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Report

Neural Substrates of Intermanual Transfer of a Newly Acquired Motor Skill

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Summary

In healthy humans, the two cerebral hemispheres show functional specialization to a degree unmatched in other animals, and such strong hemispheric specialization contributes to unimanual skill acquisition [1, 2]. When most humans learn a new motor skill with one hand, this process results in performance improvements in the opposite hand as well [3–6]. Despite the obvious adaptive advantage of such intermanual transfer, there is no direct evidence identifying the neural substrates of this form of skill acquisition [7–9]. Here, we used functional magnetic resonance imaging (fMRI) to study brain regions activated during intermanual transfer of a learned sequence of finger movements. First, we found that the supplementary motor area (SMA) has more activity when a skill has transferred well than when it has transferred poorly. Second, we found that fMRI activity in the ventrolateral posterior thalamic nucleus correlated with successful future intermanual transfer, whereas activity in the ventrolateral anterior thalamic nucleus correlated with past intermanual transfer. Third, we found that repetitive transcranial magnetic stimulation applied over the SMA blocked intermanual transfer without affecting skill acquisition. These findings provide direct evidence for an SMA-based mechanism that supports intermanual transfer of motor-skill learning.

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Results

Experiment 1

Motor-skill learning has been extensively studied with the serial reaction-time task (SRTT [10]). In this paradigm, subjects acquire the procedural knowledge needed to execute a series of actions that target a specific sequence of response locations [11]. In the first experiment carried out in the MRI scanner, we evaluated the subjects' ability to perform with the left hand before and after they received training on a 12-item finger sequence ("training sequence") with the right hand (see Figure 1A for experimental design and Supplemental Experimental Procedures available online for specific sequences utilized). Testing in the left hand consisted of three blocks: one involving randomly chosen cues ("random block") and the other two involving performance of 12-item sequences that were (a) the mirror image of the training sequence and (b) a different, unlearned sequence ("control sequence"). Sequence learning [11] for the right hand (see Supplemental Data) was calculated as the difference in response time (RT) between the last block of the training sequence and the last random block (solid line in Figure 1A). For the left hand, intermanual transfer of sequence learning was calculated in two ways: (1) as the difference in RT for the training sequence before and after right-hand practice (dashed line in Figure 1A) and (2) after practice, as the difference in RT between the training sequence and the random block. Two of the 15 subjects studied reported that some targets repeated during the SRTT training, but they were not able to reproduce the sequence.

Behavioral Measurements

Intermanual Transfer. $ANOVA_{RM}$, used to evaluate RT in the three types of blocks executed with the left hand ("Block" factor) before and after right-hand practice ("Time" factor), showed a significant effect of Block ($F = 14.9$, $p \leq 0.001$), Time ($F = 21.1$, $p \leq 0.001$), and their interaction ($F = 3.9$, $p = 0.03$; Figure 2A). Post-hoc one-way ANOVA showed a significant difference in the Block factor after ($F = 9.0$, $p < 0.01$) but not before ($F = 9.3$, $p = 0.39$) training. After training, Bonferroni corrected paired t tests showed shorter RT in the left hand in the training sequence (474.4 ± 19.3 ms) than in either the control sequence (534.2 ± 18 ms, $p = 0.03$) or the random block (570.6 ± 15.8 ms, $p < 0.01$). No differences were found between the control sequence and the random block RTs. Intermanual transfer of sequence-specific learning was substantial, although quantitatively incomplete, and was absent entirely when right-hand practice did not occur (see Figure S1). The difference between RT in the training sequence and that in the random block in the left hand increased significantly after SRTT training, another measure pointing to intermanual transfer of the training sequence (from 35.8 ± 15.5 ms to 96.2 ± 24 ms, $p < 0.01$). $ANOVA_{RM}$ showed no effect of Block ($F = 0.2$, $p = 0.7$), Time ($F = 0.07$, $p = 0.7$), or their interaction ($F = 0.003$, $p = 0.9$) on the number of errors performed by the left hand (Figure 2B).

