Done That: Short-term Repetition Related Modulations of Motor Cortex Activity as a Stable Signature for Overnight Motor Memory Consolidation

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Abstract

■ An almost universally accepted tacit expectation is that learning and memory consolidation processes must be reflected in the average brain activity in brain areas relevant to task performance. Motor cortex (M1) plasticity has been implicated in motor skill acquisition and its consolidation. Nevertheless, no consistent pattern of changes in the average signal, related to motor learning or motor memory consolidation following a single session of training, has emerged from imaging studies. Here we show that the pattern and magnitude of short-term brain activity modulations in response to task repetition, in M1, may provide a robust signature for effective motor memory consolidation processes. We studied participants during the paced performance of a finger-to-thumb opposition sequence (FOS), intensively trained a day earlier, and a similarly constructed untrained FOS. In addition to within-session "on-line" gains, most participants expressed delayed, consolidation-phase gains in the performance of the trained FOS. The execution of the trained FOS induced repetition enhancements in the contralateral M1 and bilaterally in the medial-temporal lobes, offsetting novelty-related repetition suppression effects. Moreover, the M1 modulations were positively correlated with the magnitude of each participant's overnight delayed gains but not with absolute performance levels. Our results suggest that short-term enhancements of brain signals upon task repetition reflect the effectiveness of overnight motor memory consolidation. We propose that procedural memory consolidation processes may affect the excitation–inhibition balance within cortical representations of the trained movements; this new balance is better reflected in repetition effects than in the average level of evoked neural activity. ■

INTRODUCTION

The generation of fluent, errorless, and reliable movement sequences (motor skills) requires practice (i.e., repeated experience; Adams, 1987). Practice-related gains in performance may evolve not only during the actual training experience on a novel sequence of movements but also "off-line" after practice has ended (Krakauer & Shadmehr, 2006; Karni et al., 1998). Off-line, delayed gains (DGs) in performance presumably reflect procedural (skill) memory consolidation processes that require time to evolve (Reis et al., 2013; Debas et al., 2010; Doyon et al., 2009; Song, Howard, & Howard, 2007; Robertson, Pascual-Leone, & Press, 2004). Following practice on an explicitly introduced motor sequence, the expression of DGs, in terms of faster and more accurate performance, was often dependent on sleep (Barakat et al., 2013; Doyon et al., 2009; Korman et al., 2007; Nishida & Walker, 2007; Korman, Raz, Flash, & Karni, 2003; Fischer, Hallschmid, Elsner, & Born, 2002; Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002; Maquet, 2001). Time and the affordance of sleep may be necessary to complete cellular events subserving long-term memory (Karni, 1996) such as experience-driven task-specific synaptic modifications (e.g., Xu et al., 2009; Yang, Pan, & Gan, 2009).

There is consistent evidence from functional imaging and TMS studies that motor learning is associated with substantial changes within motor-related cortical and subcortical areas (Barakat et al., 2013; Steele & Penhune, 2010; Hotermans, Peigneux, de Noordhout, Moonen, & Maquet, 2008; Krakauer & Shadmehr, 2006; Smith et al., 2006; Doyon & Benali, 2005; Fischer, Nitschke, Melchert, Erdmann, & Born, 2005; Floyer-Lea & Matthews, 2005; Penhune & Doyon, 2005; Robertson, Press, & Pascual-Leone, 2005; Grafton, Hazeltine, & Ivry, 2002; Hikosaka, Nakamura, Sakai, & Nakahara, 2002; Karni et al., 1995). For example, the magnitude of the delayed sleep-dependent improvement was linked to the recruitment of the primary motor cortex (M1) during the initial training session (Steele & Penhune, 2010). These findings support the idea that training can initiate experience-driven changes in task representations within M1 and that these changes may be crucial for the triggering of consolidation processes (Karni et al., 1995, 1998). However, functional imaging studies have provided apparently conflicting findings regarding changes in the M1 average signal in relation to motor memory consolidation following a single session of training. The average magnitude of the BOLD signals

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Journal of Cognitive Neuroscience 26:12, pp. 2716–2734
doi:10.1162/jocn_a_00675

in M1 contralateral to the trained hand was found to be either increased (Barakat et al., 2013), decreased (Fischer et al., 2005), or unchanged (Steele & Penhune, 2010). Indeed, it has been suggested that in the initial stages of motor skill acquisition M1 may have a secondary role and other representations of the task predominate (Doyon & Benali, 2005; Hikosaka et al., 2002). Here we tested whether the patterns of signal modulation in response to task repetition, rather than the average signal intensity in motor cortex per se, may provide a more reliable neural signature for motor experience and specifically for effective motor memory consolidation.

The modulation of neural activity upon task repetition is one of the most robust experience-related phenomena (Grill-Spector, Henson, & Martin, 2006; Sayres & Grill-Spector, 2006; Henson, 2003; Henson, Shallice, & Dolan, 2000; Grill-Spector et al., 1999; Karni et al., 1995, 1998; Schacter & Buckner, 1998; Wiggs & Martin, 1998; Desimone, 1996; Miller & Desimone, 1994; Miller, Li, & Desimone, 1991, 1993). This modulation can occur even without changes in the average evoked activity across trials, runs or sessions, or the entire set of repeated stimuli. Reduced physiological activity upon task repetition, repetition suppression (RS) effects, presumably reflect the optimization of processing and priming (Grill-Spector et al., 2006; Henson, 2003; Schacter & Buckner, 1998; Wiggs & Martin, 1998; Desimone, 1996); however, these effects may be performance independent (Sayres & Grill-Spector, 2006; Miller & Desimone, 1994). RS effects are transient and tend to saturate after a few iterations of the task. Repetition-driven reduction in neural activity was shown to occur in M1 in a variety of motor tasks (Valyear, Gallivan, McLean, & Culham, 2012; Hamilton & Grafton, 2009; Dinstein, Hasson, Rubin, & Heeger, 2007; Grafton & Hamilton, 2007) and was found to be related to movement sequence learning (Karni et al., 1995, 1998). In the Karni et al. (1995) study, when a new sequence of movements was performed at a given rate for the first time (the first performance block) and then repeated (the second performance block) after a short rest interval, the evoked activity in M1 contralateral to the performing hand was found to be significantly decreased in the second block (i.e., was relatively suppressed). In subsequent runs (sets), separated by short breaks, the magnitude of neural activity recovered, as indicated by the first performance block in the subsequent run. Nevertheless, the evoked signal in M1 was again reduced during the second, repeated performance block. However, as practice continued, these RS effects underwent saturation, and the pattern switched (about the seventh run) so that task repetition induced a relative enhancement (RE). This latter pattern of enhanced neural activity across performance blocks was shown to be specific to the trained sequence and was retained for at least a week (Karni et al., 1995, 1998). A pattern of enhanced physiological signal to repeated experience (RE effects) was described in perceptual systems and proposed to reflect increased attention, active working memory, or the formation of new perceptual and even lexical representation (Soldan, Zarahn, Hilton, & Stern, 2008; Henson et al., 2000; Desimone, 1996; Miller & Desimone, 1994). The within-session, experience-dependent switch in the pattern of physiological activity to repetition across performance blocks in a pair (i.e., from RS to RE) was proposed to reflect on-line learning of the specific movement sequence (Karni et al., 1995). In particular, it was hypothesized that the within-session saturation of RS effects within M1 may be related to familiarity with the component movements of the sequence, which could be retained in long-term memory, whereas RE effects may relate to the recruitment of sequence-specific procedural memory consolidation processes (Karni et al., 1998; see also Hauptmann & Karni, 2002). However, there is no evidence that the persistence of RE within M1 in subsequent sessions reflects off-line memory consolidation processes rather than a certain level of familiarity and motor experience with the component movements of the sequence per se.

The aim of the current study was to test the hypothesis that the pattern of neural signal modulation by task repetition, in motor cortex, constitutes a signature of motor experience and, specifically, of off-line skill memory consolidation.

METHODS

Participants

Thirty-two healthy young adults participated in the current study for payment: 17 participants (19–35 years, mean = 25.7, *SD* = 4.4, five women) in the fMRI group and 15 participants (n = 15, 20–35 years, mean = 25.47, *SD* = 2.73, eight women) in the control group. Both groups were trained and behaviorally tested in an identical protocol, whereas only participants of fMRI group underwent the imaging session. The control group was tested to evaluate the possible effects on subsequent performance of the additional experience afforded during the fMRI session. Two participants from the fMRI group were not included in the analysis: One had difficulties with executing the task in the scanner; another withdrew from the fMRI session for personal reasons. All participants reported no prior history of neurological or psychiatric illness or brain injury and no addiction to drugs, alcohol, or cigarettes (nonsmokers or occasional smokers). Exclusion criteria included current or chronic use of medication, any known learning disabilities, and attention deficit disorder. Only individuals with little (less than 2 years) or no formal music training participated in the current study. Professional typists were excluded as well. All participants affirmed that they had no sleep disorders and reported at least 6 hr of proper night sleep during the study period. Each participant was identified as strongly right-handed using the Edinburgh Handedness Inventory (Oldfield, 1971). Before the study, all participants gave written informed consent according to a

protocol approved by the C. Sheba Medical Center's Ethics Committee.

Design and Procedures

Participants were trained to accurately perform a given five-element finger-to-thumb opposition sequence (FOS), sequence A or sequence B, with their nondominant left hand (Figure 1A). The two FOSes consisted of identical component movements and were mirror-reversed in relation to each other. Thus, the two sequences were matched for the number of movements per digit and differed only in their order. The movement sequence was randomly assigned and then explicitly instructed. If the assigned sequence for training was A (T-FOS), then the sequence B was used as a novel untrained sequence (U-FOS) and vice versa.

