Preparatory activity in motor cortex reflects learning of local visuomotor skills

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In humans, learning to produce correct visually guided movements to adapt to new sensorimotor conditions requires the formation of an internal model that represents the new transformation between visual input and the required motor command. When the new environment requires adaptation to directional errors, learning generalizes poorly to untrained locations and directions, indicating that such learning is local. Here we replicated these behavioral findings in rhesus monkeys using a visuomotor rotation task and simultaneously recorded neuronal activity. Specific changes in activity were observed only in a subpopulation of cells in the motor cortex with directional properties corresponding to the locally learned rotation. These changes adhered to the dynamics of behavior during learning and persisted between learning and relearning of the same rotation. These findings suggest a neural mechanism for the locality of newly acquired sensorimotor tasks and provide electrophysiological evidence for their retention in working memory.

During performance of visually guided movements, the brain transforms visuospatial information into appropriate motor commands (*i.e.*, visuomotor transformation)[1–3]. Psychophysical studies suggest that when humans learn a new visuomotor transformation, an internal model of limb dynamics and kinematics is modified. Such a process would allow the motor system to achieve the desired outcome—reaching toward a visible goal—under the new conditions[4–6]. The learning of a new motor skill that requires adaptation to directional errors generalizes poorly across movement directions[7,8], workspace[9] and posture[10]. This suggests a reliance on neuronal elements with localized spatial fields[4,9,11], analogous to receptive fields in sensory systems. Such elements are common in many parts of the motor system, including the primary motor cortex where the majority of cells show directional tuning[12,13]. A few studies have investigated cortical activity while monkeys adapted to generalized novel dynamic[14–16] or kinematic[17] fields, but none have addressed the issue of learning a specific, local field. We reasoned that such learning would induce a specific and local neuronal change.

Evidence that the primary motor cortex (M1) is involved in motor learning[18] comes from both cellular[19,20] and human studies. Evidence for M1 involvement during the initial phases of learning a new motor skill comes from studies using functional neuroimaging[21,22] and transcranial magnetic stimulation (TMS)[23]. Further, behavioral and imaging studies show that consolidation occurs after learning a new motor skill, a process where the newly learned behavior shifts from an unstable to a stable state[24,25]. The early phases of consolidation were recently linked to the human primary motor cortex[26], suggesting its involvement in retaining the information in working memory until it is further redistributed for long-term memory storage. These results suggest that both during and immediately after motor learning, activity in

motor cortex should reflect recent learning and support the retention of the learned behavior.

To search for electrophysiological evidence of learning and retention of local visuomotor skills, we recorded neuronal activity in motor cortex before, during and immediately after monkeys learned a rotational mapping to one target in space. Our behavioral results indicate that monkeys, as humans, show poor generalization of the learned transformation to other directions of space. Exploring the related neuronal changes, we found that the tuning curve of neurons with preferred direction close to the learned direction was altered during the course of learning. These cells showed a relative increase in their firing rate, and did so only when the monkeys moved toward the learned direction and mainly during the preparation for movement. According to behavioral measures, the monkeys retained the learned task in working memory for at least one hour, and the altered tuning curves were indeed sustained during that time.

RESULTS

We devised a task to address several points of interest in motor learning. To test for local learning, we used only one target location (90°) during the learning epoch. We also used visuomotor rotational transformations, proposing that the directional tuning found in motor cortex can be linked to kinematic perturbations that introduce directional errors. To achieve learning on a daily basis during the whole recording period (rather than switching among pre-learned behaviors), a different rotational transformation was randomly chosen for each day from a set of four possible transformations (–90°, –45°, 45°, 90°). To observe systematic change in the activity of neurons, the same transformation was repeated (at least four repetitions for each transformation and each monkey, on different days). To compare

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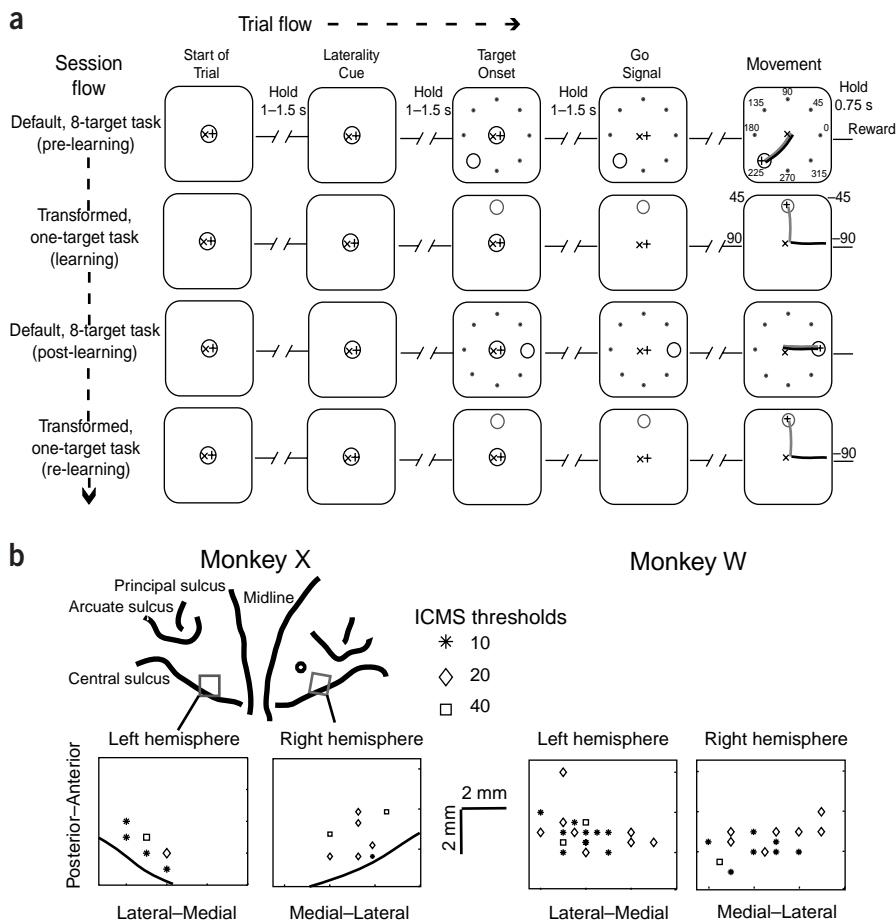
Figure 1 Experimental design and recording locations. (**a**) Session flow (top to bottom) and single trial flow (left to right). Each day (session) consisted of four different epochs shown in the four rows of the plot (see Methods for full description). The flow of a single trial is shown from left to right in each of the rows. In each trial, the monkey was first informed which hand to use in the coming trial (laterality cue). Then, after a random delay of 1–1.5 s, the target appeared (target onset) followed by another variable hold period of 1–1.5 s until the origin circle disappeared (go signal), at which time the monkey moved her arm to bring the cursor to the target. The first and third rows show the default eight-target task, in which the mapping between the visual feedback and the movement of the hand was one-to-one in both direction and amplitude. The second and fourth rows show the learning and re-learning epochs, in which only one target direction was used (upward) and monkeys were required to learn an imposed transformation (−90°, −45°, +45° or +90°) between the hand movement and the cursor (example shown is for a transform of −90°). Black lines represent movements of the hand and gray lines represent cursor movements. (**b**) Surface maps of recording sites. Anatomical reconstruction was performed for monkey X only (left). The gray squares depict the recording chambers. ICMS thresholds for eliciting single-joint movements from shoulder or elbow are shown for both monkeys.

neuronal changes on a controlled motor behavior (eliminating the possibility that changes result from differences in kinematics or dynamics), we performed a default, eight-target task (with a one-to-one mapping between cursor and hand movement) both before and after learning, and compared neuronal activity for movements with the same kinematics. Finally, to test for retention of the newly learned motor skill, we introduced the same transformation again at the end of each session ('re-learning').