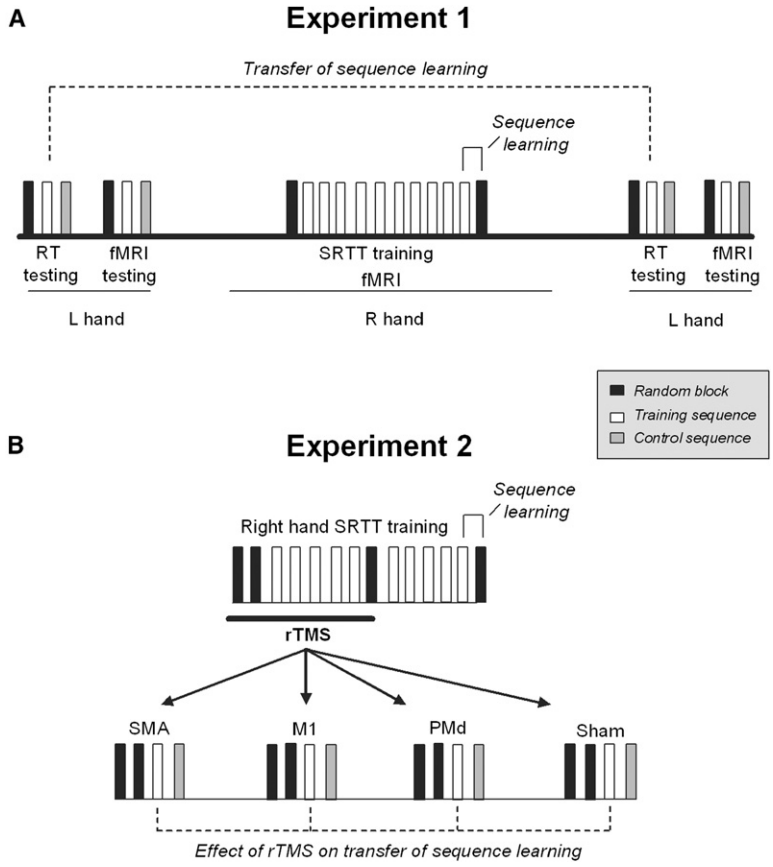

Figure 1. Experimental Design

(A) Experiment 1. Training sequence (white bars), control sequence (gray bars), and random block (black bars) were tested (RT testing) in the left hand before and after subjects practiced the SRTT task with the right hand. Left-hand SRTT task: In the first three blocks (120 key presses/block, RT testing), subjects were instructed to respond to each target presentation by pressing the appropriate key as quickly and accurately as possible. In the subsequent three blocks, targets were presented regularly (fMRI testing) every 1.5 s (96 key presses/block), and fMRI data acquisition occurred simultaneously. The order of block presentation (training sequence, control sequence, and random block) was randomized across subjects. Right-hand SRTT task: Subjects performed ten training-sequence blocks, all of them preceded and followed by one random block. For the right hand, sequence learning was calculated as the difference in RT between the last training-sequence block and the last random block (see "Sequence learning" label, solid line above bars). For the left hand, transfer of procedural sequence learning was calculated as the difference in left-hand RTs in the training sequence block before versus after right-hand training (see "Transfer of sequence learning" label, dashed line).

(B) Experiment 2. Diagram showing the order of the trial blocks performed with the right (top) and left (bottom) hands. The top section of the diagram shows the 14 blocks practiced with the right hand. Four different groups of subjects performed this task for approximately 30 min while repetitive transcranial magnetic stimulation (rTMS) or sham was being applied for the initial 15 min of training to different scalp positions on the right hemisphere. Each group received rTMS to the supplementary motor area (SMA), the right primary motor cortex (M1), the right dorsal premotor cortex (PMd), and sham. For the right hand, sequence learning was calculated as in Experiment 1 (solid line above bars at top). rTMS effects on intermanual transfer was calculated by comparing the left-hand RT in the training sequence after right-hand SRTT training across the four sites stimulated (dashed line).

fMRI Measurements

Left-hand performance. Random-effect analysis showed that, relative to rest, performance of the training sequence, control sequence, and random block with the left hand before SRTT training was associated with a bilateral increase in activity in the supplementary motor area (SMA), dorsal premotor cortex (PMd), primary visual cortex, cerebellum, and right primary motor cortex (right M1) ($p < 0.05$ FDR; Tables S1–S6). No significant differences were found among these areas when the two different sequences and random blocks were directly contrasted. After SRTT training, performance of the training sequence, control sequence, and random blocks with the left hand was associated with bilateral activation—relative to rest—in the SMA, PMd, striatum, extrastriate visual cortex (BA17 and 18), cerebellum, thalamus, and right M1 ($p < 0.05$ FDR; Tables S1–S6). Direct comparison of the training sequence, control sequence, and random block before and after training showed no significant differences in brain activity.

