Original Research Article

ASNR AMERICAN SOCIETY OF NEUROREHABILITATION

Neurorehabilitation and Neural Repair
1–13

DOI: 10.1177/15459683261454937
journals.sagepub.com/home/nnr

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Wearable Myoelectric Interface for Neurorehabilitation (MINT) to Recover Arm Activity After Stroke: A Randomized Controlled Trial

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Abstract

Background: Abnormal muscle co-activation impairs arm function after stroke. Home-based myoelectric interface for neurorehabilitation (MINT) was developed to reduce abnormal co-activation.

Objective: Evaluate MINT feasibility and effects on arm activity in a single-blind, randomized, sham-controlled trial.

Methods: Moderately-to-severely impaired chronic stroke survivors were randomized to 1 of 3 MINT groups (who played customized games requiring independent activation of 2 or 3 abnormally co-activating muscles) or a sham control group (using 1 muscle). Participants trained 90 minutes/day, 6 days/week, switching upper-arm muscle sets every 2 to 3 weeks. Feasibility was assessed using training time, repetitions, and motivation. The primary efficacy outcome was the change in Wolf Motor Function Test (WMFT) from baseline to week 6 in each MINT group compared to sham. Secondary outcomes included WMFT at week 10, WMFT subscores, Fugl–Meyer, Modified Ashworth, Motor Activity Log, reaching kinematics, co-activation, and lesion location effects.

Results: Fifty-nine participants completed training (mean: 86 ± 21 minutes/day, 315 ± 85 repetitions/day). The 3-muscle group improved WMFT by 6.8 seconds at week 6 (95% confidence interval [2.1-11.6 seconds], $P = .001$); other groups did not. Combined MINT groups improved by 4.1 seconds ([1.4-6.8 seconds], $P = .0008$). In per-protocol analysis, the 3-muscle group improved significantly more than sham on WMFT (7.5 seconds; [0.1-14.9 seconds], $P = .046$), shoulder/elbow subscores, and kinematics. At week 10, all MINT groups improved significantly, unlike sham. Reduced co-activation correlated significantly with improved arm function and movement. Stroke involving the internal capsule negatively predicted MINT response. Other secondary outcomes showed no clinically important changes.

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Discussion: MINT conditioning is feasible, reduces co-activation, and improves arm movement and activity.
Clinical Trial Registration: ClinicalTrials.gov (NCT03401762).

Keywords
stroke rehabilitation, stroke recovery, arm impairment, EMG, myoelectric, wearable, gaming, movement

Introduction

Stroke is a leading cause of permanent disability worldwide, with about 60% of survivors experiencing impairment in upper limb function 6 months after stroke.[1,2] Although rehabilitation therapies can improve function even after the initial recovery period,[3-5] only 30% of stroke survivors in the U.S. receive outpatient therapy due to resource constraints.[6] Further, higher doses of therapy are important in therapeutic improvement.[7] These facts highlight the need for new treatments that are effective, affordable, and widely accessible.

Arm impairment after stroke is due not only to weakness and spasticity but also to abnormal muscle co-activation, also called abnormal synergies,[8,9] which is not directly addressed by existing therapies. One approach attempted to address abnormal joint torque couplings using visual feedback of joint torques[10] but is impractical for use outside the lab due to the size and cost of required robotic equipment. Surface electromyography (EMG) feedback offers a potentially inexpensive and portable solution. Past studies of EMG feedback of single-muscle activity had mixed results and did not attempt to address abnormal co-activation.[11,12] Our group has developed a myoelectric computer interface that specifically targets abnormal muscle co-activation. Our initial studies on chronic stroke survivors showed that in-lab training with this interface reduced co-activation and associated arm impairment.[13-15] Further, a higher dose of training (90 minutes/day) while moving led to better outcomes than isometric training.[14]

Here, we used a wearable myoelectric interface, called myoelectric interface for neurorehabilitation (MINT), in a home-based, randomized, sham-controlled trial. MINT delivers gamified training personalized to each patient's co-activation patterns. It could ultimately provide a low-cost addition to conventional therapy and an option for individuals with limited access to outpatient rehabilitation.

We sought to optimize the MINT paradigm for the upper arm in terms of the number and ways that muscles were trained (2 vs 3 muscles simultaneously, with or without visual cues), and to validate that it was doing more than overcoming non-use (discrepancy between retained motor capacity and spontaneous daily use of the affected arm[16]). Thus, the goals of this clinical trial were to determine (1) if MINT at home is feasible, (2) if MINT can improve arm function in activities in chronic stroke survivors (primary efficacy endpoint: Wolf Motor Function Test [WMFT] at 6 weeks in each group), (3) which variant of the MINT paradigm was effective (similar to a dose-finding design[17]), and (4) whether reducing abnormal co-activation leads to greater improved arm motor activity than simply exercising individual arm muscles. Because stroke location can influence motor recovery from stroke, and to begin to understand the mechanisms behind MINT, we also explored effects of location on efficacy of MINT.

Methods

Participants

This study adhered to Consolidated Standards of Reporting Trials guidelines. The study (NCT03401762) was approved by the Institutional Review Board of Northwestern University . Written informed consent was obtained from all participants prior to eligibility screening. Recruitment was conducted through multiple channels, including the clinical neuroscience research registry, day rehabilitation centers, hospital websites, and physician referrals between January 2018 and March 2024. Inclusion criteria were over 21 years old, with moderately severe to severe upper limb impairment—Fugl–Meyer Assessment of Upper Extremity (FMA-UE) score 7 to 30—following unilateral ischemic or hemorrhagic stroke occurring at least 6 months before enrollment. Exclusion criteria were significant visual deficits impairing visibility of a laptop screen (including hemianopia), comprehension or attention deficits (assessed by 3-step commands and understanding of study procedures), multifocal infarcts, botulinum toxin in the affected arm within prior 3 months, new physical or occupational therapy initiation within prior 3 months, arm contractures, arm pain preventing participation for 90 minutes/day, or participation in other upper limb-related research studies within prior 3 months.

Randomization and Blinding

This trial used a single-blind, randomized, sham-controlled design to examine the feasibility and efficacy of MINT conditioning for improving arm activity. Participants were allocated to 1 of 3 intervention groups (described below) or to a sham control, with stratification performed according to