Behavioral findings

To determine whether learning was indeed local, we compared directional deviations of trajectories, taken at peak velocity and normalized to the transformation (signed normalized deviation, s.n.d.; see Methods). When the monkeys were returned to the default eight-target task after the learning epoch, their hand-movement trajectories deviated toward the learned-movement direction (that is, the hand movement required to move the cursor from the origin to the target during the transformation learning epoch). These deviations represent kinematic 'aftereffects,' demonstrating that an internal model has been modified during visuomotor remapping. The deviations were largest for the target used in the learning epoch (i.e. the target at 90°). Trajectories deviated to a lesser extent as a function of angular distance from this target and as a function of trial number after learning (**Fig. 2a**). Thus, the aftereffects show limited generalization across the work space, a finding that supports the notion of a local internal model and is concordant with human psychophysics[7,8].

During the learning epoch itself, more than ten trials on average were required to reach a behavioral plateau with only small and stable errors (**Fig. 2b**). As in other studies[27], learning consisted of two phases: a transient phase during the first trials followed by a slower phase. To test for retention of learning, we compared the behavior in this first learning epoch (**Fig. 2b**, black line) to the re-learning epoch (gray line) where the same transformation was introduced in the same session but after the post-learning epoch. Improvement of performance in this re-learning epoch was immediate and reached a plateau after 1–3 trials, indicating that the newly learned transformation was retained for at least 1–2 h, the duration of the post-learning epoch. The next day, however, no aftereffects were observed, indicating that learning was lost overnight. We calculated the deviation of the trajectories in the first and second trials of the pre-learning epoch (the beginning of the session) as a function of the learned transformation on the previous day (**Fig. 2c**). To further verify that learning occurred on a daily basis, we divided the recording period into early and late segments (**Fig. 2d–f**). Similar learning occurred in all segments (**Fig. 2d**) as well as similar aftereffects (**Fig. 2e,f**). The analyses in **Fig. 2c–f** thus show that the monkeys did not consolidate the newly learned transformation, allowing us to observe newly-formed neuronal changes on a daily basis and pool neurons across recording days.

To verify that behavior was indeed the same on the two default, eight-target tasks (before and after the learning epoch) we compared movement kinematics in the two epochs. We excluded the first three trials in the post-learning epoch, which showed significant aftereffects; note that trials 4 and 5 also showed small and non-significant aftereffects but only on upward (90°) direction trials. The remaining trajectories were similar in the pre- and post-learning epochs (**Fig. 3a**). Comparison of averaged velocity profiles (**Fig. 3b**) shows that although the peak velocity was slightly higher in the pre-learning
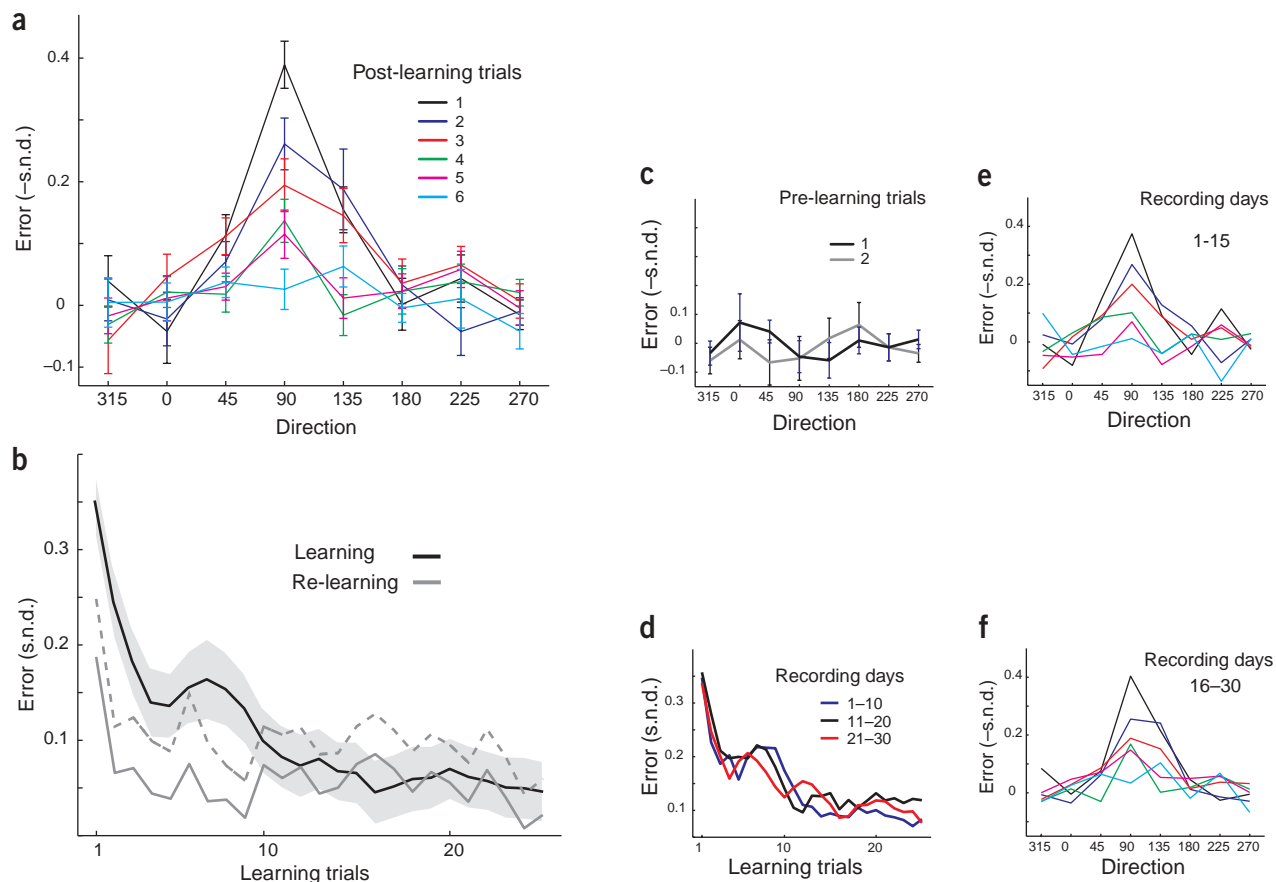
Figure 2 Movement kinematics during and after learning. (**a**) Aftereffects on standard movements in the post-learning epoch indicate the formation of a local internal model. The aftereffects are shown as signed normalized deviations (s.n.d.; see Methods). Note that aftereffects decrease as a function of angular distance from the learned target and as a function of trial number after learning. (**b**) Behavioral improvement during learning and its retention. The performance expressed in s.n.d. with two-trial moving average is shown as a function of trial number during the learning and re-learning epochs. The shaded area around the lines shows 0.95 confidence limits. Note the different temporal pattern of improvement in performance in the two epochs. During the learning epoch, performance improved slowly and reached a plateau after more than ten trials, whereas in the re-learning epoch, it improved immediately, indicating retention of the learned transformation. (**c**–**f**) Learning was washed out over night and similar learning occurred during the whole recording period. (**c**) Aftereffects on the first (black) and second (gray) trials in the pre-learning epoch normalized to the previous day learned transformation. Note the lack of aftereffects. (**d**) The same analysis and format as in **b** but calculated separately for three session groups. Each line represents a different set of ten recording days (early, mid, late). Note the similar learning curves. (**e,f**) The same analysis and format as in **a**, but calculated separately on the first half of recording days (**e**) and the second half (**f**). Note that similar aftereffects occurred in the two groups.

