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Sensorimotor Adaptation: Multiple Forms of Plasticity in Motor Circuits

Valeria Della-Maggiore[1], Sofia M. Landi[2], and Jorge I. Villalta[1]

Abstract

One of the most striking properties of the adult central nervous system is its ability to undergo changes in function and/or structure. In mammals, learning is a major inducer of adaptive plasticity. Sensorimotor adaptation is a type of procedural—motor—learning that allows maintaining accurate movements in the presence of environmental or internal perturbations by adjusting motor output. In this work, we will review experimental evidence gathered from rodents and human and nonhuman primates pointing to possible sites of adaptation-related plasticity at different levels of organization of the nervous system.

One of the most striking properties of the adult central nervous system (CNS) is its ability to undergo changes in function and/or structure. Although these plastic changes may endure, they may not always lead to the preservation of adaptive behavior as when triggered by brain injury. In mammals, however, learning is a major inducer of adaptive plasticity: the nervous system translates new knowledge into long-lasting plastic changes that lead to the formation of memories. The mechanisms by which these memories consolidate and resist degradation by newly acquired knowledge or simply decay in the absence of practice are of major interest to the field of neuroscience.

Evidence from nonhuman animals suggests that memories are consolidated through several physiological, biochemical, and molecular processes that operate at different time scales (Katche and others 2010; Kleim and Jones 2008; Luft and others 2004). For example, it has been postulated that declarative memories rely on both fast and slow consolidation phases. The fast consolidation phase takes place during and immediately after learning up to a couple of days and involves synaptic plasticity (e.g., long-term potentiation, LTP). In contrast, the slow consolidation phase takes place at the systems level and likely involves the strengthening of connections between the cortex and the hippocampus, lasting from several days to weeks and even months (Morris 2006).

Nondeclarative memories such as those induced by the acquisition of a new motor skill also seem to follow a time course of consolidation engaging differential processes and multiple levels of plasticity. One of the most popular paradigms used to study motor skill learning in rodents involves reaching to grasp food pellets with the forelimb through a small slit in the cage. Early studies show evidence indicating that improvements in performance after 5 days of training are associated with LTP of horizontal connections in the primary motor cortex (M1) (Rioult-Pedotti and others 2000), increased size of synaptic spines, and synaptogenesis (Kleim and others 2004). More recent studies using two-photon microscopy in live mice, however, indicate that new dendritic spines in the pyramidal layer of M1 emerge as fast as 1 hour posttraining in this task (Xu and others 2009), suggesting that structural plasticity goes hand in hand with the strengthening of synaptic connections. Plasticity is also expressed at the topographical level as the reorganization of motor representations in M1 (Kleim and others 2004). A recent report showing that long-term memory for skilled reaching is modulated by protein synthesis in the dorsal striatum (Wächter and others 2010) suggests that, like declarative memories, motor learning does not stay local but affects the connectivity at the systems level.

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Sensorimotor Adaptation

The acquisition of motor skills such as the ability to reach a pellet through a narrow slit requires a precise motor system that can accommodate quickly and reliably the instabilities of a changing environment. Sensorimotor adaptation is a type of procedural—motor—learning that allows maintaining accurate movements in the presence of environmental or internal perturbations by adjusting motor output. Adaptive motor learning occurs daily when, for example, we get new prescription glasses, use a new tool, wear new shoes, gain or lose significant amounts of weight, or undergo a hip replacement. It also occurs when already learned skills need to be adjusted, such as when we switch cars or play a sport in a windy weather. Finally, adaptation is also actively engaged during development as the nervous systems recalibrates to accommodate the changing biomechanical properties of our body. Depending on the amount of training, sensorimotor adaptation can lead to the modification of preexisting internal representations or the formation of new ones (Shadmehr 2005). In the context of computational motor control, these internal representations are known as "internal models," that is, neural processes that can simulate the dynamics of an effector, for example, the arm, in a given environment (Shadmehr and Mussa-Ivaldi 1994; Wolpert and Flanagan 2001). Internal models have been proposed to set the basis for the automatization of goal-directed behavior (Shadmehr 2005).

The first studies suggesting that sensorimotor adaptation is accompanied by persistent changes in brain function were psychophysical in nature. Early experimental approaches carried out during the beginning and mid-19th century resorted to the use of reversed prisms to assess the impact of perturbing the visual field on daily behavior (see Boxplot 1). Because they were aimed at evaluating the potential of the adult perceptual system to change, pioneer studies used drastic perturbations, often inverting the visual field vertically by 180° during several days or weeks (Stratton 1897). Later, Kohler studied the impact of more subtle displacements of the lateral visual field through the use of wedge prisms (Kohler 1964). Although behavioral changes were initially interpreted to reflect the modification of the perceptual visual system, the discovery that voluntary movement was necessary for adaptation (Held 1965) pointed to the sensorimotor system as the target of plasticity.

Since the early 1990s, sensorimotor adaptation has been studied extensively in the laboratory using experimental paradigms in which visual or proprioceptive feedback is altered during reaching or walking. This review will focus on the literature on reaching and pointing to visual targets. Adaptation to the distortion of visual feedback, known as visuomotor adaptation, has been studied by using reversed prisms and, most often, by rotating a cursor that represents the position of the hand on the screen relative to the real hand position. Figure 1A illustrates the setup used in our and other labs to study reaching under a visual perturbation. The subject is sitting on a chair bolted on a glass table with his forearm supported by airsleds to remove friction. The position of the fingertip is recorded with a tracking system and is displayed to the subject as a cursor. Visual target(s) and the cursor position displayed on the monitor placed on top of the setup are reflected on a mirror located at the height of the chest. In this way, the mirror provides the illusion that the target is at the same horizontal plane as his fingertip while blocking direct vision of his arm. Visual feedback on the hand is therefore entirely provided through the cursor. Other versions of visuomotor setups involve arm reaching or pointing on a digitizing tablet with or without airsleds, and finger pointing using a joystick. Adaptation to the distortion of proprioceptive feedback is normally referred to force-field adaptation or adaptation to new environmental dynamics and can be assessed by applying a force against the hand during a reaching movement through a manipulandum (Fig. 1B).