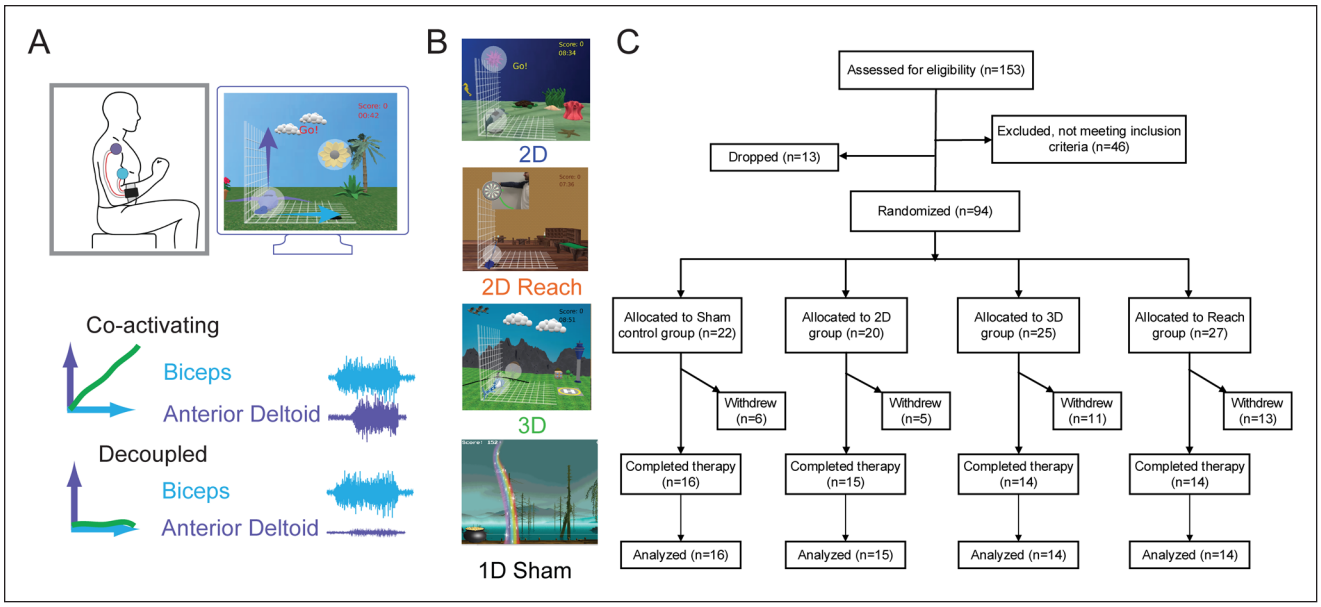

Figure 1. Myoelectric interface for neurorehabilitation (MINT) paradigm and Consolidated Standards of Reporting Trials (CONSORT) diagram. (A) *Top*, an example stroke participant used the wearable MINT device to transmit EMGs of biceps (blue) and anterior deltoid (purple) to the laptop. *Bottom*, MINT software mapped EMGs of these muscles to orthogonal components of cursor movement. In the example, biceps was mapped to the right (blue arrow) and anterior deltoid was mapped up (purple arrow). When biceps and anterior deltoid were co-activated, the cursor moved along a diagonal between the 2 directions (green). The participant was then conditioned using MINT to decouple the 2 muscles; in this example, to activate biceps independently of anterior deltoid. (B) Examples of MINT game screens for the 4 groups. In the 2D group, participants used 2 muscles mapped to the *x* and *y* directions. Similarly, in the 2D Reach group, participants were trained with 2 muscles, but they were given additional visual prompts to encourage more effort to reach in the current muscle's pulling direction. In the 3D group, participants used 3 muscles simultaneously, with each muscle separately mapped to the *x*, *y*, and *z* directions of cursor movement. Finally, in the 1D sham group, participants used only 1 muscle mapped to the *x* direction. (C) CONSORT enrollment flow chart.

age and baseline impairment severity. Randomization used permuted block sizes of 4 to preserve balance across groups.

The allocation sequence was generated in R by the study statistician, who also safeguarded its confidentiality to ensure proper concealment. A separate study member, who was not involved in outcome assessments or intervention delivery, managed group assignment. Blinding was maintained for participants and occupational therapists performing clinical assessments; staff responsible for administering MINT were necessarily aware of treatment allocation.

Identifying Abnormal Co-Activation and Group Design

Two weeks before training, participants completed a screening for abnormal muscle co-activation using a seated reaching task with EMG recordings from 12 shoulder and arm muscles involved in elbow or shoulder movement. Muscles showing the highest abnormal co-activation were identified and targeted for MINT training (see Supplemental Methods for detailed procedures and figures). Muscle-pair selection was guided by well-established literature demonstrating pathological shoulder–elbow and shoulder–scapular coupling after stroke, including anterior deltoid and biceps, biceps and triceps, anterior deltoid and trapezius,[8] as well as between anterior and posterior deltoids.[18]

Participant groups included (Figure 1(B), Figure S1): (1) 2D group, who trained with MINT using 2 muscles at a time to control a cursor (see next section for details); (2) 2D Reach group, who also used 2 muscles simultaneously to control the cursor while being cued with pictures instructing them to reach as far as possible in the direction of the target muscle; (3) 3D group, who used 3 muscles simultaneously to control the cursor; and (4) sham group, who used 1 muscle to control a cursor in 1D (see Supplemental Methods for details on group design and each group training paradigm).

MINT Conditioning

Participants were asked to use MINT 90 minutes/day, 5 days/week at home (unsupervised), and 1 day/week in lab (supervised), over 6 weeks. Each session consisted of 9 "runs" of 10 minutes each. On average, each run consisted of about 30 trials (repetitions), which were randomly ordered and balanced over target muscles. MINT included a

custom-built, wireless surface EMG acquisition system (Myomo, Inc.) that amplified, digitized, and computed the EMG envelopes, and transmitted the envelopes at 50 Hz to a laptop via Bluetooth.

MINT conditioning uses EMG envelopes to move a cursor into targets in customized games (Figure 1(A)). The EMG envelopes were mapped to orthogonal components of cursor position in either 2D (for 2D and 2D Reach groups) or 3D (for 3D group). The vector sum of these components determined the cursor position. To reach targets on the cardinal axes, participants in the experimental groups had to activate the targeted muscle independently of other muscles. Participants moved the cursor into the "home" target at the bottom left corner of the screen by relaxing the controlling muscles (Figure 1(A)). Then, an outer target appeared near one of the neighboring corners, requiring participants to activate the controlling muscle to move the cursor into the target and remain there for 0.5 seconds. Positive audiovisual feedback was provided for successfully acquiring the target within 7 seconds. MINT game design and difficulty levels are in Supplemental Methods and prior publication.[19]

Outcome Measures

Feasibility was assessed through mean daily training time, mean daily repetitions, and a modified version of the Intrinsic Motivation Inventory (IMI) survey measuring engagement and effort at the end of the 6 weeks (see Supplemental Methods).

Clinical evaluations were conducted by an occupational therapist blinded to group assignment at −2, 0, 2, 6, and 10 weeks relative to the initiation of training (Figure S1). The primary efficacy outcome was the change in the timed portion of the WMFT at the end of training (Week 6) relative to the baseline (mean of Weeks -2 and 0) for each MINT group. Consistent with standard administration of the WMFT, all timed tasks were capped at a maximum of 120 s; each task was scored at 120 seconds if a participant was unable to complete a task within this limit. We chose WMFT because, as a continuous (timed) measure of participation in functional activities, it is more sensitive to change than other discrete metrics such as the FMA-UE[20]. It also has more items relevant to upper arm function in motor activities that are independent of hand function than some other clinical scores, such as the Action Research Arm Test. We considered these properties important because this trial was (a) enrolling mostly severely impaired participants who had little or no hand function and (b) only training muscles related to elbow and shoulder function. Secondary efficacy outcomes included the change in WMFT in all MINT groups combined, WMFT at Week 10 (4-week follow-up), changes in WMFT shoulder and elbow subscores, FMA-UE (motor), Modified Ashworth Scale (MAS), and Motor Activity Log (MAL)-12. Occupational therapists were trained to perform these assessments by experienced trainers in a standardized fashion and tested to ensure at least 95% proficiency before being approved as an assessor. In addition, we computed arm kinematics during reaching.[21] (Supplemental Methods).

Behavioral metrics during training included weighted time to target (normalized by dividing by difficulty level), and co-activation between trained muscles, computed in the 1-second window before target capture. Game performance and co-activation were calculated separately for each 2-week muscle set in the 2D, 2D Reach, and sham groups; sham data excluded co-activation because only 1 muscle was recorded. For the 3D group, only the first 2 weeks of each 3-week set were included for comparability.

Effect of Stroke Location on MINT Recovery

We also explored stroke lesion location as a predictor of motor recovery following MINT conditioning by grouping participants based on involvement of specific brain regions and comparing WMFT changes across these groups (see Supplemental Materials for analysis details).

Statistical Analysis

The sample size was calculated based on a small set of preliminary data, with estimated effect size of 0.8, from our prior study.[14] For a power of 0.8 and Bonferroni-corrected alpha of .05, we estimated needing 14 participants per group to accommodate 15% attrition rate. Baseline variables (age, time post-stroke, FMA-UE, WMFT, MAS, MAL-Q, and MAL-A) were normally distributed (Lilliefors test), so a 1-way analysis of variance (ANOVA) was used to compare medians across groups at baseline (3D, 2D, 2D Reach, and Sham).