Intermanual transfer. Simple regression analysis between brain activity (estimated effect size of activation change compared to rest) and intermanual transfer to the left hand across subjects showed that pretraining functional magnetic resonance imaging (fMRI) activity in the right ventrolateral posterior (VLp) thalamic nucleus [12] correlated with the practice-dependent improvement in left-hand RT with the training sequence [MNI peak coordinate (x,y,z) = 18, −20,12, t = 4.75, $p < 0.001$ uncorrected at voxel level, $p < .05$ svc at cluster level, Figure 3A]. Similarly, fMRI activity in the right VLp thalamic nucleus correlated with the difference between training sequence and random block RTs in the left hand after training ($r = 0.6$, $p = 0.01$).

The magnitude of intermanual transfer correlated with posttraining activity in both the SMA (coordinate = 6,8,62, t = 5.37, $p < 0.001$ uncorrected at voxel level, $p < .001$ svc at cluster level, Figures 3E and 3F) and the ventrolateral anterior (VLa) thalamic nucleus (coordinate = 10, −12,6, t = 5.95, $p < .001$ uncorrected at voxel level, $p < 0.01$ svc at cluster level, Figures 3I and 3J). Activity in these areas did not correlate with performance changes in the control sequence (Figures 3G and 3K) or random block (Figures 3H and 3L). Furthermore, fMRI activity in the SMA ($r = 0.64$, $p < 0.01$) and VLa ($r = 0.8$, $p < 0.001$) correlated with the difference between training sequence and random block RTs in the left hand after training.

Experiment 2

This experiment was designed to test the effect of a transient disruption of activity in the SMA, as identified in the

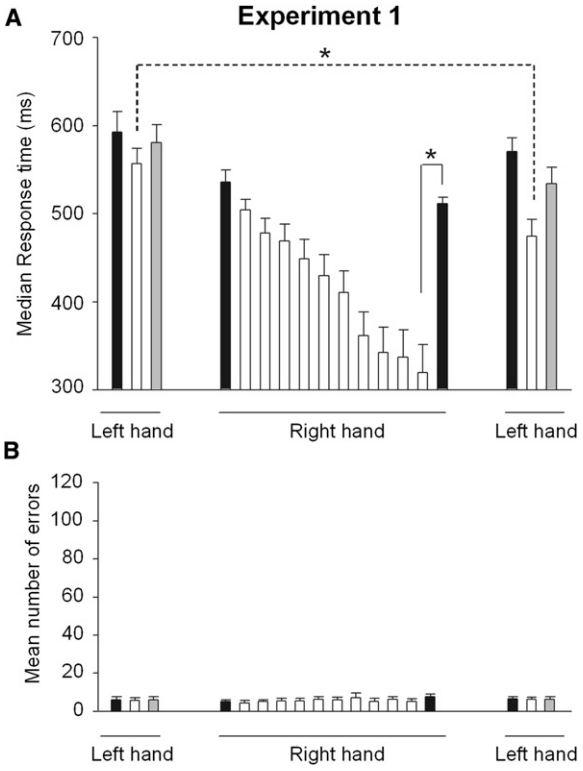

Figure 2. Experiment 1: Response Time and Mean Errors in Training Sequence, Control Sequence, and Random Block before, during, and after the SRTT Training

(A) The abscissa shows the timeline of the experiment, and the ordinate shows RT. Note the progressive shortening of RT with repeated performance of the training sequence (white bars) with the right hand. Significant (asterisk, $p < 0.05$) sequence learning with the right hand is shown in solid lines. Intermanual transfer of sequence learning in the left hand is shown as dashed lines.

(B) Mean number of errors (incorrect key presses) in each experimental block. Note the stable accuracy during the course of the experiment.

Error bars denote standard errors.

fMRI study. Additionally, we tested the effect of repetitive transcranial magnetic stimulation (rTMS) over M1, an area with potential involvement in sensorimotor processes involving the transfer hand [5, 6], and PMd, a control cortical region that was not expected to contribute substantially to the transfer process [7–9]. As in experiment 1, subjects trained for 30 min on a 12-item sequence (training sequence) intermixed with random blocks (Figure 1B). Using a stereotactic coil-positioning system, guided by each subject's anatomical MRI, we applied rTMS (900 pulses at 1 Hz for 15 min at 80% of the resting motor threshold [RMT, see Experimental Procedures and Supplemental Experimental Procedures]) over (a) SMA (n = 8), (b) right M1 (n = 8), (c) right PMd (n = 8), and (d) sham TMS (n = 8). Thus, stimulation (or the control, sham procedure) was performed for the first 15 min of the approximately 30 min during which the subjects practiced the SRTT task with the right hand. For analysis of variance, this factor was called "stimulation site," and no subjects participated in more than one group or experiment. Learning with the right hand was calculated as in experiment 1, and rTMS effects on intermanual transfer were calculated by comparison of the left-hand RT after right-hand SRTT training across the four stimulation-site groups (dashed line in Figure 1B). Eight of the 32 subjects distributed over the four stimulation and sham groups reported that some targets repeated during the SRTT training, but none of the subjects were able to reproduce the sequence.