Each participant took part in two study phases that took place on two consecutive days during the morning or early afternoon hours and were separated by 18 hr of interval. The interval between the two phases included at least 6 hr of night sleep (self-report; Figure 1B). On Day 1, each participant underwent a pretraining performance test (Pre-T), a structured training session, and an immediate posttraining performance test (Post-T). On the next day, all participants were retested on the performance of the trained sequence that was followed by a test of the untrained sequence (Overnight: T-FOS and U-FOS, respectively) using the trained (left) as well as the untrained (right) hand. The results for the untrained hand will be reported elsewhere. Participants of the fMRI group took part in the scanning session, which immediately preceded the overnight performance tests. Inside the scanner, participants repeatedly performed either the trained or the untrained sequence at an identical auditory-paced rate. Thus, both the rate of the opposition movements and the component movements composing the sequences were matched. The logic of

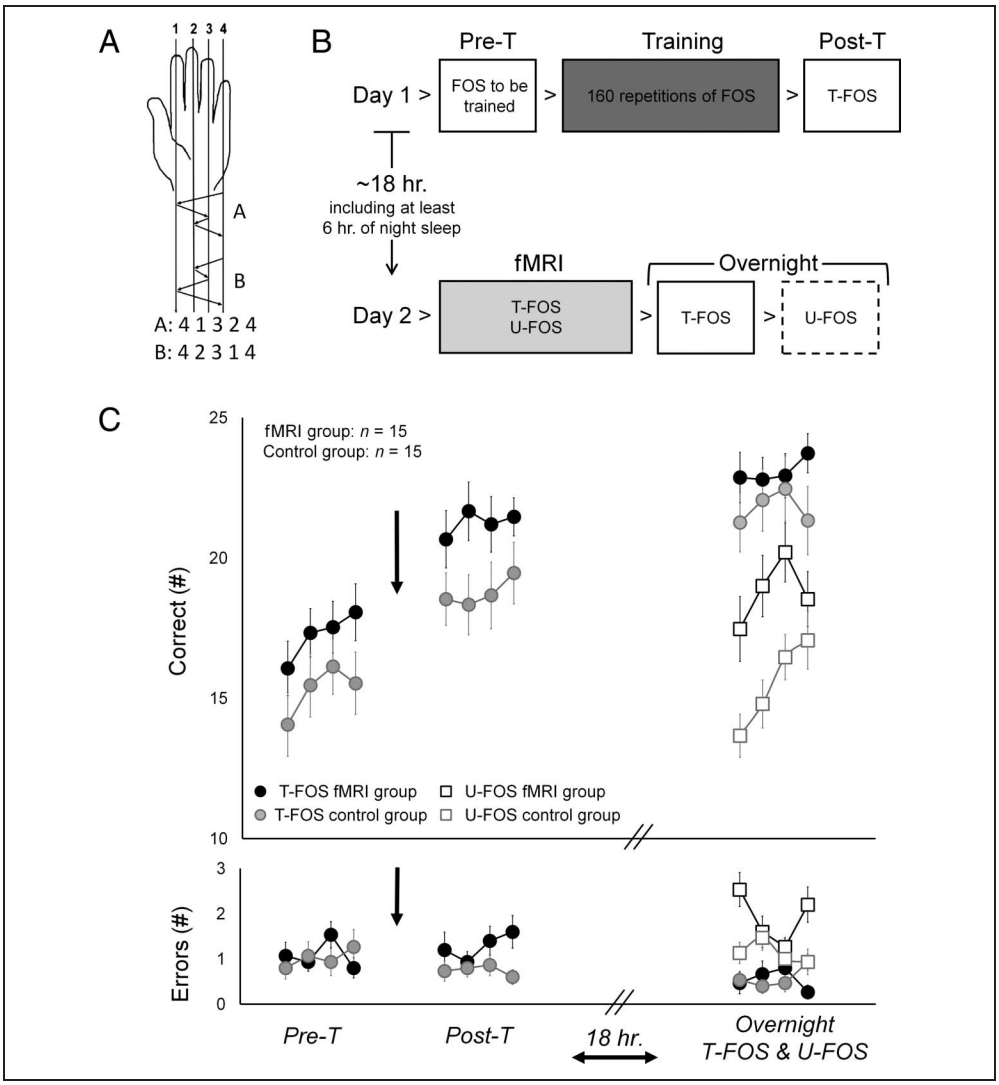

Figure 1. Study design and behavioral results. (A) FOS. The two sequences were matched for number of movements per digit and mirror-reversed in relation to each other (in terms of order). (B) The overall study design. Day 1: a pre-training performance test (Pre-T), a structured training session (Training), and an immediate posttraining performance test (Post-T). Day 2: performance tests of the trained sequence and the untrained sequence (Overnight: T-FOS and U-FOS, respectively). Only participants of the fMRI group took part in the scanning session (fMRI), immediately preceding overnight performance tests. The control (non-fMRI) group was tested to evaluate the effect of the additional experience afforded during the fMRI session on subsequent performance. (C) Performance of fMRI and control group. Two measures of performance are plotted: mean number of correct sequences (top) and mean number of errors (bottom). Each data point represents performance in a 30-sec test-block; arrow, training (160 repetitions of the FOS); bars, *SEM*. Note that experience with the two sequences inside the scanner (fMRI group) did not result in better performance of the T-FOS (compared with controls) in the subsequent test.

this design, using paced component movements, is that differences in fMRI signals would not directly reflect differences in performance speed that were expected to result from training on one but not the other sequence (Korman et al., 2003; Karni et al., 1995). It has been shown that the rate of finger movement execution can significantly (and nonlinearly) affect the evoked BOLD signals in M1 (Rao et al., 1996). In all sessions and tests, the participants performed the instructed movement sequence lying supine. The executing hand was positioned beside the trunk in direct view (palm-up) of a video camera to allow the recording of all digit movements. Visual feedback was not afforded at any time.

Training and Tests

The participants were trained and tested according to a standard FOS training protocol (Korman et al., 2003, 2007). The training session consisted of 160 repetitions of a given sequence divided into 10 training blocks. During the training, the beginning as well as the end of each training block (10 blocks, 16 repetitions of a given sequence per block) were marked by a "READY" and a "STOP" auditory signal, respectively. To ensure that the training experience afforded was identical to all participants, the initiation of each sequence during the training was cued by another auditory signal at a rate of 0.4 Hz (2.5 sec per sequence), which prior studies have shown to be a comfortable rate for young adults (Korman et al., 2003, 2007). Full explicit instruction of the sequence and general encouragement to continue accurate performance were given before each training block. Each performance test (Pre-T, Post-T, Overnight T-FOS and U-FOS) included four blocks of 30-sec duration. Each test-block was followed by a rest interval of 30 sec. Before each test-block, participants were asked to perform the movement sequence, and the block was initiated only after the FOS was accurately reproduced three times in a row. The great majority of participants successfully performed a given sequence three times in a row in their first attempt. The need for a second additional attempt was very rare and was required only when an instructed sequence was novel, that is, during the Pre-T and U-FOS performance tests. Each test-block was initiated by an auditory "READY" signal, after which participants performed the sequence continuously "as fast and as accurately as possible" until a "STOP" signal was given. Participants were instructed not to correct occasional errors. In case an occasional error occurred, an instruction "not to correct errors and to continue the task from the initial movement component of a sequence as smoothly as possible" was given. During the test, no feedback on performance was provided. The participants' performance during the test-blocks was recorded by video camera and scored off-line. For each test-block, two quantitative measures of performance were determined from these recordings: (1) the number of correctly completed sequences as a measure of speed and (2) the number of sequences with ordering errors as a measure of accuracy. The beginning of a sequence was identified by the first component movement; all incorrect opposition movements within a single trial of a sequence were counted as one error (i.e., the measure reflected the number of incorrect sequences).

fMRI Session

Participants were asked to perform one of the two possible sequences of finger movements, the sequence trained the day before (T-FOS) and the novel sequence (U-FOS; Figure 1A), using their trained (left) hand. The untrained (right) hand was subsequently tested as well; the results to be reported elsewhere. The component movements of the sequences were paced by an auditory signal at a fixed rate of 1.66 Hz to control rate-related changes in the BOLD signal (Rao et al., 1996). The paced performance enabled the assessment of signal differences as a function of the order of the component movements (sequence representation) minimizing potential differences between the sequences as well as between individuals driven by spontaneously generated performance rates.

The imaging session consisted of three consecutive runs for each sequence (T-FOS, U-FOS; Figure 3A). In this way, potential effects of proactive interference and contextual retrieval that could be caused by switching between the two sequences were minimized (Kiesel et al., 2010; Cothros, Köhler, Dickie, Mirsattari, & Gribble, 2006). The order of sequences was counterbalanced across participants. Experimental runs (each 144 sec long) were separated by a 1.5- to 2-min break, which included a verbal interaction with the participant. Participants were informed about the target sequence of finger movements, either the T-FOS or the U-FOS, to be performed in the next run, and the run was initiated only after the target FOS was accurately reproduced three times in a row by the participant. Each run consisted of two performance blocks (Perf1 and Perf2) separated by a rest interval of 30 sec. Each block was initiated by an auditory and visual "READY" cue (2 sec), after which participants performed the required FOS continuously in a paced manner for a total of eight repetitions of the FOS (24 sec). The end of the performance was marked by an auditory and visual "STOP" cue (1 sec). Each run began and ended with a rest period of 36 and 24 sec, respectively.