To compare within and between groups, linear mixed-effects models (LMEMs) were used with estimated marginal means, which also accounted for repeated measures and missing values. The outcome measures of interest were WMFT, FMA-UE, MAS, and MAL. Fixed effects included group (2D, 3D, 2D Reach, combined experimental groups, and sham) and random effects included repeated time points (baseline, Weeks 2, 6, and 10). Time was treated as a categorical variable. The covariance was unstructured to allow for different correlations between baseline and each time point. Bonferroni correction was used to adjust for multiple post-hoc pairwise comparisons. We analyzed both modified intention-to-treat (mITT; all participants who had data at week 6 timepoint) and per-protocol (participants who completed at least 30 h of training in under 10 weeks) groups. We evaluated the assumptions of LMEMs, including

linearity, normality of residuals, homoscedasticity, and appropriate specification of fixed and random effects. Overall, these assumptions were adequately satisfied for the primary model.

The assumptions were assessed using a combination of graphical and quantitative diagnostics. Normality of conditional residuals was evaluated using quantile–quantile (Q–Q) plots (Figure S2) and formally tested using the Shapiro–Wilk test, which indicated no violation of normality ($P = .20$). Homoscedasticity and independence of residuals were assessed by inspection of residuals versus fitted values (Figure S2), which did not reveal systematic patterns. In addition, likelihood ratio tests were used to evaluate homogeneity of variance across groups, supporting the assumption of equal variances.

For comparison, models using log-transformed WMFT time were also examined, consistent with prior literature. Diagnostic plots for these models (Figure S3) demonstrated greater deviation from normality, including increased dispersion from the diagonal in Q–Q plots, indicating poorer model fit relative to the untransformed WMFT specification.

Five participants were excluded from kinematic analysis due to technical recording problems; 12 were excluded from stroke location analysis due to unavailable neuroimaging. No participants were excluded from training performance analysis; missing training performance data were imputed with the last observation carried forward method. Two sample *t*-tests assessed significance of changes in kinematics and stroke-location effects.

Muscle Synergy Analysis

To investigate whether MINT conditioning altered the activation of entire muscle synergies or specific targeted muscles, we analyzed muscle synergies before and after training using electromyographic (EMG) data from 9 arm muscles during a reaching task. Synergies were extracted using non-negative matrix factorization, and changes in synergy composition and co-activation of trained muscles were compared between responders (participants in experimental groups with clinically significant WMFT improvement) and the sham group. To quantify changes in abnormal co-activation, we computed a Disparity Index (DI), which measures co-activation between 2 muscles within a synergy[15,22] (see Supplemental Methods).

Results

Participant Enrollment

Of 153 participants screened for eligibility (Figure 1(C)), 46 failed inclusion criteria and 13 withdrew before the start of training at week 0 (Figure 1(C)), leaving 94 randomized: 25 in 3D, 20 in 2D, 27 in 2D Reach, and 22 in Sham. During the course of the study, 35 subjects withdrew before week 6 of training. The main reasons for withdrawal were related to insufficient ability or desire to adhere to the protocol and family or personal issues (Table S1). Ultimately, a total of 59 participants (mITT), aged 21 to 87 years, with a mean duration of 6.4 years since stroke, completed the entire 6 weeks of training and were included in the final analysis. Two participants did not return for the follow-up visit at 4 weeks post-training. Ten participants were excluded for the per-protocol analysis (6 due to performing less than 30 hours of training, 4 due to taking more than 10 weeks). No significant differences were observed between the 4 groups (3D, 2D, 2D Reach, and Sham) for demographics or stroke-related arm function at baseline (Table 1).

Feasibility: Training Adherence and Feedback

Participants trained 86 ± 21 minutes/day of the instructed 90 minutes/day. Among those who completed training, 31% trained at least 90 minutes/day and 91% trained at least 60 minutes/day. Daily repetitions averaged 287 ± 84 in the 3D group, 315 ± 92 in 2D Reach, 356 ± 85 in 2D, and 300 ± 65 in Sham, with no significant group differences ($P > .05$, *t*-test). The list of trained muscles for all participants is reported in Table S2. The most frequently targeted pairs were BI/AD (45 subjects, 76%), AD/PD (40 subjects, 68%), and AD/Trap (31 subjects, 53%) reflecting abnormal shoulder and elbow co-activation patterns in stroke. A full distribution of muscle-pair frequencies is provided in Supplemental Table S3.

The modified IMI (7-point Likert scale) indicated high motivation, with mean enjoyment scores of 5.7 ± 1 and effort scores of 6.3 ± 0.5 (Figure S4). Mild fatigue and skin irritation were the most common adverse events, occurring in 9 participants. Details of adverse events are listed in Table S4. Participants anecdotally reported positive benefits from the MINT game, such as enhanced muscle engagement, reduced arm tension, and increased awareness of their affected arm. While some challenges with device setup and functionality were noted, the overall feedback highlighted the game's motivational impact and therapeutic value. Comprehensive feedback from participants is detailed in Table S5. We tracked phone interactions with 35 participants. Most participants required limited contact with lab staff during the week; only 6% required support more than 3 times/week.

MINT Performance and Efficacy Outcomes

Participants learned to perform MINT conditioning accurately relatively quickly, within about 5 days (Figure S5). During training, there was a 76% decrease in co-activation relative to the reaching task across all muscle pairs trained with MINT in the experimental groups (Figure S5).

Table 1. Participant Demographics.

Demographic	3D (n = 14)	2D (n = 15)	2D reach (n = 14)	Sham (n = 16)	*P*
Age (y)	60.6 ± 14.5	56.7 ± 9.2	64.7 ± 14.9	52.6 ± 12.6	.07
Gender, n (%)					
Male	11 (79)	9 (60)	11 (79)	10 (63)	
Female	3 (21)	6 (40)	3 (21)	6 (38)	
Race, n (%)					
White	6 (43)	10 (67)	8 (57)	8 (50)	
Black	7 (50)	3 (20)	6 (43)	6 (38)	
Asian	1 (7)	2 (13)	0 (0)	1 (6)	
Unknown	0 (0)	0 (0)	0 (0)	1 (6)	
Handedness					
Right	13 (93)	11 (73)	14 (100)	13 (81)	
Left	1 (7)	4 (27)	0 (0)	3 (19)	
Affected side					
Right	5 (36)	7 (47)	8 (57)	7 (44)	
Left	9 (64)	8 (53)	6 (43)	9 (56)	
Time post-stroke (y)	5.8 ± 4.7	5.7 ± 6.3	5.1 ± 6.9	7.0 ± 11.6	1
FMA-UE baseline	14.0 ± 4.3	16.7 ± 5.6	16.0 ± 4.2	17.7 ± 7.1	.3
WMFT baseline	96.3 ± 11.7	90.1 ± 13.6	91.7 ± 10.9	90.4 ± 19.2	.6
MAS baseline	0.8 ± 0.3	0.8 ± 0.3	0.7 ± 0.4	0.9 ± 0.3	.4
MAL-Q baseline	0.5 ± 0.9	0.5 ± 0.4	0.3 ± 0.4	0.6 ± 0.7	.3
MAL-A baseline	0.5 ± 0.8	0.5 ± 0.4	0.3 ± 0.4	0.6 ± 0.7	.4

Abbreviations: FMA-UE, Fugl–Meyer Assessment for Upper Extremity; WMFT, Wolf Motor Function Test; MAS, Modified Ashworth Scale; MAL-Q, Motor Activity Log–Quality of Movement; MAL-A, Motor Activity Log–Amount of Movement. Age, time, and baselines display mean ± SD. *P*-values for differences between continuous variables (age, time post-stroke, FMA-UE, WMFT, MAS, MAL-Q, MAL-A) were calculated using the 1-way analysis of variance test.

In mITT analysis of the primary efficacy measure (WMFT), the 3D group improved significantly by 6.8 seconds from baseline, exceeding the minimum clinically important difference (MCID) of 1.5 s—while the 2D, 2D Reach, and sham groups did not change significantly (Figure 2(A), Table 2). In per-protocol analysis, the 3D group improved by 7.5 seconds significantly more than sham at week 6; other experimental groups did not (Figure 2(B), Table 2). No group improved significantly more than sham in mITT analysis.