Growing evidence suggests that predictive mechanisms involved in motor control mediate adaptation. When a perturbation, for example, a force-field, is first applied to the hand during reaching (Fig. 2A), the prediction of the force required to adjust to it and reach the target will turn out to be erroneous, leading to deviated hand paths (Fig. 2B, *early adaptation*). With practice, however, prediction of the distortion becomes more accurate; subjects are able to correct for the perturbation in an anticipatory way, and hand paths approach the desired trajectory (Fig. 2B, *late adaptation*). Thus, adaptation is thought to be achieved partly by generating motor commands based on a prediction of the perturbation that will be experienced in the upcoming movement (Thoroughman and Shadmehr 1999; Tseng and others 2007).

A typical experiment is illustrated in Figure 2C. It begins with an initial baseline phase during which subjects move in the absence of the perturbation (null trials), followed by an adaptation session during which the distortion is imposed. The time course of motor error during adaptation is well characterized by an exponential function, with large level of error on the introduction of the perturbation that subsides with learning, returning to baseline levels. Removal of the perturbation after adaptation results in aftereffects, that is, the deviation of hand paths in the opposite direction. The fact that aftereffects last for several trials before performance returns to baseline levels is consistent with the formation of a memory trace for the new sensorimotor map. In one of the seminal psychophysical studies on force-field adaptation, Shadmehr and Mussa-Ivaldi (1994) first suggested that aftereffects reflect an internal model of the new environmental dynamics that develops as subjects adapt to the force-field.

BOX 1. Motor adaptation: the early years.

George Stratton belonged to the first generation of experimental psychologists. Under the initial supervision of Wundt, he performed a series of studies to investigate the ability of the perceptual system to adapt to an external perturbation of the visual field. To the right is a modern version of the inverting spectacles used by the scientist in probably the first documented experiments on visuomotor adaptation, conducted at UC Berkeley (Stratton, 1897). The study involved adapting to a full vertical inversion of the visual field. Below, is the original record of the 8-day experience. Eyes were blinfolded while glasses were off. Stratton claimed to have adapted to the perturbation by the seventh day.

Courtesy of J Bruneau,
(http://artfail.com/omnivision/)

DAY.	HOUR OF PUTTING GLASSES ON.	HOUR OF TAKING GLASSES OFF.	LENGTH OF TIME GLASSES WERE WORN.
1st	12 m.	9 p. m.	9 hrs.
2d	9 a. m,	9 p. m.	12 hrs.
3d	9 a. m.	9 p. m.	12 hrs.
4th	9 a. m.	9:45 p. m.	12 hrs., 45 mins.
5th	9:50 a. m.	10:30 p. m.	12 hrs., 40 mins.
6th	9:50 a. m.	9:45 p. m.	11 hrs., 55 mins.
7th	9:15 a. m.	9:45 p. m.	12 hrs., 30 mins.
8th	8 a. m.	12:10 p. m.	4 hrs., 10 mins.
		Total,	87 hrs.

Extracted from (Stratton, 1897), with permission

(http://www.awz.uni-wuerzburg.de/en/archive)
Ivo Kohler riding a bicycle after 7 days of wearing the inverted spectacles.

More recent studies carried out in real-life settings by Erismann and Kohler at the University of Innsbruck (Kohler, 1950;1964) during up to 125 days showed that fully adapted subjects were able to regain control of their movements after 1 week of continuously wearing vertically inverted prisms. The authors attributed this phenomenon to a progressive adjustment of the perceptual.

Based on laboratory studies conducted at Brandeis University and MIT, Held later observed (1965) that adaptation to distorted perception was only achieved when voluntary movement is allowed to the subject, suggesting that its locus is not in sensory systems, but in sensory and motor systems involved in sensorimotor coordination.

Boxplot 1. The early days of sensorimotor adaptation.

Aftereffects wash out, that is, return to baseline levels after several trials. The washout, however, does not destroy the memory formed during adaptation but temporally inhibits its expression, returning spontaneously after a time interval (Villalta and others 2013). This finding resembles the phenomenon of extinction in classical conditioning. Finally, like other types of declarative and nondeclarative learning, adaptation typically shows savings, that is, the
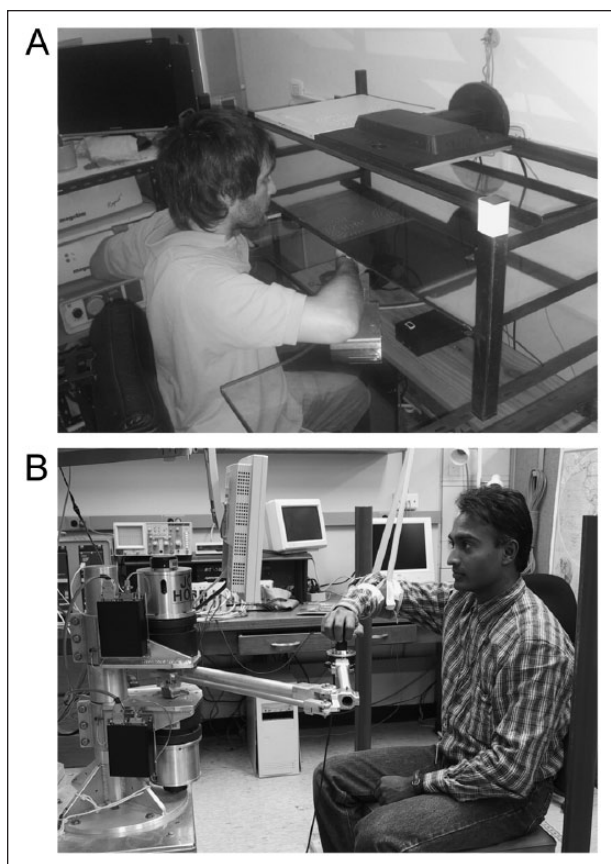
Figure 1. Adaptation paradigms used in the laboratory. (A) Illustration of a reaching setup used for visuomotor adaptation. Participants make planar reaching movements to visual targets projected on a mirror interposed between the computer monitor and the table. The position of the hand, captured by a camera placed underneath the table, is projected on the mirror as a cursor. (B) Illustration of a reaching setup used for force-field adaptation. Participants make reaching movements to visual targets displayed on the computer screen while a velocity-dependent force field is applied to the hand through the manipulandum of a robot. The position of the hand is projected on the computer screen as a cursor (Courtesy of Reza Shadmehr).

improvement in the rate of learning on a subsequent encounter with the same perturbation (Fig. 2D).

