants were instructed, encouraged, and monitored to use their paretic limbs during tasks associated with real-life ADLs by rehabilitation nurses in the rehabilitation ward.[27,33] In brief, several practical tasks including lifting and grasping water bottles, opening and shutting drawers, drawing curtains, table cleaning, grasping and releasing towels, pinching clothes pegs, holding a hairdryer, opening a pack of seasonings, and locking doors were individually and subjectively enumerated by each participant through discussions with nurses and physiatrists referring to bilateral or unilateral ADL training studies.[38,39] The frequency of each task execution was monitored with a self-assessment information sheet, and the items were modified as necessary. For the purpose of facilitation, the self-assessment sheet was daily checked, and Motor Activity Log-14 (MAL-14) was weekly scored. In addition, occupational therapists gave participants complementary homework including picking up pegs, tearing paper into pieces, drawing lines or writing letters, and reaching forward, upward, or both to move blocks. In addition, conventional physiotherapy, including the training of gait, balance and muscle strengthening, stretching of the lower extremities, and aerobic exercise using an ergometer, was applied for those participants over the same duration as the occupational therapy in order to assess whether ordinary training induces plastic changes in tibial nerve SEP.

Outcomes

Although motor functional assessments were defined as the primary outcomes in the overall interventional study, the sensory-related secondary outcomes: SEP parameters, Semmes–Weinstein monofilament, and thumb localizing tests (TLTs) were mainly analyzed in this specific study. In addition, Fugl-Meyer Assessment for the upper limb, Modified Ashworth Scale, SIAS, and MAL-14 were compared. All of the assessments were performed 1 day before and after the HANDS intervention by professional practitioners without conflicts of interest, however, the blinding was difficult in this study.

Electrophysiological assessment

SEP recording. SEP was applied as an electrophysiological sensory assessment with high reliability to clinical sensory indices including tactile sensation and proprioception.[20,40] SEPs were recorded from the bilateral median and tibial nerves using Neuropack 2300 (Nihon-Kohden, Tokyo, Japan). In accordance with the methods used in previous studies,[23,24] the active electrodes were placed at Cp3 for the median nerve and 2 cm anterior to Cp3 for the tibial nerve. In addition, SEPs were simultaneously recorded from Cp4, 2 cm anterior to Cp4 and Cz. The reference values were determined by averaging the signals from the bilateral earlobe electrodes. N13 in the median nerve and N19 in the tibial nerve were assessed at the C5 (reference: earlobe) and Th12 spinal levels (reference: 15 cm rostral to the Th12 electrode). The ground electrode was placed at the Fz position. The impedance of each electrode was maintained under 5 kΩ.

In the SEP recording, nerves were stimulated at the wrist and the posterior portion of the internal condyle, respectively. Median nerves were bilaterally stimulated with a 0.2 m^2 wave at a stimulation intensity that induced visible yet minimal muscular contraction of the abductor pollicis brevis muscle (approximately 6–10 mA). Stimulation was alternately applied to the wrist at a frequency of 2.05 Hz (i.e. 1.025 Hz for each side). Signals were recorded from −20 to 100 ms for each pulse, digitized at a sampling frequency of 5000 Hz, and band-pass filtered at 2–2000 Hz. Values applied

for the analysis were calculated as an average of two independent recordings, which were obtained for 500 sweeps *via* the addition-averaging method.[22–24]

Analysis of SEP wave forms. To count the number of central SEP peaks, we evaluated NI(N20), PI(P25), NII(N33), PII(P45), and NIII(N60) for the median nerve and N31, P35, N42, P53, and N66 for the tibial nerve. The existence of SEP peaks and the parameters were manually judged and measured by two EEG experts (a clinical technologist and a board-certified physiatrist) masked to participant's clinical information, and the average value of these two measurements was used in the analyses. Then, the latency and paretic–nonparetic amplitude ratios were analyzed. To minimize the effect of idiosyncrasies, the latency delay and the ratio amplitude were normalized by the values from the nonparetic side, and the between peak latency was applied for the assessments. With regard to the amplitude, a value of 0 was applied when the peak could not be determined. These values were calculated only for peaks that had been preserved from pretreatment.

