**Title**

Long-Term Benefits of a Tailored Strength Training Interventions on Arm Function In Chronic Stoke Survivors: A Follow-Up Study

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**Abstract (250 words max)**

**Background:** Previously, we showed that a strengthening intervention based on the presence or absence of motor evoked potentials (MEPs) in the affected upper extremity (UE) was effective in improving strength and function in chronic stroke survivors. Here, we investigated the long-term benefit of this intervention in a subset of participants (n=25) at 1-year.

**Methods:** Participants underwent transcranial magnetic stimulation (TMS) at baseline to detect the presence of MEPs in the affected UE to assess corticospinal integrity. Participants were then stratified into three training groups based on the size of the MEPs, i.e., a low (LI; MEPs<50 μV), moderate (MI; MEPs 50-120 μV) or high (HI; MEPs> 120 μV) intensity. In each group, participants performed adjusted strengthening exercises with their UE 3X/week for 4 weeks. Assessments were performed at baseline, 1-week after and, 1-year post-intervention. Assessments consisted of assessment of motor impairment (Fugl-Meyer Stroke Assessment−FMA, grip strength−GS) and UE function (Box and Block test−BBT).

A mixed ANOVA was conducted to compare changes in clinical measures over time, followed by post-hoc pairwise Wilcoxon signed rank tests with Holm-Bonferroni correction where necessary.

~~The Wilcoxon signed-rank test was applied to compare changes in clinical measures over time.~~

**Results:** Owing to the small number of participants in the LI and MI groups, these participants were merged into a single LI group (n=8). Results showed that following the MEP-based tailored training program, both the LI and HI groups maintained their gains in UL function over time [FMA: *p* = 0.18; BBT: *p* = 0.83; GS: *p* = 0.72].

**Conclusion:** Tailoring a UL training program on MEP amplitudes enables UL gains to be maintained 1 year post-intervention. These results suggest that MEP amplitude is a relevant variable to consider in exercise prescription post-stroke to allow for long-term training benefit in chronic stroke survivors.

**Keywords:** stroke, arm function, strengthening exercises, MEP, follow-up evaluation

**Introduction:**

Stroke is the third-leading cause of disability worldwide{Krishnamurthi, 2015 #503}{Krishnamurthi, 2015 #503}{Krishnamurthi, 2015 #503}{Krishnamurthi, 2015 #503}{Krishnamurthi, 2015 #503}{Krishnamurthi, 2015 #503}. Over 12 million incidents of stroke are reported around the world each year, accounting for around 891 billion in stroke-related cost (1). Paresis of the upper extremity (UE) contralesional to the affected brain areas is among the most common consequence of stroke, with long-term motor impairments occurring in about 80% of individuals (2). It is a particularly disabling condition that can impede the ability of individuals to accomplish activities of daily living (ADLs) (3).

During intensive rehabilitation, strength training interventions have been shown to be effective in promoting neuroplasticity (4), motor capabilities (5-9), and strength (4, 5, 8, 10) in acute and subacute stroke survivors. For example, Tarsová and colleagues (2008) reported significant improvement in motor impairment and activity limitations in a group of acute stroke survivors after an individualized exercises training (11). Fang and colleagues (2003) reported similar findings when comparing gains in UE function in participants in the acute phase of stroke who received 45 minutes of daily supervised physiotherapy for four weeks with those who received no physical therapy (12). These findings in the acute phase are consistent with the notion that the first 3 months is a critical window for neuroplasticity and neural reorganization (13), which also corresponds to the time where most of the recovery is seen post-stroke (14).

