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The neural correlates of learned motor acuity

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Abstract

We recently defined a component of motor skill learning as "motor acuity", quantified as a shift in the speed-accuracy trade-off function for a task. These shifts are primarily driven by reductions in movement variability. To determine the neural correlates of improvement in motor acuity, we devised a motor task, compatible with magnetic resonance brain imaging that required subjects to make finely controlled wrist movements under visual guidance. Subjects were imaged on day 1 and day 5 while they performed this task, and were trained outside the scanner on intervening days 2, 3 and 4. The potential confound of performance changes between days 1 and 5 was avoided by constraining movement time to a fixed duration. Following training, subjects showed a marked increase in success rate and a reduction in trial-by-trial variability for the trained but not for an untrained control task, without changes in mean trajectory. The decrease in variability for the trained task was associated with increased activation in contralateral primary motor and premotor cortical areas and in ipsilateral cerebellum. A global non-localizing multivariate analysis confirmed that learning was associated with increased overall brain activation. We suggest that motor acuity is acquired through increases in the number of neurons recruited in contralateral motor cortical areas and in ipsilateral cerebellum, which could reflect increased signal-to-noise ratio in motor output and improved state estimation for feedback corrections, respectively.

Introduction

Motor skill is a general term that has been used to describe improvement across a wide range of motor learning paradigms. We recently operationally defined a component of motor skill as the training-related change in the speed-accuracy trade-off function for a task (Reis et al. 2009; Shmuelof et al. 2012). We introduced the term "motor acuity" for this aspect of improvement, both to contrast it with motor learning tasks that do not emphasize improved motor execution and to draw parallels with perceptual learning (Censor et al. 2012). Functional imaging has been extensively used to investigate the neural basis of motor learning in humans, but motor acuity has been relatively neglected. The emphasis has instead been on finger sequence tasks, like the serial reaction time task (SRTT) (Grafton et al. 1995; Robertson et al. 2001; Stagg et al. 2011), and on visuomotor adaptation tasks (Diedrichsen et al. 2005; Inoue et al. 1997; Krakauer et al. 2004). In such tasks, subjects modify the selection of movements that are already skilled (such as button pressing and straight reaching movements) and so do not need to improve the acuity of the movements themselves.

A landmark study by Karni and colleagues was an exception to the emphasis on learning of sequence order and adaptation in human imaging studies (Karni et al. 1995). In this study a voxel counting method was used to show that the ability to perform a short finger-opposition sequence faster and more accurately was associated with an increased number of activated voxels in contralateral primary motor cortex compared to an unlearned sequence, even when the two sequences were matched for rate and component movements (Karni et al. 1995). The control of movement frequency is important because changes in this parameter can lead to activation changes (Jenkins et al. 1997; Orban et al. 2011; Turner et al. 1998). Since the study by Karni and colleagues, however, an association between activation changes in contralateral cortical areas and learning has been elusive. Notably, in a recent meta-analysis of 70 imaging studies of motor learning in humans, the authors found that there was no converging

71 evidence for learning-related activation in contralateral primary motor cortex (M1), once motor
72 execution was controlled for (Hardwick et al. 2013). This conclusion stands in apparent contradiction
73 with the original result by Karni and colleagues, which was not included in the meta-analysis because a
74 direct statistical comparison between learning and control tasks was not performed. The conclusion of
75 the meta-analysis also contradicts single unit and structural studies in non-human animal models that
76 have consistently shown motor learning-related changes in contralateral motor cortical areas including
77 M1 (Harms et al. 2008; Nudo et al. 1996; Rioult-Pedotti et al. 2000; Xu et al. 2009).
78
79 A potential explanation for the discrepancy between non-human animal studies that have shown
80 changes in contralateral motor cortical areas and human functional imaging studies, which for the most
81 part have not, is the nature of the motor learning tasks used. We have recently argued that sequence
82 and adaptation tasks predominantly challenge learning processes upstream of skilled motor execution
83 itself (Shmuelof and Krakauer 2011). For example, in the SRTT, the kinematics of the movements
84 themselves are very simple, and only the response time is relevant to the task (Nissen and Bullemer
85 1987). Similarly, for visuomotor rotation, the movements themselves are no more difficult to execute
86 than baseline movements and indeed show no changes in variability (Cunningham 1989; Krakauer et
87 al. 2000). It is notable that the studies included in the meta-analysis reported above were classified as
88 either SRTT variants or sensorimotor tasks. Two other prominent imaging approaches are tracking
89 tasks (Grafton et al. 2008; Miall and Jenkinson 2005; Miall et al. 2001) and bimanual coordination
90 tasks (Kelso 1984) in which subjects learn to make one-dimensional wrist movements at different
91 frequencies (Puttemans et al. 2005) or phases (Debaere et al. 2004) in each hand. Here again, it is either
92 tracking error in cursor space or synchronization between two skilled movements that is changing. In
93 neither case does execution of the movements themselves have to become faster or less variable. The
94 finger sequence task used by Karni in contrast requires a change in movement kinematics and in
95 accuracy, and therefore a change in how movements themselves are executed (Karni et al. 1995).

With the goal of studying core aspects of motor skill learning that are not captured by adaptation or sequence tasks, we recently devised a novel visually guided pointing task ("arc pointing task", APT) in which subjects control a screen cursor through a narrow semi-circular channel by rotating their hand about the wrist, using equipment that is compatible with the magnetic resonance (MR) scanner environment (Shmuelof et al. 2012). This task differs from more widely used finger sequencing tasks in that it requires precise visually guided pointing movements that are not over-learned (unlike straight reaching movements), allows for detailed trajectory kinematics to be collected throughout a single movement, and makes it possible to impose specific kinematics for single movements. The APT is, to the best of our knowledge, the first MR compatible task that allows subjects to make 2-dimensional visually guided movement trajectories with the wrist, analogous to arm reaches, which can be characterized kinematically.

In a recent psychophysical study using the APT, we showed that 3 days of practice led to a change in the speed-accuracy trade-off function for the task, driven predominantly by decreased variability around a fairly constant mean trajectory (Shmuelof et al. 2012). In the current study we sought to use functional magnetic resonance imaging (fMRI) to detect a practice-dependent change in brain activation for the APT while controlling for changes in movement execution. The experiment was performed over 5 days: subjects were scanned on day 1, trained on the APT outside the scanner on days 2, 3, and 4, and then were re-scanned on day 5. We chose to perform a multi-day study because in our previous psychophysical study, variability was still coming down after 3 days of training (Shmuelof et al. 2012) thus we reasoned that we would increase our chances of detecting the neural correlates of this change by allowing it to be as large as possible. Importantly, performance of the APT on day 1 and day 5 in the scanner was matched for kinematics: subjects performed the task at an enforced slow speed on both days and generated the same mean trajectories. In this way we were able to separate the neural

correlates of learning from the neural correlates of the improved motor ability that was achieved through such learning.