Intermanual Transfer

$ANOVA_{RM}$ showed a significant effect of stimulation site on intermanual transfer ($F = 4.17$, $p = 0.01$; Figure 4). Post-hoc analysis showed longer RTs for the left hand in the training sequence block after stimulation of the SMA (351 ± 23 ms; Figure 4A, arrow) than after right PMd (274 ± 22 ms; $p = 0.01$; Figure 4C) or sham (270 ± 29 ms; $p = 0.02$; Figure 4D) stimulation. RTs in the left hand in the training sequence were also longer after M1 (342 ± 19 ms; Figure 4B, arrow) than after right PMd (274 ± 22 ms; $p = 0.02$; Figure 4C) or after sham (270 ± 29 ms; $p = 0.04$; Figure 4D) stimulation. There were no differences in RTs when we compared the effects of SMA versus right M1 ($p = 0.7$) stimulation or when we compared PMd to sham stimulation ($p = 0.7$). The difference between training sequence and random block RT in the left hand decreased more after stimulation of the SMA (13.5 ± 9.8 ms) than after right PMd (58.5 ± 13.8 ms; $p = 0.02$) or after sham (53 ± 8.3 ms; $p = 0.02$) stimulation. The number of errors performed with the left hand were comparable in the training sequence, control sequence, and random blocks across the four STIMULATION-SITE groups ($ANOVA_{RM}$; $F = 0.4$, $p = 0.7$).

Discussion

Two novel findings emerged from this study, in which a newly acquired motor skill transferred from the practicing to the resting hand: (a) The magnitude of intermanual transfer correlated with pretraining fMRI activity in the VLp thalamic nucleus and with posttraining fMRI activity in the SMA and VLa thalamic nucleus, and (b) rTMS applied over the SMA substantially interfered with intermanual transfer of the learned task without disrupting learning.

Neural Substrates of Intermanual Transfer

Intermanual transfer of sequence learning to the resting hand first requires proper learning of the training sequence with the practicing hand [4–6]. Under our experimental conditions, procedural learning with the practicing hand was clearly documented in both fMRI and rTMS experiments (see Supplemental Data). Learning with the practicing hand was not disrupted by any form of rTMS application or sham stimulation, most likely because the intensity of rTMS was below the threshold to disrupt it, consistent with previous results ([13,14]; see also Supplemental Experimental Procedures). A proportion of the sequential learning demonstrated with the practicing hand transfers to the resting hand, a process referred to as intermanual transfer [4–6]. Although substantial behavioral evidence in this and other studies demonstrated the presence of intermanual transfer of learning in humans and nonhuman primates [3–6, 15], there is no direct evidence identifying the brain areas responsible for transferring the sequential order of the learned movements to the resting hand [7–9]. The