Sensorimotor Adaptation, Consolidation, and Memory Persistence

The consolidation hypothesis, first proposed by Muller and Pilzeker in 1900, states that new information acquired through learning is initially stored in labile memory traces that stabilize with the passage of time, becoming resistant from degradation by new learning (Lechner and others 1999). Retrograde interference has been used as a behavioral proxy to unveil the time course of memory consolidation associated with sensorimotor adaptation. An influential study by Shadmehr and Brashers-Krug (1997) showed that adapting to force-field B within 2.5 hours of having adapted to the opposite force-field A (A1) leads to retrograde interference, evidenced in naïve performance 1 week later at memory recall (A2). Yet release from interference is achieved when 5.5 hours elapse between A1 and B, suggesting that memories formed during adaption to new dynamics consolidate within such time frame. Retrograde interference has also been reported for visuomotor adaptation when a clockwise rotation (B) is learned 5 minutes after the counterclockwise rotation (A), whereas release from interference is evident when A and B are separated by 24 hours (Krakauer and others 2005). This suggests that consolidation to optical rotations takes place sometime within this long interval. No intermediate intervals have been explored. Other labs, however, have failed to replicate the findings from both these studies (Bock and others 2001; Caithness and others 2004; Goedert and Willingham 2002), showing complete interference even when 1 week was elapsed between adaptation and recall to reduce anterograde effects. These results have led to the proposal that unlike declarative memories, memories formed during sensorimotor adaptation do not undergo stabilization but a succession of active and inactive states triggered by the experimental context (e.g., Caithness and others 2004).

Regardless of the subjacent mechanism, there is no doubt that both forms of adaptation lead to the formation of long-term memories (here we refer to memories lasting 24 hours or more). Indeed, a unique session of adaptation learning leads to memory retention 5 months later (Shadmehr and Brashers-Krug 1997) and up to 1 year later (Yamamoto and others 2006). Huber and others (2004) have shown that savings observed 24 hours after re-adaptation to the same perturbation correlates with slow-wave activity during overnight sleep, providing neurophysiological evidence for sleep-induced consolidation (Huber and others 2004).

As in other types of motor learning, the intensity and frequency of practice affects the level of retention and savings. We have shown that 1 week of training on a visuomotor adaptation task leads to nearly perfect memory retention and very strong savings 1 month later (Della-Maggiore and McIntosh 2005) and up to 1 year later (Landi and others 2011) without intermediate practice, suggesting that these type of memories can be very persistent. Interestingly, simultaneous training to hit visual targets with a clay ball with and without wedge prisms (17° of lateral displacement) 4 days a week during 6 weeks leads to near perfect savings in both contexts that persist 2 years later (Martin and others 1996a). This latter study suggests that the brain can simultaneously store two neural representations, one of a perturbed visuomotor map
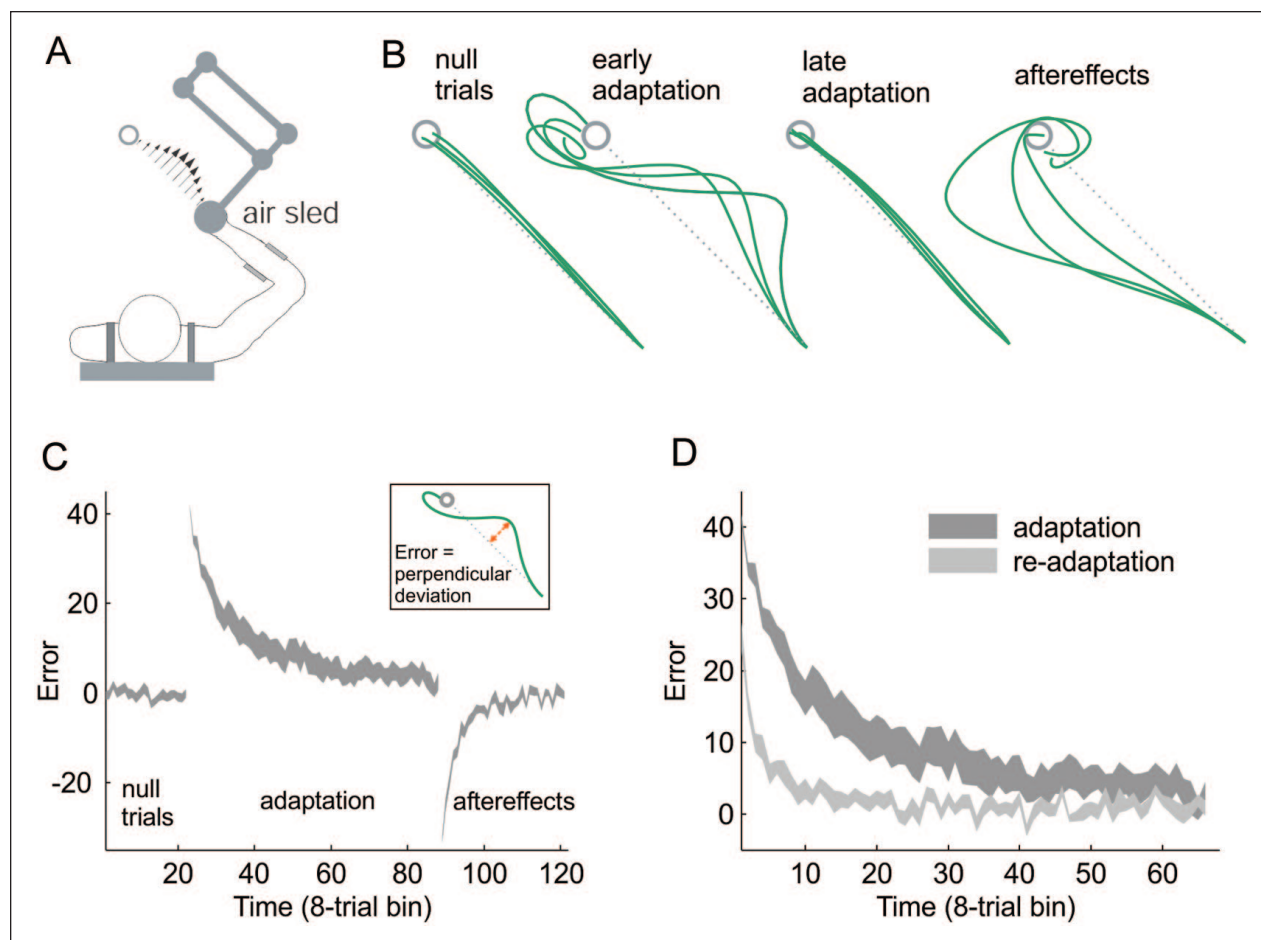
Figure 2. Psychophysics of motor adaptation. (A) Cartoon illustrating a subject adapting to a velocity-dependent force-field applied perpendicularly to the hand's movement direction during reaching to a visual target. (B) Illustration of hand trajectories produced during a force-field adaptation experiment. Shown are the hand paths corresponding to three trials of a subject making center-out reaching movements from a start point to a visual target. Hand paths are initially straight during training in the baseline period, in the absence of the perturbation (null trials). During early stages of adaptation they become deviated in the direction of the force. With practice, subjects learn to compensate the perturbation. Hand paths become straight during late adaptation phases. Aftereffects occurring when the force-field is turned off reflect the formation of a memory for the perturbation (redrawn from Della-Maggiore and others 2004) (C) Illustration of the time course of motor error during a typical adaptation experiment. Shown is the motor error computed based on the maximal perpendicular deviation of each hand path (inset) plot as a function of time (1 bin = 8 trials). Note the differences in performance during the baseline, adaptation, and aftereffects. (D) Adaptation learning shows Savings, here depicted as the improvement in the rate of learning during re-adaptation compared to the adaptation period.