Behavioral assessments

SWMT. The finer limits of the tactile sensory threshold were determined using a Semmes–Weinstein sensory tester (Sakai Medical. Co. Ltd., Tokyo, Japan). Owing to its high reliability, this method is widely applied in clinics and to the research of various diseases.[41] In summary, the monofilaments were perpendicularly applied to the palmar surface of the thumb and index finger three times by the same examiner. The force was sufficiently applied until the filament bends or twists. One or more false examination(s), in which the filament was not actually touched on the skin, were included other than in three measurements. If the participant gave incorrect answers more than once, we judged the filament strength as below threshold. Average values were recorded with the examinee in the supine position with their eyes closed.[42]

TLT. Proprioception was assessed using the TLT, which rates the accuracy of the tested limb's movement in pinching or grasping the thumb of the opposite hand during passive movement when the examinee's eyes are closed. Results are rated as follows: 0° (normal) the limb can catch the thumb without trembling; I° the limb can catch the thumb with light trembling or with correction; II° the limb cannot catch the thumb and searches the airspace several centimeters away from it, or the tested limb contacts the opposite hand and reaches the thumb *via* tracing; III the limb cannot catch the thumb but reaches airspace >10 cm away from it, or the tested limb contacts the opposite arm and reaches the thumb *via* tracing. The average of three trials was recorded as an integral number. This method was developed as an assessment for the posterior column–medial lemniscal system, and its strong correlations with deficits of deep or discriminative perceptions, including a sense of joint position and movement and tactile cutaneous localization, were reported.[43,44]

FMA for the upper limb. Motor function was evaluated using the FMA.[45] In brief, the motor function of the paretic upper extremity was assessed based on 33 independent factors of movement, each rated along a scale from 0 to 2. Subscores for proximal items (shoulder, elbow, and coordination: 42 points, FMA-p) and distal items (hand and wrist: 24 points, FMA-d) were applied for statistical analyses, as in previous studies.[34]

MAS. The spasticity of the upper extremity was assessed using the MAS for the elbow, wrist, and finger flexors.[46]

SIAS. The general status of impairment was assessed using the SIAS, which encompasses 22 categories including motor and sensory function, spasticity, and cognition.[36,37] In brief, items associated with a light touch and position sensation were scored from 0 (sensory deficit) to three (no remarkable impairment). Touch disturbances were evaluated as the degree of change relative to the unaffected side. Position disturbances were evaluated as the accuracy of passive joint movement at the index finger or thumb and great toe. Motor function was assessed across five categories: knee–mouth test, finger test, hip-flexion, knee-extension, and ankle-dorsiflexion. Performance on these five domains was rated from 0 (complete paralysis) to five (no remarkable impairment). The knee–mouth test assesses the proximal function of the upper extremity when raising the paretic arm from the knee to the mouth. Scores of one on the finger test were further categorized into three levels of impairment: 1a (mass flexion possible), 1b (mass extension possible), and 1c (minimal individual movement).