compared to the post-learning epoch (*t*-test, $P = 0.05$), no significant change existed between learned and non-learned directions. Additional analyses showed that reaction times (pre-learning, 298 ± 93 ms; post-learning, 296 ± 97 ms) and movement times (pre-learning, $1,087 \pm 219$ ms; post-learning, $1,130 \pm 249$ ms) were also similar before and after the learning epoch (*t*-test, performed separately for the two monkeys). Thus, the monkeys exhibited the same kinematics during the two identical tasks.

Neuronal findings

We analyzed neuronal activity during two time intervals: (i) preparatory activity (PA), which was measured during the 600 ms after target onset but during a hold period and (ii) movement-related activity (MRA), which was measured during the 600 ms after the go signal. We analyzed the preparatory activity of 129 motor cortex cells (38 in monkey X and 91 in monkey W) and the movement-related activity of 259 cells (104 and 155, respectively). Only cells that were recorded reliably before, during and after learning were included in the sample, to enable direct comparisons of changes in single cell activity.

Figure 4 shows the activity of one cell during the learning epoch. The firing rate of this cell increased as learning progressed (PA, left), but only after a relatively steady phase of about ten trials. Immediately following the go signal, no activity change was evident (MRA, right). The observed increase in preparatory activity could reflect the actual movement direction that gradually changes during learning. One finding that argues against this is the different temporal pattern; behavior improves during the first trials and reaches a plateau after 10–15 trials (**Fig. 2b**), whereas the increase in this cell's activity begins only after about ten trials. For this reason, we compared the population averaged activity during learning to the expected activity. The expected activity was calculated from the tuning curve of each cell in the pre-learning epoch and from the actual movement direction in a specific trial of the learning epoch. Whereas all neurons pooled together did not show any significant change in activity, only cells with a preferred direction within 30° of the learned-movement direction showed a significant deviation from their expected activity (paired *t*-test for at least three consecutive trials). In contrast, cells with other preferred directions did not show such change. For the population of neurons with pre-
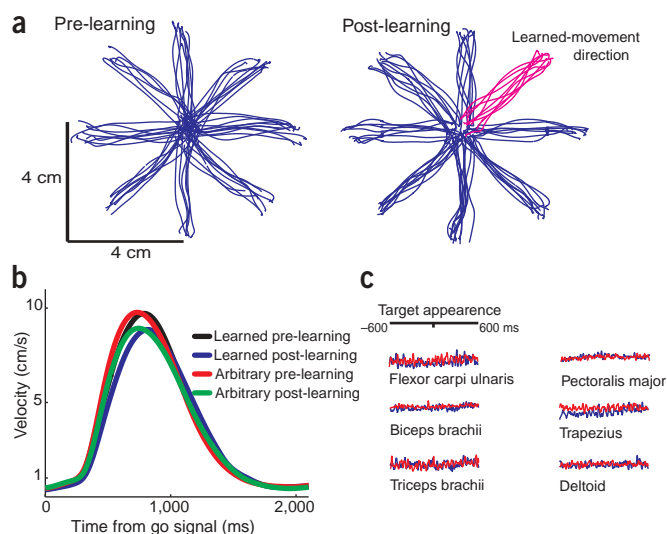
Figure 3 Similar behavior before and after learning. (**a**) Example of actual trajectories for one day (monkey W). Left, pre-learning; right, post-learning. Red trajectories are in the learned-movement direction in that session. (**b**) Averaged velocities for all recording days (monkey W), comparing pre-learning to post-learning, and learned-movement direction to all other non-learned directions. No significant difference was found between learned and non-learned directions. (**c**) Electromyographic activity confirms that monkeys did not begin movement during the hold period. Shown is EMG activity from 600 ms before to 600 ms after target onset (but before the go signal), pre- (blue) and post- (red) learning.

Figure 4 Increase in preparatory activity (PA) during learning trials, but not in movement-related activity (MRA). The figure shows activity of one motor cortex cell during the learning epoch. Left, raster plot and matching spike count in the 750 ms following the target onset (PA). Right, the same for the 750 ms following the go signal (MRA). A gradual increase of firing rate is evident (bottom to top) for PA only.

ferred directions near the learned-movement direction, the actual activity during PA increased above the expected activity only after behavior had significantly improved (*i.e.*, only after the movement direction complied with the transformation on that day; **Fig. 5a**). No change was observed for MRA and it behaved as expected during the whole learning epoch.

Several studies have suggested that early in learning, high viscoelastic forces are used to achieve the desired movement, and
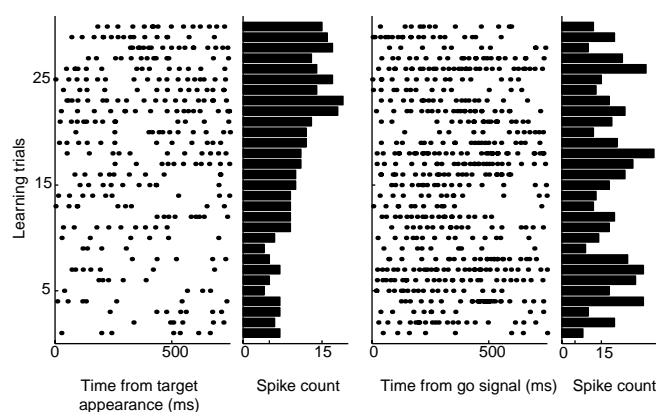
these are expressed by co-contraction and higher muscle activity. Later, as learning progresses and the contribution of the internal model increases, the role of viscoelasticity decreases[28–30]. In accord with these findings, the level of EMG activity and inter-muscle correlations decreased in the same temporal pattern as the error in behavior (**Fig. 5b**) and contrasts with that of the neural activity during learning.

