Neural Plasticity in Moderate to Severe Chronic Stroke Following a Device-Assisted Task-Specific Arm/Hand Intervention

Kevin B. Wilkins1,2, Meriel Owen1,2, Carson Ingo1, Carolina Carmona1, Julius P. A. Dewald1,2,3,4 and Jun Yao1,2*

1Department of Physical Therapy and Human Movement Sciences, Northwestern University, Chicago, IL, United States, 2Northwestern University Interdepartmental Neuroscience, Northwestern University, Chicago, IL, United States, 3Department of Biomedical Engineering, Northwestern University, Chicago, IL, United States, 4Department of Physical Medicine and Rehabilitation, Northwestern University, Chicago, IL, United States

Currently, hand rehabilitation following stroke tends to focus on mildly impaired individuals, partially due to the inability for severely impaired subjects to sufficiently use the paretic hand. Device-assisted interventions offer a means to include this more severe population and show promising behavioral results. However, the ability for this population to demonstrate neural plasticity, a crucial factor in functional recovery following effective post-stroke interventions, remains unclear. This study aimed to investigate neural changes related to hand function induced by a device-assisted task-specific intervention in individuals with moderate to severe chronic stroke (upper extremity Fugl-Meyer < 30). We examined functional cortical reorganization related to paretic hand opening and gray matter (GM) structural changes using a multimodal imaging approach. Individuals demonstrated a shift in cortical activity related to hand opening from the contralesional to the ipsilesional hemisphere following the intervention. This was driven by decreased activity in contralesional primary sensorimotor cortex and increased activity in ipsilesional secondary motor cortex. Additionally, subjects displayed increased GM density in ipsilesional primary sensorimotor cortex and decreased GM density in contralesional primary sensorimotor cortex. These findings suggest that despite moderate to severe chronic impairments, post-stroke participants maintain ability to show cortical reorganization and GM structural changes following a device-assisted task-specific arm/hand intervention. These changes are similar as those reported in post-stroke individuals with mild impairment, suggesting that residual neural plasticity in more severely impaired individuals may have the potential to support improved hand function.

Keywords: stroke, hand rehabilitation, EEG, cortical reorganization, voxel-based morphometry, functional electrical stimulation, gray matter, neuroplasticity

INTRODUCTION

Nearly 800,000 people experience a new or recurrent stroke each year in the US (1). Popular therapies, such as constraint-induced movement therapy (CIMT), utilize intense task-specific practice of the affected limb to improve arm/hand function in acute and chronic stroke with mild impairments (2, 3). Neuroimaging results partially attribute the effectiveness of these arm/hand interventions to
cortical reorganization in the ipsilesional hemisphere following training in acute and mild chronic stroke (4). Unfortunately, CIMT requires certain remaining functionality in the paretic hand to execute the tasks, and only about 10% of screened patients are eligible (5), thus disqualifying a large population of individuals with moderate to severe impairments. Recently, studies using device-assisted task-specific interventions specifically targeted toward moderate to severe chronic stroke reported positive clinical results (6–8). However, these studies primarily focus on clinical measures, but it is widely accepted that neural plasticity is a key factor for determining outcome (9–11). Consequently, it remains unclear whether moderate to severe chronic stroke [upper extremity Fugl-Meyer Assessment (UEFMA) < 30] maintains the ability to demonstrate neural changes following an arm/hand intervention.

Neural changes induced by task-specific training have been investigated widely using animal models (12). For instance, monkeys or rodents trained on a skilled reach-to-grasp task express enlarged representation of the digits of the hand or forelimb in primary motor cortex (M1) following training as measured by intracortical microstimulation (13, 14). Additionally, rapid local structural changes in the form of dendritic growth, axonal sprouting, myelination, and synaptogenesis occur (15–18). Importantly, both cortical and structural reorganization corresponds to motor recovery following rehabilitative training in these animals (19, 20).

The functional neural mechanisms underlying effective task-specific arm/hand interventions in acute and chronic stroke subjects with mild impairments support those seen in the animal literature described above. Several variations of task-specific combined arm/hand interventions, including CIMT, bilateral task-specific training, and hand-specific robot-assisted practice, have shown cortical reorganization such as increased sensorimotor activity and enlarged motor maps in the ipsilesional hemisphere related to the paretic arm/hand (21–24). These results suggest increased recruitment of residual resources from the ipsilesional hemisphere and/or decreased recruitment of contralesional resources following training. Although the evidence for a pattern of intervention-driven structural changes remains unclear in humans, several groups have shown increases in gray matter (GM) density in sensorimotor cortices (25), along with increases in fractional anisotropy in ipsilesional corticospinal tract (CST) (26) following task-specific training in acute and chronic stroke individuals with mild impairments.

The extensive nature of neural damage in moderate to severe chronic stroke may result in compensatory mechanisms, such as contralateral or secondary motor area recruitment (27). These individuals show increased contralateral activity when moving their paretic arm, which correlates with impairment (28, 29) and may be related to the extent of damage to the ipsilesional CST (30). This suggests that more impaired individuals may increasingly rely on contralateral corticobulbar tracts such as the corticoropulospinal tract to activate the paretic limb (29). These tracts lack comparable resolution and innervation to the distal parts of the limb, thus sacrificing functionality at the paretic arm/hand (31). Since this population is largely ignored in current arm/hand interventions, it is unknown whether an arm/hand intervention for these more severely impaired post-stroke individuals will increase recruitment of residual ipsilesional corticospinal resources. These ipsilesional CSTs maintain the primary control of hand and finger extensor muscles (32) and are thus crucial for improved hand function. Task-specific training assisted by a device may reengage and strengthen residual ipsilesional corticospinal resources by training distal hand opening together with overall arm use.

