

Increased functional connectivity between cortical hand areas and praxis network associated with training-related improvements in non-dominant hand precision drawing

Benjamin A. Philip and Scott H. Frey

Abstract

Chronic forced use of the non-dominant left hand yields substantial improvements in the precision and quality of writing and drawing. These changes may arise from increased access by the non-dominant (right) hemisphere to dominant (left) hemisphere mechanisms specialized for end-point precision control. To evaluate this prediction, 22 healthy right-handed adults underwent resting state functional connectivity (FC) MRI scans before and after 10 days of training on a left hand precision drawing task. 89% of participants significantly improved left hand speed, accuracy, and smoothness. Smoothness gains were specific to the trained left hand and persistent: 6 months after training, 71% of participants exhibited above-baseline movement smoothness. Contrary to expectations, we found no evidence of increased FC between right and left hemisphere hand areas. Instead, training-related improvements in left hand movement smoothness were associated with increased FC between both sensorimotor hand areas and a left-lateralized parieto-prefrontal network implicated in manual praxis. By contrast, skill retention at 6 months was predicted by changes including decreased FC between the representation of the trained left hand and bilateral sensorimotor, parietal, and premotor cortices, possibly reflecting consolidation and a disengagement of early learning processes. These data indicate that modest amounts of training (<200 min total) can induce substantial, persistent improvements in the precision and quality of non-dominant hand control in healthy adults, supported by strengthened connectivity between bilateral sensorimotor hand areas and a left-lateralized parieto-prefrontal praxis network.

1. Introduction

Some 90% of humans show a strong preference for use of the right hand in tasks that involve high levels of end-point precision (e.g. writing and drawing), which may reflect an endogenous specialization of the human left hemisphere for controlling the dynamics underlying limb trajectory (Coren and Porac, 1977, Geschwind et al., 2002, Sainburg, 2002, Shabbott and Sainburg, 2008). Remarkably, the extent to which this performance asymmetry can be altered through training remains uncertain. Apart from its basic relevance, this issue has clinical significance because many thousands of individuals are forced to rely primarily on their non-dominant hands (NDH) as a result of unilateral limb or brain injury (Larsen and Lauritsen, 1993, Nakayama et al., 1994). Notably, some 20–30% of hemiplegic stroke survivors never regain levels of dominant hand (DH) control suitable for tasks of daily life that demand high levels of precision (Heller et al., 1987, Sunderland et al., 1989).

Dominant hand amputees come to perform precision drawing and writing tasks with their NDHs at very high levels, possibly as a result of chronic forced use (Philip and Frey, 2014, Yancosek and Mullineaux, 2011). This compensation appears to involve greater recruitment of cerebellar and cortical structures including the territory formerly devoted to the amputated DH. Importantly, NDH performance was associated with increased activity within this former hand territory. This may reflect increased interhemispheric connectivity between the NDH representations and the DH representation that is specialized for precision control (Philip and Frey, 2014). However, because unilateral deafferentation induces functional changes in both cerebral hemispheres (Bogdanov et al., 2012, Calford and Tweedale, 1990, Pawela et al., 2010), it remains uncertain whether these results with amputees generalize to healthy adults, or other patient populations.

By contrast, NDH training studies involving healthy adults have tended to emphasize tasks that place few demands on the hypothesized left-hemisphere specialization for precision end-point control, instead focusing on behaviors such as finger

sequencing (Grafton et al., 2002, Karni et al., 1995), grip force tracking (Schambra et al., 2011), or wrist rotation (Shmuelof et al., 2014). A recent exception found that 11 days (660 min) of NDH training yielded improvements in visually-guided precision aiming and tracing tasks (Walz et al., 2015), accompanied by a multitude of increases in cortical and subcortical activity. Whether these changes in activity reflect experience-dependent plasticity, or are associated with differences in levels of performance before and after learning, are unclear.

We designed the present work to test two hypotheses. First, we predicted that training dosages feasible within a rehabilitation timeframe would induce significant and long-lasting improvements in NDH endpoint precision control in healthy adults. These would be reflected in decreased error rates, increased movement speed and smoothness that persist even 6 months post-training. Second, we proposed that the improvements in NDH performance reflect increased access to left hemisphere mechanisms specialized for end-point precision control (Philip and Frey, 2014, Sainburg, 2010). More precisely, we expected that training-related improvements in performance would be associated with increased functional connectivity (FC) between the cortical NDH representation and the DH representation that is specialized for precision control (Philip and Frey, 2014, Yancosek and Mullineaux, 2011). We employed a precision drawing task (PDT; Philip and Frey, 2014) that—like handwriting—is normally performed much better with the DH. We used resting state fMRI to evaluate the effects of training on functional connectivity (fcMRI), based on prior observations that motor learning can selectively modify the efficiency of resting state networks in the human brain (Albert et al., 2009, Ma et al., 2011, Vahdat et al., 2011). This approach to understanding training-related adaptations in brain has the advantage of not being confounded by pre- to post-training changes in performance, because participants perform no task during scanning.

2. Materials and Methods

2.1 Experimental Design Overview

Participants used their left non-dominant hand (NDH) to practice the precision drawing task (PDT). Each participant practiced the task for 10 days or until his or her NDH performance reached an a priori criterion ($\geq 80\%$ of their DH1 baseline speed on two consecutive training days); participants were not informed of this criterion during training. Dominant-hand (DH) baseline performance was recorded before and after NDH training. Participants underwent MRI scanning before the first PDT session ("MRI-Pre"), and one day after the final training session ("MRI-Post"). Participants returned for long-term follow-up testing 1 week, 4 weeks, and 6 months (26 weeks) after MRI-Post. During the follow-up sessions, participants performed the PDT with their NDH.

Sessions are labeled by hand and order. For example, we refer to the second NDH session as NDH2. Follow-up testing sessions were labeled NDH+1W (1 week after MRI-Post, 18 days after experiment start), NDH+4W (4 weeks after MRI-Post, 41 days after experiment start), and NDH+6M (6 months after MRI-Post, 191 days after experiment start). The first session included MRI-Pre, DH1 (dominant hand baseline), and NDH1, in that order. One day after NDH10, the participant performed a session including MRI-Post and DH2 (post-training DH performance), in that order.

2.2 Participants

We excluded individuals who were musicians, knitters, or had other hobbies involving precision bimanual skills. Twenty-two participants completed the behavioral study (age 29 ± 11 , 15 female). All were right-handed (Edinburgh scores 90 ± 16 ; Oldfield, 1971). Three participants were excluded from detailed behavioral and fMRI analyses due to non-compliance (see next paragraph for details). One participant did not complete the MRI study, and another's MRI data was discarded due to excess motion

(for details see MRI Data Analysis, 2.7). Thus, behavioral analyses were based on 19 participants (age 27 ± 8 , 13 female); except for pairwise investigations of DH data, which used 18 participants because one participant did not return for a DH2 session. MRI analyses were based on 17 participants (age 27 ± 8 , 12 female); except for analyses of long-term retention, which used the 14 participants (age 26 ± 8 , 9 female) who returned for the 6 month follow-up behavioral session. Figure 1 illustrates the pattern of participants available at each stage of the experiment.