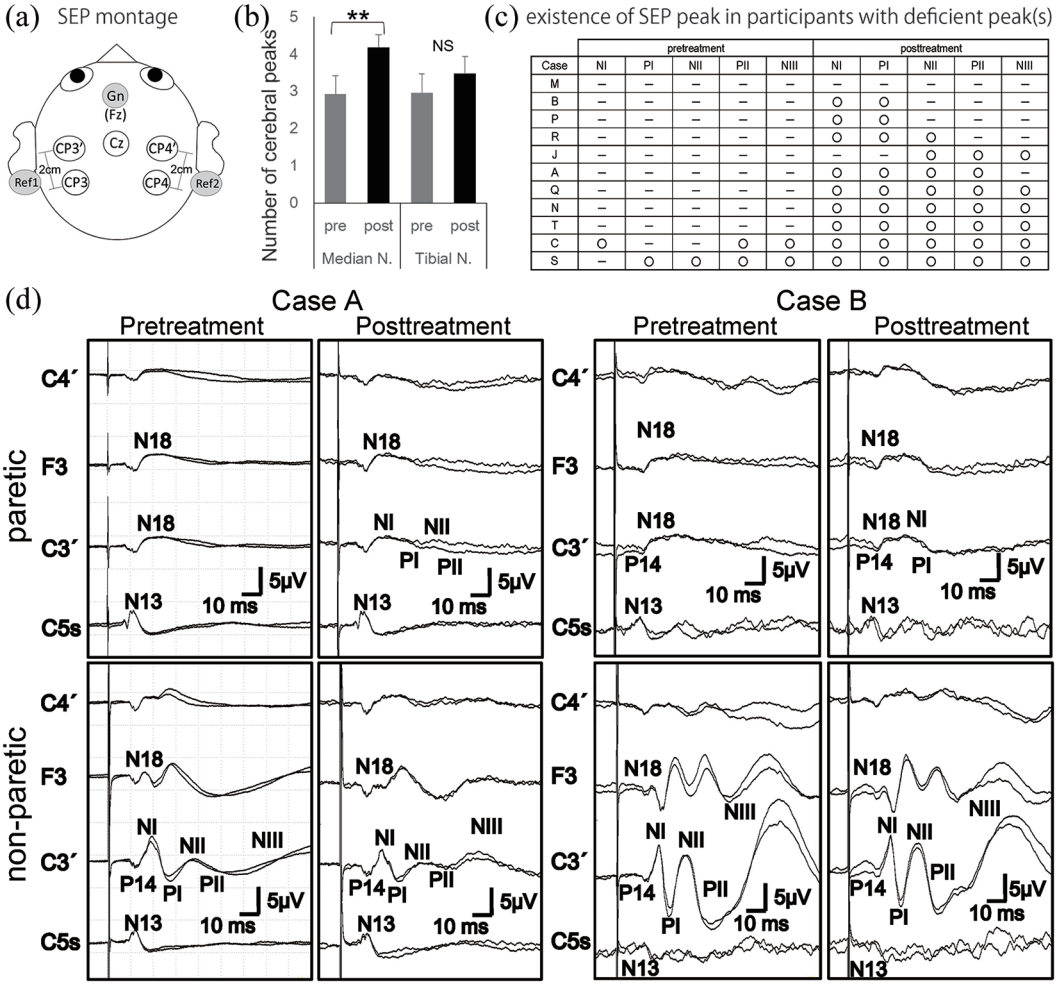

Figure 1. Features of somatosensory evoked potentials pre and post-treatment.
(a) Positions of EEG electrodes were shown. The active electrodes were placed at Cp3 for the median nerve and 2 cm anterior to Cp3 for the tibial nerve. SEPs were also simultaneously recorded from Cp4: 2 cm anterior to Cp4 and Cz. The reference values were determined by averaging the signals from the bilateral earlobe electrodes. The ground electrode was placed at the Fz. (b) Numbers of cortical peaks in the median and tibial nerves before and after hybrid assistive neuromuscular dynamic stimulation (HANDS) therapy ($n = 23$). Peak number was significantly increased in the median nerve after the intervention, but not in the tibial nerve (median nerve, $p = 0.008$; tibial nerve, $p = 0.11$, Wilcoxon signed-rank test). (c) Schematic table showing the change in the existence of the SEP peaks recorded from the median nerve in each case initial lacks SEP peak(s) ($n = 11$, circle: present, hyphen: deficient). (d) Representative median nerve SEP waves. SEP: somatosensory evoked potential.

MAL-14. The MAL-14 assesses the self-reported frequency at which the paretic upper extremity is used relative to the previous functioning, with scores ranging from 0 (not used) to five (used at the same frequency as before the onset).[47]

Statistical analyses. Wilcoxon signed-rank tests were used to compare assessment scores and the number of SEP peaks between the pre and post-treatment conditions [Table 2 and Figure 1(b)]. Paired t tests were used to compare parametric data between two conditions: latency delay [Figure 2(a)] and between peak latency [Figure 2(b)] and, ratio amplitude [Figure 2(c)]. All the analyses were carried out using SPSS version 25 (IBM Corp., Armonk, NY, USA). All data are presented as the mean ± SEM.

Results

Participant characteristics are summarized in Table 1. Table 2 shows the pretreatment and post-treatment clinical assessment scores (Table 2, $n = 23$, Wilcoxon signed-rank tests). Among the