The current study seeks to determine whether individuals with moderate to severe chronic stroke maintain the ability to show cortical reorganization and/or structural changes alongside behavioral improvement following a task-specific intervention. We hypothesize that following a device-assisted task-specific intervention, moderate to severe chronic stroke individuals will show similar functional and structural changes as observed in mildly impaired individuals, demonstrated by (i) a shift in cortical activity related to paretic hand opening from the contralateral hemisphere toward the ipsilesional hemisphere and (ii) an increase in GM density in sensorimotor cortices in the ipsilesional hemisphere.

**MATERIALS AND METHODS**

**Subjects**

Eight individuals with chronic hemiparetic stroke (age: 63.5 ± 4) and moderate to severe impairment (UEFMA: 11–24) participated in this study. Clinical information for each subject is provided in Table 1 and lesion locations in Figure 1. All individuals were screened for inclusion by a licensed physical therapist. Inclusion criteria include a UEFMA between 10 and 30 out of 66, no cognitive impairment, ability to engage in practice 1 hour per day for 6 weeks, and they must be eligible (5) thus disqualifying a large population of individuals with moderate to severe impairments.

**TABLE 1 | Subject demographics and clinical characteristics.**

| Subject | Age range (years) | Time since stroke (years) | Lesioned hemi | Lesion location | UE FMA | Pre BBT | Post BBT | Pre AROM (°) | Post AROM (°) |
|---------|------------------|--------------------------|---------------|----------------|--------|---------|----------|-------------|--------------|
| S01     | 60–65            | 9                        | L             | IC             | 23     | 0       | 6        | −20         | 11           |
| S02     | 60–65            | 8                        | R             | IC, BG         | 12     | 1       | 3        | 0           | 5            |
| S03     | 65–70            | 3                        | R             | Par, Occ, IC   | 17     | 0       | 1        | 0           | 0            |
| S04     | 60–65            | 22                       | R             | IC, BG, Thal   | 11     | 0       | 1        | 0           | 17.5         |
| S05     | 60–65            | 13                       | R             | Occ, IC        | 24     | 0       | 0        | 0           | 2.5          |
| S06     | 70–75            | 20                       | L             | IC, BG, Thal   | 13     | 0       | 0        | 0           | 1.5          |
| S07     | 55–60            | 6                        | L             | IC, BG         | 24     | 0       | 3        | 0           | 5            |
| S08     | 60–65            | 9                        | L             | IC, Thal       | 22     | 11      | 13       | 38.5        | 55           |

AROM, active range of motion; BBT, Box and Blocks Test; BG, basal ganglia; FMA, Fugl-Meyer Assessment; IC, internal capsule; Occ, occipital lobe; Par, parietal lobe; Thal, thalamus; UE, upper extremity.
or perceptual impairment, no botulinum toxin within the last 6 months, MRI compatibility, no lesion including sensorimotor cortices, the ability to elicit enough EMG activity at wrist/finger extensors, and the ability for the FES to generate a hand opening of at least 4 cm between the thumb and the index finger. This study was approved by the Northwestern University institutional review board, and all subjects gave informed consent.

**Experimental Protocols**

**Intervention**

Subjects participated in a 7-week intervention consisting of three 2-h visits per week. During the visit, subjects completed 20–30 trials of the following sequence of movements: (1) reaching out toward a jar, (2) driving the wrist/finger extensors to open the paretic hand, (3) grabbing the jar, (4) bringing the jar back toward themselves, and (5) releasing the jar. The weight, distance/height, and orientation of the jar relative to the subject were progressively altered to increase the challenge to each subject, as determined by the physical therapist. All subjects started the motor task with the arm supported by the table. Depending on ability, subjects were encouraged to progressively lift the paretic limb actively. During the task, a novel EMG-FES device, called ReIn-Hand, was used to assist paretic hand opening (see Figure S1 in Supplementary Material). This device recorded EMG activities from eight muscles (deltoid, biceps brachii, triceps, extensor communis digitorum, extensor carpi radialis (ECR), flexor digitorum profundus, flexor carpi radialis (FCR), and abductor pollicis). While the user performed the functional reaching and opening, the ReIn-Hand detected hand opening by extracting EMG features to trigger an Empi transcutaneous electrical opening, the ReIn-Hand detected hand opening by extracting EMG features to trigger an Empi transcutaneous electrical opening, the ReIn-Hand detected hand opening by extracting EMG features to trigger an Empi transcutaneous electrical opening, the ReIn-Hand detected hand opening by extracting EMG features to trigger an Empi transcutaneous electrical opening.

Pre- and Post-Intervention Tests

**Clinical Assessments**

For each subject, within 1 week prior to and following the intervention, a licensed physical therapist completed a set of clinical assessments, with the motor-related parts including UEFMA, Box and Blocks Test (BBT), and active range of motion (AROM) averaged over the II and V digit.