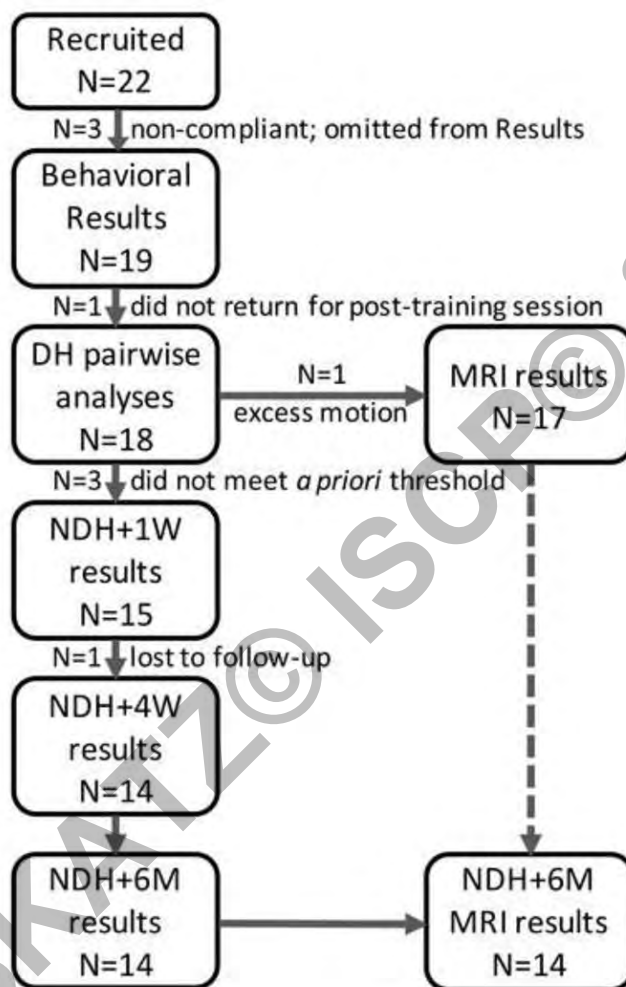


Figure 1
Flow chart of participants at each stage of analysis.
Numbers in each box indicate participants used;
numbers at arrow indicate participants lost.

As mentioned in the preceding paragraph, 3 participants were excluded from analysis due to non-compliance. A session was considered non-compliant if its success rate did not reach 90%, because a low success rate indicated the participant's failure to consistently follow task instructions ("move as quickly as possible without making any errors," and "the most important thing is to stay within the lines"). As shown in Supplementary Figure 1, three participants had ≥ 7 non-compliant sessions (7.3 ± 0.6 sessions, compared to 0.7 ± 1.1 sessions for other participants), leaving too few compliant sessions to identify post-training performance at the instructed task. All further analyses included only the 19 compliant participants.

Of the 19 participants included in our analyses, 4 did not reach the a priori performance criterion and were therefore not invited back for follow-up sessions. Of the 15 participants invited for follow-up sessions, all returned for 1-week follow-up sessions (8 ± 3 days after MRI-Post). 14 returned for 1-month follow-up session (32 ± 9 days after MRI-Post) and the 6-month follow-up session (184 ± 4 days after MRI-Post).

Three participants received fewer than 10 days of training because they substantially improved their NDH performance over a shorter period (7, 9, or 9 days respectively).

Participants were instructed at the outset not to practice outside of the training sessions. At the 6-month follow-up session, all participants confirmed that they had not changed their patterns of NDH behavior since the start of the experiment.

2.3 Precision Drawing Task

Stimuli for the PDT were identical to those previously described in Philip and Frey (2014). In brief, participants used a pen stylus to draw a line through each stimulus while remaining within the boundaries of mirror-symmetrical geometric forms (Figure 2). The PDT was presented on a Cintiq 12wx tablet with integrated 1200 * 800 screen (Wacom Co., Otone, Japan), controlled by Presentation software, v.16.0 (Neurobehavioral Systems Inc., Albany CA). This system allowed participants to draw directly on the tablet screen, during which endpoint speed and position were recorded at 30 Hz.

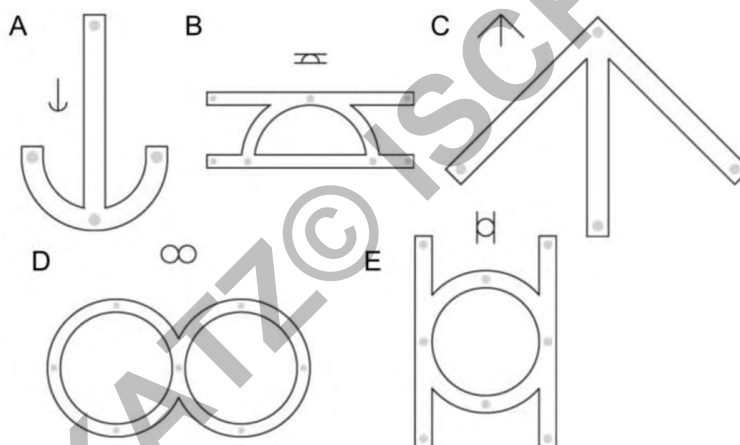


Figure 2

Sample PDT stimuli, showing 4 out of 15 possible shapes.

A: 90 mm drawing length, 5 mm width.

B: 135 mm drawing length, 3 mm width.

C: 135 mm drawing length, 5 mm width.

D: 180 mm drawing length, 3 mm width.

E: 180 mm drawing length, 4 mm width.

Each stimulus was built from 2, 3 or 4 geometric elements (lines or semicircles); each element had a drawing length of 45 mm, and thus total path lengths of 90, 180 or 360 mm. Precision requirements were manipulated by varying stimulus width (3 mm, 4 mm, or 5 mm). The full set of possible PDT stimuli entailed 15 shapes (5 of each length), each presented at all 3 widths, producing a total of 45. NDH training sessions entailed 90 trials, 2 repetitions of all 45 stimuli. DH sessions entailed 2 repetitions of 12 shapes (4 of each length) at 2 widths (3mm and 5mm), producing a total of 48 stimuli. Trials were presented in a unique pseudorandom order during each session.

Participants were instructed to move as quickly as possible without making any errors; i.e., they were instructed to prioritize error-minimization over speed. A trial was defined as an “error” if the drawn lines ever passed outside the stimulus’ margin; except for distinct accidental lines created as part of raising or lowering the pen, and for overshoots at the end of segments (following Beery & Beery, 2004). A trial was considered “incomplete” if the drawn lines did not pass fully through all open paths within the form. A trial was considered a “success” if it was neither an error nor incomplete. Both successful and error trials were used for further analyses, to keep trial counts constant across participants and training sessions. Also, if a trial’s speed exceeded ± 3 standard deviations from the mean (calculated separately for each participant and stimulus width in each session), then it was considered an outlier and not included in speed analysis.