It is important to clarify here why we chose a task, in which mean kinematics were matched before and after learning in the scanner. Although motor learning leads to improved motor performance, it is not possible to assay neural correlates of learning by comparing brain activation at different performance levels because execution-related changes confound the interpretation. Instead, we recognized that the core result of motor learning is to change motor ability, i.e. the potential or capacity to perform at higher levels. Improved motor ability presumably consists of stable changes in neural circuitry that affect how a given movement is controlled. Hence, these changes should be measurable at any level of execution.

We hypothesized that learning-induced changes in motor acuity will be a result of improved representation of the task in the cortical execution network, achieved through recruitment of additional neurons. This recruitment hypothesis would be consistent with an overall increase in task-related activation, as measured using the blood-oxygen-level-dependent signal in fMRI.

Materials and Methods

Subjects

Thirteen right-handed subjects (8 females, 18-27 years of age), naïve to the task, participated in the study. All subjects gave a written informed consent and received token compensation to participate in the study. The study was approved by the Columbia University Institutional Review Board.

MRI Acquisition

Data were acquired on a Philips Intera 3T scanner using a Philips SENSE head coil. The functional scans were acquired using a gradient echo EPI, with voxel size of 3x3x3 mm (240x240x120mm matrix). TR = 2 s, flip angle= 77°, axial slices, TE = 25ms. 40 slices were acquired in an interleaved sequence at a thickness of 3 mm (no gap). 96 volumes were collected in each experimental run. The first 2 volumes were discarded to allow magnetization to reach equilibrium. A single T1-weighted anatomical scan was also acquired for each subject (MPRAGE, 1 mm^3). The field of view covered the entire cerebrum and most of the cerebellum. The inferior part of the cerebellum was not covered in some of the subjects.

Arc-pointing task outside the scanner

Subjects participated in a protocol consisting of 5 daily sessions in the lab and 2 functional MRI (fMRI) scans on days 1 and 5. The sessions in the lab were composed of *test* sessions (days 1 and 5), where the performance of subjects in the Arc Pointing Task (APT) was assessed at 5 movement times (MTs), and *train* sessions (days 2, 3 and 4) where subjects performed the APT at the same MT (see below). The APT required subjects to guide a cursor from one circle to the other through a semi-circular channel, presented on a monitor, by moving their left (non-dominant) wrist, in a clockwise direction, without crossing the borders of the channel. The width of the channel was the same as the targets' diameter (0.7 cm). At the beginning of each trial, one of the two horizontal targets became white (start circle) and the other red (target). A left white target indicated that subjects had to make a movement through the upper semi-circular channel to the target, whereas a right white target indicated that they had to move through the lower semi-circular channel. After a variable delay, the red circle changed to green, and a tone was played indicating that subjects could start the movement. The cursor was visible throughout the movement. After the trial, the entire trajectory of the cursor appeared on the screen. During *test* and *train* sessions, subjects were required to make the movements in a predefined MT range, indicated by a computer-generated demonstration of the cursor moving through the channel

in the required MT, which was presented at the beginning of each session block. Valid movements (inside the channel, and within MT range for the constrained blocks) were followed by a pleasant sound, and rewarded with symbolic coins in proportion to the MT. During days 2-4 subjects trained by making movements in a single constrained speed range (*Train sessions,* 520-780 ms). On days 1 and 5, subjects' overall speed-accuracy trade-off function was sampled by testing their performance at 5 different MTs (*Test sessions,* 240-420 ms, 400-600 ms, 640-960 ms, 800-1200 ms, 1200-1800 ms), presented in different blocks. *Test* and *train* sessions in the lab lasted approximately one hour. For more detailed information, see (Shmuelof et al. 2012).

Arc-pointing task inside the scanner

Subjects were scanned before the *test* sessions in the lab on days 1 and 5. During the scans, subjects performed movements with their non-dominant left wrist, while lying in a supine position (Fig. 1A). They viewed, through video goggles (Resonance Technology, Los Angeles, CA), the same display of targets and cursor as in the behavioral sessions. A Qualysis (Gothenburg, Sweden) infrared camera, positioned inside the MRI room, recorded the wrist pointing direction as the position of a spherical reflective marker on the index finger's proximal interphalangeal joint (the hand was closed in a fist), at a sampling rate of 100 Hz. Subjects moved the screen cursor horizontally and vertically by pointing with their closed fist (Fig. 1B). Each subject's forearm was placed in a splint to prevent forearm supination, so that the screen x and y positions were mapped, respectively, to wrist flexion-extension and radial-ulnar deviation. A laptop computer (Apple, Cupertino, CA) was used to control the visual display and to collect cursor position data with custom software.

Study design inside the scanner

Subjects performed three experimental runs (*Localizer*, *Trained* and *Untrained*) in the scanner on day 1 and two (*Trained* and *Untrained*) on day 5 (Fig. 1C). To obtain maximum sensitivity to task effects, a block design was used. Horizontal (*Trained*) and vertical (*Untrained*, control) versions of the APT (see below) were performed in separate runs before and after training. Six movements were performed in 18 s blocks (repeated 6 times), at a slow speed (1.5 s per movement). Movement blocks were interleaved with 12 s rest periods.

During rest periods, subjects were instructed to relax their wrist and wait for the visual cue indicating the beginning of the next block. During the movement blocks, subjects performed semi-circular movements through a channel (0.7 cm wide) between two circular targets (0.7 cm diameter) separated by 4.4 cm. These dimensions refer to the position of the reflective marker as recorded by the motion capture camera. In each trial, subjects moved the cursor from one target to the other in a curved clockwise motion, attempting to keep the cursor within the arc channel (Fig. 1B). The "go" signal for each movement was a visual cue (target color changed from red to green). The instruction to the subjects was to move the cursor between the targets without crossing the boundaries of the channel, and to maintain the required MT.

During movement blocks, subjects received online feedback of cursor position, but no further information about their success or failure, or about their movement speed. To control for MT across sessions, subjects had a short training session before the experimental run, where feedback about MT was given.