**Structural Imaging of the Brain**

Within 2 weeks prior to and following the intervention, subjects participated in MRI scans at Northwestern University’s Center for Translation Imaging on a 3 TS Prisma scanner with a 64-channel head coil. Structural T1-weighted scans were acquired using an MP-RAGE sequence (TR = 2.3 s, TE = 2.94 ms, FOV 256 mm × 256 mm) producing an isotropic voxel resolution of 1 mm × 1 mm × 1 mm. Visual inspection of acquired images was performed immediately following the data acquisition to guarantee no artifacts and stable head position.

**Functional Imaging Related to Hand Opening**

Within 1 week prior to and following the intervention, subjects also participated in an EEG experiment. During the EEG experiment, participants sat in a Biodex chair (Biodex Medical Systems, Shirley, NY, USA), which restrained the trunk with straps crossing the chest and abdomen. The subject’s paretic arm was placed in a forearm-hand orthosis attached to the end effector of an admittance controlled robotic device (ACT™) instrumented with a six degree of freedom load cell (JR3, Inc., Woodland, CA, USA). At the beginning of each trial, subjects moved their hand to a home position, with the shoulder at 85° abduction, 40° flexion, and the elbow at 90° flexion angle. The subject then received an auditory cue. Following the cue, subjects relaxed at the home position for 5–7 s and then self-initiated a maximum attempted paretic hand opening with the arm resting on a haptic table.

![Lesion locations for the eight subjects overlaid on axial Montreal Neurological Institute T1 slices. The color bar indicates the number of subjects with lesioned tissue in a particular voxel. LH indicates the lesioned hemisphere.](image-url)
Subjects were instructed to avoid eye movements by focusing on a point and avoid movements of other body parts during the performance of each trial, which was visually confirmed by the experimenter. Subjects performed 60–70 trials of attempted paretic hand opening, broken into blocks (one block consisted of 20–30 trials). Rest periods varied between 15 and 60 s between trials and 10 min between blocks. The typical duration of the experiment was around 5–6 h, including ~2 h of setup, ~1 h for lunch, and ~2 h of data collection.

Scalp recordings were made with a 160-channel high-density EEG system using active electrodes (Biosemi, Inc., Active II, Amsterdam, The Netherlands) mounted on a stretchable fabric cap based on a 10/20 system. Simultaneously, EMGs were recorded from the ECR, FCR, and intermediate deltoid of the paretic arm. All data were sampled at 2,048 Hz. The impedance was kept below 5 kΩ for the duration of the experiment. Additionally, the positions of EEG electrodes on the subject’s scalp were recorded with respect to a coordinate system defined by the nasion and preauricular notches using a Polaris Krios handheld scanner and reflective markers (NDI, ON, Canada). This allowed for coregistration of EEG electrodes with each subject’s anatomical MRI data. Due to post-stroke abnormal synergy, finger/wrist extensors and flexors, and often the shoulder abductors, usually co-activate together when performing maximal hand opening (34). Therefore, in order to provide a reliable indicator of movement onset, EMGs were simultaneously recorded from the ECR, FCR, and anterior deltoid (IDL) of the paretic arm.

Data Analysis
Reorganization of Cortical Activity Related to Hand Opening
EEG data were aligned to the earliest EMG onset of the three muscles and segmented from −2,200 to +200 ms (with EMG onset at 0 ms) using Brain Vision Analyzer 2 software (Brain Products, Gilching, Germany). Data were then visually inspected for the presence of artifacts. Trials exhibiting artifacts (e.g., eye blinks) were eliminated from further analysis. The remaining EEG trials were baseline-corrected (from −2,180 to −2,050 ms), low-pass-filtered at 70 Hz, and ensemble-averaged. The averaged EEG signals were down-sampled to 256 Hz and imported into CURRY 6 (Compumedics Neuroscan Ltd., El Paso, TX, USA). The cortical current density strength (µA/mm²) in the time between 150 and 100 ms prior to EMG onset was computed using the standardized low-resolution electromagnetic brain tomography (sLORETA) method (Lp = 1) based on a subject-specific boundary element method model with the regulation parameter automatically adjusted to achieve more than 99% variance counted (36, 37). Possible sources were located on a cortical layer with 3 mm distance between each node. Although the inverse calculation was performed over the whole cortex, only the activity in bilateral sensorimotor cortices was further analyzed. Specific regions of interest (ROI) included bilateral primary sensorimotor cortices [primary motor cortex (M1) + primary sensory cortex (S1)] and secondary motor cortices [supplementary motor area (SMA) + premotor area (PM)].

To investigate the shift of cortical activity related to hand opening, we used the estimated current density strengths to calculate a laterality index [LI = (I − C)/(I + C)], where I and C are the current density strengths from the ipsilesional and contrallesional sensorimotor cortices, respectively (i.e., combined primary sensorimotor and secondary motor cortices). LI reflects the relative contributions of each cerebral hemisphere to the source activity, with a value close to +1 for an ipsilesional source distribution and −1 for a contrallesional source distribution.

Additionally, we quantified a cortical activity ratio

\[ \text{CAR} = \frac{\sum_{i} s_i}{\sum_{i} s_{\text{m}}} \]

for each of the four ROIs, where \( S \) represents the current density strength of one of the nodes, and \( n \) and \( m \) represent the number of nodes in the ROI and whole sensorimotor cortices, respectively. The cortical activity ratio reflects the relative strength from one ROI as normalized by the total combined strength of the four ROIs.