The participants' performance during the fMRI session was recorded by a video camera focused on the performing hand and evaluated by at least one trained observer, on-line and off-line. Performance was scored for accuracy, timing (i.e., initiation and termination of FOS performance), and performance rate. This experiment was realized using Cogent 2000 developed by the Cogent 2000 team at the FIL and the ICN and Cogent Graphics developed

by John Romaya at the LON, Wellcome Department of Imaging Neuroscience, and implemented in Matlab (The Mathworks, Inc., Natick, MA).

Behavioral Data Analyses

For each participant, two performance measures were calculated for each test-block: the number of correctly completed sequences as a measure of speed and the number of sequences with ordering errors as a measure of accuracy. Note that throughout the experiment, participants made very few errors. The detailed report of performance gains and their sequence specificity refers to analyses of the fMRI group data. The control group was tested to evaluate the possible effects on subsequent performance of the additional experience afforded during the fMRI session. Unless otherwise stated, the analyses were designed as within-subject comparisons. Separate repeated-measures ANOVAs for each performance measure with Test and Test-block as within-subject factors were run using Statistical Package for the Social Sciences (SPSS Statistics for Windows, Version 19.0; IBM Corp., Armonk, NY). The results were corrected for nonsphericity violation using the Greenhouse–Geisser adjustment.

To evaluate individual improvements in performance speed, an average number of correct sequences (speed) across the four test-blocks of each performance test was calculated for each participant and converted to percents relative to his or her average speed at Pre-T. Thus, speed in percents achieved by each participant at Post-T is a measure for individual within-session gains in speed. Individual DGs in speed were calculated by subtracting speed in percents achieved at Post-T from that achieved overnight for the T-FOS (i.e., Overnight T-FOS (%) − Post-T (%)). To evaluate individual improvements in accuracy, individual accuracy rates were determined for each performance test as percent of correct sequences (i.e., [average correct (#)] / [average correct (#) + average errors (#)] × 100%). Within-session and DGs in accuracy were calculated accordingly as differences between accuracy rates (i.e., Post-T (%) − Pre-T (%) and Overnight T-FOS (%) − Post-T (%) for within-session and DGs, respectively).

MRI Data Acquisition

fMRI scanning was carried out at the C. Sheba Medical Center, Tel-Hashomer, using a 3T whole-body high-definition system (GE EXCITE 3 HD) equipped with an eight-channel head coil. High-resolution full-brain 3-D structural images were acquired in the axial orientation using a T1*-weighted echo-planar sequence (repetition time = 7.3 msec, echo time = 3 msec, flip angle = 20°, field of view = 256 × 256 mm^2, matrix size = 256 × 256 voxels, voxel size = 1 × 1 × 1 mm^3). BOLD-sensitive functional images were obtained using a gradient echo-planar T2*-sequence (repetition time = 3000 msec, echo time = 35 msec, flip angle = 90°, field of view = 220 × 220 mm^2, matrix size = 64 × 64 voxels, voxel size = 3.4 × 3.4 × 3.4 mm^3, no gap, ascending) with 40 axial oblique slices, covering the whole brain.

MRI Analyses

Preprocessing

The structural and functional images were converted to Neuroimaging Informatics Technology Initiative format using MRIcron (University of South Carolina). Preprocessing and statistical analysis of the data were carried out with Statistical Parametric Mapping (SPM8; Wellcome Department of Cognitive Neurology, London, UK) operating under Matlab R2012a. For each run, the four initial scans were discarded to allow for magnetic saturation and equilibration effects. First, all images were reorientated to stereotactic space. All functional volumes were realigned using a least squares approach and a six-parameter (rigid body) spatial transformation to remove movement-related variance. To correct for nonrigid distortion, realigned functional volumes were unwarped, adjusting for interactions between movement and local field inhomogeneity (Hutton, Andersson, Deichmann, & Weiskopf, 2013; Andersson, Hutton, Ashburner, Turner, & Friston, 2001). This dynamic geometric distortion correction reduces motion-related variance and improves temporal signal-to-noise ratio (Hutton et al., 2013; Andersson et al., 2001). Following segmentation and skull-stripping of the structural data, functional images were coregistered to the individual skull-stripped 3-D anatomical image and normalized to the Montreal Neurological Institute (MNI) space using parameters obtained from the segmentation procedure. The normalized functional images were resampled to voxel dimensions of 3 mm^3. Finally, functional images were spatially smoothed with a Gaussian kernel of 8 mm FWHM to improve the signal-to-noise ratio. Before statistical analyses, head motion artifact detection routine was applied on the preprocessed data using the Artifact Detection Tools (Mazaika, Hoeft, Glover, & Reiss, 2009). No significant head motion artifacts were detected (z threshold = 2, movement threshold = 2 mm, rotation threshold = 0.05 rad).

Whole-brain and ROI Analyses

Statistical analyses of BOLD signal changes were performed using a general linear model (Friston et al., 1995). Individual models were specified separately for each sequence (T-FOS, U-FOS) using a multisession design, and each session included data from a single run (three runs). Regressors of interest (i.e., Perf1 and Perf2) were modeled as a boxcar function with a length of 24 sec convolved with the canonical hemodynamic response function. A high-pass filter of 128 sec was used to remove low-frequency noise. For the block design, inclusion of

motion covariates has a deleterious impact on general linear model sensitivity when even moderate correlation existed between motion and the experimental design (Johnstone et al., 2006). Therefore, movement parameters derived from realignment of the functional volumes were not included as covariates. Following the model parameter estimation, the linear contrasts for each sequence (T-FOS, U-FOS) were defined as follows: Perf versus Rest (i.e., main effect of performance blocks) to assess task-related changes in BOLD-fMRI signal; and Perf2 versus Perf1 to assess changes in BOLD-fMRI signal upon task repetition. To evaluate group effects of task-related activity and repetition, contrast images were introduced into second-level analyses treating participants as a random effect (one-sample t test). To assess the main effect of learning, comparison between the two sequences (T-FOS vs. U-FOS) was performed on the task-related activity (Perf vs. Rest) using a one-way within-subject ANOVA design.

Activation maps were thresholded at $p \leq .001$, uncorrected, and overlaid on the mean structural image of all participants using SPM8 and Functional Imaging Visualization Environment (nmr.mgh.harvard.edu/harvardagingbrain/People/AaronSchultz/OrthoView.html). Statistical inferences were performed on the cluster level using p values family-wise error rate (FWE)-corrected for multiple comparisons over the entire brain or on the peak level using p values FWE-corrected over a small VOI. VOIs for small volume corrections were defined for structures within the motor-related (Halsband & Lange, 2006) and resting state (Buckner, Andrews-Hanna, & Schacter, 2008) networks using Human Motor Area Template (HMAT; Mayka, Corcos, Leurgans, & Vaillancourt, 2006) and anatomical areas of Automated Anatomical Labeling (AAL; Tzourio-Mazoyer et al., 2002). VOIs relevant to the reported statistics are listed in Table 1.

ROI analyses were performed to explore individual differences in neural activity and its relevance to consolidation, using the MarsBar toolbox for SPM (Brett, Anton, Valabregue, & Poline, 2002). The ROIs were defined as spheres with a radius of 6 mm centered within significant clusters resulted from second-level analyses. The extracted betas and contrast values were introduced to SPSS for further analyses.

RESULTS

Behavioral Results

The detailed report of performance gains and their sequence specificity refers to analyses of the fMRI group data. The control group was tested to evaluate the possible effects on subsequent performance of the additional experience afforded during the fMRI session.

Performance Gains for the Trained Sequence

Training on the assigned sequence of movements resulted in both early (within-session) and delayed ("off-line," time-dependent) gains in performance (Figure 1C). Overall, repeated-measures ANOVAs with Test (Pre-T, Post-T and Overnight T-FOS) and Test-block (1–4) as within-subject factors showed significant differences in performance speed as well as in the number of errors across the three tests ($F(1.44, 20.14) = 87.48$, $p < .001$; $F(1.7, 23.85) = 4.82$, $p < .05$, the number of correct and the number of errors, respectively), indicating improvements of both speed and accuracy. There was also a significant effect of Test-block ($F(2.00, 27.99) = 4.08$, $p < .05$; $F(2.51, 35.14) = 3.10$, $p < .05$, the number of correct and the number of errors, respectively), indicating that overall performance tended to improve within the tests.

To test for within-session gains, a post hoc comparison between Pre-T and Post-T was perfomed. There were

Table 1. VOIs Used for Small Volume Corrections

N	*VOI*	*Image Calculation*
1	Right primary sensorimotor cortex	S1(R) + M1(R)
2	Left primary sensorimotor cortex	S1(L) + M1(L)
3	Supplementary motor area	SMA proper(L + R) + pre-SMA(L + R)
4	Right dorsal lateral premotor cortex	PMd(R)
5	Left dorsal lateral premotor cortex	PMd(L)
6	Right ventral lateral premotor cortex	PMv(R)
7	Left ventral lateral premotor cortex	PMv(L)
8	Right medial-temporal lobe	Hippocampus(R) + ParaHippocampal(R)
9	Left medial-temporal lobe	Hippocampus(L) + ParaHippocampal(L)

+ = union; R = right hemisphere; L = left hemisphere; S1 = primary sensory cortex (HMAT); M1 = primary motor cortex (HMAT); SMA proper = supplementary motor area proper (HMAT); pre-SMA = pre-supplementary motor area (HMAT); PMd = dorsal lateral premotor cortex (HMAT); PMv = ventral lateral premotor cortex (HMAT); Hippocampus (AAL), ParaHippocampal = parahippocampal gyrus (AAL).