Participants in all MINT groups combined improved significantly at week 6 by a mean of 4.1 seconds compared to baseline (Figure 2(A), Table 2). By week 10 (1-month post-training), all experimental groups had improved significantly on WMFT from baseline, but the sham group had not (Table 2). In particular, the 3D group continued to improve between weeks 6 and 10. Because participants were only training upper arm muscles, we also analyzed a subset of WMFT items involving movement of the elbow and shoulder only. In the mITT analysis of elbow and shoulder items, the 3D group improved significantly more than sham (by 11.9 seconds) at week 6. The other changes from baseline in mITT were not statistically greater than sham for any experimental group (Table 2). In per-protocol analysis of elbow and shoulder items only, the 3D group improved significantly more than sham at week 6 (by 16.2 seconds), and combined experimental groups also improved significantly more than sham (Figure 2(C), Table 2). The MCID was exceeded at week 6 by 10 of 14 participants (71%) in the 3D group, 7 of 14 participants (50%) in the 2D Reach group, 8 of 15 (53%) in the 2D group, and 7 of 16 participants (44%) in the sham group. Notably, even individuals with severe impairment (initial FMA$<$25, 95% of our participants) in the combined experimental groups improved by 4.3 seconds more than those with severe impairment in the sham group at week 6 ($P = .02$, 2-sample t-test). Moreover, effect sizes were moderate to large at week 6—0.7 and 1.2 in combined experimental and 3D, respectively—and increased at week 10—0.9 and 1.2 in combined experimental and 3D, respectively (Table 3). The FMA-UE improved significantly at weeks 6 and 10 in combined experimental groups but not in the sham group in mITT and per-protocol analyses. However, this improvement was less than the MCID of 5 (Table 2). The changes in FMA-UE from baseline did not differ between any experimental group and sham. Additional secondary clinical outcomes, including MAL and MAS, did not change significantly (Table S7).

We also performed a subgroup analysis according to the first muscle pair trained. Participants who started with AD/BI (n = 17), AD/PD (n = 11), AD/Trap (n = 10) improved by 5.0 ± 6.6, 2.9 ± 9.6, and 0.6 ± 4.5 seconds, respectively.

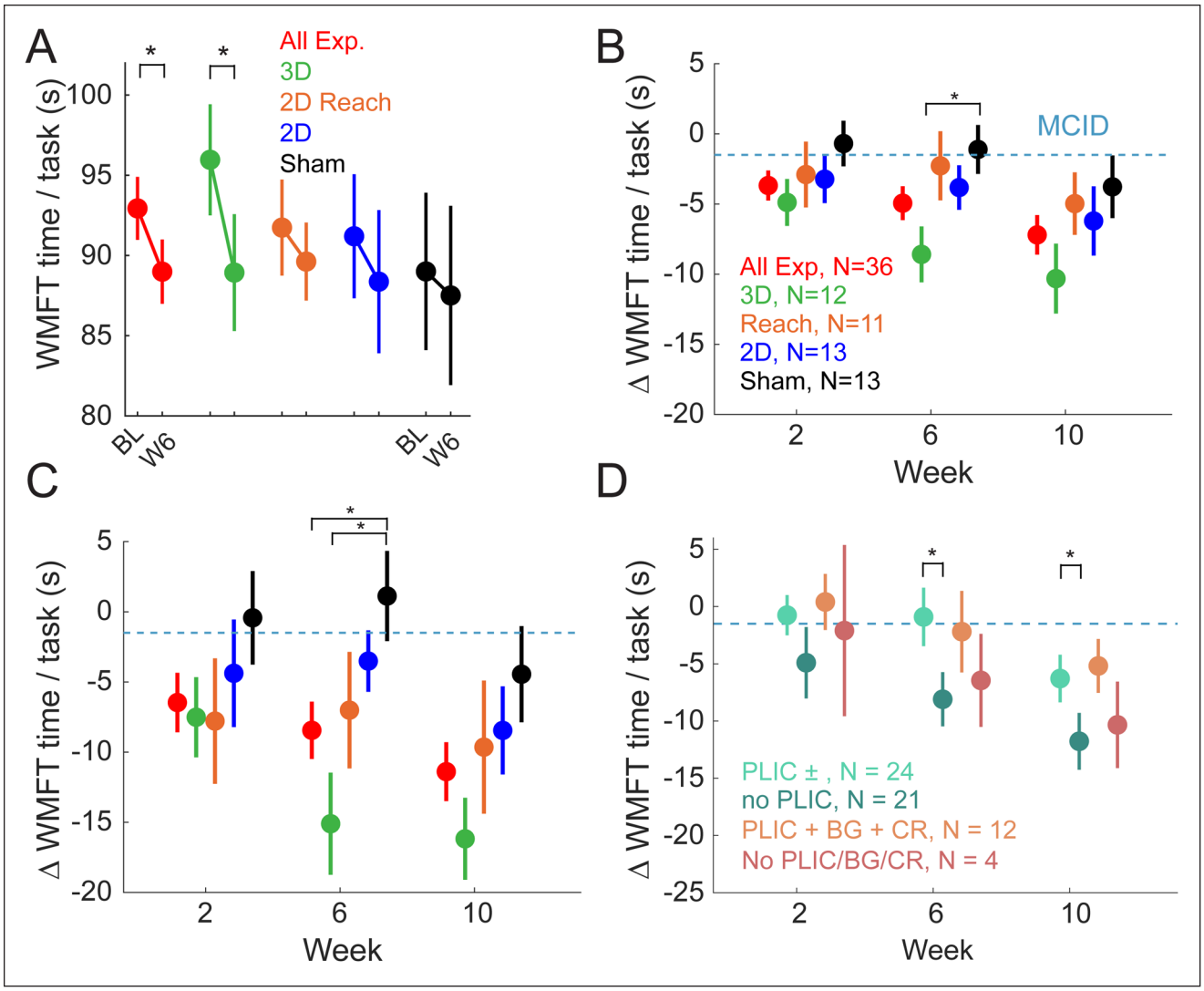

Figure 2. Effect of MINT conditioning on upper-extremity motor function. (A) Mean (±standard error) Wolf Motor Function Test (WMFT) scores at baseline (BL) and Week 6 (W6) for each group: combined experimental groups (red), 3D (green), 2D (blue), 2D Reach (orange), and sham control (black). Lower WMFT scores indicate better motor performance. (B) Mean change in WMFT score from baseline to Week 6 (ΔWMFT). Lower values represent higher functional improvement. The dashed horizontal line indicates the minimal clinically important difference (MCID). (C) Mean change in WMFT score from baseline for task items specifically involving elbow or shoulder movements, reflecting proximal motor recovery. (D) Mean change in WMFT score from baseline stratified by stroke lesion location across all participants. Abbreviations: PLIC, posterior limb of the internal capsule; BG, basal ganglia; CR, corona radiata. Asterisks (*) indicate statistically significant differences ($P < .05$). Error bars represent standard error.

These differences were not statistically significant (1-way ANOVA, $P = .32$). These findings indicate that the specific initial muscle pair did not systematically affect functional outcomes, supporting the generalizability of MINT across different abnormal co-activation patterns.

Impact of Stroke Location

We also evaluated the effect of stroke location on motor recovery with MINT conditioning. People with lesions involving at least the posterior limb of the internal capsule (PLIC; PLIC±) improved less than those without PLIC damage (No PLIC; $P = .02$; Figure 2(D)). People with lesions involving PLIC, basal ganglia, and corona radiata had a nonsignificant trend of less improvement than those whose lesions did not involve any of those regions (however, the number of participants in the latter group was very low). The proportion of PLIC involvement was 55%, 45%, and 58% for 3D, 2D, and 2D reach groups, respectively.

Table 2. Changes in WMFT and FMA-UE at Weeks 6 and 10 From Baseline, Absolute Change and Change Relative to Sham (Modified Intention-to-treat [mITT] and Per-protocol).