In order to initially familiarize subjects with the task requirements, a DH practice session preceded the DH1 session, and a NDH practice session preceded the NDH1 session. Each of these familiarization sessions consisted of 15 trials (15 shapes, 1 repetition, all at 4 mm width).

Because the number of trials per session was fixed, session duration decreased over time as participants became more skilled and increased their movement speed. NDH training sessions took 21 ± 3 minutes before training (NDH1), and 17 ± 3 minutes post-training (NDH10). Across all training sessions and participants, total training time averaged 182 ± 30 minutes.

Unlike in previous uses of the PDT (Philip & Frey, 2014), participants were given no instructions regarding use of the wrist or forearm or shoulder, and thus were allowed to hold and move the pen in any fashion they chose.

2.4 Behavioral Analysis

The tablet collected x and y position of the pen endpoint at 30 Hz. During analysis, velocity profiles for each trial were smoothed using an acausal Gaussian filter with sigma of 3 samples (90 ms).

Ratings of trial status (success, error, or incomplete) were performed by hand. A senior experimenter’s ratings were validated by a second experimenter. Raters were not blinded, because data were rated on the day of collection. For any session in which within-session agreement was below .93 or IRR was below .7 (mean – 0.5 STD from Philip and Frey (2014)), the two experimenters re-rated the session collaboratively until they reached consensus on every trial. Final ratings reached $.98 \pm .01$ agreement and $.91 \pm .04$ IRR across participants.

Four dependent measures were analyzed: speed (mm/s, mean of each trial), endpoint smoothness (positive values indicating fewer sub-movements: calculated as $-1 \times$ number of velocity peaks per 45mm element, mean of each trial), acceleration time (fraction of time spent with acceleration > 0 , mean of each trial), and success rate (number of successful trials, divided by number of completed trials; one value per session). These four variables were chosen to capture movement characteristics specialized to either hand (Pratik K Mutha, Haaland, & Sainburg, 2012), including goal-directed performance (via speed and success rate), acceleration/distance relations across multi-stage movements (via acceleration time), and arm dynamics (via smoothness). Because speed, smoothness, and acceleration time had one value per trial (as opposed to success rate which had one value per session), these three are collectively referred to as “trial-variables.”

A session was considered significantly improved from baseline for each trial-variable if that session’s mean was significantly higher than the mean performance during NDH1 (one-tailed t-test for speed and smoothness; two-tailed t-test for acceleration time due to the lack of a specific directional prediction, $\alpha = .05$). Each participant’s “post-training” performance was determined from the session NDH7-NDH10 with compliant performance (success rate $\geq 90\%$) and the highest performance for each variable.

Because 3 participants had success rates at ceiling prior to training (98–99% success on NDH1), this variable was not compared against baseline.

Acceleration time did not change consistently across training. Therefore, for brevity, analysis of acceleration time was omitted from our Results.

The difference between DH and NDH was determined pre-training as DH1 performance minus NDH1 performance, and after training as DH2 performance minus NDH post-training performance.

For follow-up sessions, two measures were used to determine successful consolidation: “retention” and “persistence.” Retention was defined as performance above pre-training baseline; a session was “retained” if the follow-up session’s mean was significantly above NDH1 (see above). Persistence was defined as $-1 \times$ the performance loss between NDH post-training and the follow-up session (two-tailed t-test for trial-variables, chi-squared test for success rate, $\alpha = .05$). DH skill was not measured during follow-up sessions.

Power analyses were performed using the MATLAB `sampsizepwr` function (The MathWorks Inc., Natick MA), using a two-tailed t-test, $\alpha = .05$, power = .90.

To measure performance changes consistently across participants and variables, each of the three trial-variables (speed, smoothness, and acceleration) were normalized to each participant’s NDH1 session by calculating a “ZNDH” score. A ZNDH score was calculated for each participant, variable, and session by: taking participant mean performance during that session, subtracting the participant’s mean during the NDH1 session, and dividing by the standard deviation during the NDH1 session. In other words, the ZNDH score reflects a Z-score based on the participant’s untrained NDH performance; this is similar to the Cohen’s d measure of effect size (Cohen, 2013), but based only on the standard deviation during the NDH1 session.

2.5 MRI sessions

Scans were performed on a Siemens (Erlangen, Germany) 3T Trio using a standard birdcage radio-frequency coil. During each fMRI session, participants lay still with their eyes open. Pre- and post-training scan sessions included: 1) T1- and T2-weighted structural scans, 2) $3 \times 5:42$ min functional runs using echoplanar imaging sensitive to the blood oxygen-level dependent contrast (BOLD-EPI), and 3) a gradient echo field map.

BOLD scans used a T2*-weighted sequence with the following parameters: TR = 2240 ms, TE = 30 ms, 64×64 voxel matrix, FoV = 256 mm, 36 contiguous axial slices acquired in interleaved order, thickness = 4.0 mm, in-plane resolution: 4.0 mm, bandwidth = 2004 Hz/pixel, 150 volumes. The initial 2 volumes in each scan were discarded to allow steady-state magnetization to be approached. Throughout the functional scans, participants were instructed to remain awake and with their eyes open and maintain fixation on a centrally presented point. Compliance was manually monitored using an Eye-Trac 6000 (Applied Science Laboratories, Bedford MA) eye-tracking camera.

High-resolution T1-weighted structural images were also acquired, using the 3D MP-RAGE pulse sequence: TR = 2500 ms, TE = 4.38 ms, TI = 1100 ms, flip angle = 8.0° , 256×256 voxel matrix, FoV = 256 mm, 176 contiguous axial slices, thickness = 1.0 mm, in-plane resolution: 1.0×1.0 mm.

DICOM image files were converted to NIFTI format using MRIConvert software (<http://lcn.uoregon.edu/~jolinda/MRIConvert/>).

2.6 Preprocessing

Structural and functional fMRI data were preprocessed and analyzed using fMRIB's Software Library (FSL v.5.0, <http://www.fmrib.ox.ac.uk/fsl/>) (S. M. Smith, et al., 2004) and involved several steps: Non-brain structures were removed using BET. Head movement was reduced using MCFLIRT motion correction. EPI unwarping was performed to correct for distortions due to magnetic field inhomogeneities using FSL PRELUDE and FUGUE, using a separate fieldmap collected following the functional runs. The data were spatially smoothed using a Gaussian kernel of 6 mm FWHM. Slice timing correction was applied. For each data set, intensity normalization was applied using "grand mean scaling", wherein each volume in the data set was scaled by the same factor to allow for valid cross-session and cross-subject statistics. A high-pass temporal filter with 200-second cut-off was applied to remove low-frequency artifacts. Independent component analysis (ICA) was conducted with MELODIC to denoise the data, following procedures detailed below. Field maps were used to apply B0 unwarping. Time series statistical analysis was carried out in FEAT v.6.00 using FILM with local autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001). Functional data were registered with the high-resolution structural image using boundary-based registration (Greve & Fischl, 2009), and resampled to $2 \times 2 \times 2$ mm resolution using FLIRT; the participant images were then registered to standard images (Montreal Neurological Institute MNI-152) using FNIRT nonlinear registration (Andersson, Jenkinson, & Smith, 2007).