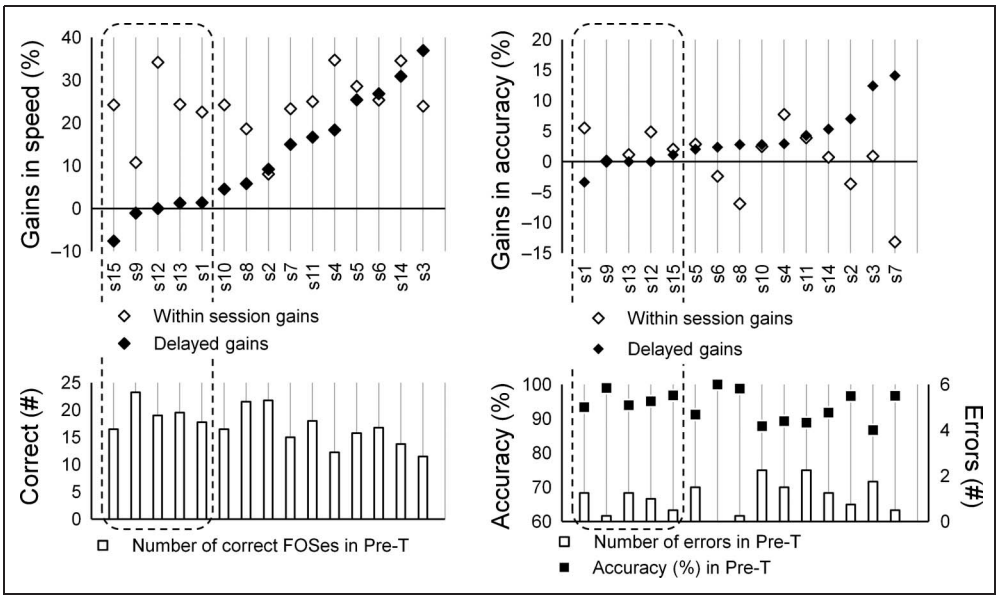

Figure 2. Individual performance of fMRI group. Each vertical line represents data of a single participant (s1–15). Dashed area, participants who failed to express DGs (<2% gains in speed). Individual speeds for each performance test were converted into percents (Pre-T = 100%). Gains in speed (%): within-session gains = Post-T (%), DGs = Overnight T-FOS (%) − Post-T (%) (top left plot). Mean number of correct sequences (speed) at Pre-T (bottom left plot). Individual accuracy rates for each performance test were determined as percent of correct sequences (i.e., [average correct (#)] / [average correct (#) + average errors (#)] × 100%). Gains in accuracy (%): within-session gains = Post-T (%) − Pre-T (%), DGs = Overnight T-FOS (%) − Post-T (%) (top right plot). Mean number of errors and accuracy (%) at Pre-T (bottom right plot).

significant within-session gains in speed with no loss in accuracy ($F(1, 14) = 196.2$, $p < .001$; $F(1, 14) = 0.49$, $p = .5$, the number of correct and the number of errors, respectively). For speed, the effect of test-block was significant before but not immediately after the training ($F(2.17, 30.41) = 4.53, p < .02$; $F(2.26, 31.60) = 1.09, p = .35$ Pre-T and Post-T, respectively), indicating that performance stabilized as a result of practice; however, there was no significant test by test-block interaction. Importantly, additional gains in performance speed developed overnight (Overnight T-FOS compared to Post-T: $F(1, 14) = 14.42, p < .01$). These DGs in speed were paralleled by a significant reduction in the absolute number of errors ($F(1, 14) = 9.18$, $p < .01$). The concurrent gains in both speed and accuracy indicate skill acquisition rather than speed–accuracy tradeoff, that is, participants were not trading one aspect of performance for the other. On average the overnight gains (DGs) in speed were 1.83 ± 0.48 additional sequences per test-block, the number of errors, that were very low throughout, dropped from 1.8 ± 0.26 (mean ± *SEM*, Post-T) to 0.55 ± 0.15 (Overnight T-FOS) per test-block. However, although all of the participants gained in speed within the session, five participants failed to show additional overnight improvements (DGs) in speed and accuracy (Figure 2); in the control group, one participant did not improve in speed overnight. The performance levels of these participants were not exceptional at any of the performance tests. Failure to express DGs overnight was not related to the initial performance levels, the saturation of within-test improvements in speed, or the absolute speed achieved overnight for the T-FOS.

Specificity of Performance Gains

The gains in performance expressed after the training were sequence specific (Figure 1C). Participants were unable to express the gains attained for the T-FOS in the performance of the matching untrained sequence (U-FOS). The performances of the T-FOS at both post-training and overnight test were significantly faster than the performance of the U-FOS ($F(1, 14) = 12.33, p < .01$; $F(1, 14) = 39.47, p < .001$; Overnight U-FOS compared with Post-T and Overnight T-FOS, respectively) as well as significantly more accurate ($F(1, 14) = 5.51, p < .05$; $F(1, 14) = 26.67, p < .001$; Overnight U-FOS compared with Post-T and Overnight T-FOS, respectively). However, a day after the training, the fMRI group performed the U-FOS significantly faster ($F(1, 14) = 6.24, p < .05$) but less accurate than the T-FOS before the training ($F(1, 14) = 11.04, p < .01$).

Effects of Additional Experience in the Scanner

Comparison with the control group (trained and tested with an identical protocol but without the added experience of the neuroimaging session afforded, on both sequences, preceding the overnight performance tests) showed that the fMRI group had no significant advantage

in the performance of the T-FOS at any test (Figure 1C). A repeated-measures ANOVA with Group (fMRI and control) as a between-subject factor showed no significant Group effect ($F(1, 28) = 2.216$, $p = .148$; $F(1, 28) = 1.045$, $p = .32$, the number of correct and the number of errors, respectively) and no significant Group × Test interaction ($F(1.56, 43.65) = 1.578$, $p = .22$; $F(1.79, 50.05) = 1.32$, $p = .28$, the number of correct and the number of errors, respectively). There was, however, a significant main effect of Test ($F(1.56, 43.65) = 168.29$, $p < .001$; $F(1.79, 50.05) = 4.19$, $p < .05$, the number of correct and the number of errors, respectively) indicating robust gains in performance, speed, as well as accuracy, across the three tests for both groups. Significant differences in performance between the two groups were found only for the U-FOS with a significantly faster but less accurate performance in the fMRI group ($F(1, 28) = 6.82$, $p = .01$; $F(1, 28) = 6.97$, $p = .01$, the number of correct and the number of errors, respectively). Thus, experience with the two sequences inside the scanner did not result in better performance of the T-FOS in the subsequent test but had an effect on the performance of the U-FOS.

fMRI Results

During the fMRI session, participants were instructed to perform either the trained or the untrained sequence following paced auditory cue. Each run consisted of two performance phases of the same sequence (T-FOS or U-FOS) designed as blocks (Perf1 and Perf2) and separated by a brief rest interval (Figure 3A).

Neural Correlates of Previous Experience

The second-level analyses were run twice, once on the data from all participants ($n = 15$) and again on the data from only those participants who expressed DGs in speed overnight (DGs group, $n = 10$). Analyses referring to both groups are presented in Figures 3, 4, 5, and 6 and Tables 2 and 3. There were no significant differences in task-related neural activity evoked by the two sequences (T-FOS vs. U-FOS) in both analysis groups. However, activity within extensive cortical areas was modulated differentially across performance blocks for the trained and the untrained sequences. Analyses of the data from all participants showed that, during the T-FOS performance, relative decreases in BOLD-fMRI signals from the first to the second, repeated performance blocks (i.e., RS effects: Perf1 > Perf2) were significant only within the calcarine (Figure 3B, top; Table 2.1). Additional RS effects for the T-FOS were evident within the right cerebellum (Crus1) and small clusters located in the superior parietal gyri but were not significant on the cluster level. The U-FOS, however, induced significant RS effects in multiple brain areas (Figure 3B, bottom; Table 2.2). These RS effects were significant within the SMA, the bilateral pre- and postcentral

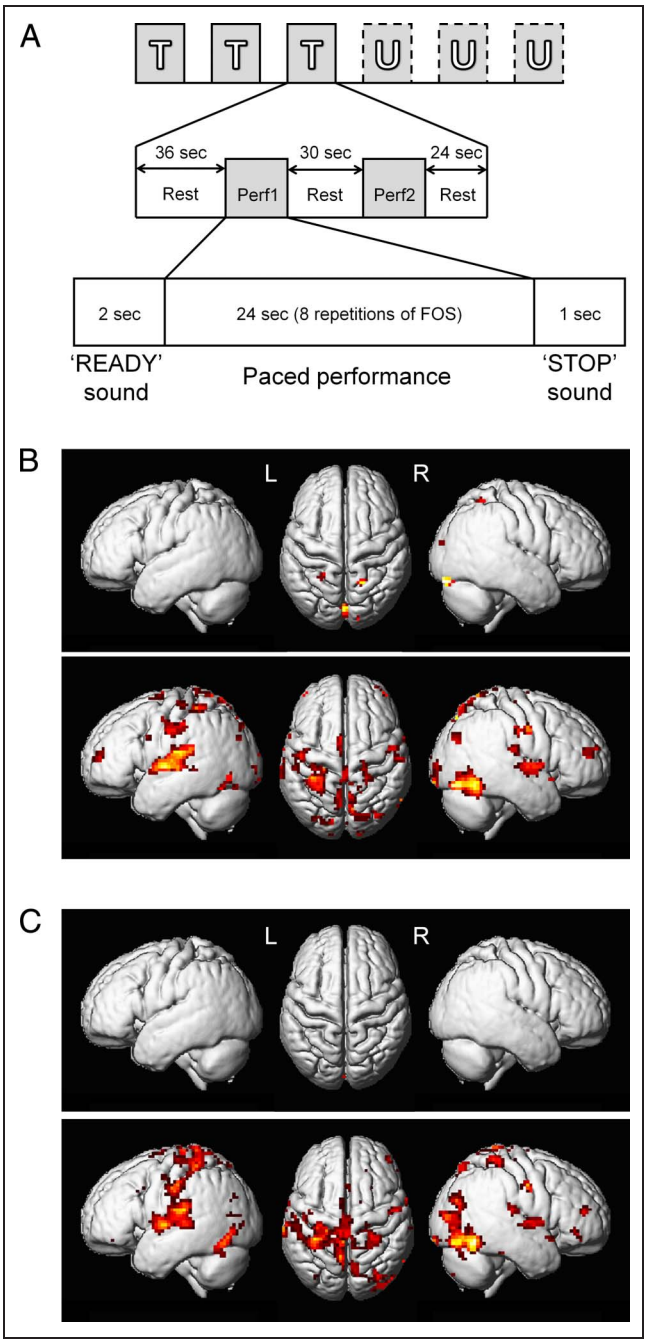

Figure 3. fMRI session design and RS effects. (A) The fMRI session design. T = T-FOS; U = U-FOS; Perf1, Perf2 = two blocks of FOS performance. Note that both sequences were performed at an identical auditory-paced rate of 1.66 Hz per movement. (B, C) Activation maps showing RS effects for all participants ($n = 15$, B) and for participants expressing DGs ($n = 10$, C) for both sequences (top, T-FOS; bottom, U-FOS). Activation maps are shown over the surface rendered from the mean structural image of all participants, thresholded at $p < .001$ (uncorrected).