<< << < Figure 1 > >> >>

Tasks

Subjects performed three types of movement task. The *Trained* task consisted of APT movements as described above with the two targets arranged along a horizontal line, in the same configuration as during the behavioral training in the lab. The *Untrained* task differed in the target arrangement, which was vertical (rotated in 90°), and was never practiced outside of the scanner. In both tasks, movements were always made in a clockwise direction (Fig. 1B). In addition, subjects performed a *Localizer* task on day 1, which served as a functional localizer to identify brain areas involved in planning and execution of visually guided left wrist reaching movements. Subjects had to guide a cursor between a start target (diameter 0.7 cm) presented at the center of the screen and targets (diameter 0.7 cm) presented 3.5 cm to the left and to the right of the start target by making a sequence of straight out-and-back visually guided movements. As for the APT experiments, this task had a block design: 6 out-and-back movements were performed in each 18 s block.

Imaging analysis

Preprocessing and computing activation maps were all performed using Brain Voyager QX 1.10 (Brain Innovation, Maastricht, The Netherlands). Before statistical analysis, head motion correction using trilinear interpolation, high-pass temporal filtering in the frequency domain (three cycles/total scan time) and spatial smoothing (FWHM = 8mm) were applied to remove drifts and to improve the signal-to-noise ratio. The first two functional images of each run were discarded to allow for stabilization of the signal. Functional images were incorporated into the three-dimensional datasets through trilinear interpolation and transformed into Talairach space and Z-normalized. Group analysis was performed using a random-effects multi-subject General Linear Model (GLM). Regressors were defined as a boxcar function peaking during each block, convolved with a two-gamma hemodynamic response function. The Task-by-Day interaction analysis was performed using Brain Voyager QX ANOVA/ANCOVA module.

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244

245 *Voxel-based analysis*

246 We constrained the voxel-based analysis to the execution network for visually guided wrist movement
247 using a mask generated from the multi-subject contrast map of the functional localizer scan obtained
248 during performance of the *Localizer* task on Day 1 (straight reaching movements>rest, $p<0.05$). To
249 correct for multiple comparisons, a cluster threshold of 112 contiguous functional voxels was used for
250 the mask contrast and a cluster threshold of 19 contiguous functional voxels was used for the rest of the
251 contrasts. The thresholds were computed using a Brain Voyager QX Cluster-level Statistical Threshold
252 Estimator plugin by running 1000 iterations of a Monte-Carlo simulation to estimate the probability of
253 getting a cluster of a given size by chance (taking into account the number of activated voxels and
254 spatial smoothing).

255

256

257 *Global Ranking analysis*

258 We designed a non-parametric analysis to capture global changes in activation following training. This
259 analysis was based on individual unmasked and unsmoothed images. For each voxel, the contrast for
260 the day effect comparing the *Trained* and *Untrained* tasks was computed based on first level standard
261 General Linear Model (Friston et al. 1994) images computed in SPM5
262 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5) following slice time correction, high pass filter (5
263 cycles per scan) and image normalization to a standard brain using 4^{th} degree B-spline interpolation.
264 Ranks (integers representing orderings for all contrast estimates in the ROI) were calculated regardless
265 of condition for each subject. The sum of the ranks across conditions is the sum of the integers from 1
266 to the number of voxels in the image (V) times the number of conditions (C), which is equal to
267 C*V(C*V+1)/2. This ranking procedure is identical to calculating a Wilcoxon rank sum statistic. The

subject-specific proportion of the rank values devoted to each condition was then calculated and subsequently averaged over subjects within conditions. The average proportion in the first condition was retained as a test statistic. A low value of this statistic generally represents lower activation contrast values for this condition relative to the other and vice versa for a high value. A null distribution was obtained by permuting the condition labels within subjects and recalculating the statistics values. The result is a robust non-parametric test of contrast differences using the ensemble of voxels rather than separate interaction tests per voxel.

Behavioral analysis

Custom routines written within the Igor software package (Wavemetrics, Lake Oswego, OR) were used to compute error rate, MT, peak speed, and average trajectory. Cursor position data was low-pass filtered (zero-lag, 3rd-order Butterworth filter, cutoff frequency 14 Hz). A trial was considered an error if the cursor's radial position exceeded the channel's boundaries or if the cursor did not reach the target by the end of the trial duration (1.5 s). Error rate is the fraction of error trials out of all trials. Error rate, MT and peak speed comparisons were performed using paired *t*-tests for the behavioral data from the scanner and an ANOVA for the behavioral data obtained in the laboratory. For average trajectory and variance calculations, we discarded from each movement the first and last 10° of cursor position, corresponding to the area within the initial and final targets (polar coordinate angle relative to an origin midway between the two targets). Trajectories were then interpolated to 200 points, using linear interpolation. Correction for multiple comparisons when comparing the averaged trajectories and the trial-by-trial variability measures was conducted using a Random field Gaussian distribution correction for temporal correlation in the data (Shmuelof et al. 2012). This analysis focused on the time-normalized radial position of the cursor, which was the task relevant control variable, using paired *t*-tests run repeatedly for every normalized time point (n = 200). To correct for the probability of false positives due to multiple comparisons, we addressed temporal correlations in the data that resulted

from temporal smoothing. Corrected thresholds were thus computed based on the estimated number of truly independent samples present within the sampled vector using random field theory (Worsley et al. 1992).

Results

Subjects showed improvement in the Trained APT both in and outside the scanner

Subjects showed a significant improvement in APT performance across the tested range of movement times MTs when assessed outside the scanner after 3 days of training (comparison of performance on days 1 and 5, $p<0.001$, Fig. 2A). Consistent with our previous report (Shmuelof et al. 2012), the improvement generalized to MTs not experienced during training.

During the imaging sessions on days 1 and 5, subjects performed both the *Trained* (horizontal arc, Fig. 1B) and *Untrained* tasks (vertical arc). The *Untrained* task was introduced to control for a possible order effect: putative learning-related imaging effects for the *Trained* task on day 5 might instead be a non-specific effect of performing the same task twice in the scanner regardless of training. If activation changes were merely due to an order effect, comparable activation changes would be seen from day 1 to day 5 for the *Untrained* task. Subjects showed improvement in accuracy for the *Trained* APT performed in the scanner from day 1 to day 5 ($p = 0.007$, Fig. 2B) with no associated change in MT ($p = 0.38$, Fig 2B), peak movement speed ($p = 0.362$), and mean trajectory ($p>0.05$ throughout the trajectory, see methods). Crucially, the *Trained* task showed a decrease in trial-by-trial variability, with a maximal F value of 16.278 ($p<0.001$, Fig. 2C,E). The improvement in performance in the scanner is consistent with the behavioral results obtained outside the scanner (Fig. 2A). The observed reduction in variability is consistent with our previous behavioral work that showed reduction in trial-by-trial variability following training in the APT (Shmuelof et al. 2012). The *Untrained* task did not show

changes in movement speed, MT, mean trajectory, and mean variability across days (p = 0.29, and p = 0.31, and p>0.05, respectively, Fig 2B).