MELODIC ICA was used to identify artifactual components for removal. Components were rejected if they clearly met one of the following criteria: (1) preponderance of suprathreshold voxels in non-brain areas, including ventricles or a "halo" outside the brain; (2) spin history effects, specifically activations that appear in alternating slices; (3) time course dominated by distinct temporal spikes; (4) components covering the majority of 1–2 slices, but not neighboring slices; or (5) Nyquist ghosts. Only the 20 components with the highest contributions were tested for rejection. 8.6 ± 2.7 components were rejected per run, representing 22.3% of total components (881/3954).

2.7 MRI data analysis

As noted above, one participant was excluded from fMRI data analysis due to excess motion (peak instantaneous translation > 2mm/volume).

FSL analysis of fcMRI data was performed following Vahdat, et al. (2011) and Makin, et al. (2013). Regions of interest (ROIs) in sensorimotor hand area were determined for each participant, by inverse-warping normative ROIs from standard space to each individual participant (Philip and Frey 2014). These normative ROIs were defined using data from a functional localizer task in which an independent sample of 17 healthy adults (mean age = 52 years, range 29–62, 4 female, 1 left-handed) performed an aurally-paced, thumb-finger sequencing task with eyes closed (J. C. Smith & Frey, 2011). Spherical ROIs (5 mm radius) were centered on the peak activations in the left hemisphere ($X = -38, Y = -24, Z = 54$) and right hemisphere ($X = 38, Y = -24, Z = 54$).

At the first level (i.e. for each functional scan), FSL's Featquery was used to identify the time course of changes in image intensity across all voxels in each ROI, after ICA and other preprocessing steps. These ROI time courses served as the explanatory (predictor) variables (EVs). Temporal derivatives were included to account for minor differences in timing. First-level contrasts of parameter estimates (COPEs) were calculated separately for each seed region, so that e.g. measurements of FC with the left-seed ROI were independent of any FC changes involving the right-seed ROI.

The first-level analysis also included ten covariates of no interest to regress out non-neural changes, selected independently in each functional scan: (1) the time course of a voxel in white matter: anterior corpus callosum, or posterior corpus callosum if no voxel could be definitively identified as wholly in anterior corpus callosum; (2) the time course of a voxel in CSF: posterior horn

of left lateral ventricle, or anterior horn if no voxel could be definitively identified as wholly in posterior horn; (3) the time course of a voxel outside the brain, superior to the anterior end of the third ventricle; (4) the time course of the whole-brain average; (5–10) motion covariates from MCFLIRT motion correction, encompassing three dimensions of translation and three of rotation. All covariates received the same temporal filtering as the fMRI data (Hallquist, Hwang, & Luna, 2013).

The top-level analysis followed previously successful methods for detecting FC changes across learning (Vahdat, et al., 2011). Two regressors were used. First, a participant regressor, to regress out consistent participant-specific effects; this regressor was constant for each participant, across all six runs (three runs \times 2 sessions: pre- and post-training). The second regressor, which is the regressor of interest, modeled each participant's behavioral change across training. This applied regressor of interest, after orthogonalization with respect to the other regressor, was set to $-(\text{behavior})/2$ for the scans on session 1, and $+(\text{behavior})/2$ for the scans on session 2. Thus, the contrast of interest in the generalized linear model (GLM) was a graded variable based on each subject's behavior.

For each seed region, three separate analyses were performed to identify areas that exhibited changes in functional connectivity: (1) between pre-training and post-training scans, with no explicit behavioral regressor; (2) between pre-training and post-training, and correlated with smoothness learning; (3) between pre-training and post-training, and correlated with smoothness retention. Speed learning and retention were omitted because of the absence of hand-specific speed learning (see Results 3.2); this choice was made before the start of MRI analyses. "Smoothness learning" for fcMRI analysis was defined as the ZNDH for each participant's best session, mean-removed across participants. "Smoothness retention" was defined as ZNDH performance during NDH+6M session (i.e., performance difference between pre-training and 6-month follow up).

At the top level, Z-statistic images were thresholded at $Z > 2.3$, with clusterwise correction at $p < .05$. Multi-fiducial mapping in Caret v5.64 (<http://www.nitrc.org/projects/caret/>) was used to overlay group statistical maps onto a population-average, landmark- and surface-based (PALS) atlas for visualization (van Essen, 2005). Slice views were produced using Mricron version 12/2009 (<http://www.mccauslandcenter.sc.edu/mricro/mricron/>).

To measure the influence of hand-nonspecific fcMRI changes across the training period, the full analysis was repeated using seed regions defined by repetitive movements of the feet (instead of the hands). These ROIs were 5mm radius spheres centered on the voxel of peak activation in the left hemisphere ($X = -4, Y = -28, Z = 72$) or right hemisphere ($X = 6, Y = -24, Z = 74$) during toe flexion movements.

Correlations between the two seed regions were measured by calculating the Pearson r between the average timecourse of all voxels in the left hemisphere hand seed and the average timecourse of all voxels in right hemisphere hand seed. The resulting r value was Fisher's z -transformed to stabilize variance and allow further statistical analysis.

To determine whether training-related changes in FC were associated with reduced noise or increased signal, we calculated the temporal signal-to-noise ratio (tSNR; Van Dijk, Sabuncu, & Buckner, 2012) pre- and post-training. For each voxel, the tSNR was calculated as the mean signal value divided by the standard deviation of the voxel's signal intensity over time. A run's tSNR value was calculated as the average tSNR within a mask defined by all areas significantly correlated with the seed region at the group level, separately for each seed region.

3. Results

3.1 Successful Performance of the Precision Drawing Task

Error rates averaged $4.2 \pm 2.0\%$ (range: 1.2–8.6%), and $0.4 \pm 0.3\%$ of trials were discarded as incomplete (range: 0–1.1%). Outliers accounted for $4.4 \pm 2.3\%$ of trials during speed analysis (range: 1.3–8.9%). The low rates of errors and of incomplete trials indicate that participants performed the PDT successfully.

3.2 Evidence for Training-related Changes in Performance

As predicted, we found statistically significant improvements between pre- and post-training tests in NDH: smoothness (paired-sample t-tests: $t(18) = 6.29$, $p < .0001$), speed ($t(18) = 7.91$, $p < .0001$), and success rate ($t(18) = 3.71$, $p < .01$). These group results were consistent across individuals: all 19 participants who completed the protocol exhibited significantly increased NDH success rate, while 18 (95%) showed increased speed, and 17 (89%) displayed increased smoothness.

As illustrated in Figure 3A, we detected significantly increased speed in the group after 4.6 ± 2.3 training sessions, and smoothness after 5.4 ± 2.5 sessions (mean \pm std of first NDH session with performance significantly greater than baseline). A one-way ANOVA revealed a significant effect of Session (10 levels, one per training session) for both NDH speed ($F(9,180) = 9.02$, $p < .0001$) and NDH smoothness ($F(9,180) = 8.22$, $p < .0001$); for both variables, post-hoc tests (Tukey's HSD) revealed significant differences between session 1 and sessions 7–10.