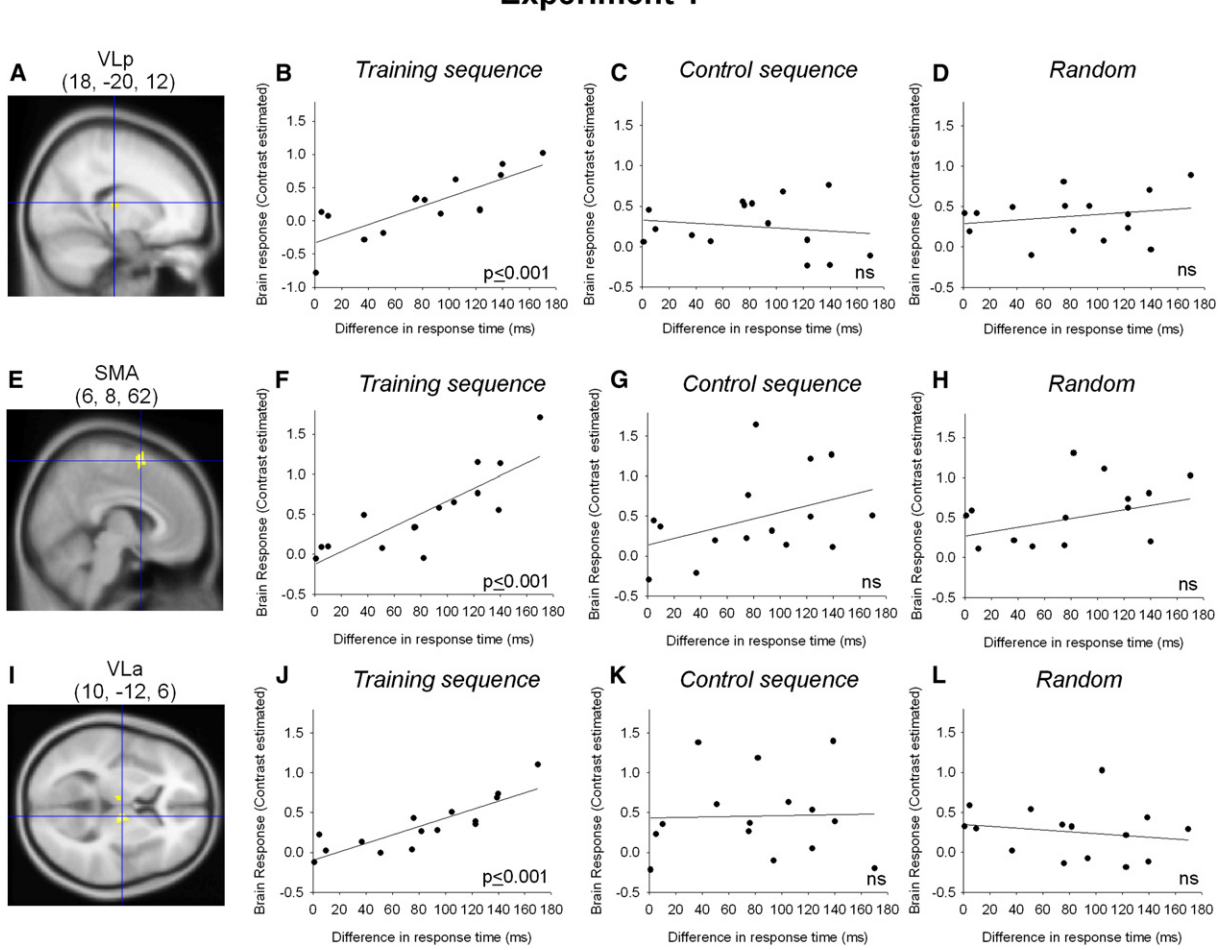

Figure 3. Experiment 2: Pre- and Post-Training fMRI Activity with Intermanual Transfer of Sequence Learning

(A) Pretraining fMRI activity in the ventrolateral posterior nucleus of the thalamus (VLp) increased significantly with transfer of the training sequence to the left hand. (E and I) Brain regions where posttraining fMRI activity increased with transfer of the learned sequence to the left hand. (E) SMA. (I) Ventrolateral anterior nucleus of the thalamus (VLa). In all graphs, the abscissa indicates the difference in left-hand training sequence RTs before versus after right-hand SRTT training; positive values indicate RT decreases. Note that the data composing the abscissa always come from a comparison of pretraining and posttraining RTs for the training sequence (dashed line in Figure 1A), regardless of whether the ordinate shows the brain response (contrast estimated) for the training sequence (B, F, and J), the control sequence (C, G, and K), or the random block (D, H, and L). The results show that the increased pre-training fMRI activity in the VLp was associated with more successful intermanual transfer of the training sequence (B) but not the control sequence (C) or random block (D) to the left hand, whereas the increased posttraining fMRI activity in the SMA and VLa was associated with more successful intermanual transfer of the training sequence (F and J) but not the control sequence (G and K) or random block (H and L) to the left hand. R values represent Pearson's correlation coefficient.

purpose of our investigation was to provide insight into the mechanisms underlying this process.