Structural Changes in GM Density
Anatomical T1 data were analyzed with FSL-voxel-based morphometry (VBM) 1.1 (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM; Oxford University, Oxford, United Kingdom) (38) using FSL tools (39). First, T1 images for participants who have left hemisphere lesions were flipped to ensure that the lesions of all subjects were in the right hemisphere. The T1 images were then brain-extracted using the Brain Extraction Tool and segmented into GM using FAST4. The resulted GM partial volume images were aligned to Montreal Neurological Institute (MNI) 152 standard space using the affine registration tool FLIRT and averaged to create a study-specific GM template. Subsequently, individual GM partial volume images in native space were non-linearly registered to this template using FNI RT, modulated to correct for local expansion or contraction due to the non-linear component of the spatial transformation, and then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm. Finally, a voxel-wise General Linear Model was applied with Threshold-Free Cluster Enhancement (40) to detect changes in GM density following the intervention. Voxel-based threshold of changes in GM density was set at \( p < 0.001 \) uncorrected.

Statistical Analysis
Statistics were performed using SPSS (IBM, V23). Clinical and neural measures were examined for normality using a Shapiro–Wilk test. A Wilcoxon signed rank test was used if assumptions of normality were not met. A paired \( t \)-test was performed on LI. A 2 (time) × 4 (region) repeated measures ANOVA was performed on the cortical activity ratio. We performed post hoc paired \( t \)-tests when a main ANOVA effect was found. Significance was set at \( p < 0.05 \). Individual data are depicted for all significant findings.

RESULTS
Changes in Arm/Hand Function following EMG-FES Task-Specific Training
Table 1 shows pre and post BBT and AROM scores. Notably, most subjects initially scored a 0 on the pre-assessment BBT and
showed 0° of AROM due to the severity of their motor impairments at the arm/hand. The clinical data violated the assumptions of normality based on the Shapiro–Wilk test. Therefore, a Wilcoxon signed rank test was used and reported a significant increase in BBT following the intervention (average increase of 1.9 blocks per minute, \( p = 0.03 \); Table 1) and AROM (average increase of 9.9°, \( p = 0.03 \); Table 1), indicating improvement of paretic arm/hand control, although FMA did not change.

Cortical Reorganization Related to the Hand

Figure 2A shows an example of ensemble-averaged EEG for the 160 channels for Subject 1. There is a clear baseline from roughly −2 to −1.5 s prior to EMG onset and then a slow increase in electrical potential when approaching EMG onset, consistent with the Bereitschaftspotential. The reconstructed cortical activity for Subject 1 while performing hand opening on the table is depicted in Figure 2B pre-intervention and in Figure 2C post-intervention. This subject showed bilateral activity in sensorimotor cortex prior to the intervention as seen in Figure 2B and dominant ipsilesional activity following the intervention as seen in Figure 2C. We quantified the pre- and post-intervention LI in each of the participants (see results in Figure 3). A paired \( t \)-test found a significant increase in LI following the intervention \([t(7) = 3.09, p = 0.02]\), signifying a post-intervention shift toward the ipsilesional hemisphere.

To further investigate regions responsible for the post-intervention LI changes, we quantified the pre- and post-intervention cortical activity ratios for primary sensorimotor (M1/S1) and secondary motor (SMA/PM) cortices (see results in Figure 4). A 2 (time) × 4 (region) repeated measures ANOVA found a significant time × region interaction \([F(1,7) = 3.47, p = 0.03]\). Post hoc paired \( t \)-tests found that following the

![Figure 2](image-url)
intervention, there was a decrease in the cortical activation ratio in contralesional M1/S1 ($p = 0.04$) and a trending increase in ipsilesional SMA/PM ($p = 0.06$) related to paretic hand opening.

**GM Density**

Following the intervention, subjects displayed significantly greater GM density in M1 and S1 in the lesioned hemisphere ($x = 52, y = -16, z = 30, t$-value = 2.55, $p < 0.001$) and a decrease in GM density in M1 and S1 in the non-lesioned hemisphere ($x = -46, y = -20, z = 60, t$-value = 2.41, $p < 0.001$; $x = -44, y = -18, z = 36, t$-value = 2.79, $p < 0.001$) as depicted in Figures 5A, B.

Additionally, subjects displayed greater GM density in the thalamus in the lesioned hemisphere ($x = 2, y = -20, z = 10, t$-value = 3.13, $p < 0.001$) as shown in Figure 5C. A complete list of significant regions is provided in Table S1 in Supplementary Material.

**DISCUSSION**

The present study investigated neural changes in individuals with moderate to severe stroke following an EMG-FES-assisted task-specific arm/hand intervention. Specifically, we found a shift of sensorimotor cortical activity related to hand opening from contralesional to ipsilesional cortex, along with structural changes in the form of increased ipsilesional M1/S1 and decreased contralesional M1/S1 GM density. Although similar device-assisted hand/arm training in this population has been investigated before to examine behavioral improvements (7, 41, 42), this study provides evidence for corresponding neural changes even in this more severe chronic population.