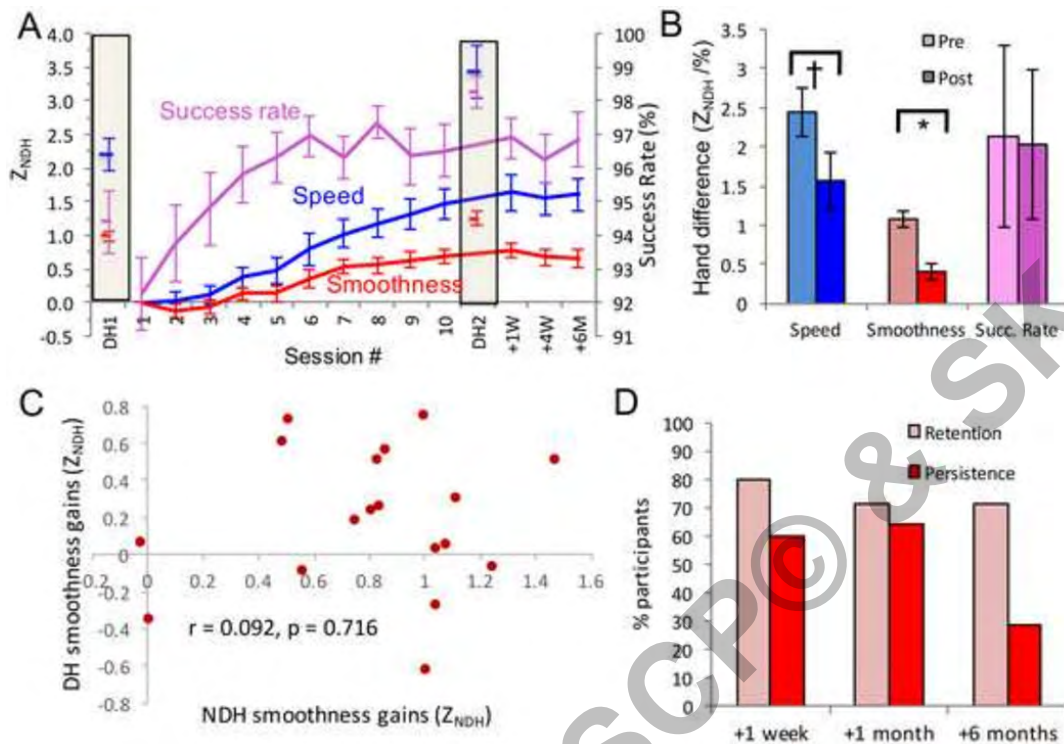


Figure 3

PDT behavior. A: Increased speed, smoothness, and success rate across training, as well as persistence/retention during follow-up sessions. Group means \pm SEM. Speed and smoothness in Z_{NDH}, success rate in %. B: Hand differences (NDH - DH) pre-training and post-training, demonstrating significant NDH-specific learning for smoothness and trend for speed. *: $p < .001$. †: $p = .069$. C: Hand-specificity of NDH smoothness learning confirmed by near-zero correlation between NDH smoothness gains and DH smoothness gains. D: Long-term changes in NDH smoothness, measured as % of participants at each follow-up session. "Retention" defined as significantly increased from pre-training baseline. "Persistence" defined as no significant change from post-training peak.

To address whether these effects were exclusive to the trained NDH, we also tested whether DH performance changed across training. We found significant increases in DH speed ($t(17) = 3.51$, $p < .01$) and DH success rate ($t(17) = 3.41$, $p < .01$), and a trend toward increased DH smoothness ($t(17) = 1.99$, $p = .064$). Power analysis suggests that the trend toward increased DH smoothness would require 50 participants to reach significance at the current effect size. We also tested whether intermanual performance asymmetry (i.e. the "hand asymmetry") narrowed between pre-training and post-training. For smoothness, the hand asymmetry narrowed significantly ($t(17) = 4.17$, $p < .001$). Speed exhibited a non-significant trend toward a narrower hand asymmetry post-training ($t(17) = 1.94$, $p = .069$; power analysis indicates $N = 28$ for significance). We found no significant change in the hand asymmetry for success rate ($t(17) = 0.13$, $p = .907$), likely due to near ceiling performances by several individuals (Figure 3B). Comparing the pre-post difference between hands (i.e., the "training effect"), we found similar results: for speed, the effect was numerically higher for the NDH ($Z_{NDH} = 1.74 \pm 0.91$) than the DH (1.34 ± 1.13), but the difference did not reach statistical significance ($t(34) = 1.14$, $p = 0.26$); whereas for smoothness, the NDH training effect ($Z_{NDH} = 0.82 \pm 0.39$) exceeded the DH training effect (0.31 ± 0.34) by a statistically significant margin ($t(34) = 4.24$, $p < .001$). Taken together, while both hands showed some performance improvements across training, only movement smoothness had NDH-specific improvements.

To confirm the NDH specificity of smoothness improvements, we measured the relationship between smoothness gains across

training in the NDH (where they were statistically significant) vs. DH (where they were not). As shown in Figure 3C, we found no intermanual correlation for smoothness gains ($r = 0.092$, $p = 0.716$). Therefore, hand-nonspecific smoothness improvements were not confounded with hand-specific improvements.

Across days, success rates were not significantly correlated with speed or smoothness for any participant (Bonferroni-corrected $\alpha = .05$), demonstrating that speed-accuracy tradeoffs do not explain the improvements in performance across training. Because of near-ceiling success rates throughout much of training ($\mu > 95\%$ from NDH4 onward), we did not further analyze day-by-day success rates.

In summary, consistent with our hypothesis, our participants clearly improved NDH skill during 10 days of training. This is especially evident in endpoint smoothness, a key indication of skill learning that is hypothesized to reflect the dominant left hemisphere advantage for inter-segmental limb control (Sainburg, 2005), and as such holds particular interest for measuring acquisition of new skills with the NDH (Sainburg, 2002; Shabbott & Sainburg, 2008). We also detected significant pre- to post-test improvements in the untrained DH. Taken together, these results indicate that training led to significant NDH-specific improvements in movement smoothness.

3.3 Long-Term Persistence and Retention of NDH Skill

Despite discontinuing practice, most participants continued to show significant training-related benefits for one or more measures of NDH skill even 6 months after the end of NDH training. For smoothness, our measure of NDH-specific skill, 80% of participants (12/15) retained performance (remained above pre-training baseline) 1 week after the end of training, while 71% (10/14) retained performance 1 month after training, and 71% (10/14) after 6 months. A subset of participants showed full persistence of their post-training smoothness (i.e., no significant decrease from their post-training peak): 60% (9/15) after 1 week, 64% (9/14) after 1 month, and 29% (4/14) after 6 months. These results are summarized in Figure 3D. Despite discontinuing practice, most participants continued to show significant training-related benefits for NDH skill even half a year after the end of NDH training.