There is growing evidence that intense rehabilitation interventions can also reduce motor impairments on in chronic stroke survivors. For instance, Sun and colleagues (2018) showed that training of the less-affected UE in chronic stroke survivors also led to gain in the affected UE. Further, using transcranial magnetic stimulation (TMS), it was shown that this cross-education was associated with neuroplastic changes in the ipsilesional hemisphere such as shortened cortical silent period and reduced transcallosal inhibition from both hemispheres (4). Beaulieu and colleagues (2019) investigated the effect of aresistance training interventionin a group of 14 chronic stroke survivors. One group received the training paired with transcranial direct stimulation (tDCS), while the other received the training with a sham tDCS (6). The intervention consisted of 60-min of exercises, three times per week for four weeks, targeting the affected UE. Various outcome measures were assessed, including the Fugl-Meyer Assessment (FMA) for the UL, the Box and Block test, and the Motor Activity Log (MAL). Although using tDCS did not lead to additional functional gains, both groups showed improvement in response to progressive resistance exercise. In a recent report, our group described the results of a strengthening intervention targeting the UE in a large sample of chronic stroke survivors (n=90). Participants were regrouped into three intensity groups based on the size of TMS-elicited motor evoked potentials (MEPs) in the affected hand, which provided an index of corticospinal integrity (CSI) and of potential responsivity to training. Our results showed that adjusting the training intensity on the basis of MEP size led to clinically significant gains in the affected UE both in terms of reduced impairments and improved function for all participants, regardless of the stroke severity at baseline (15, 16).

In the present report, our goal was to extend our previous results to determine whether the gains in arm function observed immediately following the 1-month training intervention, were maintained the long term at 1-year follow-up. There are still controversies as to whether the improvements gained from exercise interventions have long-term beneficial effects in post-stroke populations (17-26). Wu and colleagues (2016) compared the long-term recovery trajectories in three groups of participants: [1] robot-assisted therapy, [2] intensive comparison training aiming to match the robot-assisted therapy, and [3] usual care (26). Both intervention groups underwent one-hour functional UE supervised training 3 times per week for 12 weeks until about 36 sessions were completed. Post-training, those in the intervention groups demonstrated greater improvement in UE function relative to the control group; however, at follow-up 36-week, no difference was detected. On the other hand, Stinear and colleagues (2007) investigated the effects of a 30-day training program in participants in the chronic stage and showed that gains in UE function were maintained up to three years post-intervention. Interestingly, the participants who maintained their gains in this study also exhibited MEPs in response to TMS (27) and thus had preserved CSI. As stated earlier, our own investigation provided further evidence that the presence of MEPs in the affected extremity is indeed a critical factor influencing the outcomes of rehabilitative exercises targeting arm and hand function (15, 16). In this report, we describe our observations collected from a subset of participants who completed the strengthening intervention and were re-assessed at 1-year follow-up to determine whether the gains they experienced in their UE were still detectable in the long-term.

**Methods:**

A detailed description of the study’s protocol is given elsewhere (15). In brief, participants were allocated to three training intensity groups based on the size of MEPs (peak-to-peak amplitude) elicited by supramaximal (1.3 motor threshold) TMS pulses applied over the hand motor area of the lesioned hemisphere using the first dorsal interosseous (FDI) as the target muscle. Participants with MEPs <50 μV were allocated to a low-intensity (LI:) group, those with MEPs between 50-120 μV to a moderate-intensity (MI) group and those with MEPs > 120 μV to a high-intensity (HI). In each training group, the strength training program consisted of lifting dead weights specifically targeting the shoulder, elbow flexors, and wrist extensors of the affected arm. At the beginning of each week of training, participants’ 10 RM (the maximal load that could be lifted 10 times consecutively) was assessed to estimate their 1RM (28). The estimated 1RM was then used to calculate the baseline at which participants began the upcoming week of training: those in the LI group began at 35% of their 1RM, while MI and HI participants began at 50% and 70%, respectively. The intensity of training was increased by 5% weekly for the duration of the intervention, so that at the end of the 4 weeks, participants in the LI group trained at 50% 1 RM, while the MI and HI groups, respectively, trained at 65% and 85% 1RM. The training also targeted grip strength using the Jamar® hydraulic hand dynamometer.