Our first result was that the magnitude of intermanual transfer of sequence learning correlated with posttraining fMRI activity in both the SMA and VLa thalamic nucleus. SMA is well placed to perform this function [16, 17]. It has dense transcallosal commissural connections with both M1 and premotor areas in the opposite hemisphere, as well as with the contralateral SMA [18]. The SMA is also strongly and reciprocally connected to the VLa nucleus of the thalamus, and the present results show that activity in this nucleus also correlates with the magnitude of intermanual transfer. The homology of VLa with the oral ventrolateral nucleus (VLo) in macaque monkeys is well established [19], and evidence from nonhuman primates shows that VLa receives GABAergic inputs from the internal segment of the globus pallidus in the basal ganglia [20]. The finding of greater VLa and SMA activation in association with more successful intermanual transfer in our study (Figure 3B and F) supports a role for this VLa–SMA axis, as well as the basal ganglia, in intermanual transfer of procedural knowledge. Based on its anatomical and physiological connections, it is possible that VLa exerts a modulatory role on interactions between the SMA and other cortical targets in both cerebral hemispheres [20], a proposal consistent with the documented role of the VLa in the selection of correct motor responses to visual cues [21].

Unlike the VLa results, which showed a posttraining fMRI correlation with transfer that had already occurred, the VLp nucleus of the thalamus showed a pretraining fMRI correlation with the magnitude of future intermanual transfer. VLp receives strong inputs from the cerebellum [20, 22], which has been implicated in error

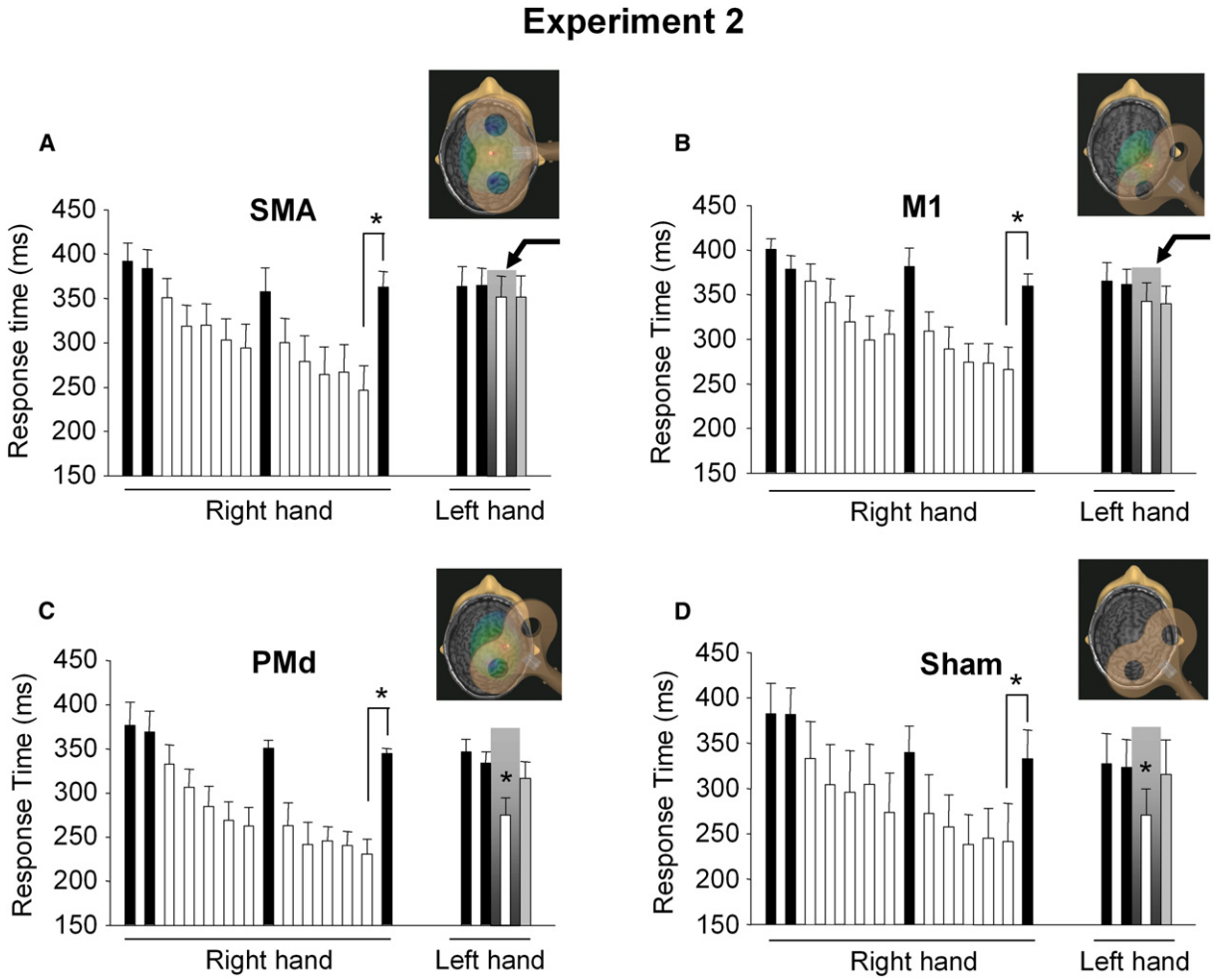

Figure 4. Experiment 2: Effects of rTMS on Intermanual Transfer of Sequence Learning