There was a significant difference in the degree of improvement for the *Trained* compared to the *Untrained* task (p = 0.049, Fig 2B). The small improvement for the *Untrained* task, although not significant (p=0.15), likely reflects partial generalization from the horizontal to the vertical task. It should be emphasized that we were looking for neural and behavioral differences between the *Trained* and *Untrained* tasks; such differences are not dependent on an absence of changes for the *Untrained* task.

< < < < < Figure 2 > > > > >

Skill learning was associated with changes in contralateral motor cortical areas and the ipsilateral cerebellum

The functional imaging data were analyzed using a General Linear Model (Friston et al. 1994). We were specifically interested in learning-related activation changes in brain areas associated with execution of wrist movements. Therefore the voxel-wise analysis was constrained to the execution network for visually guided pointing movements of the left wrist. We used a localizer scan based on straight reaching movements of the left wrist on day 1 to identify the wrist movement network (Fig. 3A, Table 1). Notably, the mask was constructed based on the averaged contrast image from the *Localiz*er scan using a low threshold of p=0.05 (cluster-size correction of 112 functional voxels), resulting in an inclusive mask of the execution network for wrist reaching movements.

Separate contrast maps were generated for a comparison between task-related activation patterns for days 1 and 5 (p<0.01, cluster size correction of 19 contiguous functional voxels) within the task mask

(Fig. 3A, Table 1) for the *Trained* (Fig. 3B, Table 1) and *Untrained* (Fig. 3C) tasks. Training on the horizontal APT was associated with increased activation in contralateral primary motor cortex (M1), contralateral dorsal premotor cortex (dPMC) and contralateral anterior intraparietal cortex (AIP), supplementary motor cortex (SMA) and in the ipsilateral cerebellum (Fig. 3B, Table 1). There were no significant reductions in activation following training within the task mask. For the *Untrained* vertical APT, there were no significant activation increases or decreases (Fig. 3C).

< < < < < Figure 3 > > > > >

In order to quantitatively test whether acquisition of skill could be associated with a net global increase in activation across all voxels in the unmasked brain, we designed a non-parametric ranking procedure to compare the distributions of activation for all unthresholded voxels before and after training (see Methods). For every subject, day 5 and day 1 activation values for the *Trained* task from every voxel were ranked together. The proportion of ranks for day 5 activation values was then computed and compared to a null distribution, obtained by permuting condition labels within subjects. The average proportion of ranks across subjects for day 5 observations was 0.52, which was significantly higher than chance (p=0.03, see Methods), indicating a global increase in activation for the *Trained* task following training. A similar analysis for the *Untrained* task did not indicate a global change in activation following training (0.5, p=0.68).

Increases in activation were greater for the Trained task

While the voxel-wise and ROI results showed that the *Trained* horizontal APT was associated with significant changes in activation and the *Untrained* vertical APT was not, these results are not sufficient to establish a selective learning effect for the *Trained* APT as compared to the *Untrained*

APT. To reach this conclusion it is necessary to show a significant day-by-task interaction (Nieuwenhuis et al. 2011). There were significant day-by-task interactions for the voxel-wise analysis in contralateral dPMC, in SMA and in the ipsilateral cerebellum (Fig. 3D, Table 1).

Given the low sensitivity of the voxel-based analysis, we also used a global multivariate approach to show a day-by-task interaction for activation across all unthresholded and unmasked voxels. For the global interaction measure we used the same ranking analysis as described above, but this time ranked according to day 5-day 1 activation values in each voxel for both the *Trained* and *Untrained* tasks together. The average proportion of ranks across subjects for the *Trained* task turned out to be 0.53, indicating that voxels changed more for the *Trained* than the *Untrained* task. Permutation analysis shows that average proportion of ranks is significantly different than the null distribution (p=0.03). Figure 4 demonstrates the shift of the distribution of the day5-day1 activation pattern for the *Trained* task compared to the *Untrained* task for a single subject.

<<<<< Figure 4 >>>>>

In summary, when kinematics were successfully constrained on day 1 and day 5 (same MT and average trajectory) for both the *Trained* horizontal APT and the *Untrained* vertical APT, there were significant learning-related increases in activation for the *Trained* task in contralateral motor cortical areas and in the ipsilateral cerebellum. Corroborating these results, a global test of activation across all voxels showed that there was greater activation overall for the *Trained* task compared to the *Untrained* task.

Discussion

We sought to dissociate brain activation related to motor learning from brain activation related to motor execution. We were specifically interested in the neural correlates of decreased movement variability (improved motor acuity) when controlling visually guided cursor trajectories with the wrist. We found learning-related increases in activation in contralateral motor cortical areas and in the ipsilateral cerebellum, when the task was performed with matched kinematics on the pre- and post-training days.

We have recently suggested that it is motor acuity that requires learning-related changes in contralateral primary and premotor cortical areas (Krakauer and Mazzoni 2011; Shmuelof and Krakauer 2011). Studies of motor learning in rodents have consistently shown changes in contralateral M1 after practice on visually guided pellet prehension tasks (Greenough et al. 1985; Kargo and Nitz 2004; Kleim et al. 2002; Xu et al. 2009). These changes, which take days to weeks to develop, include expansion in motor maps, long-term potentiation, and synaptogenesis. In one study, rats were trained on a pellet prehension task over 12 days. Over the first 6 days, pellet retrieval success rates were associated with changes in the action selected and changes in the ratio of muscle activation for a particular EMG pattern. Reduction in the variability of the muscle recruitment pattern only occurred over days 7 to 12 and it was only this reduction in variability that correlated with improvements in signal-to-noise ratio (SNR) in M1 cells (Kargo and Nitz 2004). This result is entirely consistent with our results: the APT was designed to emphasize variability reduction over action selection. This result also provides a potential explanation for why so many human imaging studies have not shown learning-related changes in contralateral motor cortical areas after controlling for execution. The kind of learning seen in the first 6 days in the rat study is probably what is being emphasized in most human studies, namely adaptation and action selection rather than motor acuity.

In previous work we have shown that training on the APT at slow speeds leads to improvements at untrained fast speeds (Shmuelof et al. 2012). We suggested that this generalization supports a representation of skilled movements that can be scaled across a range of difficulty (speed) levels. This idea is supported by our present result that learning-related activation was detectable even when performing at a slow speed. One possibility is that specific arrangements of controllers in M1 can be learned and associated with task-specific synergies. A fairly simple scalar input control onto these cortical representations could then allow these synergies to scale across speeds (d'Avella et al. 2008; Overduin et al. 2012). The degree of task specificity of these synergies is yet to be determined. The lack of a significant task-by-day interaction in M1 may support a partial overlap between learned synergies for the two tasks performed with the same effector. Thus we would conjecture that the non-significant interaction effect for the trained versus untrained task in M1 is due to generalization rather than a lack of learning-related changes in this region.