Retention and persistence results from other behavioral measures are shown in Supplementary Figure 2. Smoothness retention was not predicted by pre-training smoothness or smoothness gains across training, as shown in Supplementary Figure 3.

3.4 Upper-extremity specificity of functional connectivity MRI

For each of the below-described analyses of normatively defined cortical hand areas, we repeated the analysis with a normative foot seed substituting for the hand seed from the same hemisphere. Only 1.2% of all voxels (for individual analyses: median 0%, range 0–3.2%) achieved significance for both hand and foot, suggesting that the results reflect primarily hand-specific changes in functional connectivity. No further discussion of results from the foot seeds is presented.

3.5 No changes in functional connectivity between left and right sensorimotor hand representations

To identify training-related FC changes between bilateral sensorimotor cortices, we measured the correlation between the two seed regions. We measured whether this value: (1) differed between pre- and post-training via t-test, (2) correlated pre-training with smoothness learning or retention, (3) correlated post-training with smoothness learning or retention, or (4) whether the across-training difference correlated with smoothness learning or retention.

None of these possible relationships showed a significant effect ($p > 0.2$). Therefore, we found no evidence for training-related

changes in FC between left and right hand sensorimotor representations.

3.6 Functional connectivity changes do not arise from changes in signal variability

To identify whether FC changes across training arose from changes in variability, we compared temporal signal to noise (tSNR) between voxels with significant FC in pre- and post-training scans. We performed 2×2 ANOVA (Session: Pre, Post; Seed: Left, Right) and found no statistically significant effects of Session ($F(1,64) = 0.78$, $p = .380$), Seed ($F(1,64) = 2.14$, $p = .149$) or interaction ($F(1,64) = 0$, $p = .954$). Changes in tSNR across training showed no statistically significant correlations with smoothness learning or retention ($r^2 < .21$, $p > .07$). Therefore, we found no evidence that changes in signal variability drove our functional connectivity results.

3.7 Non-dominant hand performance-related increases in functional connectivity between sensorimotor hand representations and left ventral parieto-premotor circuit

We identified brain areas that significantly changed FC with our normative hand seed areas between pre-training and post-training scans, and were correlated across participants with NDH smoothness gains across learning. We found learning-related strengthening of FC between the trained left hand's (right hemisphere) sensorimotor representation and the left supramarginal gyrus (SMg) and superior parietal lobule (SPL), as well as bilateral postcentral gyri (putative primary somatosensory cortex: S1), frontal operculum (putative rostral PMv; ventral premotor cortex), middle frontal gyrus (MFg), and rostral dorsolateral prefrontal cortex (dlPFC); note that the FC increases in SPL and PMv while bilaterally present, were left-asymmetric (Figure 4A, warm colors). Conversely, FC decreased with right parietal operculum (putative secondary somatosensory cortex: S2), precentral sulcus, temporal pole, bilateral occipital cortex, and supplementary motor area (SMA) (Figure 4A, cool colors).

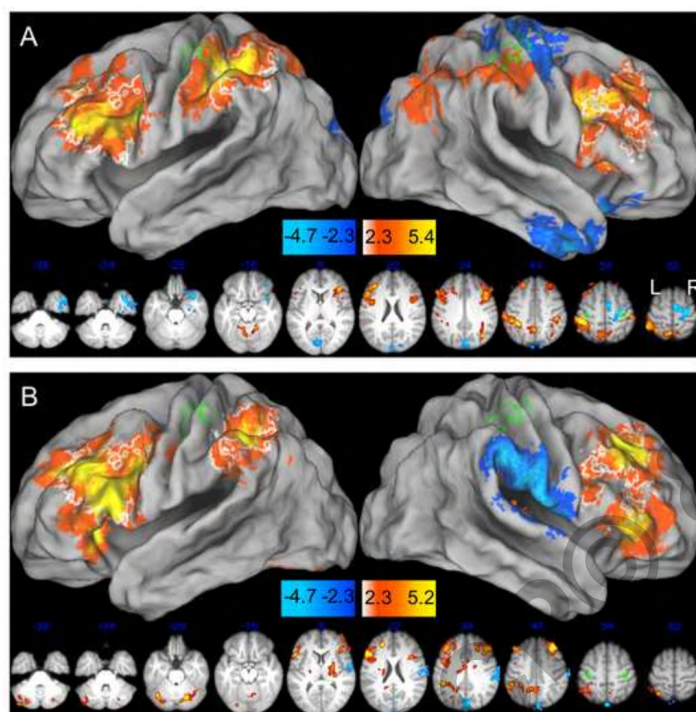


Figure 4

Changes in functional connectivity with normative hand seeds, across training and correlated with smoothness learning. Green outlines indicate bilateral seed regions. White outlines indicate areas that changed connectivity with both seeds (i.e., significant in both A and B). A: Changed connectivity with trained left hand's (right hemisphere) seed, including increased connectivity with left SMg and SPL, bilateral S1, vPMC, dIPFC, and superior cerebellum; and decreased connectivity with right S2, precentral sulcus, temporal pole, bilateral occipital cortex, and SMA. B: Changed connectivity with untrained right hand's (left hemisphere) seed, including increased connectivity with left SMG and vPMC, bilateral dIPFC, cerebellar hemispheres, and precuneus; and decreased connectivity with right S1, S2, anterior SMg, and bilateral occipital cortex.

The untrained right hand's representation (left hemisphere) also showed learning-related increases in FC with the left SMg and PMv, as well as bilateral rostral prefrontal cortex, cerebellar hemispheres, and precuneus (Figure 4B, warm colors). For the same right hand seed, we found decreased FC with right postcentral gyrus (putative S1) precentral gyrus (putative dorsal premotor cortex, PMd), anterior SMg, and parietal operculum (putative S2); and bilateral occipital cortex. (Figure 4B, cool colors).

In sum, performance improvements were accompanied by increased FC between either hand representation and the left SMg, left PMv, and right MFg (Figure 4, white outlines). The trained left hand representation also showed increased FC with the right PMv, while the untrained right hand representation exhibited increases in bilateral cerebellar connectivity. These findings are consistent with the view that increased skill from unilateral NDH training affects the strength of resting connectivity between the contra- and ipsi-lateral cortical hand representations and key parieto-frontal regions involved in manual praxis within the motor-dominant left cerebral hemisphere.

3.8 Non-dominant hand retention-related changes in functional connectivity with sensorimotor hand representations

We identified brain areas that significantly changed FC with our normative hand seed areas across training, and were correlated across participants with retention of smoothness learning 6 months post-training. In other words, areas where changes during training predicted skill 6 months later.

We found selective retention-related FC decreases between the trained left hand's (right hemisphere) sensorimotor hand representation and bilateral precentral gyrus (putative bilateral PMd and right M1), postcentral gyrus (putative S1), bilateral superior parietal lobule (SPL), left thalamus, and SMA (Figure 5A). In other words, reduced FC within the cortical sensorimotor network—particularly decreased FC between the trained left-hand representation and bilateral sensorimotor cortex—predicted long-term retention of skill.