All participants also underwent clinical assessment of their UE by an experienced therapist who was blinded regarding group allocation. The assessment was performed at three time points: at baseline, prior to training (T1), immediately after the intervention (T2), and at one-year follow-up (T3). The assessment included the following primary outcome measures: [1] the Fugl-Meyer stroke assessment for UL impairment (FMA) (29), [2] the Box and Block test (BBT) (30), and [3] grip strength, measured in kg (average of three trials). Several secondary outcome measures were also considered, including a self-reported quantity and quality of use of the paretic UL, quantified by the Motor Activity Log (MAL) (31), and the active range of motion (AROM) in flexion at the affected shoulder, elbow, and wrist (Fig.1).

A flowchart of a group of individuals

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**Statistical Analysis**

Due to the small number of participants in the LI and MI groups, data of these two groups were combined to create a larger LI treatment group. Henceforth, the LI group refers to eight participants who underwent either LI- or MI-intensity training.

Sociodemographic characteristics between the LI and HI groups were compared using the Mann-Whitney U Test for continuous variables and Chi-square tests of independence for proportions. Descriptive statistics were used to characterize the sample at baseline, and the Mann-Whitney U Test was used again to evaluate between-group differences in outcome measures at baseline. As for change in the sample over time, the mixed ANOVAs with a covariant in participant ID were used to compare observations at all measurement periods.

95% confidence intervals (CIs) for the mean difference between functional measurements at T2 and T3, and between T2 and T1 were computed with a bootstrapping approach. Specifically, the difference between measurements was resampled for each primary outcome measure 100,000 times, and the 95% CI was constructed by taking the 2.5th and 97.5th percentile of the resulting distribution. ANCOVAs were conducted for each outcome variable, with each variable’s measurement at baseline as a covariate, to assess the impact of intervention group on the mean difference between evaluations. The significance level was set to be p < 0.05 for all tests. All statistics were computed using R Statistical Software (version 4.0.1) (32).

**Results:**

This report is about a subset of participants (n=26) who were reassessed at a one-year follow-up clinical evaluation (Fig. 1). Of these, one was excluded because of experiencing a second stroke within one year after the completion of the initial intervention. The demographic characteristics of the remaining 25 participants are summarized in Table I. There were no significant differences in demographic characteristics or history of stroke between the LI and HI-intensity training groups. At the time of the follow-up assessment, participants had a mean age of 66 ± 8 years, and the time since stroke was 4 ± 4 years. Most participants were male (72%), and about half of them had a stroke on the left side of the brain. The most common type of stroke was ischemic (76%).

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| **Table I: Sociodemographic Characteristics by Training Group [Mean ± SD]** | | | |
| Characteristic | LI (n = 8) | HI (n = 17) | p-value\* |
| Age (years) | 66 ± 9 | 66 ± 9 | 1.00 |
| Handedness (right/left) | 7/1 | 13/4 | 0.91 |
| Sex (male/female) | 5/3 | 13/4 | 0.80 |
| Time since stroke (years) | 4 ± 5 | 5 ± 4 | 0.32 |
| Side of stroke (right/left) | 4/4 | 8/9 | 1.00 |
| Type of stroke (ischemic/hemorrhagic/other) | 7/1/0 | 12/4/1 | 0.60 |
| \*Mann-Whitney U Test for continuous variables, Chi-square test for independence for proportions | | | |

An ANOVA was conducted for each outcome measure and confirmed between-group differences at baseline. Participants in the HI intervention group demonstrated significantly stronger performance on these measures at baseline, except for AROM at the shoulder and elbow (Table II).