**Shift toward Ipsilesional Hemisphere**

As expected, before the intervention, subjects showed cortical activity predominantly from the contralesional hemisphere related to open the paretic hand, as reflected by the overall negative LI. This contralesional activity may suggest an increased reliance on low-resolution contralesional corticobulbar pathways such as the corticoreticulospinal tract (31, 43) for general paretic arm function. In fact, more severely impaired subjects actually tend to involuntarily close the hand and activate shoulder muscles when asked to open (35), which may reflect this increased reliance on ipsilateral corticobulbar pathways that innervate primarily flexor hand and proximal muscles compared to extensors (44). These
pathways lack sufficient innervation to extensor muscles of the hand to produce appropriate hand opening (45) and are often associated with greater motor impairment (29, 31).

Effective hand/arm interventions in mildly impaired post-stroke individuals have reported a post-intervention shift toward ipsilesional sensorimotor areas (46, 47). This shift is thought to be a beneficial since it may indicate increased use of ipsilesional CSTs, which maintain the primary innervations to the extensor muscles of the hand (32). Intervention-induced shifts toward the ipsilesional hemisphere have rarely been investigated in more
severely impaired post-stroke individuals, especially not for arm/hand training partially due to the lack of inclusion of these subjects in arm/hand interventions. In this study, we found that a ReIn-Hand-assisted arm/hand intervention induced a positive change in LI. Our results suggest that even moderate to severe chronic stroke subjects maintain the ability to show similar cortical reorganization back toward the ipsilesional hemisphere following task-specific training as seen in more mild subjects. This ipsilesional shift may suggest decreased recruitment of contralesional corticobulbar pathways and increased reliance on ipsilesional CSTs during paretic hand opening, which may allow for greater functionality at the hand as seen by the increase in BBT and AROM. Additionally, it could reflect increased ability to actually drive hand opening when instructed rather than involuntary closing and activating proximal muscles (35). It is worth noting that only six out eight participants exhibited this intervention-induced shift despite all showing improvements on either BBT or AROM, possibly reflecting compensatory behavioral strategies following the intervention rather than recovery in these two participants.

**Changes in Cortical Activity Driving LI Shift**

We calculated the cortical activity ratio in each sensorimotor region to further elucidate which regions were contributing to the LI shift. Following the intervention, subjects showed decreased activity in contralesional primary sensorimotor cortex (M1/S1) and a trending increase in ipsilesional secondary motor cortex (SMA/PM).

Increased contralesional primary sensorimotor cortex activity is associated with greater impairment following stroke (48, 49) and greater damage to CST (50, 51). Therefore, this decreased activity could reflect either decreased recruitment of contralesional descending motor pathways or changes in interhemispheric balance between primary sensorimotor cortices (52) and thus allow for increased functional usage of the affected hand.

Stroke patients tend to activate secondary motor areas more following greater CST damage (51) and show positive correlations between ipsilesional secondary motor area activation and recovery (53, 54). The increased recruitment of ipsilesional SMA/PM may be due to increased recruitment of direct projections to the spinal cord (55), although these connections are not as efficacious as connections from M1 to the spinal cord (56). Alternatively, plasticity within intrinsic cortico-cortical neuronal connections in M1 (57) may allow increased communication between SMA/PM and M1 following injury. Thus, ipsilesional secondary motor areas may serve as a potential avenue for functionally relevant cortical reorganization via either descending or intrinsic connections in addition to removal of contralesional cortical activity.

**Increased GM Density in Ipsilesional Sensorimotor Cortex**

Previous work demonstrated significant decreases in GM volume in ipsilesional precentral gyrus following a subcortical stroke, which was associated with greater impairment (58). However, following task-specific training, mild chronic stroke subjects showed increases in GM density in ipsilesional sensorimotor cortex (25), and increases in perilesional GM density were associated with better recovery in acute stroke (59). Similarly, we found increased ipsilesional M1/S1 GM density following the intervention in our moderate to severe stroke population. Additionally, a significant positive correlation was found between changes in LI and changes in GM density in ipsilesional M1/S1 following the intervention ($R^2 = 0.70, p < 0.05; \text{Figure S2 in Supplementary Material}$), showing that activity shifting to the ipsilesional hemisphere was associated with increased ipsilesional M1/S1 GM density.

Increases in GM density may suggest potential synaptogenesis, dendritic growth, or gliogenesis at the cortex (60). Thus, these changes may be due to new synapse formation and dendritic growth commonly seen in animal training models (61). Additionally, these subjects likely experienced cortical atrophy prior to the intervention due to disuse of the paretic limb, which may have been partially remedied following the intervention due to increased use of the paretic arm/hand. Despite greater damage to ipsilesional descending motor tracts, these severely impaired individuals demonstrate the ability to reorganize ipsilesional primary sensorimotor cortices.

In these more severely impaired post-stroke individuals, we also found intervention-induced decreases in contralesional M1/S1 GM density, which were not reported before in mildly impaired individuals. This decrease may be specific to more severe patients since post-stroke, increased use of the contralesional hemisphere occurs to a greater degree in severely impaired individuals compared with milder individuals (29). The decrease in GM density in contralesional M1/S1 may indicate a decrease in dendritic complexity or synapses in these areas (62). These structural changes may be a result of decreased activation in these areas due to decreased recruitment during movement or overall decreased use (63, 64). Alternatively, they may be due to decreased tonic activity in these contralesional sensorimotor areas, which is thought to be a contributor to hyperexcitability in the brainstem and subsequent increased tone in this population (65, 66).