To further establish that neuronal changes occurred only in preparation for movement and only in a specific subpopulation of cells (*i.e.*, those with preferred direction near that of the learned-movement direction), we compared tuning curves from the pre-learning epoch with those from the post-learning epoch. We did not find any systematic or significant changes in the neurons' preferred direction (bootstrap procedure), and preferred directions were uniformly distributed (Rayleigh test). We then compared the actual tuning curves of single cells (**Fig. 6a,b**) and found that for cells with
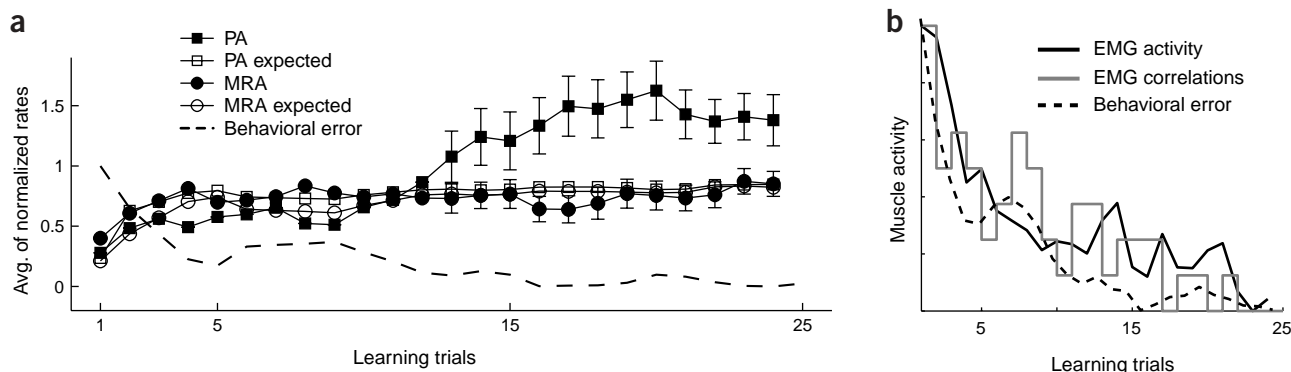

Figure 5 Temporal pattern of changes in neuronal and muscular activity during learning. (**a**) Preparatory activity (*n* = 17) and movement-related activity (*n* = 37) of cells with preferred direction within 30° of the learned-movement direction, comparing average expected activity (±s.e.m.). Expected activity was calculated as the activity from the pre-learning tuning curve in the actual movement direction during the learning trial. The dashed line represents behavioral performance, as expressed by s.n.d., during the learning epoch (same as in **Fig. 2b** but scaled to allow for comparison of temporal pattern). Note that for this group of cells, with PDs near the required movement direction, the expected activity increases as performance improves, and trajectories become closer to the required movement direction. However, the observed preparatory activity clearly exceeds the expected as learning progresses. (**b**) Reduction in muscle activation correlates with improvement in performance. Muscle activation (total r.m.s. normalized to each muscle maximal activity and averaged over muscles) is shown in black and the number of significant positive correlations between muscle pairs is shown in gray. The performance function (s.n.d.) is the same as in **a**, but all graphs are scaled to allow for comparison of temporal pattern.
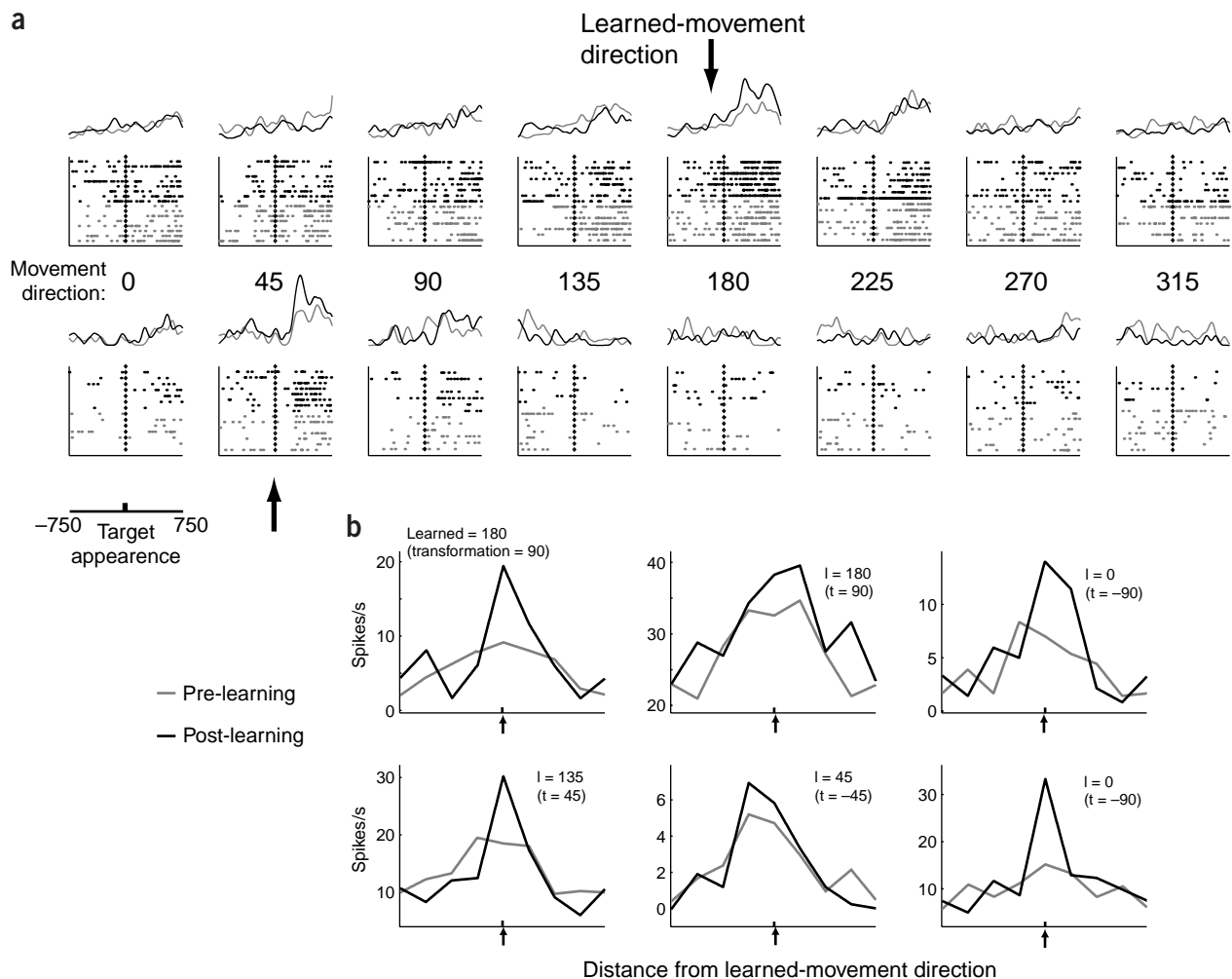
Figure 6 Learning-induced changes in single cells. (**a**) Raster plots and peri-stimulus time histograms showing activity of two cells during movements in eight directions. The pre-learning is shown in gray (dots and lines) and post-learning in black. All plots were aligned to the target onset, thus preparatory activity starts at time 0. Note that activity is enhanced only for the preferred direction of the cell. Upper cell (monkey W): PD in pre-learning is 163° and post-learning 169°; lower cell (monkey X): pre-learning is 31° and post-learning is 48°. (**b**) Directional tuning curves of six cells in the preparatory period. The abscissa represents the distance from the learned-movement direction in each cell's session (marked by arrow). Top row, cells from monkey W; bottom row, cells from monkey X; upper-left graph is same cell as top row in **a**. Note that the enhancement in firing rate is centered on the learned-movement direction and that the preferred directions of the cells are near this direction.

preferred direction near the learned-movement direction, enhancement in firing rate was centered on this direction.