	Mean change by group				Mean change by group compared to sham			
	Week 6		Week 10		Week 6		Week 10	
Group	Mean (95% CI)	*P*	Mean (95% CI)	*P*	Mean (95% CI)	*P*	Mean (95% CI)	*P*
WMFT–MITT–all items								
2D	−3.2 (−7.8 to 1.4)	.3	−5.8 (−10.4 to −1.2)	**.007**	−1.6 (−8.0 to 4.8)	1	−1.8 (−8.4 to 4.7)	1
3D	−6.9 (−11.6 to −2.1)	**.002**	−9.4 (−14.1 to −4.6)	**<.0001**	−5.2 (−11.7 to 1.2)	.2	−5.4 (−12.1 to 1.2)	.2
2D reach	−2.1 (−6.9 to 2.6)	1	−5.4 (−10.1 to −0.7)	**.02**	−0.5 (−7.0 to 6.0)	1	−1.4 (−8.1 to 5.2)	1
All Exp.	−4.1 (−6.8 to −1.4)	**.0008**	−6.9 (−9.6 to −4.2)	**<.0001**	−2.4 (−7.6 to 2.7)	.9	−2.9 (−8.3 to 2.5)	.7
sham	−1.6 (−6.0 to 2.8)	1	−4.0 (−8.6 to 0.7)	.1				
WMFT–per-protocol–all items								
2D	−3.8 (−8.9 to 1.3)	.2	−6.2 (−11.3 to −1.1)	**.01**	−2.7 (−10.0 to 4.5)	1	−1.9 (−9.3 to 5.6)	1
3D	−8.6 (−13.9 to −3.3)	**<.0001**	−10.3 (−15.6 to −5.0)	**.01**	−7.5 (−14.9 to −0.1)	**.047**	−6.0 (−13.6 to 1.7)	.2
2D reach	−2.3 (−7.8 to 3.3)	1	−5.0 (−10.5 to 0.6)	.1	−1.2 (−8.7 to 6.4)	1	−0.6 (−8.4 to 7.2)	1
All Exp.	−4.9 (−8.0 to −1.8)	**.0004**	−7.2 (−10.2 to −4.1)	**<.0001**	−3.8 (−9.8 to 2.2)	.4	−2.8 (−9.1 to 3.4)	1
sham	−1.1 (−6.2 to 4.0)	1	−4.4 (−9.8 to 1.1)	0.2				
WMFT—MITT—elbow/shoulder items								
2D	−2.8 (−10.4 to 4.7)	1	−8.2 (−15.8 to −0.7)	**.02**	−2.9 (−13.4 to 7.6)	1	−3.2 (−13.9 to 7.5)	1
3D	−11.9 (−19.6 to −4.1)	**.0008**	−15.0 (−22.8 to −7.2)	**<.0001**	−11.9 (−22.6 to −1.3)	**.02**	−10.0 (−20.9 to 1.0)	.1
2D reach	−6.3 (−14.1 to 1.5)	.2	−10.8 (−18.6 to −3.0)	**.002**	−6.4 (−17.0 to 4.3)	.5	−5.8 (−16.7 to 5.2)	.7
All Exp.	−7.0 (−11.4 to −2.5)	**.0004**	−11.3 (−15.8 to −6.9)	**<.0001**	−7.1 (−15.6 to 1.5)	.2	−6.3 (−15.2 to 2.6)	.3
sham	0.1 (−7.2 to 7.4)	1	−5.0 (−12.7 to 2.6)	.4				
WMFT—per-protocol—elbow/shoulder items								
2D	−3.5 (−11.7 to 4.6)	1	−8.5 (−16.6 to −0.3)	**.04**	−4.6 (−16.2 to 6.9)	1	−3.2 (−15.1 to 8.7)	1
3D	−15.1 (−23.6 to −6.6)	**<.0001**	−16.2 (−24.7 to −7.7)	**.003**	−16.2 (−28.0 to −4.5)	**.003**	−10.9 (−23.0 to 1.2)	.1
2D reach	−7.0 (−15.9 to 1.8)	.2	−9.6 (−18.5 to −0.8)	**.03**	−8.1 (−20.2 to 3.9)	.4	−4.4 (−16.8 to 8.0)	1
All Exp.	−8.5 (−13.4 to −3.6)	**<.0001**	−11.4 (−16.3 to −6.5)	**<.0001**	−9.7 (−19.2 to −0.2)	**.04**	−6.2 (−16.1 to 3.8)	.5
sham	1.1 (−7.0 to 9.3)	1	−5.3 (−13.9 to 3.4)	.5				
FMA-UE–MITT								
2D	1.6 (−0.1 to 3.3)	.06	1.4 (−0.3 to 3.1)	.1	0.5 (−1.8 to 2.9)	1	0.5 (−2.0 to 2.9)	1
3D	1.6 (−0.2 to 3.3)	.1	1.5 (−0.2 to 3.2)	.1	0.5 (−1.9 to 2.9)	1	0.5 (−1.9 to 3.0)	1
2D reach	1.7 (−0.0 to 3.5)	.06	1.7 (−0.0 to 3.5)	.06	0.6 (−1.8 to 3.0)	1	0.7 (−1.7 to 3.2)	1
All Exp.	1.6 (0.6 to 2.6)	**<.0001**	1.5 (0.6 to 2.5)	**.0004**	0.5 (−1.4 to 2.5)	1	0.6 (−1.4 to 2.6)	1
sham	1.1 (−0.5 to 2.7)	.4	1.0 (−0.7 to 2.7)	.6				
FMA-UE–per-protocol								
2D	1.8 (−0.1 to 3.7)	.06	1.7 (−0.2 to 3.5)	.1	0.2 (−2.5 to 2.9)	1	0.3 (−2.4 to 3.1)	1
3D	1.3 (−0.7 to 3.2)	.4	1.4 (−0.5 to 3.4)	.3	−0.4 (−3.1 to 2.3)	1	0.1 (−2.7 to 2.9)	1
2D reach	1.5 (−0.6 to 3.5)	.3	2.0 (−0.0 to 4.0)	.05	−0.2 (−2.9 to 2.6)	1	0.7 (−2.2 to 3.5)	1
All Exp.	1.5 (0.4 to 2.6)	**.004**	1.7 (0.6 to 2.8)	**.001**	−0.1 (−2.3 to 2.1)	1	0.4 (−1.9 to 2.7)	1
sham	1.6 (−0.3 to 3.5)	.1	1.3 (−0.7 to 3.3)	.4				

Abbreviations: W6, Week 6; W10, Week 10; WMFT, Wolf Motor Function Test; FMA-UE, Fugl–Meyer Assessment of the Upper Extremity; All Exp, combined experimental groups, CI, confidence interval; MITT, modified intention to treat.
Mean and 95% CI and adjusted *P*-value reported.
Bolded items were statistically significant at the significance level of .05.

Table 3. Effect Size of Change From Baseline in WMFT at Week 6 and Week 10 for Modified Intention-to-treat and Per-protocol Analyses.

Effect size				
	Modified intention-to-treat		Per-protocol	
	Week 6—Baseline	Week 10—Baseline	Week 6—Baseline	Week 10—Baseline
2D	0.6	0.8	0.6	0.7
3D	1.2	1.2	1.4	1.2
2D Reach	0.4	0.7	0.4	0.6
All Exp.	0.7	0.9	0.8	0.8

Abbreviations: WMFT, Wolf Motor Function Test. All Exp, combined experimental groups.
Effect sizes were computed as change in WMFT divided by the standard deviation of the sham group.