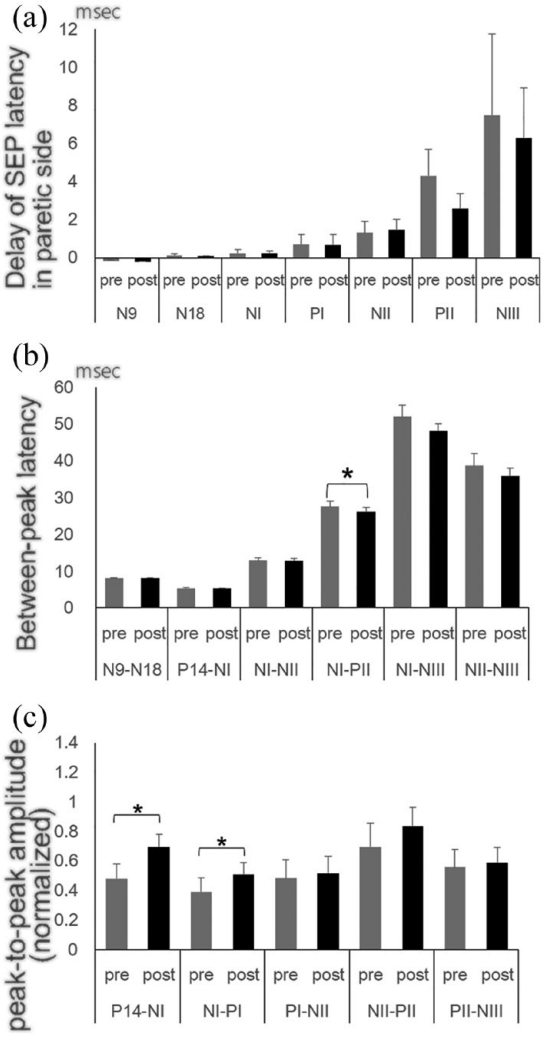

Figure 2. Detailed analysis for median nerve somatosensory evoked potentials (SEPs).
(a) Graph showing the delay in latencies in the paretic side compared with the nonparetic side, at pre and post-treatment. Values were calculated in regard to initially observed peaks ($n = 23$, N9 and N18: $n = 13$, NI, PI, and NII: $n = 14$, PII, and NIII). Although significant differences were not detected in any of the peaks, a weak trend was observed in the PII peak ($p = 0.093$, t test). (b) Between peak latencies on the paretic side. Values were calculated in regard to initially observed peaks ($n = 23$, N9–N18: $n = 13$, P14-NI, NI-PII, NI-NIII, and NII-NIII: $n = 12$, NI-NII). Significant shortening in the latency of NI–N45 was observed after the intervention (*: $p < 0.05$, t test). (c) Standardized peak-to-peak amplitude in the paretic side (paretic/nonparetic). No significant difference was observed between pre and post-treatment ($n = 13$).

Table 1. Patient characteristics.

Age	**52.1 ± 14.5 years**
Sex	Female ($n = 13$), Male ($n = 10$)
Diagnosis	Ischemia ($n = 10$), hemorrhage ($n = 12$) subarachnoid hemorrhage ($n = 1$)
Hemiparetic side	Left ($n = 13$), right ($n = 10$)
Days after onset	740.4 ± 517.0
SIAS score	Knee–mouth: 2.83 ± 0.39 Finger test: 1.29 ± 0.32 Hip-flexion: 3.30 ± 0.56 Knee-extension: 3.00 ± 0.60 Ankle-dorsiflexion: 1.91 ± 0.85

sensory assessments, significant improvement was observed for the TLT only ($p = 0.018$). However, significant recovery of motor function in the upper extremity was observed based on all four sub-scores of the FMA [distal scores (B: hand joint and C: hand and finger) and proximal scores (A: shoulder, elbow, and forearm function and D: coordination and speed of gross proximal movement)] (Supplementary Table 1. FMA-distal, $p < 0.001$: FMA-proximal, $p < 0.001$: FMA-total, $p < 0.0001$). No significant changes in spasticity were detected at the elbow, wrist, or finger joints using the MAS ($p > 0.05$). MAL-14 results indicated that practical daily use of the paretic upper extremity significantly improved following the intervention ($p < 0.0001$). With the SIAS, significant functional recovery was only observed for finger function ($p = 0.033$). No remarkable adverse events were observed during this intervention.

When comparing the number of pre and post-treatment central SEP peaks after NI, we observed significant recovery in the median nerve, although no such difference was observed for the tibial nerve [Figure 1(b) median nerve: pretreatment 2.91 ± 0.51; post-treatment 4.17 ± 0.34; $p = 0.0077$, tibial nerve: pretreatment 2.96 ± 0.51; post-treatment 3.43 ± 0.46; $p = 0.11$, Wilcoxon signed-rank test]. Figure 1(c) summarizes the existence of the SEP peaks for participants with deficient SEP peak(s) before the intervention [Figure 1(c), $n = 11$]. The numbers of participants where new peaks appeared were as follows: NI ($n = 8/10$ participants), PI ($n = 8/10$), NII ($n = 7/10$), PII ($n = 5/9$), and NIII ($n = 4/9$). There was only one nonresponder in our sample. No patients showed a loss of peak(s) after the intervention. Representative median nerve SEP waves are shown in Figure 1(d),

Table 2. Sensory functional changes induced by HANDS therapy.