This specific elevation of the tuning curve is reflected at the population level, as illustrated in **Fig. 7**, which depicts the PA at the learned-movement direction of all cells as a function of the angle between each cell's PD and the learned-movement direction. Comparing the population activity before and after learning, indicates that only cells with a PD near the learned-movement direction showed an increase in firing rate after learning. Comparing with the same finding during learning (**Fig. 5a**), a significant difference was found between pre- and post-learning epochs only for cells with PDs within 30° of the learned-movement direction (2-way ANOVA and post-hoc analysis). To verify that these cells change their activity mainly in the neighborhood of their PD, we aligned each cell tuning curve around its PD and found that the averaged PD aligned tuning curve also showed increased activity only around its center. We also extended the database of cells by removing the criterion of cosine fit, which added 48 directionally tuned cells for a total of 177 cells. For this extended population of cells as well, almost all

cells with PD within 30° from the learned-movement direction show elevated activity at this direction (**Fig. 8a–c**).

As a control, we conducted the same analysis for non-learned directions (**Fig. 8d**). When the distances between the PD and movement direction are relative to an arbitrarily selected direction, no change is present. None of the seven other movement directions was associated with a change in tuning. We further tested whether learning-induced changes were observed only in the PA by performing the same analyses as in **Fig. 7**, this time for MRA . No change was observed in movement-related activity (**Fig. 8e**, diamonds).

Previous studies have shown that excessive training can induce changes in representation maps of motor cortex[31,32]. This raises the possibility that the observed effect in our study results from the mere repetition of a given movement during the learning epoch. To control for this possibility, we conducted sessions with a repetitive, control condition, which entailed a one-target task without angular transformations. Here, the target direction was either 180° or 90°, in separate sessions. Cells recorded in these sessions did not show
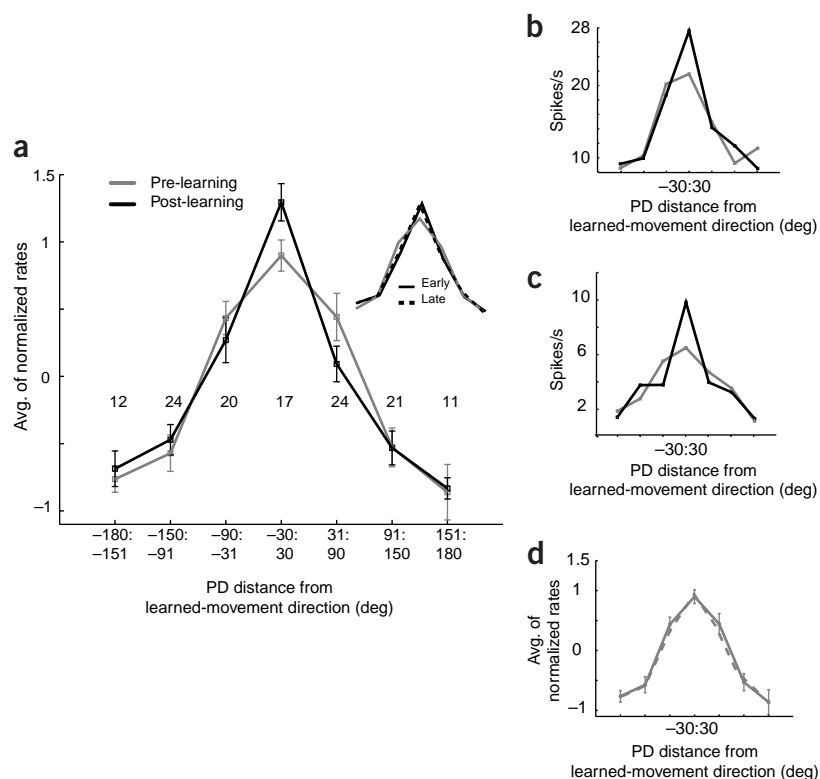
Figure 7 Learning-induced changes as revealed by comparing population activities before and after learning. Population averages of preparatory activity (PA) in the learned-movement direction (± s.e.m.). (**a**–**c**) Gray lines show activity during the pre-learning epoch and black line the post-learning epoch. The abscissa shows the cells' PD distance from that direction. (**a**) Normalized rates are shown in the main plot, with the numbers of cells in each entry. Inset, the first three trials (solid black) in the post-learning epoch (but after excluding the first three trials showing significant aftereffects) and the last three trials (dashed black) indicating that the change persisted during the whole post-learning epoch. The red solid line was shifted slightly to the right for presentation. (**b**) Same as the main plot in **a** for non-normalized firing rates. (**c**) Same as the main plot in **a**, with each cell normalized to its baseline activity but not scaled. (**d**) This plot shows that the effect shown in **a**–**c** was washed out over night. Dashed gray line shows pre-learning activity from a given session but normalized to the previous session's learned-movement direction. Solid gray line is identical to the one in the main plot of **a**. Note that unlike other comparisons in this report, it compares two different cell populations, thus it is a qualitative rather than a quantitative result.

changes in their activity (**Fig. 8e**, squares and circles). We therefore conclude that the change of tuning in the post-learning epoch was caused by the learning of new visuomotor transformations during the learning epoch. Two of the aforementioned findings support this conclusion: first, the change was not observed during movement-related activity and second, the kinematics and dynamics of movements were similar after learning.

In line with the retention of behavioral improvement (faster learning in the re-learning epoch, **Fig. 2b**), we did not observe any washout of changes in activity in the post-learning epoch. Although only a small number of trials (6–9) was available for statistics, the two examples in **Fig. 6a** show that the cells' enhanced activity remained the same during the whole post-learning epoch. To test this at the population level, we divided the post-learning trials into two groups: 'early' (the first three trials but following the first three trials with significant aftereffects) and 'late' (the last three trials). The same trend of change was apparent in both phases (**Fig. 7a**, inset). We verified it using a bootstrap method, sampling with replacement of trials and cells and comparing the obtained distribution of differences to the 'true' difference between early and late ($P = 0.3$, n.s.). This sustained pattern of activity might serve in retention of the newly acquired skill until it can be further consolidated. However, no traces of the learned transformation were found the following day (**Fig. 2c–f**), indicating that consolidation was never complete. In parallel, we found that the neuronal effect observed during and after learning was not observed on the following day (**Fig. 7d**).