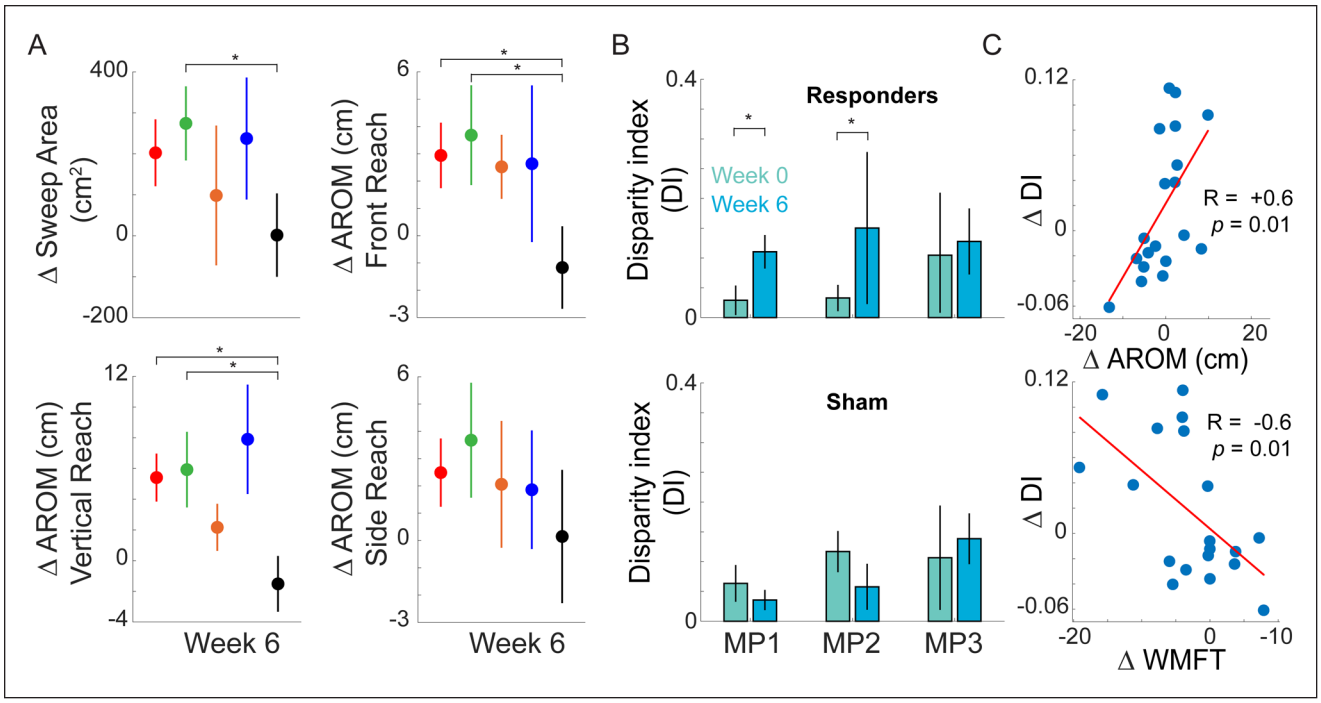

Figure 3. Effect of MINT conditioning on reaching kinematics and muscle coordination. (A) Mean change from baseline to Week 6 in reaching kinematic measures for each group: combined experimental groups (red), 3D (green), 2D (blue), 2D Reach (orange), and sham control (black). *Top left*: sweep area (movement workspace area; larger values indicate improved movement extent). *Top right*: active range of motion (AROM) during front reaching. *Bottom left*: AROM during vertical reaching. *Bottom right*: AROM during side reaching. Positive values represent improvement relative to baseline. (B) Mean (±SE) disparity index (DI), a measure of abnormal muscle co-activation/synergy coupling, at baseline (Week 0) and Week 6. Data are shown separately for responders (*top row*) and sham participants (*bottom row*) for each pair of trained muscles. Higher DI values indicate reduced abnormal coupling and improved muscle coordination. (C) Correlations between changes in DI (Week 6–baseline) and functional improvements. *Top*: association between change in DI and change in combined front and vertical AROM. *Bottom*: association between change in DI and change in WMFT score. Data are shown for all participants (experimental and sham combined).
Asterisks (*) indicate $P < .05$. Error bars represent standard error.

Kinematic Outcomes

For a more sensitive measure of movement changes, we measured wrist kinematics relative to the shoulder during various reaching movements (Figure 3(A)). At week 6, in the sweep task, the 3D group improved significantly compared to sham (275-cm² difference, $P = .03$, *t*-test; Figure 3(A)) and combined experimental groups showed a nonsignificant trend of improvement in sweep area compared to sham (201 cm²; $P = .08$). Active range of motion (AROM) in forward reaching improved by more than sham in the 3D (4.8 cm, $P = .02$; Figure 3(A)) and combined experimental groups (4 cm, $P = .03$). AROM in vertical reaching improved by more than sham in both 3D (7.4 cm, $P = .01$; Figure 3(A)) and combined experimental groups (6.9 cm, $P = .007$). In side reaching, the 3D group and combined experimental groups showed nonsignificant trends of improvement versus sham (3.0 and 2.0 cm, $P = .1$ and .2, respectively; Figure 3).

Muscle Synergy Analysis and Co-Activation Outcomes

After 6 weeks of MINT conditioning, the number and composition of synergies did not change in either responders or sham. Responders showed an average of 2.6 ± 0.9 synergies at baseline and 2.4 ± 0.8 at week 6, while sham participants had 2.9 ± 0.9 and 2.8 ± 0.9, respectively. However, muscle weights within synergies did change significantly due to training. Specifically, in responders the disparity index (DI) increased significantly in muscle pairs 1 and 2 ($P = .00004$ and .005) but not pair 3 ($P = .33$; Figure 3(B)). DI did not change significantly for any muscle pairs ($P = .94$, .88 and .22 for muscle pair 1, 2 and 3, respectively) in sham group participants. This means that responders decreased the co-activation specifically between the muscles trained, and did not affect the other muscles in the synergy. Moreover, increased DI correlated with increased active range of motion ($R = .6$, $P = .01$) and improved WMFT ($R = -.6$, $P = .01$; Figure 3(C)).

Discussion

In this randomized, sham-controlled trial, wearable MINT conditioning proved feasible, enabling high-dose, high-repetition, at-home training that was rated as enjoyable and motivating. MINT conditioning reduced abnormal co-activation between trained muscle sets during training. MINT conditioning also significantly enhanced arm activity in the 3D group and all groups combined, while the sham intervention did not. Participants in the 3D group, but not the 2D groups, improved function more than sham in per-protocol analysis, and particularly in the elbow and shoulder-related movements, which were the most relevant to the muscles trained. Experimental groups combined did not improve their activity significantly more than sham groups. MINT, but not sham, conditioning also improved arm active range of motion in multiple reaching tasks. Finally, reduction in within-synergy co-activation (increased DI) during reaching correlated significantly with improvements in both activity and AROM. This indicated that MINT enhanced movement by reducing abnormal co-activation rather than by overcoming long-term non-use.

The 3D group's 6.9-second WMFT improvement, with shoulder and elbow subscores improving by 11.9 seconds, is clinically meaningful, approaching gains seen in constraint-induced movement therapy (10-second improvement) in moderately impaired stroke survivors (mean FMA: 43) in the subacute period. In contrast, our cohort had severe impairment (mean FMA: 16) and was enrolled at an average of 6 years post-stroke, underscoring MINT's potential for this underserved population. Unlike vagus nerve stimulation[4] or spinal/cerebellar stimulation,[23,24] which showed modest benefits in severely impaired individuals, MINT offers a non-invasive, wearable option for those with restricted rehabilitation access. While some studies using conventional, or high-intensity,[8] occupational therapy have shown improvement in arm movement in the chronic stage of stroke,[5,25] most of those studies were performed in mildly or moderately impaired stroke survivors.

MINT reduced abnormal co-activation during both training and reaching. This is a novel mechanism of action for stroke rehabilitation therapy, with only a few prior uncontrolled trials attempting to reduce abnormal co-activation[13,14,26,27] or abnormal joint coupling[28] in the past. Combined with our prior study involving in-lab myoelectric interface training, our results indicate that reducing abnormal co-activation can improve arm movement. The fact that reduced co-activation (increased DI) correlated highly with both functional gains and AROM strongly suggests that reducing co-activation led to improved movement. The fact that wrist AROM relative to the shoulder—which factors out trunk movement—did show improvement from MINT indicates that the functional improvement was not compensation, but rather true improved movement. This contrasts with many studies of task-oriented therapies in chronic stroke (though some did show evidence for reduced impairment, for example, Queens Square, VNS-REHAB[4,7]; however, those populations were less impaired overall than our study population).