We found that training in the APT was associated with increases in activation in motor cortical areas and the cerebellum without any significant decrease in activation (Fig. 2B). In contrast, previous studies of motor learning that have focused on average activity changes, as we did here, have shown both increases and decreases in activation in several brain areas (Kelly and Garavan 2005; Petersen et al. 1998; Steele and Penhune 2010; Wu et al. 2004). Increased accuracy and precision in motor performance with training is presumably driven by increased signal-to-noise (SNR) in brain representations. There is evidence from the perceptual learning literature that there are at least two cortical mechanisms for increasing SNR (Reed et al. 2011; Yang et al. 2009). Training-related improvements in frequency discrimination in rats are first associated with auditory cortex map expansion and then with map renormalization (Reed et al. 2011). The expanded representation may improve encoding through summation over more units, while selective stabilization of specific dendritic spines during the renormalization phase may be associated with improved encoding through

441 selection of the most informative units, i.e. through reduction in the noise correlations between task-
442 related units (Bejjanki et al. 2011). Increased accuracy and precision in motor performance with
443 training, as for perceptual learning, is presumably also driven by increased SNR in brain
444 representations. It may be that the reported bi-directionality of brain activation responses in motor
445 learning tasks (Dayan and Cohen 2011; Hardwick et al. 2013) reflects the fact that the SNR can be
446 improved by either increases in the number of neurons recruited for a task or selection of a subset of
447 neurons specifically tuned to the task. The former would lead to increases in average activation and the
448 latter to decreases. The relative balance of these competing mechanisms for a learned representation
449 may be dependent on a variety of factors that include the task itself and the time spent practicing the
450 task. Thus we propose that in our task, motor acuity was associated with an increase in the number of
451 neurons recruited. It is possible that with more prolonged training we would have seen activation return
452 to day 1 levels (Puttemans et al. 2005; Reed et al. 2011; Xu et al. 2009). It should be noted that
453 although statistical maps cannot distinguish increased extent (more voxels) from increased intensity
454 (increased activation of same number of voxels), the latter would decrease, not increase, SNR.
455
456 A new approach to the study of learning is to use multi voxel pattern analysis (Cox and Savoy 2003;
457 Kamitani and Tong 2005). Using this approach it has been shown that improvement in perceptual
458 orientation discrimination was associated with increased orientation discrimination in the BOLD signal
459 taken from visual areas, without any changes in average activation in the same areas (Jehee et al. 2012).
460 In the motor domain, it has recently been shown that those areas that showed the largest learning-
461 related increases in classification accuracy of four separate trained finger sequences were in areas that
462 showed no changes in average activation (Wiestler and Diedrichsen 2013). Areas that did show a
463 change in average activation for the direct contrast between trained versus untrained sequences, showed
464 decreases in activation (bilateral PMd and along the intraparietal sulcus) and no increases. How to
465 reconcile these results with our and other studies (in multiple species) that suggest a predominant role

for contralateral motor cortical areas for skill? In the study by Wiestler and Diedrichsen, subjects executed sequences faster by overlapping presses of each individual finger (Wiestler and Diedrichsen 2013). There was no measure of precision of either the individual finger presses or of the two-finger transitions. Thus it could be argued that subjects were learning to choose the specific finger transitions needed for each sequence through a better representation of each sequence, i.e., faster selection of the required transitions. The ability to quickly execute any particular transition may, however, already have been at ceiling before learning even begun. The decrease in mean activation in this case could be a result of the reduction in the cognitive effort required to select the right sequence of finger presses. Indeed, such automatization effects in sequence learning have been shown to be associated with reduction in activation in cortical motor areas (PMD, SMA and parietal regions) (Puttemans et al. 2005; Wu et al. 2004). Thus sequence tasks may for the most part emphasize action selection over action execution. In our task, in contrast, it is clear to subjects from the outset what action is needed, down to the sub-movements, and it is the variability of this single action that needs to be reduced with training. An increase in neural bandwidth may only be needed when speed and accuracy of a particular action increases and not when the only difference is whether the actions are released in parallel rather than serially.

It is important to avoid the error of reverse inference when speculating about the meaning of the activations observed in an imaging study (Poldrack 2006). Our main prediction was that contralateral motor cortical areas would show a learning effect if the task emphasized the requirement for motor acuity. That said we were agnostic as to whether we would see a learning effect in the ipsilateral motor cerebellum or not; we observed increased activation in lobule V of the anterior lobe, which has been shown to be involved in visuomotor rotation learning (Donchin et al. 2012). The cerebellum is a critical structure for adaptation; returning behavior to baseline levels in the setting of external perturbations and maintaining a calibrated forward model of an ever-changing plant (Barash et al. 1999; Tseng et al.

2007). What is not clear is the degree to which the cerebellum is involved in improving motor acuity. We have recently shown that feedback responses improve from day 1 to day 5 in the APT (Shmuelof et al. 2012). Such improved feedback responses could occur through improved state estimation by the cerebellum. In this framework, the decrease in variability seen with learning could be due to more precise feedback corrections enabled by the cerebellum and increased SNR via increased neuronal recruitment in motor cortical areas. The learning-related activation we observed in the cerebellum was medial to the previously reported hand area in superior cerebellar cortex (lobules V and VI) (Grodd et al. 2001; Kuper et al. 2012; Rijntjes et al. 1999). Indeed we saw cerebellar activation in this hand area in our *Localizer* task (Figure 3A). Changes in activation associated with learning a new internal model also occur outside the cerebellar hand area (Imamizu et al. 2000). The results of this previous study and our current study suggest that both acquisition of a new forward model and improvement of state estimates in an existing forward model may depend on the same cerebellar representation.

An alternative explanation for our results could be that the activation differences are driven by differences in observed errors before and after training. Indeed both motor cortical areas and the cerebellum have been shown to have error-related activation (Diedrichsen et al. 2005; Imamizu et al. 2000; Schlerf et al. 2012). Critically, however, in these cases, activation increases as errors increase and, in the case of the cerebellum, occurs in the hand area. Here we show that activation increased with training as errors *decreased* and this activation was medial to the previously reported error-related cerebellar hand area activations.