The increases in GM density seen in the thalamus in our results may be due to the repeated use of electrical stimulation throughout the intervention. Although we focused on the motor changes in this study, it is likely that these subjects show sensory neural changes as well due to the augmented afferent feedback generated by the EMG-FES device. Therefore, it is not surprising to see changes in the thalamus due to its central role as a sensory relay station for both the cutaneous and proprioceptive sensory modalities (67).

**Limitations**

The main limitation of the current study is the small sample size. Despite the relatively small n, we observed consistent patterns of functional and structural changes. These changes signify the importance of examining the potential neural mechanisms found here in a larger population of moderate to severe chronic stroke subjects. Additionally, there was no control group in the present study. However, this study was aimed at investigating whether this population maintained the ability to show neural changes following an intervention, rather than answering the question
of what is the optimal intervention for this population. Another potential confounding factor from the task-specific intervention is the amount of stretching. However, stretching on its own is unlikely to drive the functional and structural changes found in this study (68), even though it may temporarily reduce the stretch reflex activation of wrist and finger flexors (69). Additionally, reduced flexion synergy and subsequent decreased involuntary shoulder abduction/adduction force generation during hand opening (34) could contribute to intervention-induced changes in LI.

One of the primary long-term goals of the current study is to substantially increase the population included in task-specific therapy. Although the current ReIn-Hand device allowed our cohort of moderate to severe chronic stroke individuals to participate in task-specific training, it does require both detectable extensor EMGs to drive the device and responsiveness to FES to create sufficient hand opening. In our experience, limiting our inclusion criteria to an FMA ≥10 satisfied these requirements in most of initially screened participants (18 out of 20). However, due to the current sample size, it is difficult to accurately specify the portion of individuals who could utilize the ReIn-Hand device. However, considering that only ~5% of nearly 800 post-stroke individuals in the Clinical Neuroscience Research Registry hosted by the Rehabilitation Institute of Chicago and Northwestern University exhibit FMA scores less than 10, it clearly substantially increases coverage compared with conventional task-specific training.

CONCLUSION

The present study shows the ability of even moderate to severe chronic stroke subjects to show cortical reorganization at both the functional and structural levels following a device-assisted task-specific intervention in a manner resembling that seen in mild chronic stroke subjects. Despite the tendency to focus on acute or mild chronic stroke patients in hand function rehabilitation, the current study encourages the continued push to use devices to involve moderate to severe chronic stroke subjects in task-specific arm/hand rehabilitation.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Northwestern University Institutional Review Board with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by Northwestern University Institutional Review Board.

AUTHOR CONTRIBUTIONS

KW helped with design of the intervention and neuroimaging pre-/posttests, acquired the EEG data, ran intervention sessions, conducted EEG and VBM data analysis, contributed to interpretation, and was primary author of the manuscript. MO acquired MRI data, aided in the VBM data analysis, and contributed to interpretation and manuscript writing. CI aided in MRI data acquisition, VBM data analysis, and contributed to interpretation and manuscript writing. CC helped with the design of the intervention, ran intervention sessions, acquired the EEG data, conducted pre/post clinical assessments, conducted clinical measure data analysis, and contributed to interpretation. JD helped with the design of the intervention and neuroimaging pre-/posttests and provided interpretation to the data as well as contributions to manuscript writing. JY was the primary designer of the intervention and neuroimaging pre-/posttests, ran the intervention sessions, aided in the acquisition of the EEG data, aided in EEG analysis, provided interpretation to the data, and contributed to manuscript writing.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://journal.frontiersin.org/article/10.3389/fneur.2017.00284/full/#supplementary-material.

REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics – 2015 update: a report from the American Heart Association. Circulation (2015) 131(4):e29–322. doi:10.1161/CIR.0000000000000157
2. Wolf SL, Winston CJ, Miller JP, Taub E, Uswatte G, Morris D, et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. JAMA (2006) 296(17):2095–104. doi:10.1001/jama.296.17.2095
3. Taub E, Uswatte G, Elbert T. New treatments in neurorehabilitation based on basic research. Nat Rev Neurosci (2002) 3(3):228–36. doi:10.1038/nnr754
4. Favre I, Zeffiro TA, Detante O, Krainik A, Hommel M, Jaillard A. Upper limb recovery after stroke is associated with ipsilesional primary motor cortical activity: a meta-analysis. Stroke (2014) 45(4):1077–83. doi:10.1161/STROKEAHA.113.003168
5. Kwakkel G, Veerbeek JM, van Wegen EE, Wolf SL. Constraint-induced movement therapy after stroke. Lancet Neurol (2015) 14(2):224–34. doi:10.1016/S1474-4422(14)70160-7
6. Page SJ, Levine PG, Basobas BA. “Reps” aren’t enough: augmenting functional electrical stimulation with behavioral supports significantly reduces impairment in moderately impaired stroke. Arch Phys Med Rehabil (2016) 97(5):747–52. doi:10.1016/j.apmr.2016.01.004
7. Klamroth-Marganska V, Blanco J, Campen K, Curt A, Dietz V, Ettlin T, et al. Three-dimensional, task-specific robot therapy of the arm after