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| **Table II: Differences Between Groups at Baseline** | | | |
|  | LI (n = 8) | HI (n = 17) | p-value\* |
| FMA (normal = 66) | 42 ± 16 | 61 ± 13 | 0.003 |
| BBT (# of blocks in 60 seconds) | 19 ± 17 | 49 ± 16 | 0.003 |
| GS (in kg) | 16.6 ± 14.4 | 35.1 ± 12.2 | 0.008 |
| MAL AOU (normal = 5) | 2.04 ± 1.78 | 4.14 ± 1.45 | 0.016 |
| MAL QOU (normal = 5) | 1.88 ± 1.63 | 3.83 ± 1.44 | 0.031 |
| Shoulder AROM flexion (°) | 117 ± 47 | 147 ± 37 | 0.085 |
| Elbow AROM flexion (°) | 138 ± 7 | 138 ± 9 | 0.884 |
| Wrist AROM flexion (°) | 39 ± 23 | 67 ± 21 | 0.004 |
| \*Mann-Whitney U Test | | | |

FMA = Fugl-Meyer Assessment; BBT = Box and Block Test; GS = Grip Strength; MAL AOU = Quantitative Motor Activity Log; MAL QOU = Qualitative Motor Activity Log; AROM = Active Range of Motion

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Mean differences between assessments in outcome measures for all participants are shown in Table III. Overall, irrespective of the intervention groups, participants maintained their improvement in all primary outcome measures from post-treatment to follow-up [FMA: V = 65, p = 0.18, d = 0.033; BBT: V = 145.5, *p* = 0.83, d = 0.007; GS: V = 137, p = 0.72, d = - 0.028; MAL AOU: V = 41, *p* = 0.1851, d = 0.012; MAL QOU: V = 117, *p* = 0.058, d = 0.087].

Table III: Mean Differences Between Follow Ups

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|  | F † | Pr(> F) † | T3 - T2 Δ | 95% CI | T3 - T1 Δ | 95% CI | T2 - T1 Δ | 95% CI |
| FMA | 14.25 | 1.53E-05 | 0.1807 | (-0.40, 1.36) | 0.0005\* | (1.44, 4.00) | 0.0047\* | (0.88, 3.64) |
| BBT | 1.909 | 0.16 | // | // | // | // | // | // |
| GS | 11.276 | 0.0001 | 0.7209 | (-1.77, 0.82) | 0.0004\* | (1.54, 3.87) | 0.0011\* | (1.55, 3.83) |
| MAL AOU | 4.975 | 0.0111 | 0.1852 | (-0.19, 0.18) | 0.0237\* | (0.03, 0.60) | 0.0041\* | (0.13, 0.49) |
| MAL QOU | 21.569 | < 0.0001\* | 0.0582 | (0.015, 0.28) | < 0.0001\* | (0.40, 0.87) | < 0.0001\* | (0.31, 0.66) |
| Shoulder AROM | 5.625 | 6.50E-03 | 0.1574 | (-2.24, 5.16) | 0.0089\* | (2.44, 14.81) | 0.0134\* | (1.68, 12.76) |
| Elbow AROM | 1.102 | 3.41E-01 | // | // | // | // // // | | | | |  |  |
| Wrist AROM | 0.582 | 5.63E-01 | // | // | // | // // // | | | | |  |  |
| † F-statistic corresponding to Follow Up in two-way ANOVA with MEP group and Follow Up as main effects and a  covariate in Participant ID | | | | | | | | | |
| Δ P-value of post-hoc Wilcoxon signed-rank test with Holm-Bonferroni correction for multiple comparisons.  \* denotes significance for all tests. | | | | | | | | | |

ANCOVAs were conducted for each outcome measure in Table III, accounting for intervention group and covarying against baseline measurement of each outcome measure.Maintenance of improvements at one-year follow up occurred similarly for both groups [FMA: F(1, 22) = 1.016, *p* = 0.325, ηp2 = 0.124; BBT: F(1, 22) = 0.552, *p* = 0.465, ηp2 = 0.006; GS: F(1, 22) = 1.969, p = 0.18, ηp2  = 0.060; MAL AOU: F(1, 22) = 0.711, *p* = 0.408, ηp2  = 0.058; MAL QOU: F(1, 22) = 0.22, *p* = 0.644, ηp2 = 0.041].