Conclusion

We show that improvements in motor acuity over days are associated with learning-related increases in activation in areas within the baseline execution network: contralateral motor cortical areas and the ipsilateral cerebellum. A global non-localizing analysis confirmed that learning was associated with net increases in activation. Thus the observed decreases in movement variability could be accounted for by

a learning-related increase in the number of neurons recruited for the task. We conclude that when humans perform a task that in many ways can be considered an analog for visually guided reaching, learning-related changes occur within the execution network in a manner analogous seen in rodent and non-human primate models (Nudo et al. 1996; Xu et al. 2009).

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Captions of figures

Table 1

Execution and Learning related brain activation. Summary of activation loci for execution and learning related contrasts.

Figure 1

a. Experimental setup in the MRI scanner. Subjects performed the same APT task while lying supine, and moving their left wrist. The position of the marker was captured by the infrared camera that was positioned in the scanner room. Subjects received feedback through goggles.

b. Sample hand paths from the *Trained* (top) and *Untrained* (Bottom) tasks, recorded in the scanner, before (grey) and after (black) training. The task was to move the cursor in a clockwise direction from one circle to the other through a circular channel, without crossing the channel's boundaries. Day 1 trajectories show greater trial-to-trial variability than day 5 trajectories for the *Trained* task but not for the *Untrained* task.

c. Experimental protocol. Subjects participated in a 5 day protocol, which was composed of 5 daily sessions in the lab and 2 MRI scans on days 1 and 5. After the MRI sessions a speed-accuracy tradeoff functions (SAF) for the APT was derived for each subject.

Figure 2

a. Performance in the sessions in the lab before (grey, day 1) and after (black, day 5) training. Error-rate (fraction of movements outside the channel) is plotted against average movement time for the five imposed MTs. This plot illustrates the group's speed-accuracy tradeoff function (SAF) and its change after practice. Subjects showed reduction in error rate in all measured speeds, i.e., a shift across the SAF to a higher level of performance. Error bars denote SEM.

b. Performance measures from the *Trained (T)* and *Untrained (UT)* tasks (performed in the scanner). Error rate reduction following training for the *Trained* (solid bars) and *Untrained* tasks (empty bars, left). Subjects did not modulate MT in both tasks following training (middle). Improvement was greater for the *Trained* task (right). Error bars denote SEM.

c. Average trial-by-trial variability from day 1 (gray) and day 5 (black) scanning sessions of the *Trained* task. Averaged variability is plotted against normalized time. Following training, there is a reduction in variability mainly during the first half of the movement. Error bars denote SEM.

d. Average trial-by-trial variability from day 1 (gray) and day 5 (black) scanning sessions for the *Untrained* task. Averaged variability is plotted against normalized time. Variability for the *Untrained* task does not change with time.

e. Comparison of variability measures across days. Day effect (F values) as a function of normalized time. Dotted horizontal line represents the threshold (corrected for multiple comparisons) above which F values are statistically significant. Significant changes in variability can be seen for the *Trained* task (solid line) but not for the *Untrained* task (dashed line).

Figure 3

a. BOLD activation increase associated with the wrist localizer task. Voxel-based and ROI analyses were masked by mean activation pattern for straight reaching movements with the left wrist (*Localizer* scan, wrist movements>baseline). Average activation patterns are shown on inflated brain surfaces. Average activation in the cerebellum is shown on a coronal slice (y=-50). Reaching movement with the wrist was associated with a broad increase in activation in both hemispheres, in visual and motor areas and in the cerebellum.

b. Contrast map for the *Trained* task. Subjects were scanned while performing the *Trained*, horizontal arc task before and after training (on days 1 and 5). A contrast analysis between day 1 and day 5 activation patterns within the task mask (subset a) is shown. Increase in activation following training is shown in red-yellow colors, decrease in activation is shown in blue-green colors (color coding is shown in bottom right corner of the figure). Training in the APT was associated with increased activation in the right primary motor, premotor and supplementary motor cortices. Reduction of activation following training was not detected.

c. Contrast map for the *Untrained*, vertical arc task. A contrast analysis for the *Untrained* task within the task mask did not result in any significant change in activation.

d. Task by training interaction analysis. An interaction analysis (using ANCOVA) between training (day 1 versus day 5) and task (*Trained* versus *Untrained*) within the task mask resulted in significant activation in premotor dorsal and supplementary motor cortex.

Figure 4

Sample of the global interaction analysis from a single subject. Distribution of the training effect (day 5–day 1) of all voxels for the *Trained* (black) and *Untrained* (grey) tasks. The *Trained* distribution is shifted to the right of the *Untrained* indicating fewer negative values and more positive values relative to the untrained.

732

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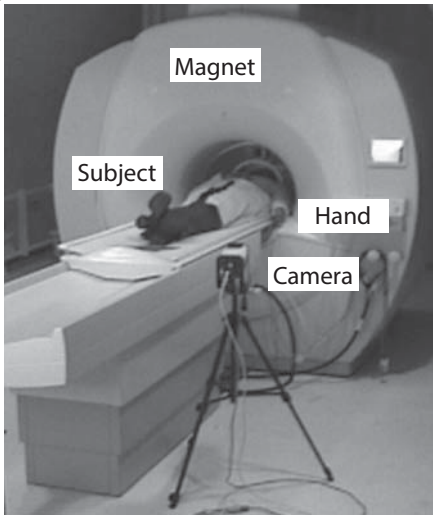
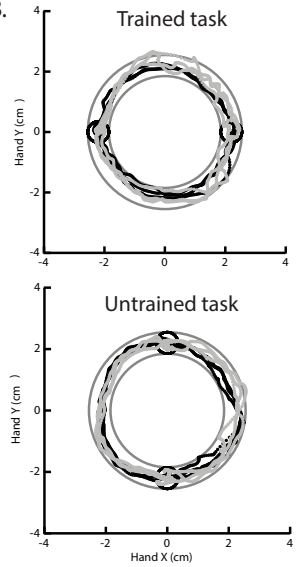
A.