While arm activity as measured by WMFT did improve significantly from MINT, secondary measures of impairment (FMA) and participant-reported activity (MAL) did not. This difference could be because these are insensitive measures of improvement, especially for severely impaired individuals (nearly our entire study population). For example, significant improvement in reaching AROM could be achieved, which is functionally important to stroke survivors, without changing the FMA subscore on shoulder abduction or flexion from a 1, if the elbow is only able to be extended to 170°. The MAL is heavily biased toward items involving finger movement, which most of our participants lacked. This study trained only shoulder and elbow-related muscles and we did not expect to see improvement in more distal function, so it is not surprising that we did not see large improvements in these measures in severely impaired patients. The WMFT assessed multiple items not including the hand (ie, shoulder and elbow items, which showed the most improvement in experimental groups vs sham), and is a timed test, which is more sensitive to change than discrete measures.

We found that participants whose strokes involved the PLIC, a proxy for damage to the corticospinal tract, did not improve as much from MINT conditioning. This aligns with results from prior studies that analyzed effects of stroke location.[29-32] This may suggest that some residual corticospinal tract function is important for overcoming abnormal co-activation. Future studies will examine this question further.

This study design examined different variants of the MINT paradigm. The 3D variant's improvement may stem from greater motor learning complexity or prolonged training on the most abnormally co-activating muscle sets (3 vs 2 weeks). While the 2D Reach group did not improve as much as 3D overall, it did improve more than 2D in shoulder and elbow function. It is possible that encouraging reaching also loaded shoulder muscles more, resulting in more co-activation,[9,29] and thus increased task difficulty. Optimizing timing of shoulder loading may be important to consider in future studies of MINT. The fact that the 2D groups did not show significantly more improvement than sham may have been due to smaller effect sizes than anticipated in these groups based on our prior study.[14] It is possible that there were more participants in this study with greater damage to the corticospinal tract than in the prior study. The greater improvement in 3D group participants suggests that longer training on the most co-activating muscle sets may have led to a greater improvement in activity. Participants in this study performed—with minimal supervision—more than

300 repetitions per day, many more than typically done in conventional therapy (either in clinic or at home) though less total than a prior study of telerehabilitation therapy in subacute stroke.[33] Dosage (including the number of muscle sets to train and total time to train) and intensity are important factors to consider in future studies of MINT. The current MINT study targeted proximal muscles, as abnormal co-activation is most prominently described in these muscle groups. Testing MINT in distal muscles, such as wrist extensors and flexors, which also show abnormal co-activation,[34] as well as proximal muscles, may lead to greater functional improvement. Further, we expect that MINT will be most beneficial, and transfer better to daily activity, when combined with other therapies. Combining MINT with task-specific training, as well as strategies such as behavioral contracts, homework assignments focused on daily activities, and real-life progress tracking, may enhance the integration of trained movements into activities of daily life. Furthermore, integrating MINT with neuromodulation techniques, including brain or spinal cord stimulation or pharmacologic enhancement, may enhance effectiveness by promoting neuroplasticity and facilitating motor recovery. Participants showed continued improvement even 1 month after MINT, indicating that its effects may persist beyond the training period. This pattern is consistent with recovery models suggesting that once patients achieve a sufficient level of motor control, they may enter a positive cycle in which better movement leads to greater spontaneous arm use and further neural adaptation.[35,36]

Future studies will be necessary to illuminate what criteria may best predict response to MINT conditioning. Based on our secondary analyses, such criteria might include the amount of co-activation, preserved corticospinal tract function, and intrinsic motivation. Other limitations of the study included a relatively high withdrawal rate and non-universal enjoyment of the game. Motivation, concentration, and training intensity are critical to improving function after a stroke.[37,38] While mITT participants rated the MINT games favorably overall, some participants did have trouble using this early system design, due to computer illiteracy and equipment breakdown. Few participants required frequent support, highlighting self-sufficiency. While the withdrawal rate was relatively high (37%), most reasons were unrelated to MINT conditioning or devices but rather to personal, illness, or logistical scheduling issues. Moreover, participants trained much more independently in this study than in most trials, including telerehabilitation.[33] The current design of the MINT device is somewhat bulky, requires clipping leads to electrodes and frequent replacing of electrodes, which presented challenges for some severely impaired users. We are addressing these concerns and creating a more accessible and user-friendly design for future iterations of MINT. Improving usability, motivation, and robustness is a goal of upcoming studies. Completely wireless sensors without requiring frequent home replacement are also being developed, which will reduce setup burden and prevent placement errors, especially for difficult-to-reach muscles like deltoids. These improvements should help with effectiveness in real-world clinical use.

This study also has other limitations inherent to clinical trials of sensorimotor retraining. Home-based, EMG-guided rehabilitation must contend with variability in sensor placement, signal quality, and training environment, which may reduce consistency of the intervention across participants. Additionally, group-level treatment effects may not fully represent the heterogeneous responses observed at the individual level. Participants differ in lesion location, cognitive status, and motivation—all of which may influence responsiveness to therapy. Future studies with larger samples, refined hardware and user experience, and more detailed stratification will be important to better understand individual treatment responsiveness.

We acknowledge the distribution of residuals from WMFT is often skewed from normal and that other studies often use logarithmic transformation or nonlinear models to address this issue. However, in this study, the residuals of WMFT were more normally distributed than the residuals of the log of WMFT. Therefore, logarithmic transformation of the data was not performed for a primary analysis. A secondary analysis using log-transformed WMFT showed similar trends to those using original WMFT. Analyzing the original WMFT scores also better preserves the interpretability of results.

Despite these limitations, this study suggests that wearable, home-based MINT conditioning to reduce co-activation has potential benefit for arm movement and activity after stroke and warrants further study. Although not studied here, MINT could potentially improve access. A pilot study also suggests that MINT may similarly help leg function.[26] Benefits could perhaps increase further if MINT were combined with other therapies that target strength, excitability (ie, stimulation), motor learning,[39] or task-specific training.

Acknowledgments

We thank our participants for their valuable time and effort. We thank R. James Cotton, Jeffrey Nie, and James Nie for their efforts in kinematic data recording; to Murad Alqadi and Tyler Jacobson for their assistance with recruitment and data collection; and to Torin Kovach for his contributions to game design. We also thank Michael Ellis and Veronica Rowe for training our occupational therapists on outcome evaluations.

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Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was funded in part by National Institutes of Health Grants R01NS099210, R01NS112942, R01HD113270, and NSF CAREER Award (# 2145321).

Declaration of Conflicting Interests

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

Supplementary Material

Supplementary material for this article is available on the *Neurorehabilitation & Neural Repair* website along with the online version of this article.