Regarding range of motion, only the affected shoulder maintained an improvement until T3 for both intervention groups (V = 207.5, *p* < 0.01) (Fig. 2 & 3). The active range of motion of neither the elbow nor the wrist changed over time (Fig. 3).

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| |  |  |  |  | | --- | --- | --- | --- | | **Table III: Mean Differences Between T2 and T3** | | | | |  | T3 - T2 | 95% CI | P-Value † | | FMA | 0.48\* | (-0.40, 1.32) | 0.325 | | BBT | 0.16\* | (-2.16, 2.44) | 0.465 | | GS | -0.43\* | (-1.77, 0.82) | 0.175 | | MAL AOU | 0.02\* | (-0.19, 0.18) | 0.408 | | MAL QOU | 0.138\* | (0.015, 0.28) | 0.644 | | \*Wilcoxon signed-rank test (p > 0.05) | | | | | † ANCOVA (covariate = baseline measure) | | | |   FMA = Fugl-Meyer Assessment; BBT = Box and Block Test; GS = Grip Strength; MAL AOU = Quantitative Motor Activity Log; MAL QOU = Qualitative Motor Activity Log |

**Discussion:**

To the best of our knowledge, the present study is the first to evaluate the long-term effects of a tailored, MEP-based UL strength training intervention in chronic stroke survivors.  On average, participants maintained post-intervention improvements in UL strength and function until at least 1-year follow-up. Participants’ gains were not modulated by their level of impairment, as measured by their intervention group.

**The Long-term Efficacy of Rehabilitation Therapies in Individuals with Chronic Stroke**

Our results are in line with the studies having found long-term benefits of rehabilitation interventions in chronic stroke survivors. Ramos-Murguialday and colleagues showed that, following a 4-week intervention of both Brain-Machine-Interface (BMI) training and physiotherapy, a cohort of individuals with chronic stroke outperformed a control group at a one-year follow-up as assessed by the FMA (19). The intervention took place every weekday and consisted of 1 hour of BMI training, where the participant’s paretic UL was moved by a robotic orthosis, either in response to sensorimotor rhythms (intervention group) or at random (control), followed by an hour of physiotherapy. Sale and colleagues showed that serial robotic training resulted in a long-term improvement in UL function as measured at one-year follow-up in individuals with chronic stroke, traumatic brain injury, and spinal cord injury (24). Specifically, participants who underwent a 2nd round of robot-assisted therapy, beginning three months after the termination of initial treatment, demonstrated improved scores on the Box and Block Test and Frenchay Arm Test compared to the control group. Given that robotic training allows for intense training, and that our intervention individualized training according to the person's own recovery potential to guarantee optimal training intensity, it may be thought that in order to achieve or maintain post-training gains, intensity plays an important role for chronic stroke patients.

**The Effect of Stroke Severity on Recovery Potential**

In our study, participants’ maintenance of gains in UL function was not affected by the severity of their stroke, as measured by MEP amplitude. This result contradicts existing literature concerning the question of whether stroke severity modulates recovery potential (10, 27, 33-35). For example, Stinear and colleagues used MEP amplitude and FA of the CST to predict the state of post-stroke participants’ UL function and their functional recovery potential (27). They found that the presence of MEPs modulated the potential for recovery, as those with MEPs could see functional recovery as late as three years post-stroke, while recovery in those without MEPs was heavily dependent on damage to the CST. Likewise, Prabhakaran and colleagues modelled the recovery of forty-one individuals with acute ischemic stroke of varying severity, as measured by UL FMA score at baseline (34). Clinical variables, including age, sex, lesion location, infarct volume, time between evaluations, and stroke severity, were found to be strong predictors of recovery for only individuals with mild-to-moderate impairment post-stroke; those with severe impairment demonstrated little recovery. Most recently, Bonkhoff and colleagues*,* reaffirmed the distinction between the recovery patterns of individuals with moderate stroke and those with severe stroke (36). Considering those with UL FMA scores less than 45, the authors constructed a Bayesian hierarchical model to predict participants’ change in FMA score over the period of six months. While both the moderate and severe groups were found to experience a similar average change in FMA score over time, it was concluded that for individuals with severe stroke-related impairments, they recovered more the smaller their impairment level was, while for better-recovered stroke survivors, they recovered more the larger their initial impairment (36).