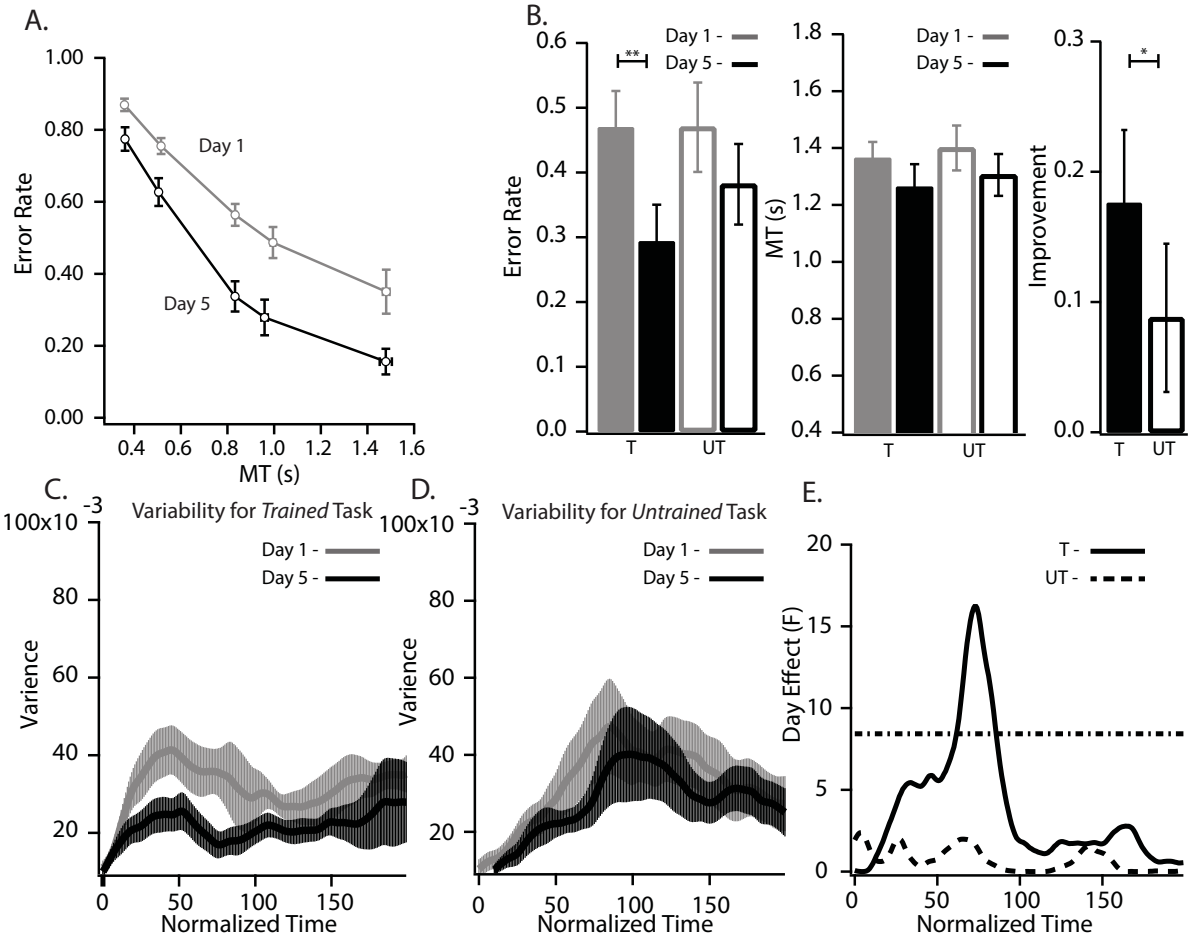


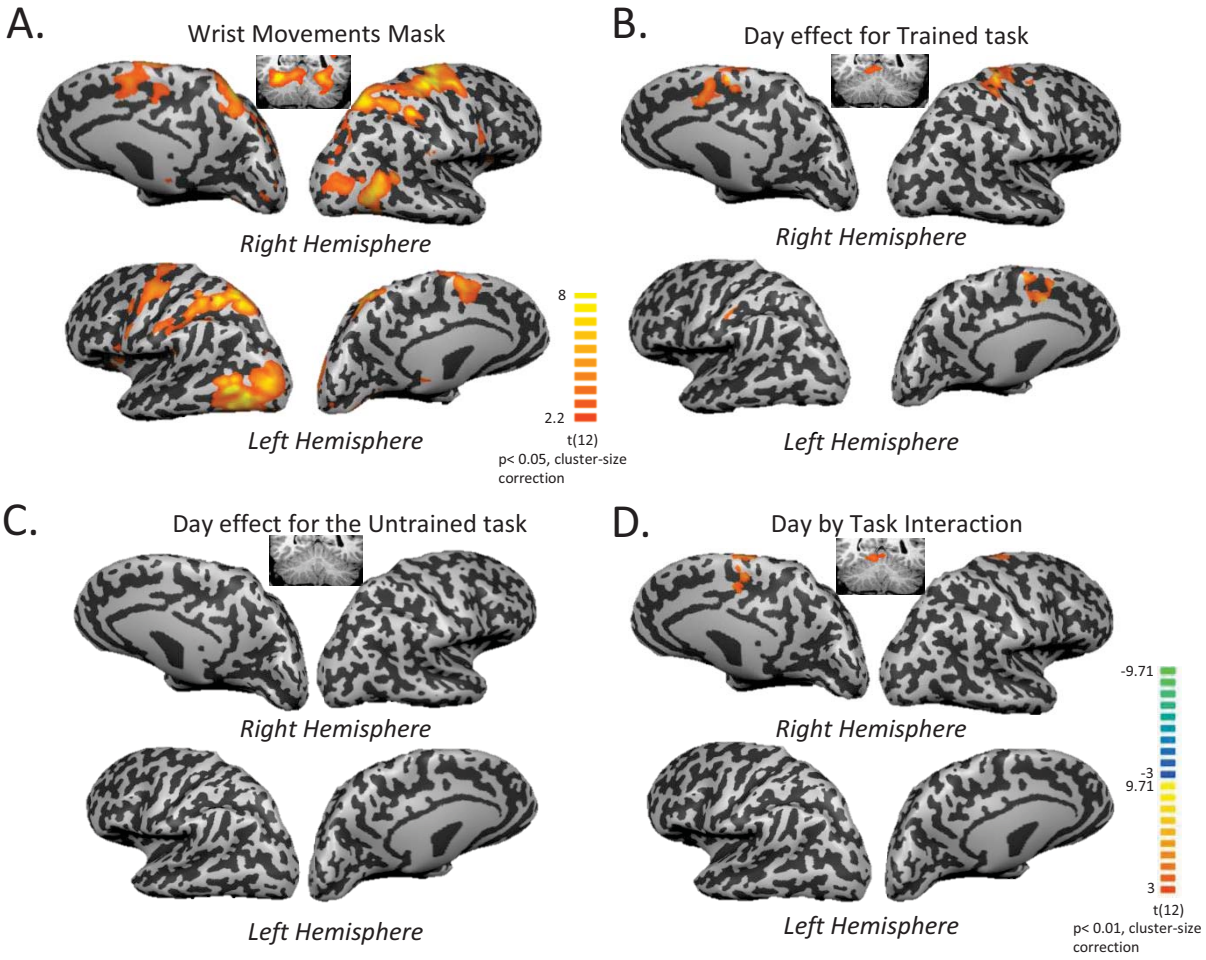
B.