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stroke: a multicontext, parallel-group randomised trial. *Lancet Neurol* (2014) 13(2):159–66. doi:10.1016/S1474-4422(13)70305-3
8. Singer BJ, Vallence AM, Cleary S, Cooper J, Loftus AM. The effect of EMG triggered electrical stimulation plus task practice on arm function in chronic stroke patients with moderate-severe arm deficits. *Restor Neurol Neurosci* (2013) 31(6):681–91. doi:10.3233/RNN-130319
9. Krakauer JW, Carmichael ST, Corbett D, Wittenberg GF. Getting neurorehabilitation right: what can be learned from animal models? *Neurorehabil Neural Repair* (2012) 26(8):923–31. doi:10.1177/1545968312440745
10. Pekn M, Pekny M,Nilsson M. Modulation of neural plasticity as a basis for stroke rehabilitation. *Stroke* (2012) 43(10):2819–28. doi:10.1161/STROKEAHA.112.654228
11. Starkey ML, Schub ME. How plastic is the brain after a stroke? *Neuroscientist* (2014) 20(4):359–71. doi:10.1177/1073858413514636
12. Nudo RJ. Recovery after brain injury: mechanisms and principles. *Front Hum Neurosci* (2013) 7:887. doi:10.3389/fnhum.2013.00887
13. Nudo RJ, Millgren GW, Jenkins WM, Merzenich MM. Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. *J Neurosci* (1996) 16(2):785–807.
14. Kleim JA, Barbay S, Nudo RJ. Functional reorganization of the motor cortex following motor skill learning. *J Neurophysiol* (1998) 80(6):3321–5.
15. Gibson EM, Purger D, Mount CW, Goldstein AK, Lin GL,Wood LS, et al. Neuronal activity promotes oligodendrogenesis and adaptive myelination in the mammalian brain. *Science* (2014) 344(6153):252904. doi:10.1126/science.1252304
16. Kleim JA, Barbay S, Cooper NR, Hogg TM, Remple MS, et al. Motor learning-dependent synaptogenesis is localized to functionally reorganized motor cortex. *Neurobiol Learn Mem* (2002) 77(1):63–77. doi:10.1006/nlme.2000.4004
17. Maier IC, Baumann K, Thallmair M,Weinmann O, Scholl J, Schub ME. Constraint-induced movement therapy in the adult rat after unilateral corticospinal tract injury. *J Neurosci* (2008) 28(38):9386–403. doi:10.1523/JNEUROSCI.1697-08.2008
18. Biernaskie J, Corbett D. Enriched rehabilitative training promotes improved forelimb motor function and enhanced dendritic growth after focal ischemic injury. *J Neurosci* (2001) 21(14):5272–80.
19. Nudo RJ, Wise BM, SiFuentes F, Millgren WK. Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. *Science* (1996) 272(6598):1791–4. doi:10.1126/science.272.6598.1791
20. Tamakoshi K, Ishida A, Takamatsu Y, Nakashima H, Shimada H, et al. Motor skills training promotes motor functional recovery and induces synaptogenesis in the motor cortex and striatum after intracerebral hemorrhage in rats. *Behav Brain Res* (2014) 260:34–43. doi:10.1016/j.bbr.2013.11.034
21. Sawaki L, Butler AJ, Leng X, Wassenaar PA, Mohammad YM, Blanton S, et al. Sequencing bilateral and unilateral task-oriented training versus task-oriented training alone to improve arm function in individuals with chronic stroke. *Neurorehabil Neural Repair* (2013) 27(9):920–8. doi:10.1177/1545968312440745
22. Saito T, Van Kaick S, Mehrholz J, Leidner O, Eickhoff C, Pohl M. Best conventionalfusion therapy versus modular impairment-oriented training for arm paresis after stroke: a single-blind, multicenter randomized controlled trial. *Neurorehabil Neural Repair* (2009) 23(7):706–16. doi:10.1177/1545968309335974
23. Yao J, Chen A, Carmona C, Dewald JP. Cortical overlap of joint representations contributes to the loss of independent joint control following stroke. *Neuroimage* (2009) 45(2):490–9. doi:10.1016/j.neuroimage.2008.12.002
24. Zaaimi B, Edgley SA, Soteropoulos DS, Baker SN. Changes in descending motor pathway connectivity after corticospinal tract lesion in macaque monkey. *Brain* (2012) 135(Pt 7):2277–89. doi:10.1093/brain/aw2115
25. Baker SN. The primate corticospinal tract, hand function and functional recovery. *J Physiol* (2011) 589(23):5603–12. doi:10.1113/jphysiol.2011.215160
26. Askim T, Indredavik B, Vangberg T, Haberg A. Motor network changes associated with successful motor skill relearning after acute ischemic stroke: a longitudinal functional magnetic resonance imaging study. *Neurorehabil Neural Repair* (2009) 23(3):295–304. doi:10.1177/1545968308322840
27. Michielsen ME, Selles RW, van de Geest JN, Eckhardt M, Yavuzer G, Stam HI, et al. Motor recovery and cortical reorganization after mirror therapy in chronic stroke patients: a phase II randomized controlled trial. *Neurorehabil Neural Repair* (2011) 25(3):223–33. doi:10.1177/1545968310385127
28. Ward NS, Brown MM, Thompson AJ, Frackowiak RS. Neural correlates of motor recovery after stroke: a longitudinal fMRI study. *Brain* (2003) 126( Pt 11):2476–96. doi:10.1093/brain/awg145
49. Calautti C, Naccarato M, Jones PS, Sharma N, Day DD, Carpenter AT, et al. The relationship between motor deficit and hemisphere activation balance after stroke: a 3T fMRI study. Neuroimage (2007) 34(1):322–31. doi:10.1016/j.neuroimage.2006.08.026