There are several reasons for the discrepancy between the results of our study and those of previous studies. By having tailored our UL strength training intensity to participants’ recovery potential, our intervention may have been uniquely useful in allowing gains in UL function for more severe chronic stroke. In comparison, existing research reflects other, more generic interventions and are thus less effective for recovery from severe stroke than the intervention used in the present study (10, 27, 34, 36). Also, our study concerns exclusively those in the chronic phase of stroke, and it is possible that the differences in recovery potential between those of mild to severe stroke are attenuated as one moves into the chronic phase of recovery (10, 34, 35). Another reason might be the exclusion criteria of the present study. Individuals presenting significant spasticity or pain intensity at the affected UL, along with major sensory deficit or hemineglect, were excluded from the study. It is possible that individuals disproportionately contribute to the variation in recovery patterns between severe and less-severe stroke survivors, and thus the present study lacks variation between the groups. Finally, in a previous study of Milot and colleagues*,* where the authors compared the predictive power of fMRI, diffusion-tensor imaging, and MEPs elicited from TMS in predicting UL motor recovery following an 8-week robotic training intervention (33), it was found that MEP magnitude at baseline was the most significant predictor of change in BBT scores between pre- and post-intervention. It was also noted that participants with lower MEP amplitude at baseline experienced greater improvements in BBT scores. The authors attributed this effect to participants having more room to improve with training. It is possible that a similar effect is being observed in the present study for our more severely impacted participants. Further looking at the data, it was noted that in the entire cohort, three out of four participants that showed a decline in UL function following training were in the HI training group, thus having better recovered from their stroke.

Overall, our results reaffirm that modulating strength training programs by a biomarker of CST integrity leads to UL strength and functional improvements, irrespective of the individual’s initial severity of stroke. Additionally, we found that improvement in active range of motion in the paretic shoulder, on average, was maintained over time, as opposed to elbow and wrist range of motion which saw no improvement. Because of the shoulder’s critical importance in the functional use of the UL (37), this finding further suggests that considering MEP amplitude in the prescription of post-stroke strength training exercises is crucial to optimize short and long-term training response and recovery in the chronic phase of a stroke.

**Study Limitations**

As for the study limitations, FMA scores were high for many participants in the HI training group, which may have introduced a ceiling effect and concealed the subtle improvements in motor impairment otherwise made by these participants. Additionally, because the follow-up study was conducted throughout two different sites, potential inconsistencies in data collection may have occurred. However, the research team involved in data collection all underwent training before any data was collected to limit this potential problem. The exclusion criteria of the study, which precluded the participation of post-stroke individuals who were unable to perform the training program limits the generalizability of the results in the population of chronic stroke survivors. The uneven distribution of participants across treatment intensity groups, in addition to the relatively small sample size of the study, may also be considered a confounding factor, although the relevant statistical methods (ANOVA and ANCOVA) do not assume similarly sized groups.

**Conclusion**

Individuals with chronic stroke whose UL strength training intervention was tailored by a biomarker of corticospinal integrity, by means of MEP amplitude, saw improvements in functional ability and strength of the UL that were sustained for at least one year following the intervention. Moreover, the present study supports the growing body of evidence that long-term functional recovery is a feasible goal for patients with chronic stroke and suggests that rehabilitation is a worthwhile endeavor for those with more severe stroke impairments.

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**Conflict of Interest Statement**

The Authors declare that there is no conflict of interest.

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**Clinical Messages (2-4 bullet points, 50 words or less)**

* Gains in affected UL function can be maintained at 1-year post-training in chronic stroke survivors.
* Tailoring a UL strength training program based on the integrity of the corticospinal tract to ensure optimal training intensity allows for maintaining post-training UL gains regardless of stroke severity status.

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