gyri, as well as the inferior and superior parietal cortex. Additional clusters with significant RS effects for the U-FOS were located in the middle and posterior cingulate cortex as well as within the middle superior and posterior inferior temporal gyri. Identical analyses of the

Table 2. RS Effects (All Participants)

Label		MNI Coordinates			Size (Voxels)	z Score	p
		x	y	z			
1. RS for T-FOS (Perf1 > Perf2)							
Calcarine	R	12	−88	7	149	4.48	$.02_{FWE}$
Calcarine	L	−6	−82	10		3.92	
2. RS for U-FOS (Perf1 > Perf2)							
Precentral	L	−21	−28	58	204	3.51	$.001_{FWE}$
Postcentral*[2]	L	−30	−37	52		4.32	
Parietal_Inf	L	−27	−46	52		3.82	
Parietal_Sup	L	−33	−46	58		3.50	
Precentral*[5]	L	−39	−7	49	108	3.90	$.03_{FWE}$
Postcentral	L	−45	−13	40		3.47	
Parietal_Inf*[2]	L	−45	−25	37		3.77	
Precentral*[6]	R	48	−7	40	70	3.97	.01
Precentral	R	21	−19	64	271	3.29	$< .001_{FWE}$
Postcentral	R	21	−43	49		4.20	
Postcentral*[1]	R	21	−28	55		4.02	
Cingulum_Mid	R	9	−31	46		4.17	
Cingulum_Mid	R + L	0	−37	46		3.87	
Supp_Motor_Area*[3]	L	−3	2	64	59	3.81	.02
Parietal	R	21	−79	52	239	4.34	$< .001_{FWE}$
Precuneus	R	6	−76	58		3.70	
Precuneus	L	–	−55	70		3.56	
Temporal_Sup	L	−54	−10	1	425	4.51	$< .001_{FWE}$
Temporal_Mid	L	−51	−37	−2		3.39	
SupraMarginal	L	−60	−28	22		3.55	
Insula	L	−36	−19	4		3.23	
Temporal_Inf	R	51	−58	−17	367	4.31	$< .001_{FWE}$
Temporal_Mid	R	60	−64	−2		3.39	
Occipital_Inf	R	42	−76	−17		4.01	
Cerebellum_6	R	21	−79	−17		3.39	
Rolandic_Oper	R	63	5	4	95	4.00	$.04_{FWE}$
Temporal_Sup	R	57	−4	1		3.99	
Calcarine	L	−3	−100	−14	123	3.93	$.02_{FWE}$
Calcarine	R	15	−94	1		3.87	
Lingual	R	15	−97	−11		3.38	

Labeling clusters (the most significant local maxima for each area) obtained from activation maps thresholded at $p < .001$ (uncorrected) using AAL (Tzourio-Mazoyer et al., 2002). *[N]Significant peak at $p < .05$ level FWE-corrected over a small VOI; [N] refers to a VOI used for small volume correction as listed in Table 1; p_{FWE} = cluster-level FWE-corrected over the entire brain; p = cluster-level uncorrected.

DGs group showed no significant RS effects for the T-FOS and similar RS effects during the U-FOS performance (Figure 3C).

Importantly, relative increases in BOLD-fMRI signals across performance blocks (i.e., RE effects: Perf1 < Perf2) were found only for the T-FOS (Figures 4 and 5, Table 3). The analysis of data from all participants showed significant RE effects within a dorsal part of the right (contralateral) sensory-motor cortex somewhat lateral to the hand knob (lateral M1; Figure 4A) and bilaterally in the medial-temporal lobe (MTL)—an area including the parahippocampal cortex and the hippocampus (Figure 5). In a similar analysis restricted to the DGs group REs upon repeated performance of the T-FOS occurred in the right sensory-motor cortex and included the knob of the right precentral gyrus, that is, the M1 hand area (Yousry et al., 1997; Figure 4B). Note that the RE effects in bilateral MTL reflected smaller negative BOLD signals versus rest upon task repetition (Figure 5, bottom plots). However, within the right sensory-motor

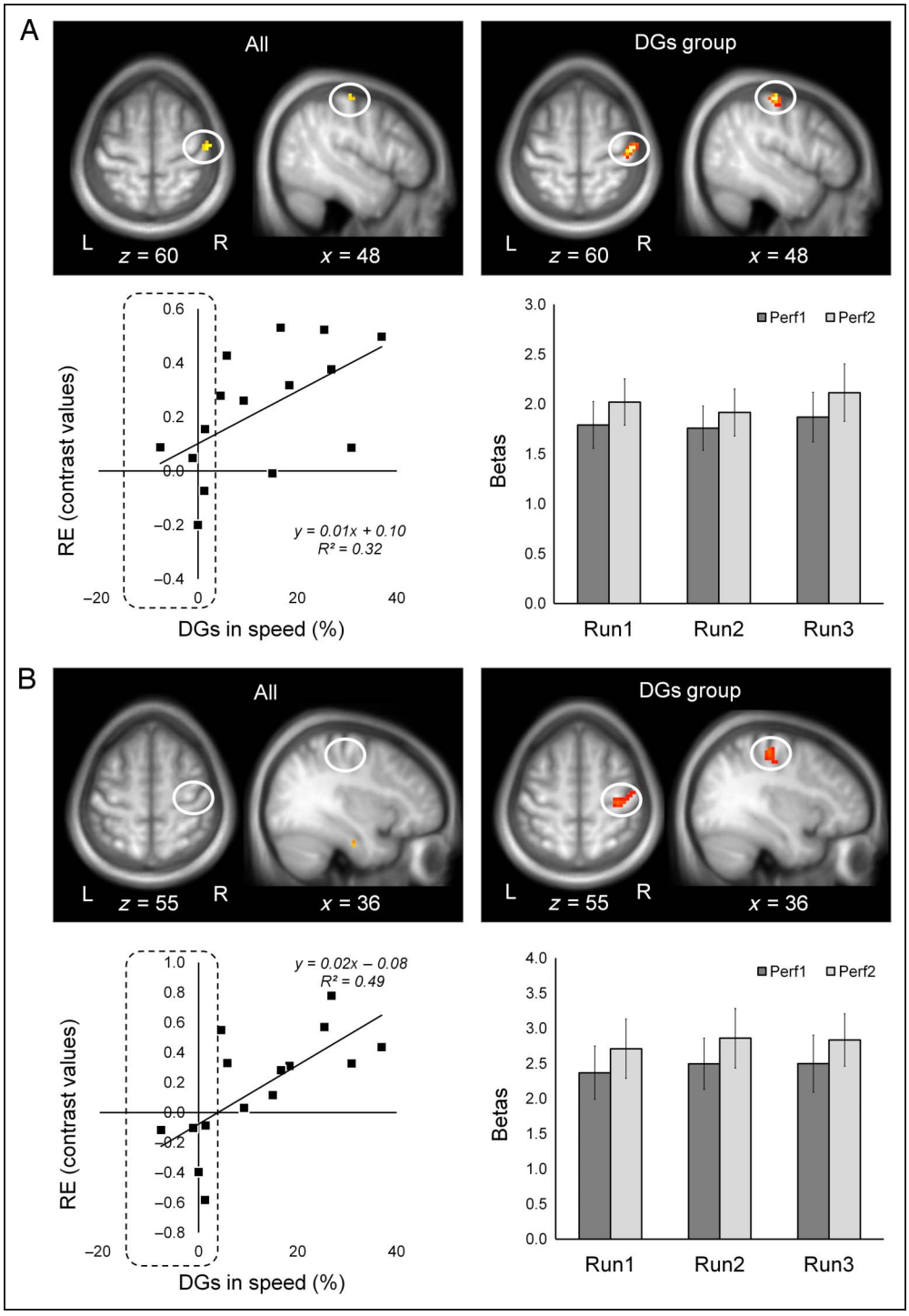

Figure 4. RE effects within the right (contralateral) M1. Activation maps showing RE effects for all participants (n = 15, top left) and for participants expressing DGs (n = 10, top right). Activation maps are shown over the mean structural image of all participants, thresholded at $p < .001$ (uncorrected). Individual contrast values for RE effects (Perf1 < Perf2, y axis) versus DGs (%, x axis) (left plots); dashed area, participants who failed to express DGs (<2% gains in speed). Mean signals (betas) for each performance block of the T-FOS (right plots); bars, *SEM*. Contrast values and mean signals (betas) were extracted from spherical ROIs with a radius of 6 mm. (A) lateral M1, sphere ROI centered at [48 −16 60], mean signals (betas) refer to the data from all participants (right plot). (B) M1 hand area (knob), sphere ROI centered at [36, −25, 55], mean signals (betas) refer to the data from DGs group (right plot). Note that RE effects within the knob of the central gyrus were induced only in participants expressing DGs.