DISCUSSION

The present results demonstrate a modification in the activity and spatial tuning functions of neurons in the motor cortex as a result of learning a local visuomotor skill. This altered activity reflects learning and retention of the newly acquired internal model, one that converts

visuospatial cues into the motor commands required for hand movements and/or joint rotations to achieve the goal. The finding that only cells with PDs near the learned-movement direction modified their activity reflects the specificity of the elements comprising the local internal model, as suggested by recent theoretical work[33–35], psychophysical findings[9,11,36] and electrophysiological evidences from altered load conditions[15,37]. This finding provides a possible neuronal basis for the psychophysical finding that the learning of a sensorimotor mapping, one that introduces directional errors, is local[7–10]. A possible explanation for the elevation of the activity of cells with PDs near the direction of the required hand movement is that such elevation can serve to 'win' over the 'default' choice (*i.e.*, to move the hand in the direction of the target).

The neuronal changes were observed only in advanced phases of learning and lasted for the remaining of the learning epoch when behavior was stable, muscle activity was reduced and inter-muscle correlations decreased. These findings are consistent with studies showing that neuronal changes during movement preparation lag behavioral changes[17,38]. It is also consistent with the notion that early in learning new dynamics, vicsoelastic properties are used to help produce the correct movement and that only in later phases an internal model is formed to represent the newly learned environment[28,30]. Our findings suggest that the motor system may also use similar mechanisms (co-contraction) for enhanced motor control at early stages of learning new kinematics.

The changes we observed persisted when the monkeys returned to performance of the default task, even after the behavioral aftereffects disappeared, and were sustained until the relearning of the same transformation. This finding is congruent with the retention of behavioral improvement found in the re-learning epoch and suggests that the primary motor cortex stores the newly acquired skill in working memory[26]. The neuronal changes were washed out over

Figure 8 Learning-induced changes were specific and were not observed for mere repetition of movement, for non-learned directions, or for movement-related activity. (**a**–**c**) To further verify the learning-induced changes, we used an extended database of cells by removing the criterion for cosine fit ($n = 177$). Histograms of changes in firing rate in the learned-direction (post- minus pre-learning) for cells with a preferred direction within 30° of the learned direction (**a**) and for the rest of the cells (**b**). The small horizontal bar below the histograms designates the 0.95 confidence interval for the population mean. (**c**) Same analysis as in **Fig. 7a**, but on this extended database. (**d**) Averaged preparatory activity of cells when aligned to an arbitrary, non-learned direction. The abscissa shows the cells' PD distance from that direction (same format as in **Fig. 7**). Activities were similar for pre- and post-learning epochs, indicating that learning a specific direction did not affect other directions. (**e**) Cells did not change their movement-related activity (diamonds), nor was there an effect after mere repetition of movement (squares, preparatory activity; circles, movement-related activity). The abscissa shows the absolute PD distance from the learned-movement direction or from the repeated-movement direction.
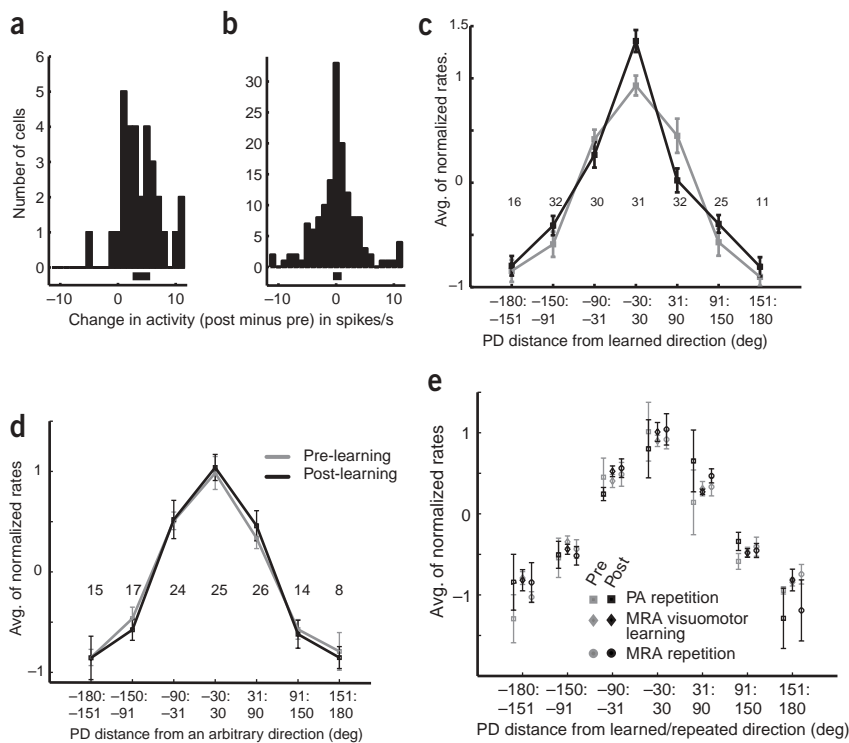
night, reinforcing the finding that no aftereffects were observed on the next day and that similar learning behavior occurred during the whole recording period. The lack of behavioral aftereffects and improvement in skill performance from day to day implies that the learned skill did not undergo consolidation, where a newly learned skill is transferred for longer-term memory storage[24,25]. This absence of consolidation can be attributed to two factors. First, the four different randomly chosen transformations were an incentive not to consolidate, as behavior learned the previous day could interfere with learning of the current transformation. Second, consolidation might require a sufficient number of training trials. For example, prism adaptation studies have shown that 50 trials are sufficient to induce immediate aftereffects, but over 250 trials are required for longer-lasting (24 h) consolidation[39].

Whereas higher attention is required during learning, there is evidence to suggest that the observed changes cannot be solely attributed to this factor. First, attention was needed during movement execution (at least in the first learning trials, where deviations were high and attending to the visual feedback was crucial), yet the observed effect only occurred for the preparatory activity and not for movement-related activity. Second, attention is expected to be higher at the onset of learning, yet no change occurred before performance reached a plateau. Finally, no change in neuronal activity was observed for the direction of the target presented during learning—upward (90°)—the direction which requires increased attention and for which behavioral aftereffects were observed.

The fact that the change in our study occurred selectively during movement preparation and not during execution of movement might reflect the modification of internal models of movement kinematics rather than dynamics. These changes in activity may be driven by inputs from premotor areas—areas that show extensive preparatory activity, are more involved in coding kinematic aspects of movement and are thought to compute visuomotor transformations[40–44]. A recent study described changes in cell PDs after adaptation to perturbed dynamics in

an eight-direction task. In line with the dynamics versus kinematics suggestion, this study showed that the changes in the primary motor cortex occurred during execution of movement[14], but in premotor cortices, changes were observed during the preparation for movement as well[16]. Although the difference in results could stem from other task-related differences, such as the kinematic variable[45] (direction vs. velocity-dependent fields) or local versus global learning (eight targets instead of one), it could also suggest that a different modification occurs for learning new kinematics and learning new dynamics[27,46].