and the other of an unperturbed visuomotor map. Thus, after long-term training the motor system acquires the ability to switch between these maps with minimal adaptation time and aftereffects.

Multiple Levels of Plasticity

Where in the motor system are long-term memories for new sensorimotor maps stored? In this section, we will review experimental evidence gathered from rodents and human and nonhuman primates pointing to possible targets of adaptation-related plasticity at different—neuronal and

systems—levels of organization. For practicality, we will distinguish between functional and structural plasticity, the former including persistent changes in neuronal activity, regional brain activity, and functional connectivity, and the latter referring to changes in neuronal morphology, gray matter concentration of cortical regions, and the integrity of white matter tracts.

Functional Plasticity at the Neuronal Level

Neurons in several motor areas are directionally tuned, that is, they respond more strongly when movements are

executed in one direction of space, their preferred direction (PD), than when they are executed in other directions (e.g., Georgopoulos and others 1982). Electrophysiological studies in monkeys have shown that reaching under a force-field (Gandolfo and other 2000) shifts the preferred direction of individual neurons in M1 to encode the direction of the compensatory force. However, these changes may not necessary reflect plasticity but, for example, changes in muscle activity resulting from the applied load. Inspired by Shadmehr and Mussa-Ivaldi's (1994) seminal work on force-field adaptation, the same laboratory carried out an experiment to identify neuronal correlates for the formation of an internal model in neurons of the primary motor cortex (Li and others 2001). For this purpose, they trained macaques on the same center-out reaching paradigm for one session while recording from M1 neurons and the arm muscles involved in reaching. In accordance with a study carried out in humans (Thoroughman and Shadmehr 1999), the preferred direction of the muscles shifted in the direction of the perturbation during adaptation but in the opposite direction during the washout, that is, when the force-field was turned off. Among all recorded cells, the authors identified two types of neurons with memory-like activity that did not match the muscle activity. Type I memory cells were characterized by a shift of their PD in the direction of the force-field that took place toward the *end* of adaptation and persisted throughout the washout. Type II cells were silent during adaptation but changed their tuning curve in the direction of the perturbation during the washout. Interestingly, at the population level, the PD of these two types of neurons balanced each other, leading to a pattern of tuning that resembled that of the muscle. Based on these findings, the authors proposed that single neurons change their tuning properties during motor learning whereas the neuronal population compensates these changes to preserve performance.

The use of chronic stable recordings has recently allowed to confirm these results and, furthermore, reveal that long-term training during five daily sessions leads to a persistent shift in the directional tuning curves of a subset of neurons (Richardson and others 2012). The persistence of this tuning profile throughout the baseline condition preceding the adaptation session—when kinematics are back to normal—is consistent with long-lasting plasticity. Similar results have been found when the perturbation is applied during reaching in only one of eight movement directions (Arce and others 2010b). At the population level, firing rates of neurons in M1 appear to be modulated based on the distance of their PD from the learned movement direction, with maximal activity in directions that oppose the perturbing force and minimal activity in the direction of the force (Arce and others 2010a). This spatial pattern of neuronal activity has been postulated to produce an adapted population vector.