References

1. Grefkes C, Fink GR. Recovery from stroke: current concepts and future perspectives. *Neurol Res Pract*. 2020;2(1):17. doi:10.1186/s42466-020-00060-6
2. Kwakkel G, Kollen BJ, van der Grond J, Prevo AJH. Probability of regaining dexterity in the flaccid upper limb: impact of severity of paresis and time since onset in acute stroke. *Stroke*. 2003;34(9):2181-2186. doi:10.1161/01.STR.0000087172.16305.CD
3. Cramer SC. Repairing the human brain after stroke: I. Mechanisms of spontaneous recovery. *Ann Neurol*. 2008;63(3):272-287. doi:10.1002/ana.21393
4. Dawson J, Liu CY, Francisco GE, et al. Vagus nerve stimulation paired with rehabilitation for upper limb motor function after ischaemic stroke (VNS-REHAB): a randomised, blinded, pivotal, device trial. *Lancet*. 2021;397(10284):1545-1553. doi:10.1016/S0140-6736(21)00475-X
5. Kwakkel G, Veerbeek JM, van Wegen EEH, Wolf SL. Constraint-induced movement therapy after stroke. *Lancet Neurol*. 2015;14(2):224-234.
6. Ayala C. Use of outpatient rehabilitation among adult stroke survivors — 20 states and the district of Columbia, 2013, and four states, 2015. *MMWR Morb Mortal Wkly Rep*. 2018;67:575-578. doi:10.15585/mmwr.mm6720a2
7. Ward NS, Brander F, Kelly K. Intensive upper limb neurorehabilitation in chronic stroke: outcomes from the Queen Square programme. *J Neurol Neurosurg Psychiatry*. 2019;90(5):498-506. doi:10.1136/jnnp-2018-319954
8. Dewald JPA, Pope PS, Given JD, Buchanan TS, Rymer WZ. Abnormal muscle coactivation patterns during isometric torque generation at the elbow and shoulder in hemiparetic subjects. *Brain*. 1995;118(2):495-510. doi:10.1093/brain/118.2.495
9. Twitchell TE. The restoration of motor function following hemiplegia in man. *Brain*. 1951;74(4):443-480. doi:10.1093/brain/74.4.443
10. Ellis MD, Holubar BG, Acosta AM, Beer RF, Dewald JPA. Modifiability of abnormal isometric elbow and shoulder joint torque coupling after stroke. *Muscle Nerve*. 2005;32(2):170-178. doi:10.1002/mus.20343
11. Wolf SL. Electromyographic biofeedback applications to stroke patients: a critical review. *Phys Ther*. 1983;63(9):1448-1459. doi:10.1093/ptj/63.9.1448
12. Glanz M, Klawansky S, Stason W, et al. Biofeedback therapy in poststroke rehabilitation: a meta-analysis of the randomized controlled trials. *Arch Phys Med Rehabil*. 1995;76(6):508-515. doi:10.1016/S0003-9993(95)80503-6
13. Wright ZA, Rymer WZ, Slutzky MW. Reducing abnormal muscle coactivation after stroke using a myoelectric-computer interface: a pilot study. *Neurorehabil Neural Repair*. 2014;28(5):443-451. doi:10.1177/1545968313517751
14. Mugler EM, Tomic G, Singh A, et al. Myoelectric computer interface training for reducing co-activation and enhancing arm movement in chronic stroke survivors: a randomized trial. *Neurorehabil Neural Repair*. 2019;33(4):284-295. doi:10.1177/1545968319834903
15. Seo G, Kishta A, Mugler E, Slutzky MW, Roh J. Myoelectric interface training enables targeted reduction in abnormal muscle co-activation. *J NeuroEngineering Rehabil*. 2022;19(1):67. doi:10.1186/s12984-022-01045-z
16. Hirsch T, Barthel M, Aarts P, et al. A first step toward the operationalization of the learned non-use phenomenon: a Delphi study. *Neurorehabil Neural Repair*. 2021;35(5):383-392. Accessed July 28, 2025. https://pubmed.ncbi.nlm.nih.gov/33703971/
17. Winstein C, Kim B, Kim S, Martinez C, Schweighofer N. Dosage matters. *Stroke*. 2019;50(7):1831-1837. doi:10.1161/STROKEAHA.118.023603
18. Roh J, Rymer WZ, Perreault EJ, Yoo SB, Beer RF. Alterations in upper limb muscle synergy structure in chronic stroke survivors. *J Neurophysiol*. 2013;109(3):768-781. doi:10.1152/jn.00670.2012
19. Hung NT, Paul V, Prakash P, et al. Wearable myoelectric interface enables high-dose, home-based training in severely impaired chronic stroke survivors. *Ann Clin Transl Neurol*. 2021;8(9):1895-1905. doi:10.1002/acn3.51442
20. Sivan M, O'Connor RJ, Makower S, Levesley M, Bhakta B. Systematic review of outcome measures used in the evaluation of robot-assisted upper limb exercise in stroke. *J Rehabil*

Med. 2011;43(3):181-189. Accessed July 28, 2025. https://pubmed.ncbi.nlm.nih.gov/21305232/
21. Nie JZ, Nie JW, Hung NT, Cotton RJ, Slutzky MW. Portable, open-source solutions for estimating wrist position during reaching in people with stroke. *Sci Rep*. 2021;11(1):1. doi:10.1038/s41598-021-01805-2
22. Roh J, Lee SW, Wilger KD. Modular organization of exploratory force development under isometric conditions in the human arm. *J Mot Behav*. 2019;51(1):83-99. doi:10.1080/00222895.2017.1423020
23. Powell MP, Verma N, Sorensen E, et al. Epidural stimulation of the cervical spinal cord for post-stroke upper-limb paresis. *Nat Med*. 2023;29(3):689-699. doi:10.1038/s41591-022-02202-6
24. Baker KB, Plow EB, Nagel S, et al. Cerebellar deep brain stimulation for chronic post-stroke motor rehabilitation: a phase I trial. *Nat Med*. 2023;29(9):2366-2374. doi:10.1038/s41591-023-02507-0
25. Rodgers H, Bosomworth H, Krebs HI, et al. Robot assisted training for the upper limb after stroke (RATULS): a multicentre randomised controlled trial. *Lancet*. 2019;394(10192):51-62.
26. Khorasani A, Hulsizer J, Paul V, Gorski C, Dhaher YY, Slutzky MW. Myoelectric interface for neurorehabilitation conditioning to reduce abnormal leg co-activation after stroke: a pilot study. *J NeuroEngineering Rehabil*. 2024;21(1):1-9. doi:10.1186/s12984-024-01305-0
27. Marin-Pardo O, Donnelly MR, Phanord CS, Wong K, Pan J, Liew SL. Functional and neuromuscular changes induced via a low-cost, muscle-computer interface for telerehabilitation: a feasibility study in chronic stroke. *Front Neuroergonomics*. 2022;3:1046695. doi:10.3389/fnrgo.2022.1046695
28. Keller T, Ellis MD, Dewald JPA. Overcoming abnormal joint torque patterns in paretic upper extremities using triceps stimulation. *Artif Organs*. 2005;29(3):229-232. doi:10.1111/j.1525-1594.2005.29041.x
29. Shelton FDNAP, Reding MJ. Effect of lesion location on upper limb motor recovery after stroke. *Stroke*. 2001;32(1):107-112. doi:10.1161/01.STR.32.1.107
30. Cassidy JM, Tran G, Quinlan EB, Cramer SC. Neuroimaging identifies patients most likely to respond to a restorative stroke therapy. *Stroke*. 2018;49(2):433-438. doi:10.1161/STROKEAHA.117.018844
31. Stinear CM, Barber PA, Petoe M, Anwar S, Byblow WD. The PREP algorithm predicts potential for upper limb recovery after stroke. *Brain*. 2012;135(8):2527-2535. doi:10.1093/brain/aws146
32. Stinear CM, Byblow WD, Ackerley SJ, Smith MC, Borges VM, Barber PA. PREP2: a biomarker-based algorithm for predicting upper limb function after stroke. *Ann Clin Transl Neurol*. 2017;4(11):811-820. doi:10.1002/acn3.488
33. Cramer SC, Dodakian L, Le V, et al. Efficacy of home-based telerehabilitation vs in-clinic therapy for adults after stroke: a randomized clinical trial. *JAMA Neurol*. 2019;76(9):1079-1087. doi:10.1001/jamaneurol.2019.1604
34. Ellis MD, Lan Y, Yao J, Dewald JPA. Robotic quantification of upper extremity loss of independent joint control or flexion synergy in individuals with hemiparetic stroke: a review of paradigms addressing the effects of shoulder abduction loading. *J NeuroEngineering Rehabil*. 2016;13(1):95. doi:10.1186/s12984-016-0203-0
35. Han CE, Arbib MA, Schweighofer N. Stroke rehabilitation reaches a threshold. *PLoS Comput Biol*. 2008;4(8):e1000133. doi:10.1371/journal.pcbi.1000133
36. Ballester BR, Ward NS, Brander F, Maier M, Kelly K, Verschure PFMJ. Relationship between intensity and recovery in post-stroke rehabilitation: a retrospective analysis. *J Neurol Neurosurg Psychiatry*. 2022;93(2):226-228. doi:10.1136/jnnp-2021-326948
37. Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. *J Speech Lang Hear Res*. 2008;51(1):S225-S239. doi:10.1044/1092-4388(2008/018)
38. Schmidt RA, Lee TD. *Motor Control and Learning: A Behavioral Emphasis*. 3rd ed. Human Kinetics; 1999:xvi, 493.
39. Cheng LY, Che T, Tomic G, Slutzky MW, Paller KA. Memory reactivation during sleep improves execution of a challenging motor skill. *J Neurosci*. 2021;41(46):9608-9616. doi:10.1523/JNEUROSCI.0265-21.2021