METHODS

Animals, recordings and behavioral task. Two female rhesus monkeys (*Macaca mulatta*, ~4.5 kg) were implanted with recording chambers (27×27 mm) above both the right and left hemispheres. Animal care and surgical procedures complied with the *NIH Guidelines for the Care and Use of Laboratory Animals* (1996) and with guidelines supervised by the Institutional Committee for Animal Care and Use at Hebrew University. The monkeys were seated in a dark chamber, and eight microelectrodes were lowered into each hemisphere. The electrode signals were amplified, filtered and sorted (MCP-PLUS, MSD, Alpha-Omega), and all spike shapes were sampled at 24 kHz. The monkeys operated two *x*–*y* manipulanda to control two cursors (+ for the right hand; × for the left) on a video screen 50 cm away. Wrist cuffs minimized distal movements.

As illustrated in **Fig. 1a**, each trial began when the monkey centered both cursors on the origin (central circle) for at least 1 s. One of the cursors then turned green, indicating the hand to be used in the trial (laterality cue). After a variable hold period of 1.0–1.5 s, a target (circle of 0.8 cm diameter) appeared at one of eight possible positions 4 cm from the origin (**Fig. 1a**, middle column). After an additional 1.0–1.5 s hold period, the origin disappeared (go signal), prompting the monkey to move the green cursor in a straight trajectory (limited by an invisible virtual corridor 0.8 cm in width) to reach the target in less than 2 s. After another hold of 750 ms, a liquid reward was delivered.

In each session, the monkey performed a default eight-target task before (pre-learning epoch) and after (post-learning epoch) a transformed one-target task (learning epoch), and then repeated the transformed one-target

task (re-learning epoch). This re-learning epoch was used to assess retention of the learned motor skill. In the default task (**Fig. 1a**, first and third rows), the target was chosen randomly in each trial from among the eight possible positions. In the transformed one-target task (**Fig. 1a**, second and fourth rows), the upward target (designated 90°) was presented on every trial, and an angular transformation was applied to the relation between hand movement and the direction of cursor movement on the video screen. The transformation was the same during both epochs of a given session but randomly chosen out of four possibilities (–90°, –45°, +45° or +90°) at the beginning of each day. Note that during the learning epoch for the angular transform illustrated (–90°), a hand movement at an angle of 0° (*i.e.*, a rightward hand movement) was required to move the cursor from the origin to the target at 90° (*i.e.*, an upward cursor movement). The phrase 'learned-movement direction' refers to the direction of hand movement needed to bring the cursor to the target for these visuomotor remappings. There were four possible learned-movement directions in this study: 0°, 45°, 135° and 180°, associated with the –90°, –45°, +45° and +90° transforms, respectively. Monkeys were trained for several months with the default eight-target task but did not see the transformations before the recordings.

Surface electromyogram (EMG) recordings were taken from the following muscles: flexor carpi ulnaris and radialis, extensor carpi ulnaris and radialis, biceps brachii, triceps brachii, deltoid, trapezius, pectoralis major, latissimus dorsi, rhomboid, teres major and oblique abdominal extensors (several of these shown in **Fig. 3c**).

Penetration locations were verified by magnetic resonance imaging (MRI; Biospec Bruker, 4.7 tesla). At the end of each session, we examined the activity of neurons evoked by passive manipulation of the limbs and applied intracortical microstimulation (ICMS; 50 ms of 200-μs cathodal pulses at 300 Hz) to evoke movements. In monkey X, we also made anatomical observations to verify the accurate penetration sites relative to the central sulcus.

Data analysis. We selected single neurons for analysis on the basis of several inclusion criteria: (i) ability to isolate their spikes; (ii) penetration sites where ICMS evoked single-joint shoulder or elbow movements at ≤40 μA; (iii) at least five trials in each direction both pre- and post-learning; (iv) the lack of significant change in activity during the first hold period for the pre-learning epoch vs. the post-learning epoch (Mann-Whitney U-test); (v) the results of a one-way ANOVA showing a significant effect for direction; and (vi) a cosine fit that exceeded $R^2 = 0.5$. For comparing pre-learning and post-learning population activities (as in **Fig. 7**), we normalized each cell's actual firing rate by its baseline and depth of modulation:

$$r\_normalized\,(d) = \frac{r(d) - a}{b}$$

where d is the movement direction, and a and b are the baseline and the modulation-depth respectively, as calculated by a cosine fit[12] ($r(d) = a + b\cos(d - d_0)$). We verified that choosing cells based on R^2 statistics did not bias our results by replacing the criteria (*f*) with a uni-modality test. We studied cells that were activated during contralateral and ipsilateral movements, and after verifying that each of the two populations produced similar results, we pooled all the cells together.

The deviation in trajectories was assessed by a 'signed normalized deviation' (s.n.d.), calculated as a directional deviation—the required hand direction minus the actual hand direction (taken at peak velocity), normalized by the transformation in the session (–45, –90, +45 or +90). Note that both the denominator and numerator are signed; thus a positive number only occurs when both deviation and transformation have the same sign, indicating that improvement in performance matched the transformation in sign and magnitude (**Fig. 2b**). A negative number results when the deviation and the transformation have opposite signs, showing that aftereffects match the transformation.

The statistical significance throughout this report is accepted at the $P < 0.01$ level, unless otherwise mentioned. We used both parametric (*t*-test and ANOVA) and non-parametric (Mann-Whitney and Kruskal-Wallis) methods for all statistical tests.