Likewise, adaptation to a visuomotor rotation increases the activity of those motor neurons of which the preferred direction is the solution in hand space to compensate for the optical rotation (Paz and others 2003; Wise and others 1998). As in force-field adaptation, neuronal activity in M1 increases during late stages of learning and gets stronger in the solution direction as adaptation progresses. Changes in directional tuning have also been observed for visuomotor adaptation (Paz and others 2003). The results suggest that a local memory for the new visuomotor map with little or no generalization to untrained directions is represented in M1 neurons. Paz and Vaadia (2009) have proposed that these persistent changes in tuning curves may be brought about by Hebbian plasticity between visual and motor neurons that fire together during late stages of learning. Based on electrophysiological recordings (Bremner and Andersen 2012) and an imaging study carried out by our group (Barany and others 2014), we hypothesize that the "visual" target of plasticity is the posterior parietal cortex, a key cortical area where information regarding the target location and the state of the effector are thought to integrate to generate a movement vector.

Altogether, the electrophysiological work points to M1 as a key node in the formation of motor memories. The late emergence of changes in tuning curves and the persistence of these changes over several training sessions when kinematics are restored to native coordinates suggest that this region may be relevant in the stabilization of newly formed sensorimotor maps, in other words, in the process of motor memory consolidation.

Functional Plasticity at the Systems Level: PET and fMRI

Over the past decades, several studies aimed at identifying changes in brain activity elicited during *one* session of visuomotor adaptation. Early positron emission tomography (PET) work (Clower and others 1996) reported the activation of the contralateral posterior parietal cortex (PPC) during reaching with wedge prisms (left supramarginal gyrus). The posterior parietal cortex has long been linked to the processing of sensorimotor transformations necessary to plan spatially guided movements (Battaglia-Mayer and others 2003; Bernier and Grafton 2010; Snyder and others 1997). Interfering with sensorimotor coordination is thus likely to increase the metabolic demand of the area. Several PET and functional magnetic resonance studies (fMRI) later confirmed the participation of PPC during the acquisition phase of visuomotor adaptation (Diedrichsen and others 2005; Ghilardi and others 2000; Graydon and others 2005; Grefkes and others 2004; Krakauer and others 2004).

An increment in cerebellar activity is also characteristic of early stages of visuomotor and force-field adaptation

(Diedrichsen and others 2005; Krakauer and others 2004). Imamizu and others (2000) have shown that during adaptation to an optical rotation involving a computer mouse, activity increases in several regions of the cerebellum. Interestingly, activity surrounding the posterior fissure, initially proportional to the error rate, remains high once adaptation reaches the asymptote, suggesting that the cerebellum is relevant both for error correction and learning. These imaging results are in agreement with neuropsychological evidence indicating that extensive cerebellar damage compromises both the rate of learning and retention in several adaptation paradigms (Martin and others 1996b; Maschke and others 2004; Smith and Shadmehr 2005; Werner and others 2009). The implementation of ballistic experimental designs precluding the occurrence of corrective submovements confirmed that both adaptation and retention are impaired in cerebellar patients even when movement kinematics are barely compromised. Based on these findings, it has been proposed that the role of the cerebellum is not unique to error correction but involves sensory prediction error, that is, the ability to process the mismatch between the predicted sensory outcome based on an efferent copy of the motor command and the actual sensory feedback (Miall and others 2007; Tseng and others 2007). The former could be conveyed to the cerebellum through the posterior parietal cortex (Della-Maggiore and others 2004; Desmurget and others 1999).

Other regions of the motor network that increase activity during visuomotor adaptation include the premotor cortex (Krakauer and others 2004; Seidler and others 2006), the putamen, and the globus pallidus (Graydon and others 2005; Seidler and others 2006). Finally, prefrontal regions including dorsal and ventral portions of the right prefrontal cortex (Seidler and others 2006; Seidler and Noll 2008) and the pre-SMA (Krakauer and others 2004) appear to be systematically recruited during early stages of adaptation, which may reflect a change in strategy to counter the perturbation, or the inhibition of the old visuomotor map necessary to move in native visuomotor coordinates (Della-Maggiore and Mcintosh 2005).

Long-Term and Offline Imaging. The functional studies reviewed above indicate that several of the regions normally active during the execution of reaching or pointing increase their activity on the introduction of a sensorimotor perturbation. It is important, however, to distinguish among the specific components of the action that contribute to the functional changes identified in these structures. When interested in detecting plastic changes triggered by one learning session, the "online" approach is limited because, during execution, changes in activity are accompanied by changes in kinematics and dynamics that are very difficult to control for. In addition, as learning proceeds, newly formed memories can be retrieved online. Thus, execution, memory consolidation, and retrieval are simultaneously captured in the same brain scan. This leaves the experimenter with a confounded picture where plastic changes are not easily identified.

One way to get around this limitation is to track changes in brain activity across *several* training sessions. The rationale of this approach is based on the fact that as adaptation progresses motor error returns to baseline levels. Thus, although the time course of changes in brain activity may be influenced by kinematic and dynamic confounds during the initial phases, as learning progresses, persistent increments in activity are likely to reflect plasticity. With this aim in mind, several years ago we carried out a longitudinal PET study to identify changes in brain activity and functional connectivity that took place before and after adaptation to a complex optical rotation that involved changing the angle of perturbation depending on the movement direction (Fig. 3). Of note, the perturbation remained the same throughout the training session for each direction. Subjects continuously tracked the position of a target on a computer screen using a cursor controlled with their right hand with a joystick (Fig. 3A). Vision of the hand was blocked. The participants' task was to keep the distance between target and cursor as short as possible at all times. The experimental design is illustrated in Figure 3B. Six PET images were acquired from an experimental group and a control group in two different sessions, at the beginning and at the end of 6 days of training (4 blocks of 13 minutes per day). On day 0, all subjects performed an unperturbed version of the task until performance reached an asymptote. The average of the distance between target and cursor for the last block was used as a measure of baseline. On day 1 the experimental group was exposed to the visuomotor rotation. The control group performed the task in the absence of the perturbation throughout the whole experiment. Five PET images were acquired every 11 minutes on day 1 and one PET image was acquired on day 6.