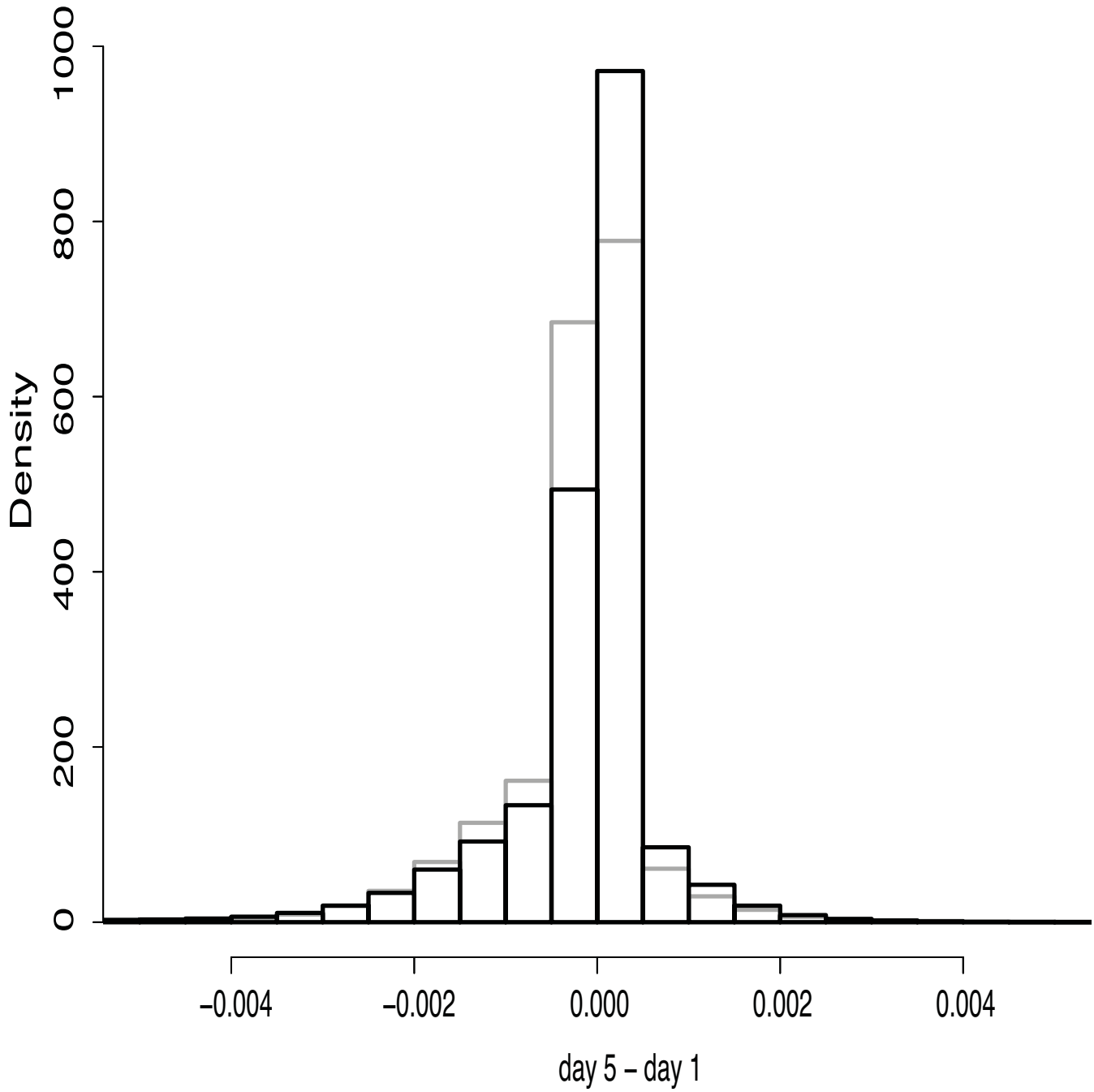


C.

Day:	1	2	3	4	5
MRI:	Pre-training: Trained, Untrained, Localization				Post-training: Trained, Untrained
Lab:	Pre-training Test-Deriving SAF	Training	Training	Training	Post-training Test-Deriving SAF


A.
Error Rate
MT (s)
Day 1
Day 5
B.
Error Rate
MT (s)
Improvement
Day 1 -
Day 5 -
**
*
T
UT
C.
Variability for *Trained* Task
Varience
Normalized Time
D.
Variability for *Untrained* Task
Varience
Normalized Time
E.
Day Effect (F)
T -
UT -
Normalized Time


A.
Wrist Movements Mask
Right Hemisphere
Left Hemisphere
8
2.2
t(12)
p< 0.05, cluster-size correction
B.
Day effect for Trained task
Right Hemisphere
Left Hemisphere
C.
Day effect for the Untrained task
Right Hemisphere
Left Hemisphere
D.
Day by Task Interaction
Right Hemisphere
Left Hemisphere
-9.71
-3
9.71
3
t(12)
p< 0.01, cluster-size correction


Density
0
200
400
600
800
1000
−0.004
−0.002
0.000
0.002
0.004
day 5 − day 1

Region	Cluster size (mm3)	Talairach coordinates			t-value
		Peak X	Peak Y	Peak Z	
Wrist movement day 1> baseline (Localizer task, p<0.05, cluster size correction)					
lPMC	10763	33	-13	52	6.45
SMA	10506	4	-8	54	7.25
rM1	24365	25	-23	48	10.65
rAIP	12858	22	-56	48	9.72
lAIP	13167	-20	-62	54	11.37
rLOG	18251	43	-70	7	10.43
lLOG	23615	-44	-71	3	13.99
rPut	7092	22	4	6	6.52
lPut	4427	-26	1	0	4.78
rCBL - lob VI	14729	31	-59	-18	10.43
lCBL - lobe VI	21287	-29	-53	-18	12.82
lCBL - lobe V	18534	-2	-59	-12	10.62
***Trained* task day 5 > day 1 (p<0.01, cluster size correction)**					
rM1	2811	19	-21	63	3.29
rdPMC	1378	23	-8	57	4.11
SMA	5006	-4	-14	54	7.53
rAIP	596	-44	-37	47	2.06
lCBL - lob V	1340	2	-50	-9	4.70

Task by Day Interaction (p<0.01, cluster size correction)					
rdPMC	1619	11	-14	66	3.71
SMA	1065	-4	-14	54	4.57
lCBL - lob V	2104	-5	-47	-12	5.02