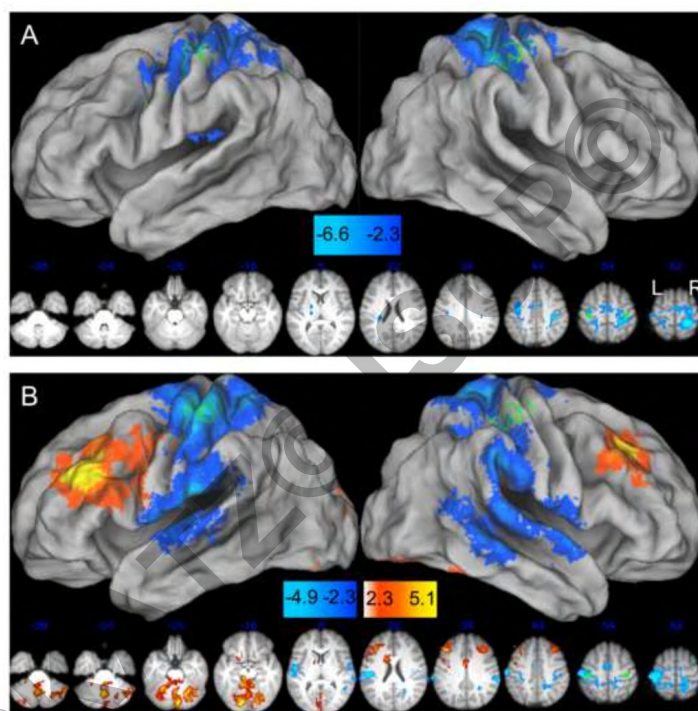


Figure 5

Changes in functional connectivity with normative hand seeds, across training and correlated with smoothness retention at 6 months post-training. Green outlines indicate bilateral seed regions. A: Changed connectivity with trained left hand's (right hemisphere) seed, including decreased connectivity with bilateral PMd and S1, right M1, bilateral SPL, and SMA. B: Changed connectivity with untrained right hand's (left hemisphere) seed, including increased connectivity with dIPFC, anterior cingulate gyrus, and cerebellum; and decreased connectivity with precuneus, bilateral SPL, and left S1 and S2.

The untrained right hand's (left hemisphere) sensorimotor hand representation exhibited increased FC with bilateral dIPFC and MFG, bilateral cerebellar hemispheres and vermis, and the anterior cingulate gyrus (Figure 5B, warm colors). For the same right hand seed, we found decreased FC with left precentral gyrus (putative M1), postcentral gyrus (putative S1), bilateral parietal operculum (putative S2), and SMg, right precuneus, bilateral SPL, and SMA (Figure 5B, cool colors).

4. Discussion

This project is the first to demonstrate that a relatively short period of training can produce significant and enduring improvements in drawing with the NDH, and to show that these performance improvements are associated with changes in functional connectivity between bilateral hand areas and higher-level parieto-frontal regions implicated in the representation of praxis. A relatively short period of training (10 days, ~180 minutes total per individual) was sufficient to induce substantial improvements in NDH speed, accuracy and smoothness, including limb-specific improvements in NDH smoothness. These improvements in smoothness persisted for at least 6 months after the end of training.

Contrary to our expectations, we detected no learning-related changes in FC directly between independently defined cortical hand representations. Instead, training-related improvements in performance were associated with changes in FC between bilateral hand representations and regions involved in acquired manual skills (praxis). Conversely, long-term (6 months post-training) retention of NDH improvements in movement smoothness were predicted by FC changes that included decreased FC between the trained hand's cortical representation and bilateral superior parieto-frontal sensorimotor areas, which may indicate a time-dependent consolidation of skill representations.

4.1 Training-Related Improvement of Non-Dominant Hand Skill

Our results demonstrate that even modest amounts of training can provide substantial and enduring improvements in NDH precision drawing in healthy adults. Performance improved simultaneously in speed, accuracy, and smoothness, and thus cannot be dismissed as changing speed-accuracy tradeoff.

In the untrained DH, speed and accuracy also improved significantly between pre- and post-training assessments, which may reflect general familiarization with the paradigm, changes in limb-independent levels of representation, and/or inter-limb transfer of learning. The difference between the NDH and DH in movement smoothness narrowed significantly over the course of training, which was not the case for either speed or accuracy. Therefore, only smoothness showed clear evidence of training-related improvements specific to the NDH (Figure 2B). NDH-specific learning in the smoothness domain is particularly interesting because PDT smoothness may depend on the coordination intersegmental dynamics (e.g. across finger and wrist joints), and control of movement dynamics may be a specialization of the left motor cortex, which is primarily responsible for distal movements of the right DH (Geschwind, et al., 2002; Liepmann & Maas, 1905; Sainburg, 2002).

The training-related improvements in NDH smoothness could arise from two potential mechanisms. One possibility is improved inter-hemispheric transfer: access by the non-dominant right hemisphere to left-lateralized mechanisms, such as those endogenously specialized for the control of limb dynamics (Philip & Frey, 2014; Sainburg, 2010). Alternatively, intra-hemispheric refinement: the capacity of the non-dominant right sensorimotor cortex for the control of movement dynamics may itself have improved. Learning-related changes in FC between pre- and post-training scans help to differentiate between these two interpretations.

4.2 Improvements in NDH skill are associated with increased functional connectivity involving bilateral hand areas and parieto-frontal regions implicated in representation of manual praxis

We found a striking but unpredicted similarity between the network of brain regions exhibiting increased FC associated with increased NDH-specific skill, and areas previously implicated in the representation of manual praxis. We hypothesized that improvements in left hand performance would be associated with increased access by the trained left hand's (right hemisphere)

hand area to the ipsilateral (left hemisphere) hand area; instead, significant improvements in NDH smoothness were associated with increased FC between bilateral sensorimotor hand areas and higher-level regions implicated in the representation of acquired manual skills, including left-asymmetrical bilateral increases in FC between sensorimotor hand areas and cortex within and adjacent to the IPS and PMv (Figure 4).

Both hand areas exhibited left-asymmetrical increases in FC with cortex in and along the IPS, and in the PMv, as well as in bilateral MFG (Figure 4). These areas play a role in planning and production of familiar skilled movements (praxis) with either limb, and damage to these areas has long been associated with the development of limb apraxia (Geschwind, et al., 2002; Goldenberg, 2013; Haaland, Harrington, & Knight, 2000; Heilman, Rothi, & Valenstein, 1982; Johnson-Frey, Newman-Norlund, & Grafton, 2005; Liepmann & Maas, 1905; Oldfield, 1971). Therefore, we suggest that in the current investigation, training increased efficiency of communication between left-asymmetrical regions of parieto-frontal cortex that represent the acquired drawing skill and the bilateral hand areas involved in sensorimotor control of the NDH.