On average, subjects achieved visuomotor adaptation within 3 days (Fig. 3C). All subjects from the experimental group showed aftereffects. Visuomotor adaptation was associated with a shift in the relationship between brain activity and performance that took place throughout adaptation (Fig. 3D, bottom plot). This pattern was specific to the experimental group. Brain areas depicted in yellow in the figure, correlated positively with the brain-behavior correlation profile displayed in the plot, whereas regions depicted in blue correlated negatively with this brain-behavior profile. Specifically, during early stages of adaptation, improvements in performance were associated with greater activity in dorsolateral and ventrolateral
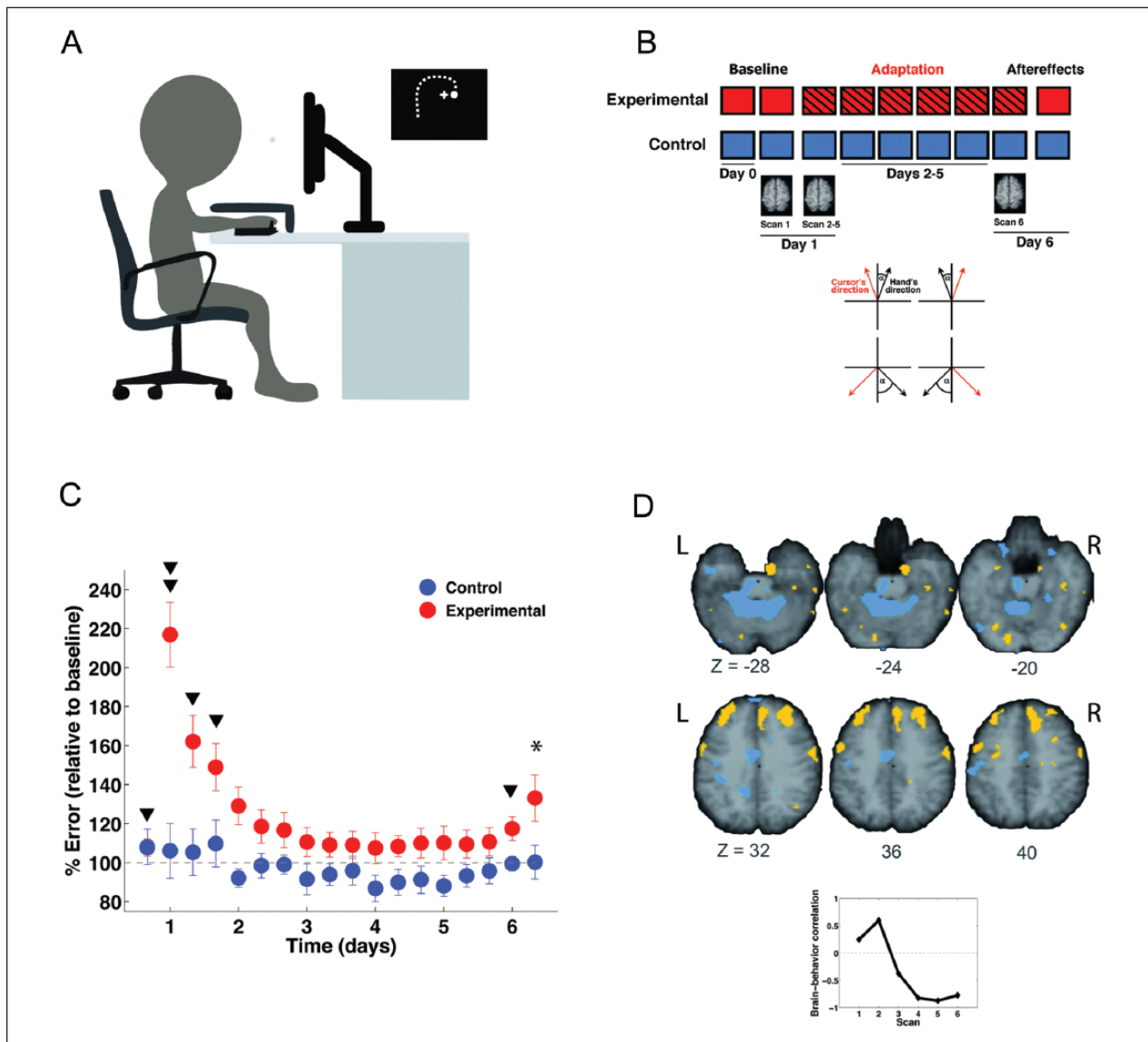
Figure 3. Functional changes induced by long-term adaptation. (A) Participants used a joystick with their right hand to track the random movement of a visual target on a computer screen (filled circle). The position of the hand was displayed as a cursor (+). Vision of the hand was blocked. (B) The experiment was 7 days long. All subjects carried out the visuomotor task in the absence of the perturbation on day 0 until a plateau was reached. On day 1, they performed one additional block of baseline during which they were PET scanned. A complex visuomotor perturbation consisting in rotating the cursor position by the specular image of the hand position was applied during the second block of practice in experimental subjects (see plot in the bottom). The rotation varied with the direction of movement. Two PET scans were obtained during the second block and two additional scans during the third and fourth blocks. A sixth scan was acquired after 6 days of practice, once adaptation was achieved. Aftereffects were recorded by removing the perturbation in the last block. Control subjects performed the same task without the perturbation and were scanned at the same time points. (C) Shown is the mean visuomotor error (distance between target and cursor) ± SE of each 13-minute block throughout the experiment. Arrowheads indicate the blocks during which PET images were obtained. Aftereffects are illustrated with an asterisk. (D) Shown are the results from conducting a partial least square analysis in which the relationship between brain activity and behavior was examined across groups. Shown is the spatial pattern of activity identified by the analysis (top) and the corresponding experimental effects (bottom). For simplicity, only the profile corresponding to the experimental group is shown in the plot because this effect was driven entirely by this group. The latter represents the correlation between brain activity depicted in the images and the level of performance. Regions in yellow correlated positively whereas regions in blue correlate negatively with the profile of the plot. (C) and (D) were redrawn from Della-Maggiore and McIntosh (2005).