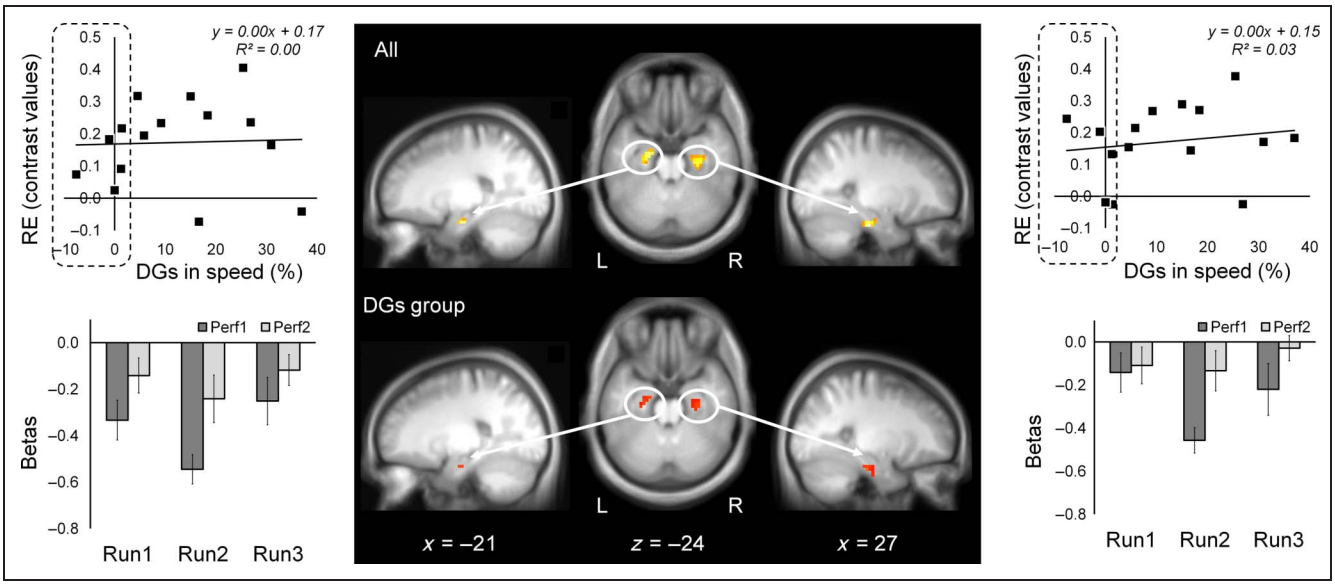

Figure 5. RE effects within MTL. Activation maps showing RE effects for all participants (n = 15, top middle) and for participants expressing DGs (n = 10, bottom middle). Activation maps are shown over the mean structural image of all participants, thresholded at $p < .001$ (uncorrected). Individual contrast values for RE effects (Perf1 < Perf2, y axis) versus DGs (%, x axis) (top plots); dashed area, participants who failed to express DGs (<2% gains in speed). Mean signals (betas) for each performance block of the T-FOS for all participants (bottom plots); bars, *SEM*. Contrast values and mean signals (betas) were extracted from spherical ROIs with a radius of 6 mm. Left MTL, sphere ROI centered at [−21, −13, −23] (left); right MTL, sphere ROI centered at [27, −22, −26] (right).

cortex, the RE effects were the result of enhanced positive BOLD signals versus rest (Figure 4, right plots).

ROI and Correlation Analyses—The Expression of DGs

ROI analyses were performed on spheres centered within the clusters showed significant RE effects (Figures 4 and 5). The choice of spheres was driven by the findings of two separate local maxima within M1 in the group analyses; note that the focus within the M1 hand knob was significant only in the DGs group. To this end, mean signals (betas) for each block as well as individual contrast values for the main task effect (Perf > Rest) and repetition enhancement effect (Perf1 < Perf2) were extracted from each ROI. Mean betas for each block for both sequences (T-FOS and U-FOS) are shown in Figure 6. Repeated-measures ANOVAs with Task (T-FOS and U-FOS) and Repetition (Perf1 and Perf2) as within-subject factors,

Table 3. Repetition Enhancement Effects

		All Participants (n = 15)				*DGs Group (n = 10)*			
		MNI Coordinates				*MNI Coordinates*			
Label		*x*	*y*	*z*	*p*	*x*	*y*	*z*	*p*
1. RE for T-FOS (Perf1 < Perf2)									
Postcentral (+)	R	51	−19	64	.02^{*1}	51	−19	64	.05$_{FWE}$
Precentral (+)	R	–	–	–	–	36	−25	55	∧
ParaHippocampal (−)	R	27	−22	−26	< .01^{*8}	27	−22	−26	.05^{*8}
Hippocampus (−)	L	−21	−13	−23	< .01^{*9}	–	–	–	–
ParaHippocampal (−)	L	–	–	–	–	−18	−13	−23	.08^{*9}
2. RE for U-FOS (Perf1 < Perf2)									
No significant results	–	–	–	–	–	–	–	–	–

Labeling clusters obtained from activation maps thresholded at $p < .001$ (uncorrected) using AAL (Tzourio-Mazoyer et al., 2002). p_{FWE} = cluster-level FWE-corrected over the entire brain; $p^{*[V]}$ = peak-level FWE-corrected over a small VOI, $^{[V]}$ refers to a VOI used for small volume correction as listed in Table 1; ∧ = for the cluster-level p values, areas within the same cluster as area listed above; (+) = increased task-related activity versus rest; (−) = decreased task-related activity versus rest.

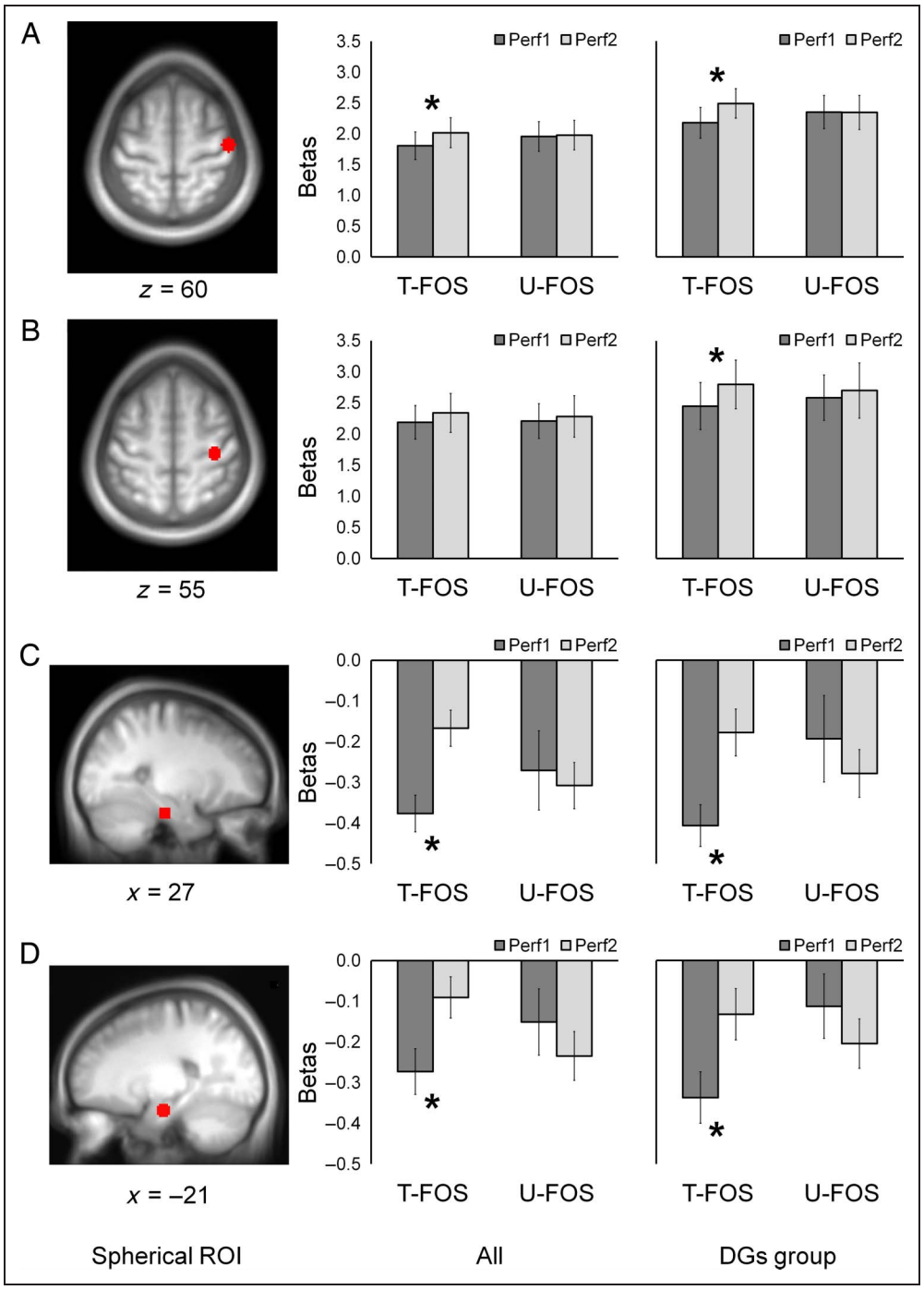

Figure 6. Mean betas extracted from regions with RE effects. Spherical ROIs with a radius of 6 mm centered within clusters with significant RE effects are shown over the mean structural image of all participants. Mean signals (betas) for each performance block (Perf1 and Perf2) and each sequence (T-FOS and U-FOS) averaged across three runs for all participants (left plots) and DGs group (right plots): bars, *SEM*. *$p \leq .01$ level. (A) Rght (contralateral) lateral M1, sphere ROI centered at [48 −16 60]. (B) Right (contralateral) M1 hand area (knob), sphere ROI centered at [36, −25, 55]. (C) Left MTL, sphere ROI centered at [−21, −13, −23]. (D) Right MTL, sphere ROI centered at [27, −22, −26].