The FC changes associated with the dominant left hemisphere are unsurprising in the context of the ipsilateral hand area's role in control of the non-dominant limb (Dassonville, Zhu, Ugurbil, Kim, & Ashe, 1997; J Diedrichsen, Wiestler, & Krakauer, 2013) and in skills that involve coordination of both distal and more proximal limb segments (Verstynen, Diedrichsen, Albert, Aparicio, & Ivry, 2005), which is certainly true in drawing.

Moreover, our finding of a role for the left PPC in PDT skill learning matches lesion studies that demonstrated a left PPC role for visuomotor adaptation (P. K. Mutha, Sainburg, & Haaland, 2011a, 2011b). We had not anticipated this common result, because PDT learning presumably depends on visuomotor skill learning and improvements in online feedback-driven control, whereas these lesion studies indicated no link between left PPC function and online error correction. Based on our unanticipated results, the left PPC's role in praxis (as described above) may support visuomotor learning for tasks as diverse as ballistic arm movements and precision drawing skill.

Our findings parallel previous task-based fMRI studies of adults born left-handed but forced to write with their non-dominant right hand. These individuals showed a correlation between NDH penmanship skill and involvement of the left (non-dominant) sensorimotor and premotor cortex in bilateral skilled and unskilled movements, whereas PMd and SMg remained asymmetrically lateralized to the right (dominant) hemisphere (Klöppel, Vongers, van Eimeren, Frackowiak, & Siebner, 2007). While it is difficult to compare task-based fMRI results with resting-state fMRI, we found FC increases in a similar network: between bilateral sensorimotor cortices and overlapping posterior parietal and rostral premotor regions of the dominant hemisphere. These common findings suggest that improvements in NDH performance may involve experience-dependent changes in ipsilateral higher-level centers of the dominant hemisphere.

4.3 Retention and Persistence of Training-related Improvements in Performance

Strikingly, our participants' performance improvements continued long after training ceased, with 77% of participants still showing increased NDH smoothness after 6 months. Long-term retention of NDH skill would maximize the clinical benefit gained from a single course of rehabilitation therapy. However, our training protocol entailed much less time than current upper limb rehabilitation protocols post-stroke, which (though possibly suboptimal for driving neuroplasticity) involve hundreds of movement repetitions during daily sessions (Lang, et al., 2009; Lang, Wagner, Edwards, & Dromerick, 2007).

An important question is whether an approach like ours might benefit the many individuals who are forced to rely on the NDH for precision skills as a result of injury or disease (Larsen & Lauritsen, 1993; Nakayama, et al., 1994). As discussed in the Introduction, 20–30% of hemiplegic stroke survivors never regain use of their dominant hand (DH) for tasks of daily life such as

writing or drawing. Chronic DH amputees often achieve a very high level of performance with the NDH on these tasks (Philip & Frey, 2014), and NDH-specific training may facilitate this adaptation. Extensions to patients are planned to extend this work to patients with DH dysfunction from other conditions such as orthopedic injury, stroke, and peripheral nerve damage.

4.4 Retention of Non-Dominant Hand Smoothness Associated with Changes in Intra- and Inter-hemispheric Functional Connectivity

Unexpectedly, we found a network of FC changes across training that predicted long-term (6 month) retention of NDH skill. The trained hand's cortical representation showed retention-related decreases in FC with a bilateral network of parieto-frontal sensorimotor areas, including PMd, S1, SPL, and SMA, as well as right M1 (Figure 5A). This finding complements earlier studies indicating a focusing of network activity as skills become well-learned: while activity within M1 may expand with over-training, areas involved in the early learning processes cease their involvement in behavior (e.g. S. Grafton, Hazeltine, & Ivry, 1995, 1998; Ma, et al., 2011; Ungerleider, Doyon, & Karni, 2002).

The untrained hand's representation showed retention-related decreases in FC with left S1/S2, precuneus, and bilateral SPL; and retention-related increased FC with dIPFC, anterior cingulate gyrus, and cerebellum (Figure 5B). Retention-related increases in FC with the untrained hand representation are difficult to interpret, particularly in the context of whole-brain MRI results detected outside hypothesized networks. However, both hand sensorimotor areas showed retention-related decreases in FC with bilateral S1, possibly indicating reduced need for somatosensory feedback in a highly-trained skill.

Interestingly, few areas showed FC changes correlated with both learning and retention, consistent with our behavioral finding that initial learning did not correlate with long-term retention. We found one FC change involving the trained hand representation that occurred for both learning and retention: decreased FC with the right PMd. This area plays a role in learning continuous (non-chunkable) components of finger movement sequences during the first four days of learning, but its role in later stages of learning remains unknown (Jörn Diedrichsen, 2015). As mentioned above, later stages of learning involve a focusing of task-based cortical networks, wherein areas including PMd and SMg play a role during early learning but not for well-learned skills (Ma, et al., 2011; Ungerleider, et al., 2002). Therefore, the disengagement of PMd from motor output areas during rest could reflect a broad (i.e. evident during task and rest) consolidation-related shift from relatively early stages of learning a continuous drawing task to a more well-learned (and thus more likely to persist) movement under control of M1 and subcortical structures.

4.5 Limitations and Future Directions

Throughout this manuscript, we have interpreted changed coupling between brain areas as changed FC. However, coupling could change for other reasons: increased coupling could reflect a decrease in a non-shared input, while reduced coupling could reflect increased noise. Our methods cannot disambiguate these possibilities.

Our study only involved training of the left NDH. Therefore, we cannot categorically rule out effects of natural variability, or general effects related to practicing skilled unimanual movements with either hand. However, these shortcomings should be ameliorated by our decision to focus only on FC changes associated with increased skill in the NDH, especially since training-related changes in DH skill would likely be much subtler due to ceiling effects from lifelong use of the DH for precision manual skill.

Our study also cannot distinguish between NDH-specific and left-hand-specific effects. Hand dominance and left/right lateralization are separable (Gonzalez, Ganel, & Goodale, 2006), so future studies should include left-handed participants to distinguish between these two forms of lateralization.

Finally, because our study measured BOLD activity during resting state, it remains possible that cortical activity during task performance follows a pattern distinct from the changes that we detected during rest.

4.6 Conclusions

We elicited substantial and persistent improvements in non-dominant hand skill with ten days of training. If these behavioral results generalize to other movements or related skills, this training protocol could improve performance with the non-dominant hand after irreversible unilateral impairment of the dominant hand due to stroke, nerve injury, or other disability.

Improved performance across training was associated with an increased role for the left-asymmetric praxis network. Combined with previous results, these suggest that non-dominant hand skill learning may depend on ipsilateral higher-level centers of the dominant (here, left) hemisphere.

We found a network of areas where decreased functional connectivity with the motor cortex predicted long-term retention of skill. If this relationship is causal, neuro-stimulation techniques could potentially facilitate cortical plasticity in this network and enhance the retention of a non-dominant hand skill training protocol.

Highlights

- 10 days of training led to improved skill with the non-dominant left hand.
- Skill gains were retained for 6 months after the end of training.
- Successful learning was associated with a left hemisphere cortical network.
- Retention was predicted by early disengagement of motor-learning areas.
- Modest training (< 200 min total) can improve non-dominant hand control.

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Footnotes

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