Via a stereotactic coil-positioning system guided by MRI within each individual, rTMS was applied over: (A) SMA, (B) MI, (C) pMD, and (D) sham (placebo stimulation with coil positioned over right M1). In all graphs, the abscissa shows the time course of the experiment, and the ordinate shows RTs of the training sequence (white bars), control sequence (gray bars), and random blocks (black bars). Note the progressive shortening of RT with the right-hand training during performance of the training sequence in all four groups (solid connecting lines in [A] through [D], asterisk, $p < 0.05$). In contrast to the similarity among groups during sequence learning with the right hand, intermanual transfer to the left hand (gray shaded areas in [A]–[D]) differed among the groups. Sequence-specific transfer was substantially decreased with SMA and M1 stimulation, as shown by the similar RTs in the training sequence and random blocks after the SRTT ([A and B], arrows in shaded areas), but not with PMd and sham rTMS stimulation, as shown by the shorter RTs in the training sequence than in random blocks ([C and D], asterisks in gray shaded areas). The latter two groups (C and D) show significant intermanual transfer (asterisk, $p < 0.05$), whereas the former groups (A and B) do not. The pictures above each bar graph show the calculated center of the rTMS-induced field and the target anatomical position determined by the MRI-guided frameless stereotaxic coil-positioning system in a representative subject. Error bars denote standard errors.

prediction and correction [23]. There is evidence that VLp neurons also contribute to error prediction [24], and it is well established that this region is strongly interconnected with the SMA [20, 25]. The present results suggest that greater VLp activity prior to training contributes to successful intermanual transfer. Transfer is assessed after training, but it is likely to develop as the training progresses. Accordingly, a possible account for this relationship is that VLp is not simply "quiet," or waiting for learning to occur, at the start of SRTT training. Rather, under the influence of cerebellar inputs, it may play a role in generating a prediction of the future finger movement, and this could operate from the start of training. Before SRTT training and in its early stages, VLp's predictions could tune SMA's activity in a way that promotes transfer; a greater magnitude of VLp activity might promote more successful transfer. After training, at the time of transfer testing, this tuning process would presumably be completed, and VLp's contribution would decrease as that of VLa and SMA increases. This division of labor would be especially valuable if VLa (reflecting its basal ganglia inputs) and VLp (reflecting its cerebellar inputs) processed error signals of different types, an idea consistent with the finding that the cerebellum plays its largest role in trial-to-trial adjustments in the process of motor learning, whereas the basal ganglia contributes more to online adjustments during a movement [26]. Taken together, these fMRI observations suggest novel differentiated roles for the mixed thalamic input from the basal ganglia

and cerebellum to the SMA in the development of successful intermanual transfer of sequential learning in humans; cerebellar input (via VLp) might condition trial-to-trial learning in a manner suitable to future transfer, and basal ganglia input (via VLa) might contribute to online adjustments during transfer testing.

Our second set of results relates to the understanding of the consequence of a virtual lesion as implemented by rTMS on the ability of subjects to transfer the learned motor sequence to the resting hand. The fMRI results in our investigation clearly demonstrated a correlation between posttraining SMA activity and successful intermanual transfer. To better understand the functional significance of this association between posttraining SMA fMRI activation and successful intermanual transfer, we studied—in different groups of subjects—the consequences of disruption of activity in SMA, as well as the consequences of sham rTMS and a control cortical region PMd, which was not expected to contribute substantially to the transfer process [7–9]. The results of this experiment showed a significant decrement in transfer when rTMS disrupted SMA, but not with disruption of PMd or with sham stimulation. These findings revealed a critical role (beyond association) for SMA activity in successful intermanual transfer of sequence learning. The crucial functional role of SMA in successful intermanual transfer of sequence learning demonstrated here is consistent with findings in patients with lesions involving the anterior part of the corpus callosum, which links both SMAs [27].