in all participants, showed significant RE effect within the lateral M1 with a trend toward Repetition × Task interaction ($F(1, 14) = 7.22, p < .05$; $F(1, 14) = 3.64, p = .08$, Repetition and Repetition × Task interaction, respectively) as well as significant Repetition × Task interaction within the MTL bilaterally ($F(1, 14) = 7.03, p < .05$; $F(1, 14) = 9.07, p < .01$, left and right MTL, respectively). Post hoc analyses performed separately for each movement sequence, in line with the whole-brain analyses, showed that RE effects within the lateral M1 and MTL were significant for the T-FOS ($F(1, 14) = 12.10, p < .01$; $F(1, 14) = 42.52$, $p < .001$; $F(1, 14) = 30.69, p < .001$, lateral M1, left and right MTL, respectively) but were not significant for the U-FOS ($F(1, 14) = 0.20, p = .65$; $F(1, 14) = 0.18, p = .68$; $F(1, 14) = 1.33, p = .27$, lateral M1, left and right MTL, respectively). Significant RE effects within the M1 hand area were found only for the DGs group with significant Repetition × Task interaction (Repetition: $F(1, 9) = 10.31, p = .01$; Repetition × Task: $F(1, 9) = 4.87, p = .055$). Post hoc analyses performed separately for each sequence showed that RE effects within the M1 hand area were restricted to the T-FOS within the DGs group ($F(1, 9) = 23.05, p = .001$; $F(1, 9) = 1.25, p = .29$, T-FOS and U-FOS, respectively).

The linear correlation analyses revealed the existence of a strong positive relationship between overnight improvements in speed (DGs) and RE effects during the T-FOS performance within the right M1 hand area (Figure 4B, left plot; Table 4). Moreover, in line with the results of the whole-brain and ROI analyses on the group level, only participants who expressed DGs were characterized by increased BOLD signal upon repetition within this region (i.e., positive values for RE effects within the M1 hand area; Figure 4B, left plot). There was also positive relationship between DGs and RE effects within the right lateral M1, but this effect failed to be significant after a Bonferroni correction (Figure 4A, left plot; Table 4). However, the magnitude of RE effects during the T-FOS performance within the MTL was not correlated with the expression of DGs (Figure 5, top plots; Table 4). No significant correlations were found between repetition effects (Perf1 < Perf2) and participants' absolute speed achieved overnight in any of the ROIs tested (Table 4). There were also no significant correlations between the neural activity evoked in the four ROIs (Perf > Rest) and either the DGs or the absolute speed achieved overnight for the T-FOS; there was a positive correlation of activity within the lateral M1 and the DGs, but this effect failed to be significant after a Bonferroni correction (Table 4).

DISCUSSION

The current results suggest that the pattern of neural activity modulation upon task repetition (across performance blocks in a pair), rather than the magnitude of the average evoked signal per se, reflected the effectiveness of overnight memory consolidation following motor learning. A clear pattern of RE in the evoked BOLD-fMRI signals characterized the paced performance of the sequence of finger-to-thumb opposition movements intensively trained a day earlier. These RE effects were observed within the sensory-motor cortex contralateral to the performing hand as well as in the MTL bilaterally. Moreover, the magnitude of RE effects within the contralateral M1 correlated with the DGs in the performance of the T-FOS. Taken together these results suggest that the modulation of the BOLD signal upon task repetition constitute a reliable neural signature for off-line memory consolidation processes.

The performance of the trained sequence a day after the initial training was significantly faster and more accurate than the performance of the untrained sequence, composed of identical opposition movements (Figure 1C). During the scanning session these differences in the rate of sequence executions were minimized by requiring participants to perform the component movements at a comfortable but externally paced rate. Thus, the differences in neural activity were not directly related to faster task execution but rather reflected differences in the order of the component movements—trained versus untrained (Karni et al., 1995). The brain areas activated for the T-FOS were not different from those activated for the U-FOS. On the other hand, upon repetition after the brief rest interval, the U-FOS induced significant reductions in the BOLD signal within extensive brain areas, whereas reduced activity upon repeated performance of the T-FOS was significant only within the calcarine (presumably reflecting the fact that the visual cues for task performance were novel, i.e., presented to the

Table 4. Correlations between Contrast Values and Behavioral Measures for the T-FOS

ROI	*RE vs. DGs (%)*	*RE vs. Correct (#)*	*Act vs. DGs (%)*	*Act vs. Correct (#)*
Right lateral M1 centered at [48, −16, 60]	$r = .56$	$r = .02$	$r = .61$	$r = .18$
	$p = .03$*	$p = .95$	$p = .02$*	$p = .54$
	$p_{cor} = .11$		$p_{cor} = .08$	
Right M1 hand area centered at [36, −25, 55]	$r = .70$	$r = .12$	$r = .47$	$r = .04$
	$p < .01$**	$p = .68$	$p = .08$	$p = .89$
	$p_{cor} = .01$**			
Right MTL centered at [27, −22, −26]	$r = .17$	$r = .24$	$r = .47$	$r = .20$
	$p = .55$	$p = .40$	$p = .08$	$p = .47$
Left MTL centered at [−21, −13, −23]	$r = .45$	$r = .02$	$r = .24$	$r = .42$
	$p = .87$	$p = .95$	$p = .39$	$p = .12$

RE = repetition enhancement effects (Perf1 < Perf2); Act = task-related activity (Perf > Rest); DGs (%) = DGs in speed (Overnight T-FOS (%) − Post-T (%)); correct (#) = the average number of correct sequences achieved overnight during the T-FOS performance test; p_{cor} = values corrected for multiple tests (four correlation analyses for each ROI) using Bonferroni adjustments.

*$p \leq .05$ level.

**$p \leq .01$ level.

participants for the first time during the imaging session; Grill-Spector et al., 1999). RS for the untrained sequence was apparent in most of the task-related areas, in line with previous studies (Hamilton & Grafton, 2009; Grill-Spector et al., 1999; Buckner et al., 1998). RS is considered a neural correlate of behavioral priming and novelty (Grill-Spector et al., 2006; Henson, 2003; Schacter & Buckner, 1998; Wiggs & Martin, 1998; Desimone, 1996) and was observed in both block design (Grill-Spector et al., 1999; Karni et al., 1995; Raichle et al., 1994; Squire et al., 1992) and event-related (Sayres & Grill-Spector, 2006; Henson et al., 2000; Buckner et al., 1998) studies across various time intervals (Grill-Spector et al., 1999; Fahy, Riches, & Brown, 1993; Miller et al., 1991). Repetition-related reductions in neural activity may reflect a process of selection whereby neurons that poorly represent the task-relevant features of the initial experience drop out upon repeated experience (Desimone, 1996; Miller et al., 1993). From this point of view, only cells carrying critical information for task performance continue to produce robust activation at later stages of practice. As practice continues, task-relevant units may actually be enhanced after a certain amount of experience (practice; Karni et al., 1995, 1998) offsetting the initial suppression–selection process (Desimone & Duncan, 1995). Novelty and priming effects in both behavior and the brain are of a transient nature and, as a rule, saturate after a rather limited number of repetitions (Hauptmann & Karni, 2002; Karni et al., 1995, 1998; Raichle et al., 1994; Karni & Sagi, 1993; Miller et al., 1991). Training beyond the saturation of repetition priming was proposed as a critical requirement for the expression of DGs in performance (Hauptmann & Karni, 2002; Karni et al., 1998).

In the current study, all participants were trained according to a standard FOS training protocol to ensure adequate practice (Korman et al., 2003, 2007). Rapid changes in performance were observed before the training (Pre-T); these effects were saturated as a result of practice (Post-T). Given the identical structure of the two sequences, the counterbalancing and previous imaging studies (Karni et al., 1995, 1998), it is reasonable to assume that the initial performance of the to-be-trained sequence was characterized by RS effects. These effects were likely to be saturated by the end of the training session (Karni et al., 1995, 1998). The imaging results of the current study clearly indicate, therefore, that on the day after the initial training session the saturation of RS for the T-FOS was maintained in all participants. Thus, the training afforded in the current study was sufficient for saturating RS effects, for the T-FOS, irrespective to the ability to express DGs. Nevertheless, five participants failed to express DGs in performance overnight (Figure 2). Failure to express DGs overnight was not related to the initial performance levels, the saturation of within-test improvements in speed or the absolute speed achieved overnight for the T-FOS. Thus, insufficient training or relatively slow or inaccurate performance cannot explain the lack of additional gains overnight. The magnitude of DGs in motor sequence tasks was shown to be sleep-dependent regardless to the time of day during which training, retest, and sleep were afforded (Korman et al., 2003, 2007; Nishida & Walker, 2007; Fischer et al., 2002; Walker et al., 2002). Failures to express DGs may have resulted from individual differences in the recruitment of the motor network in general and of M1 in particular during the training experience (Steele & Penhune, 2010). However, individual differences in posttraining experience (Tibi, Eviatar, & Karni, 2013; Balas, Roitenberg, Giladi, & Karni, 2007; Brown & Robertson, 2007) and in susceptibility to interference (Korman et al., 2007; Brashers-Krug, Shadmehr, & Bizzi, 1996) as well as differences in posttraining sleep (Korman et al., 2003, 2007; Fischer et al., 2002; Walker et al., 2002) and sleep structure (Barakat et al., 2013; Karni, Tanne, Rubenstein, Askenasy, & Sagi, 1994; Maquet, 2001) may critically affect the expression of DGs.