1. Soechting, J.F. & Flanders, M. Sensorimotor representations for pointing to targets in three-dimensional space. *J. Neurophysiol.* **62**, 582–594 (1989).
2. Kalaska, J.F., Scott, S.H., Cisek, P. & Sergio, L.E. Cortical control of reaching movements. *Curr. Opin. Neurobiol.* **7**, 849–859 (1997).
3. Buneo, C.A., Jarvis, M.R., Batista, A.P. & Andersen, R.A. Direct visuomotor transformations for reaching. *Nature* **416**, 632–636 (2002).
4. Shadmehr, R. & Mussa-Ivaldi, F.A. Adaptive representation of dynamics during learning of a motor task. *J. Neurosci.* **14**, 3208–3224 (1994).
5. Kawato, M. Internal models for motor control and trajectory planning. *Curr. Opin. Neurobiol.* **9**, 718–727 (1999).
6. Wolpert, D.M. & Ghahramani, Z. Computational principles of movement neuroscience. *Nat. Neurosci.* **3** (Suppl.), 1212–1217 (2000).
7. Gandolfo, F., Mussa-Ivaldi, F.A. & Bizzi, E. Motor learning by field approximation. *Proc. Natl. Acad. Sci. USA* **93**, 3843–3846 (1996).
8. Pine, Z.M., Krakauer, J.W., Gordon, J. & Ghez, C. Learning of scaling factors and reference axes for reaching movements. *Neuroreport* **7**, 2357–2361 (1996).
9. Ghahramani, Z., Wolpert, D.M. & Jordan, M.I. Generalization to local remappings of the visuomotor coordinate transformation. *J. Neurosci.* **16**, 7085–7096 (1996).
10. Baraduc, P. & Wolpert, D.M. Adaptation to a visuomotor shift depends on the starting posture. *J. Neurophysiol.* **88**, 973–981 (2002).
11. Shadmehr, R. & Moussavi, Z.M. Spatial generalization from learning dynamics of reaching movements. *J. Neurosci.* **20**, 7807–7815 (2000).
12. Georgopoulos, A.P., Kalaska, J.F., Caminiti, R. & Massey, J.T. On the relations between the direction of two-dimensional arm movements and cell discharge in primate motor cortex. *J. Neurosci.* **2**, 1527–1537 (1982).
13. Kakei, S., Hoffman, D.S. & Strick, P.L. Muscle and movement representations in the primary motor cortex. *Science* **285**, 2136–2139 (1999).
14. Li, C.S., Padoa-Schioppa, C. & Bizzi, E. Neuronal correlates of motor performance and motor learning in the primary motor cortex of monkeys adapting to an external force field. *Neuron* **30**, 593–607 (2001).
15. Gribble, P.L. & Scott, S.H. Overlap of internal models in motor cortex for mechanical loads during reaching. *Nature* **417**, 938–941 (2002).
16. Padoa-Schioppa, C., Li, C.S.-R. & Bizzi, E. Neuronal correlates of kinematics-to-dynamics transformation in the supplementary motor area. *Neuron* **36**, 751–765 (2002).
17. Wise, S.P., Moody, S.L., Blomstrom, K.J. & Mitz, A.R. Changes in motor cortical activity during visuomotor adaptation. *Exp. Brain Res.* **121**, 285–299 (1998).
18. Sanes, J.N. & Donoghue, J.P. Plasticity and primary motor cortex. *Annu. Rev. Neurosci.* **23**, 393–415 (2000).
19. Hess, G. & Donoghue, J.P. Long-term depression of horizontal connections in rat motor cortex. *Eur. J. Neurosci.* **8**, 658–665 (1996).
20. Rioult, P.M., Friedman, D., Hess, G. & Donoghue, J.P. Strengthening of horizontal cortical connections following skill learning. *Nat. Neurosci.* **1**, 230–234 (1998).
21. Karni, A. *et al.* Functional MRI evidence for adult motor cortex plasticity during motor skill learning. *Nature* **377**, 155–158 (1995).
22. Jenkins, I.H., Brooks, D.J., Nixon, P.D., Frackowiak, R.S. & Passingham, R.E. Motor sequence learning: a study with positron emission tomography. *J. Neurosci.* **14**, 3775–3790 (1994).
23. Muellbacher, W., Ziemann, U., Boroojerdi, B., Cohen, L. & Hallett, M. Role of the human motor cortex in rapid motor learning. *Exp. Brain Res.* **136**, 431–438 (2001).
24. Shadmehr, R. & Holcomb, H.H. Neural correlates of motor memory consolidation. *Science* **277**, 821–825 (1997).
25. Brashers-Krug, T., Shadmehr, R. & Bizzi, E. Consolidation in human motor memory. *Nature* **382**, 252–255 (1996).
26. Muellbacher, W. *et al.* Early consolidation in human primary motor cortex. *Nature* **415**, 640–644 (2002).
27. Krakauer, J.W., Ghilardi, M.F. & Ghez, C. Independent learning of internal models for kinematic and dynamic control of reaching. *Nat. Neurosci.* **2**, 1026–1031 (1999).
28. Thoroughman, K.A. & Shadmehr, R. Electromyographic correlates of learning an internal model of reaching movements. *J. Neurosci.* **19**, 8573–8588 (1999).
29. Nezafat, R., Shadmehr, R. & Holcomb, H.H. Long-term adaptation to dynamics of reaching movements: a PET study. *Exp. Brain Res.* **140**, 66–76 (2001).
30. Osu, R. *et al.* Short- and long-term changes in joint co-contraction associated with motor learning as revealed from surface EMG. *J. Neurophysiol.* **88**, 991–1004 (2002).
31. Nudo, R.J., Milliken, G.W., Jenkins, W.M. & Merzenich, M.M. Use-dependent alter-

ations of movement representations in primary motor cortex of adult squirrel monkeys. *J. Neurosci.* **16**, 785–807 (1996).

32. Plautz, E.J., Milliken, G.W. & Nudo, R.J. Effects of repetitive motor training on movement representations in adult squirrel monkeys: role of use versus learning. *Neurobiol. Learn. Mem.* **74**, 27–55 (2000).

33. Poggio, T. & Girosi, F. Theory of networks for learning. *Science* **247**, 978–982 (1990).

34. Schaal, S. & Atkeson, C.G. Constructive incremental learning from only local information. *Neural Comput.* **10**, 2047–2084 (1998).

35. Pouget, A. & Snyder, L.H. Computational approaches to sensorimotor transformations. *Nat. Neurosci.* **3** (Suppl.), 1192–1198 (2000).

36. Thoroughman, K.A. & Shadmehr, R. Learning of action through adaptive combination of motor primitives. *Nature* **407**, 742–747 (2000).

37. Kalaska, J.F., Cohen, D.A., Hyde, M.L. & Prud'homme, M. A comparison of movement direction-related versus load direction-related activity in primate motor cortex, using a two-dimensional reaching task. *J. Neurosci.* **9**, 2080–2102 (1989).

38. Mitz, A.R., Godschalk, M. & Wise, S.P. Learning-dependent neuronal activity in the premotor cortex: activity during the acquisition of conditional motor associations. *J. Neurosci.* **11**, 1855–1872 (1991).

39. Yin, P.B. & Kitazawa, S. Long-lasting aftereffects of prism adaptation in the monkey. *Exp. Brain Res.* **141**, 250–253 (2001).

40. Alexander, G.E. & Crutcher, M.D. Preparation for movement: neural representations of intended direction in three motor areas of the monkey. *J. Neurophysiol.* **64**, 133–150 (1990).

41. Crammond, D.J. & Kalaska, J.F. Modulation of preparatory neuronal activity in dorsal premotor cortex due to stimulus-response compatibility. *J. Neurophysiol.* **71**, 1281–1284 (1994).

42. Wise, S.P., Di Pellegrino, G. & Boussaoud, D. The premotor cortex and nonstandard sensorimotor mapping. *Can. J. Physiol. Pharmacol.* **74**, 469–482 (1996).

43. Shen, L. & Alexander, G.E. Preferential representation of instructed target location versus limb trajectory in dorsal premotor area. *J. Neurophysiol.* **77**, 1195–1212 (1997).

44. Kakei, S., Hoffman, D.S. & Strick, P.L. Direction of action is represented in the ventral premotor cortex. *Nat. Neurosci.* **4**, 1020–1025 (2001).

45. Tong, C., Wolpert, D.M. & Flanagan, J.R. Kinematics and dynamics are not represented independently in motor working memory: evidence from an interference study. *J. Neurosci.* **22**, 1108–1113 (2002).

46. Flanagan, J.R. *et al.* Composition and decomposition of internal models in motor learning under altered kinematic and dynamic environments. *J. Neurosci.* **19**, RC34 (1999).