One additional consideration relates to the interpretation of rTMS-induced changes in behavior as evidence of a causal link between activity in the stimulated region (in this case SMA) and the specific behavior being disrupted (in this case intermanual transfer) [28, 29]. It should be kept in mind that the behavioral consequences of rTMS over SMA could represent the consequences of focal disruption of activity in this region [14], of disruption of its interconnected areas [30], and/or of disruption of the ability of the remainder of the brain to compensate for SMA disruption. Interestingly, although fMRI activity in M1 failed to correlate with successful intermanual transfer either before or after learning, rTMS over M1 disrupted intermanual transfer of the sequential learning, possibly through its well-known [31–33] functional connections with SMA.

Conclusion

In summary, this study provides direct evidence for the involvement of an SMA-based mechanism in intermanual transfer of a form of procedural knowledge: the learning of movement sequences. The present data also point to a differential and time-dependent contribution of two different thalamic nuclei—one that channels information from the cerebellum (VLp) and one that does so from the basal ganglia (VLa). This information provides evidence for previous proposals about the functions of neural networks that involve the dorsal thalamus [34]. These neural networks, which involve the SMA–VLa and SMA–VLp cortico-thalamocortical loops, provide an important adaptive advantage to healthy humans: the ability to apply skills obtained with the dominant hand to the opposite one as necessary for achieving goals.

Experimental Procedures

Participants

Fifteen right-handed healthy volunteers (two females and 13 males with a mean age of 24.7 ± 2.8 years) were studied in experiment 1, and 32 different subjects (12 females and 20 males with a mean age of 27.5 ± 6.3 years) participated in experiment 2. In experiment 2, eight subjects were assigned to each of four different stimulation-site groups, including: (a) SMA (n = 8), (b) right M1 (n = 8), (c) right PMd (n = 8), and (d) sham TMS (n = 8). All subjects gave written, informed consent, and the experiments were approved by the National Institute of Neurological Disorder and Stroke Institutional Review Board (Bethesda, USA) and the local ethics committee of the National Institute for Physiological Sciences (Okasaki, Japan).

fMRI Procedure

As illustrated in Figure 1A, subjects first performed three kinds of trial blocks with the left hand (RT testing in Figure 1A): (a) the mirror image of the training sequence, (b) a different, unlearned sequence (control sequence), and (c) a random block. The GO signal was displayed on a computer screen (one asterisk and three dots evenly spaced horizontally, all appearing simultaneously). The position of the asterisk, which varied among the four possible locations each time a display appeared, indicated the required key press. Then, the asterisk positioned at the right end of the screen corresponded to position 1 (in which position 1 corresponded to the index finger, position 2 to the middle finger, position 3 to the ring finger, and position 4 to the little finger). After the correct key was pressed, the next display of three dots and one asterisk appeared on the computer screen. If subjects made an error by pressing an incorrect key, the program enforced a delay until the correct key was pressed. Subjects were instructed to respond as quickly and accurately as possible to the asterisk's presentation. Response times were measured and defined as the time interval between the GO signal and the correct key press. In the next three blocks (training sequence, control sequence, and random block) (fMRI testing in Figure 1A) the asterisk was presented regularly, every 1.5 s, so that comparability of fMRI data before and after SRTT training would be maximized [2]. See Supplemental Data for details about fMRI procedures and analysis.

rTMS Procedure

Subjects in experiment 2 did not participate in fMRI experiments. rTMS was delivered over SMA, right PMd, right M1 and with a sham procedure to four different groups of subjects (eight subjects per group) in four separate sessions via a Magstim rapid stimulator (Rapid Magstim company, Dyfed, UK) through a figure-of-eight coil (loop diameter, 9 cm; type no.: 8809). A stereotactic frameless Nexstim Navigation Brain Stimulation System (NBS) was used for precisely locating the target brain position in each individual's structural MRI (see Supplemental Experimental Procedures for site localization). rTMS was applied during SRTT with the right hand (Figure 1B) at a frequency of 1 Hz. A total of 900 pulses were applied for 15 min at 80% of RMT during the initial part of the SRTT training. At the beginning of each experiment, we determined the right M1 RMT, defined as the lowest intensity of TMS output required for evoking MEPs of at least 50 μV in peak-to-peak amplitude in at least three of five consecutive trials. See Supplemental Data for details about rTMS procedure and analysis of behavioral measurements.

Supplemental Data

Additional Results and Experimental Procedures as well as two figures and five tables are available at http://www.current-biology.com/cgi/content/full/17/21/1896/DC1/.

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