The current results indicate that the failure to express overnight DGs was related to the absence of RE within the M1 hand representation area across performance blocks of the T-FOS. There is evidence for focal increased excitability, paralleled by surround inhibition within the motor system that contributes to the selection of voluntary movements (Sohn & Hallett, 2004). Horizontal intracortical axon collaterals that interconnect the entire M1 hand representation area (Huntley & Jones, 1991) may be involved in the coordination of patterns of motor output to multiple muscles. Although much shorter time intervals (compared with the rest interval within each run afforded in the current study) were used in animal studies, there is evidence for summation (enhancement) effects suggesting local modulations of interconnections under some repeated activation protocols (Baker, Olivier, & Lemon, 1998). Given the notion of sleep-dependent resetting of the overall excitatory–inhibitory balance during the consolidation phase (Tononi & Cirelli, 2006), we conjecture that the local circuitry underlying the execution of the trained movement sequence may undergo such resetting during a successful consolidation interval that includes sleep. Given our behavioral and imaging results, this resetting is presumably specific for the trained and successfully consolidated sequence of movements. Nevertheless, there were no RS effects in the contralateral motor hand area for the execution of the same movements arranged in a different, novel, order (U-FOS; Figures 3, bottom, and 6B). This absence of RS effects within the contralateral motor hand area a day after training may reflect the prior experience with movement components of this sequence. The results of Karni et al. (1995, 1998) have shown that, during the initial phase in the motor skill acquisition, some of the repetition-dependent BOLD signal modulations (RS) in M1 contralateral to the performing hand could be ascribed to the overlap in the representation of the component movements. Thus, RS effects may reflect the identity of the component movements irrespective of their order when

both sequences are introduced concurrently (Karni et al., 1998). In the current study, the untrained sequence was introduced to the participants after the trained sequence was extensively practiced a day earlier. Thus, the novelty of the component movements of the U-FOS in terms of M1 activity may have been reduced.

It is not known whether the modulation of neural activity upon task repetition is dependent on the length and nature of the rest interval inserted between the two performance intervals. The number and rate of task iterations (the block length) may also be important factors in the modulation of BOLD signal to task repetition. Adaptation studies in the visual system showed that the magnitude of repetition effects was increased with longer exposures to the stimuli (Grill-Spector et al., 1999) and decreased with longer ISIs (Henson et al., 2000; Grill-Spector et al., 1999). Single cell recordings in studies using the DMS task, with multiple intervening items between the sample and matching test stimulus, showed that activity within visual processing regions exhibited RS as well as match enhancement (Miller & Desimone, 1994; Miller et al., 1991, 1993). These effects bridged up to six intervening stimuli (~8 sec) within a trial (Miller et al., 1991). However, there was no modulation of responses when a sample on one trial was repeated on the next trial following the intertrial interval (1–2 sec), ruling out temporal contiguity alone as the explanation of the sample-match effects (Miller & Desimone, 1994; Miller et al., 1993). It has been suggested that the failure of repetition effects to carry across trials in the DMS task indicates the presence of an active reset mechanism that reboots the memory traces to avoid cross-trial interference or to prime neural cells with the memory of a sample (Miller et al., 1993). In the current study, repetition enhancement effects across blocks in a pair could be reproduced in successive runs, which were separated by breaks (1.5–2 min) dedicated to verbal interaction with participants (Figures 4 and 5). This suggests that such an interval was sufficient to recover the repetition effects in line with previously reported results (Karni et al., 1995, 1998). One cannot rule out that the verbal interaction with the participants during the break between runs was also a factor in the recovery of the repetition effects.

There is consistent evidence from animal and human studies that M1 plays a central role in the long-term retention of motor skills following multisession training (Mandelblat-Cerf et al., 2011; Matsuzaka, Picard, & Strick, 2007; Floyer-Lea & Matthews, 2005; Kleim et al., 2004; Penhune & Doyon, 2002; Karni et al., 1995, 1998; Kleim, Barbay, & Nudo, 1998; Nudo, Milliken, Jenkins, & Merzenich, 1996). Moreover, it has been recently shown that extended practice of the motor skill stabilizes the M1 activity pattern (Huang et al., 2013) and is associated with reduced metabolic activity in M1 (Picard, Matsuzaka, & Strick, 2013). However, a number of studies suggest that regions other than M1, for example, cerebellum and BG (Lehéricy et al., 2005; Doyon et al., 2002), as well as the hippocampus (Albouy et al., 2008), contribute to early phases of acquisition of motor skill. Although some studies reported an increase in M1 activation even after a single session of training (Albouy et al., 2012; Orban et al., 2010; Honda et al., 1998), these effects can be ascribed to enhance task execution, for example, an increase in speed of performance, rather than to the effects of sequence learning per se (Orban et al., 2010; Honda et al., 1998). In the current study, the rate of sequence execution during scanning was identical in all participants and for both sequences (paced performance). Moreover, there was no significant correlation between the individuals' actual performance speed for the T-FOS overnight and the magnitude of either average activity or repetition effects in M1.

Time-dependent changes in performance, such as the expression of DGs, were hypothesized to reflect neuron-level memory consolidation processes (Karni, 1996; Karni & Sagi, 1993). Recent studies, using in vivo transcranial two-photon microscopy to examine changes within pyramidal neurons in the mouse motor cortex, showed that synaptic connections rapidly respond to motor experience in a novel task with the formation of new dendritic spines (Xu et al., 2009; Yang et al., 2009). The extent of spine remodeling in motor cortex correlated with delayed behavioral improvement (Xu et al., 2009; Yang et al., 2009). Moreover, new spines that were induced during the early stage of learning tended to stabilize (Xu et al., 2009), suggesting lasting experience-specific synaptic reorganization within motor cortex.

Studies of repetitive TMS indicate that M1 is implicated in the initiation of long-term motor memory (Richardson et al., 2006), including presumably early stages (5–30 min after training) of motor skill consolidation following training (Hotermans et al., 2008; Baraduc, Lang, Rothwell, & Wolpert, 2004; Muellbacher et al., 2002). However, after practice on the motor sequence task inhibition to the contralateral M1, induced by repetitive TMS, abolished only the daytime improvements (Robertson et al., 2005) and did not fully abolish the early posttraining boost effect in performance (Hotermans et al., 2008). Brain structures other than M1 may have a role in off-line memory processes: importantly, the corticostriatal networks (Doyon & Benali, 2005; Lehéricy et al., 2005) and even interactions with the hippocampus (Albouy et al., 2008, 2013; Hobson & Pace-Schott, 2002).

A recent study (Steele & Penhune, 2010) suggests that the recruitment of M1 during the initial training session predicts the overnight improvement of performance. However, Steele and Penhune (2010) found no significant difference in the average M1 activation overnight, that is, before and after the consolidation phase following initial training—a result that is in line with the current findings. Thus, the magnitude or extent of BOLD signals within M1 may not reflect familiarity with a movement sequence or procedural memory consolidation processes; both conditions, however, are reflected in the pattern of neural activity upon task repetition.

There were T-FOS-specific RE effects in the MTL. One should note that the MTL modulation pattern is somewhat different from that of M1 because the evoked signals were negative (compared with rest). Thus, the repetition of the T-FOS induced less suppression of the MTL activity. The MTL is part of the resting state (default) network, exhibiting consistent activity decreases during task performance compared with rest (Buckner et al., 2008; Raichle et al., 2001). The suppression of the resting state network has been shown to be reduced when a task becomes more familiar (McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003), less difficult (McKiernan et al., 2003), and well practiced (Kincses et al., 2008). The decrease in task-induced deactivation as a function of task repetition was previously reported during repeated exposure to visual stimuli of familiar and unfamiliar objects and may reflect reduced requirements for attention and cognitive control (Soldan et al., 2008). It has been suggested that cognitive control may impede procedural mnemonic processes (Brown & Robertson, 2007). Recent studies suggest that hippocampal activity may be correlated with the ability to engage procedural memory processes (Albouy et al., 2008, 2013). We propose that the emergence of RE within M1 contralateral to the performing hand and the decreased deactivations upon task repetition within the MTL reflect two aspects of procedural memory: the formation of a differential neural representation for the trained sequence and the decreased demand on control and attention processes in the execution of the trained sequence, respectively.

Altogether, our results suggest that delayed performance gains, but not absolute performance levels, are related to changes in the way the brain repeatedly generates a movement sequence after its consolidation in memory. We propose that procedural memory consolidation processes may affect the excitation–inhibition balance within cortical representations of the trained movements; this new balance is better reflected in repetition effects than in the average level of evoked neural activity. We conjecture that the local circuitry underlying the execution of the trained movement sequence may undergo a resetting during a successful consolidation interval. This resetting relates to the movement sequence rather than the component movements. Thus, the mode of the neural activity in motor cortex to repeated task iterations constitutes a neural signature for motor experience and specifically for the effectiveness of motor memory consolidation processes.

Acknowledgments

E. G. was partially supported by a fellowship from the E. J. Safra Brain Research Center for the Study of Learning Disabilities. We thank Tammi Kushnir, Ph.D., director of research at the C. Sheba Medical Center, for her technical and administrative support.

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