		Pretreatment	Post-treatment	*p* value
SWMT	Thumb	4.07 ± 1.24	4.13 ± 1.43	0.43
	Index finger	4.17 ± 1.39	4.15 ± 1.40	0.64
TLT		1.26 ± 1.05	0.87 ± 0.97	0.018

HANDS, hybrid assistive neuromuscular dynamic stimulation; SWMT, Semmes–Weinstein monofilament test; TLT, thumb localizing test.

which clearly shows the post-treatment NII peak, as well as a suspected NIII peak at C3 in case A, and also the post-treatment NI peak in case B.

We then analyzed each component of the SEP wave (i.e. latency and amplitude) of the median nerve. In the nonparetic side, no significant changes were observed in the between peak latencies of central SEP peaks and N18, which is generated at the caudal most brain-stem,[48] and in the voltage differences between each neighboring peak (Supplementary figure 1(a), (b), *t* test). Then, to normalize the latencies with regards to idiosyncrasies, the latency delay on the paretic side was compared between pre and post-treatment. Although significant differences were not detected in any of the peaks, a weak trend was observed in PII peak (Figure 2(a) PII latency: pretreatment 4.29 ± 1.37; post-treatment 2.59 ± 0.78; $p = 0.093$, *t* test). In the latencies between specific sections (i.e. between peak latency), a significant reduction was observed at NI-PII on the paretic side after the intervention (Figure 2(b), NI-PII between peak latency: pretreatment 27.64 ± 5.38; post-treatment 26.25 ± 4.22; $p = 0.045$, *t* test), and no significant changes were observed for any other pairs of peaks. To investigate changes in amplitude between neighboring SEP peaks, we calculated the amplitude ratios between the paretic and nonparetic sides. A significant increase was detected in the ratios of P14-NI and NI-PI, and no significant differences were observed for the latter peaks (Figure 2(c), P14-NI amplitude: pretreatment 0.482 ± 0.099; post-treatment 0.696 ± 0.085; $p = 0.022$, NI-PI amplitude: pretreatment 0.391 ± 0.098, post-treatment 0.051 ± 0.079; $p = 0.026$, *t* test). However, no remarkable differences were detected in these values among the SEPs recorded from tibial nerves (Supplementary Figure 2).

Discussion

In this study, we studied the effect of HANDS therapy on sensory and motor recovery in patients with chronic stroke. To the best of our knowledge, this study is the first to focus on changes in sensory processing using electrophysiological methods in conjunction with NMES training in this patient population.

Following the interventions, we observed significant improvements in behavioral assessment scores for proprioception, but not for tactile sensation. These results may be explained by the finding that recovery of proprioception increases during the chronic phase and the recovery of tactile sensation decreases in the relatively early phase.[7] Because IVES amplifies the electrical activity and contraction of the target muscle, this process probably stimulates proprioceptive perception.[33] In addition, the occupational therapy performed in this study involved sensorimotor training (i.e. passive stretching with muscular contraction), which may have contributed to this trend by helping to integrate afferent proprioceptive stimuli and actual movement, that is, the sensorimotor feedback loop is activated and strengthened in a task-specific manner by HANDS therapy. Because SEPs reflect tactile sensation and proprioception,[20] our findings suggest that the observed functional recovery is due to the recovery of the proprioceptive system.

Of note, while a significant improvement was observed in the median nerve SEPs after the HANDS intervention, no significant or remarkable changes were detected from the tibial nerves in lower extremities where basic physiotherapy was given over the same intervention period. Consistent with a previous report,[17] this result implies that conventional rehabilitation does not

sufficiently induce somatosensory plasticity detectable with SEP in chronic stroke patients.

Interpretation of SEP recovery

In general, it is widely accepted that the NI component originates from the primary sensory area because it is only observed in the contralateral post-rolandic scalp, while the NI-PII is characterized as a postcentral cortical component.[22,49] Previous studies indicate that greater numbers of postcentral peaks are associated with better sensory perception.[22] These findings suggest that the observed restoration of SEP peaks corresponds to plasticity in the primary sensory cortex itself and the associated improvements in signal processing. The improvements observed in the present study may be due to two aspects of the intervention. First, 8 of the 10 participants without initial NI or PI peaks exhibited restoration of these peaks following the intervention [Figure 1(c)], accompanied by the increase in the amplitudes of P14-NI and NI-PI. In addition to the restoration of later peaks, improvements may have been related to decreased latency of later components. A significant decrease in the latency gap was observed between NI and PII, along with a possible simple decrease in PII latency [Figures 2(a) and (b)].