prefrontal cortex, frontal eye fields, and extrastriate areas of the dorsal visual pathway (brain regions depicted in yellow in Fig. 3D). These regions were activated bilaterally. However, during later stages of adaptation, improvements in performance were associated with lower activity in these areas but greater activity in a sensorimotor network including the left (contralateral) sensorimotor cortex, left cingulate motor area, anterior cerebellum, and left posterior parietal cortex (regions colored in blue in Fig. 3D). Crucially, this pattern persisted during the second scanning session, that is, after adaptation was achieved and performance returned to baseline levels, suggesting that this network may be associated with the formation of a motor memory for the new sensorimotor map. Further examination of the functional connectivity through correlational analysis revealed that the learning-related shift in brain activity from attentional to motor areas was associated with a progressive increment in the functional connectivity of a network including the anterior cerebellum, contralateral sensorimotor, and posterior parietal cortex that remained strong after visuomotor adaptation was achieved. Our study suggests that the connectivity of this network undergoes plastic changes associated with visuomotor adaptation.

Another way to get around the confound associated with scanning during execution is to scan the brain at rest. Resting-state fMRI has become increasingly popular over the past few years. It consists of identifying spontaneous oscillations in the blood oxygen level dependent signal (BOLD) while subjects lie at "rest," that is, in the absence of external stimulation and without performing any task. Resting-state oscillations have been interpreted to reflect the energy demands of neuronal populations that, by firing synchronously, have wired together through synaptic plasticity (Lewis and others 2009). Exploratory analysis of resting-state activity has reliably identified eight different networks at the individual level and at the group level (e.g., Beckmann and others 2005). The fact that these functional networks map into the underlying anatomy (Hagmann and others 2008) and are altered by callosotomy (Johnston and others 2008) provide strong evidence supporting the existence of a neural origin for resting-state activity.

Recently, Albert and collaborators have used resting-state fMRI to examine, offline, learning-related changes associated with visuomotor adaptation (Albert and others 2009). The authors compared a rest scan obtained 4 minutes after adapting to an optical rotation with a rest scan obtained before performing the task. The analysis identified two neural networks that showed learning-related changes as compared to a control group that was not exposed to the perturbation: the default-mode frontoparietal network, which was more functionally connected in the experimental than in the control group, and

a cerebellar network, not identified among the reliable resting-state networks, which was only detected in the experimental group. The identification of the latter network is in line with the imaging and patients' studies mentioned above and, furthermore, suggests that the cerebellum may be involved in early stages of memory consolidation. It is important to take into consideration, however, that the low intensity of training chosen for this study (only 11 minutes of adaptation) may have not sufficed to engage brain networks necessary for long-term memory. On the other hand, the lack of a link between functional connectivity and improvements in performance questions the specificity of this network to the formation of motor memories.

Functional Plasticity at the System Level: TMS and TDCs

It is important to remark that functional imaging is correlational in nature and, therefore, cannot disambiguate if a certain region undergoes plastic changes supporting long-term memory or indirectly contributes to plasticity in other region(s) as part of the network. The advent of transcranial magnetic stimulation (TMS), a noninvasive technique designed to interfere with brain activity within a physiologically relevant timeframe (100 ms), provided neuroscientists with a powerful tool to dissect the cortical mechanisms underlying the formation of motor memories. By interfering with neuronal processing of the target area TMS can be used in humans to establish a causal link between brain activity and performance. Another technique that has gained great popularity is transcranial direct current stimulation (TDCS), which, depending on the polarity of the delivered current, enhances (anodal) or decreases (cathodal) corticospinal excitability. In contrast with TMS, TDCS cannot be used in event-related designs but needs to be applied for a continuous period of 15 to 30 minutes to have a detectable impact on behavior.