50. Schaechter ID, Perdue KL, Wang R. Structural damage to the corticospinal tract correlates with bilateral sensorimotor cortex reorganization in stroke patients. Neuroimage (2008) 39(3):1370–82. doi:10.1016/j.neuroimage.2007.09.071

51. Ward NS, Newton JM, Swayne OB, Lee L, Thompson AJ, Greenwood RJ, et al. Motor system activation after subcortical stroke depends on corticospinal system integrity. Brain (2006) 129(Pt 3):809–19. doi:10.1093/brain/awl002

52. Greffkes C, Fink GR. Reorganization of cerebral networks after stroke: new insights from neuroimaging with connectivity approaches. Brain (2011) 134(Pt 5):1264–76. doi:10.1093/brain/awr053

53. Hubbard II, Carey LM, Budd TW, Levi C, Mc Elduff P, Hudson S, et al. A randomized controlled trial of the effect of early upper-limb training on stroke recovery and brain activation. Neurorehabil Neural Repair (2015) 29(8):703–13. doi:10.1177/1545968314562647

54. Johansen-Berg H, Dawes H, GUY C, Smith SM, Wade DT, Matthews PM. Correlation between motor improvements and altered fMRI activity after rehabilitative therapy. Brain (2002) 125(Pt 12):2731–42. doi:10.1093/brain/awf282

55. Macpherson J, Wiesendanger M, Marangoz C, Miles TS. Corticospinal neurons of the supplementary motor area of monkeys. A single unit study. Exp Brain Res (1982) 48(1):81–8. doi:10.1007/BF00239574

56. Maier MA, Armand J, Kirkwood PA, Yang HW, Davis JN, Lemon RN. Differences in the corticospinal projection from primary motor cortex and supplementary motor area to macaque upper limb motoneurons: an anatomical and electrophysiological study. Cereb Cortex (2002) 12(3):281–96. doi:10.1093/cercor/12.3.281

57. Sanes JN, Donoghue JP. Plasticity and primary motor cortex. Annu Rev Neurosci (2000) 23:393–415. doi:10.1146/annurev.neuro.23.1.393

58. Cai J, Ji Q, Xin R, Zhang D, Na X, Peng R, et al. Contralesional cortical structural reorganization contributes to motor recovery after sub-cortical stroke: a longitudinal voxel-based morphometry study. Front Hum Neurosci (2016) 10:393. doi:10.3389/fnhum.2016.00393

59. Abela E, Seiler A, Missimer JH, Federspiel A, Hess CW, Sturzenegger M, et al. Grey matter volumetric changes related to recovery from hand paresis after cortical sensorimotor stroke. Brain Struct Funct (2015) 220(5):2533–50. doi:10.1007/s00429-014-0804-y

60. Zatorre RJ, Fields RD, Johansen-Berg H. Plasticity in gray and white: neuroimaging changes in brain structure during learning. Nat Neurosci (2012) 15(4):528–36. doi:10.1038/nn.3045

61. Murphy TH, Corbett D. Plasticity during stroke recovery: from synapse to behaviour. Nat Rev Neurosci (2009) 10(12):861–72. doi:10.1038/nrn2735

62. Sowell ER, Thompson PM, Tessner KD, Toga AW. Mapping continued brain growth and gray matter density reduction in dorsal frontal cortex: inverse relationships during postadolescent brain maturation. J Neurosci (2001) 21(22):8819–29.

63. Zito K, Svoboda K. Activity-dependent synaptogenesis in the adult mammalian cortex. Neuron (2002) 35(6):1015–7. doi:10.1016/S0896-6273(02)00903-0

64. Langer N, Hanggi J, Muller NA, Simmen HP, Jancke L. Effects of limb immobilization on brain plasticity. Neurology (2012) 78(3):182–8. doi:10.1212/WNL.0b013e318236c6b6.

65. Brown P. Pathophysiology of spasticity. J Neurol Neurosurg Psychiatry (1994) 57(7):773–7. doi:10.1136/jnnp.57.7.773

66. Li S, Francisco GE. New insights into the pathophysiology of post-stroke spasticity. Front Hum Neurosci (2015) 9:192. doi:10.3389/fnhum.2015.00192

67. Kandel ER, Schwartz JH, Jessell TM, Siegelbaum SA, Hudspeth AJ. Principles of Neural Science. 5th ed. New York: McGraw-Hill Companies, Inc. (2013).

68. Teasell R, Foley N, Salter K, Bhogal S, Jutai J, Speechley M. Evidence-based review of stroke rehabilitation: executive summary, 12th edition. Top Stroke Rehabil (2009) 16(6):463–88. doi:10.1310/tsr1606-463

69. Schmit BD, Dewald JP, Rymer WZ. Stretch reflex adaptation in elbow flexors during repeated passive movements in unilateral brain-injured patients. Arch Phys Med Rehabil (2000) 81(3):269–78. doi:10.1016/S0003-9993(00)90070-4

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