Recovery of earlier cortical components may be due to plastic changes, as represented by the restoration of NI peaks, which was probably induced by increased sensory input due to electrical stimulation and functional use. Researchers have reported that high-frequency somatosensory stimulation induces an increase in the amplitude of the NI-PI component, and improvements in behavioral perception, in healthy controls.[21] Because IVES involves the application of electrical stimulation to muscles and sensory terminals, similar effects might occur using this modality. In addition, because IVES directly amplifies electrical activity and promotes actual contraction of the target muscle by stimulating muscular proprioception in a synchronous manner,[33] sensory feedback is provided in a more physiological manner, which may explain the observed enhancements in recovery.[50] Previous studies have reported that a home based exercise program combined with toxin A botulinum injections, which not only reduce spasticity but also increase daily functional use of the paretic limb, promotes the restoration of NI-PI amplitude.[51,52] Based on these findings, we speculate that proprioceptive perception from muscle spindles and central neuroplasticity underlie these changes. In combination, the accumulated evidence suggests that intensive occupational and ADL training together with a significant increase in daily use of the paretic limb are vital to induce plastic changes.

Previous studies have reported that changes in later cortical components including NI-PI or PI-NII reflect plastic changes in sensorimotor integration.[53,54] The shortening of the NI-PII latency gap observed in this study may reflect such improvements. In addition, among all of the sensory tests only TLT scores, which reflect proprioception and sensorimotor integration,[44] were improved by HANDS therapy. However, SEPs recorded around the primary sensory cortex alone provide only a limited view of cortical plasticity due to HANDS therapy. Future studies should utilize combined imaging and electroencephalography to provide further insight into the mechanisms underlying NEMS-based rehabilitative interventions for chronic stroke.

Study limitations

This study possesses some limitations to note. First, our study was an interventional study without appropriate control participants. Therefore, it is impossible to determine if NMES, or a different aspect of the therapeutic treatments composing HANDS therapy, resulting in the improvements observed, even though the tibial nerve SEPs from lower extremities can be regarded as a control to some extent. Second, although this study has enough power to detect significant changes in behavioral and electrophysiological assessments, the number of included participants was too small to perform stratified analyses of SEP waveforms or the severity of the sensory disturbance. Third, we cannot exclude the possibility of selection bias. Fourth, our participants do not represent the entire population of stroke survivors. Fifth, our intervention was carried out as inpatient treatment, the feasibility of which will differ between countries. Although we required participants to be monitored and facilitated the use of their paretic limb in their ADL, such NMES-based treatment could possibly be carried out on an outpatient basis as in a previous study.[31] Sixth, our intervention allowed four participants to receive botulinum toxin A injections when required (Supplementary Table 2), which may affect the feature of SEP.[25]Further analyses excluding these participants demonstrated

approximately the same statistical results, all of the significant differences were preserved and an additional two others were detected: shortenings of PII latency (pretreatment 4.29 ± 1.37; post-treatment 2.59 ± 0.78; $p = 0.027$) and N9-N18 between peak latency (pretreatment 8.2 ± 0.1; post-treatment 8.1 ± 0.1; $p = 0.040$). The former implies that more robust somatosensory cortical plasticity was induced by HANDS therapy, while the latter appears difficult to interpret due to the very small variance. It is well known that the initial tonus weakening does not occur for several days[55] and that the change could be statistically detectable from 3–6 weeks after the injection.[56] Therefore, it is suggested that the influence of botulinum therapy on somatosensory plasticity was limited during the rest of the intervention, even though some motor functional improvements were induced. Seventh, our results lack the quantitative data in terms of the amount of IVES stimulation, hand opening repetitions, or actual time of voluntary ADL training with the HANDS system which makes it difficult to evaluate the dose responsibility.

Conclusion

The results of this study demonstrate that HANDS therapy, which utilizes closed-loop NMES, promotes motor and sensory (proprioceptive) recovery in patients with chronic stroke. We observed the restoration of the NI peak in the majority of patients with poor pretreatment SEP responses, which may reflect plastic changes in the primary somatosensory cortices. In addition, we observed a shortening of PII latency, suggesting that HANDS therapy modifies sensorimotor processing. These findings indicate that neurorehabilitation induces sensory and motor-related brain plasticity *via* the activation of a sensorimotor feedback loop. In addition, our results emphasize the importance of assessing sensory function using behavioral and electrophysiological methods, even when rehabilitative methods for stroke are targeted toward motor recovery.

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Conflict of interest statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental material

Supplemental material for this article is available online.

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