TMS can be applied as single, double, or triple pulses during the movement (on-line mode) or repetitively (rTMS) prior or after training (off-line mode). Inspired on the physiological and imaging findings reviewed above, a few TMS studies have examined the role of the primary motor cortex in motor adaptation. Single pulses of TMS applied over this region at the offset of reaching affects the immediate retention of memories during visuomotor adaptation, as evidenced in the faster rate of decay of aftereffects (Hadipour-Niktarash and others 2007). This finding has been corroborated by a TDCS study showing that 15 minutes of anodal stimulation over M1 during training has no effect on the rate of learning but enhances memory retention immediately after visuomotor adaptation (Galea and others 2011). On the other hand, a similar protocol to that applied by Hadipour-Niktarash and
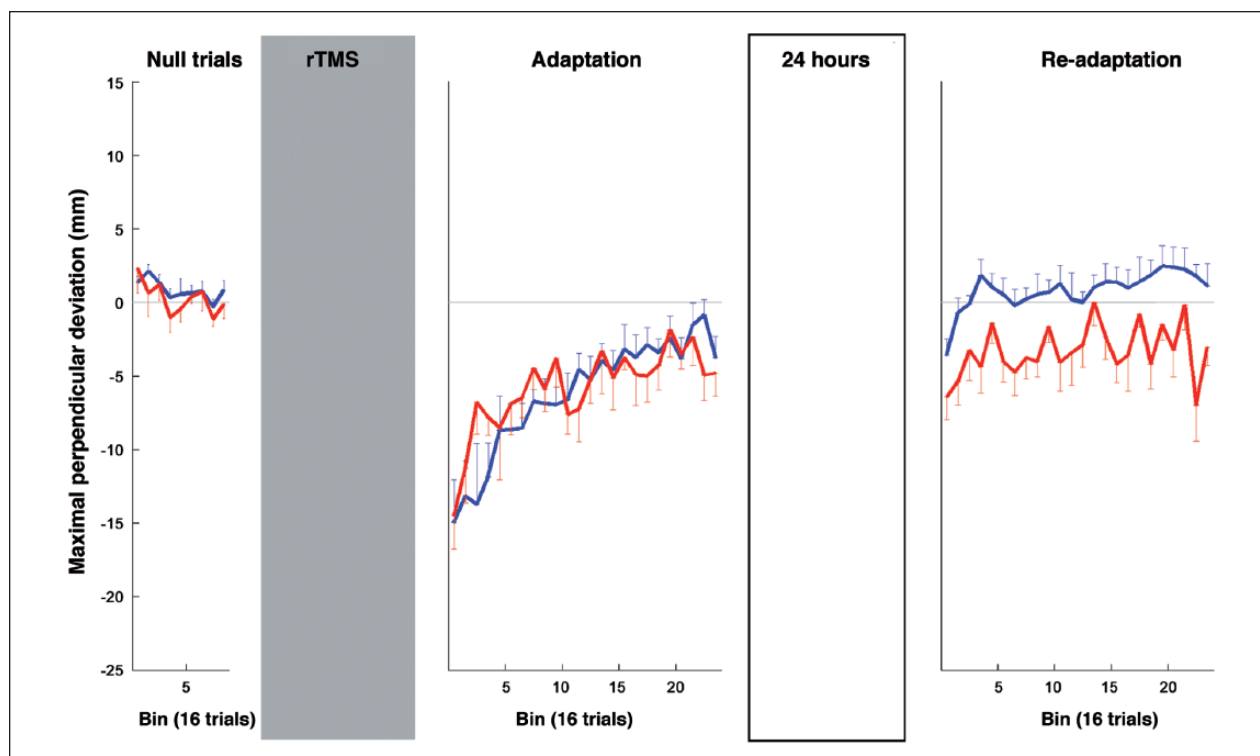
Figure 4. Primary motor cortex is necessary for the formation of long-term memories. Shown is the mean motor error ± SE averaged every 16 trials for experimental (red) and control (blue) groups during force-field adaptation. Experimental subjects were subjected to 15 minutes of 1-Hz rTMS before adaptation, whereas the control group was untreated. TMS affected retention in the experimental but not the control group, evidenced at test, during re-adaptation to the same field 24 hours later. Redrawn from Richardson and others (2006).

others (2007) has been shown to affect the peak force applied by the subject during late stages of force-field adaptation, once performance approaches a plateau (De Xivry and others 2011).

The studies mentioned above explored memory retention immediately after learning. The role of M1 on long-term memory formation of new sensorimotor maps (i.e., memories that last 24 hours or more) was first explored using repetitive TMS (Fig. 4). The application of an rTMS protocol known to decrease corticospinal excitability (15 minutes at 1 Hz) immediately prior to force-field adaptation has no effect on movement execution or learning but impairs memory retention measured 24 hours later during re-adaptation (Richardson and others 2006). This effect is more pronounced in the movement direction of the muscle directly stimulated with TMS, in this case, the biceps. The application of rTMS over M1 also reduces anterograde interference during sequential adaptation to opposite force-fields (Cothros and others 2006). Recently, we have shown that washing out behavioral gains prior to re-adaptation to an optical rotation interferes anterogradely with the retrieval of the visuomotor map learned 24 hours earlier (Villalta and others

2013). Interestingly, the application of rTMS on M1 following the protocol used by Richardson and others (2006) reduces the amount of anterograde interference compared to a sham group (Fig. 5), suggesting that masking of the memory for the perturbation takes place in this region of the cortex. Thus, in agreement with the neurophysiological literature reviewed above, M1 appears to intervene during late stages of adaptation and has a fundamental role in the formation and the expression of long-term memories for this kind of learning.

TDCS has also been applied to assess the role of the cerebellum in visuomotor adaptation. Fifteen minutes of anodal stimulation of the ipsilateral cerebellar cortex increases the speed of learning but has no effect on memory retention (Galea and others 2011). TMS can also be used in combination with electromyography to infer the connectivity between two regions. In particular, cerebellar connectivity can be measured by assessing the size of motor evoked potentials induced after sequentially stimulating the ipsilateral cerebelar cortex and the contralateral M1 following a 5-ms interval. In agreement with the TDCS experiment mentioned above, the connectivity of the lateral cerebellum increases during early stages of

adaptation to an abrupt optical rotation but not during performance on random or gradual perturbations, or during unperturbed trials (Schlerf and others 2012). The finding that the cerebellar cortex is most active during successful compensation of the perturbation is in agreement with the observation that cerebellar patients are much slower than healthy controls at motor adaptation to abrupt perturbations (Martin and others 1996b; Smith and Shadmehr 2005), but adapt similarly when the perturbation is introduced gradually (Criscimagna-Hemminger and others 2010).

Based on the preponderant role of the posterior parietal cortex in imaging studies of adaptation, we conducted an experiment to identify the contribution of the PPC to force-field adaptation (Della-Maggiore and others 2004). Single pulses of TMS applied 40 ms after the onset of a reaching movement spares initial stages of learning but significantly affects late stages of adaptation (Fig. 6). TMS stimulation also affected retention measured immediately after learning as evidence in the very first trial after removing the perturbation. Retention was not assessed at 24 hours. The region of the left posterior parietal cortex targeted in our study (superior bank of the middle intraparietal sulcus), which is functionally connected to the dorsal premotor cortex (Chouinard and others 2003), receives both proprioceptive and visual inputs in the monkey (Battaglia-Mayer and others 2001). This makes it a suitable neural substrate to compute an error signal using the position of the hand based on central (Sperry 1950) and/or peripheral (proprioceptive, visual) information, and the target as inputs. A recent study provides strong evidence suggesting that this region may in fact be crucial to process proprioceptive feedback (Reichenbach and others 2014). Our results are in line with the proposed role of the PPC in state estimation during voluntary movement (Desmurget and others 1999).

Structural Plasticity at the Neuronal and System Levels

At the systems level, functional imaging and, more conclusively, TMS studies indicate that both the primary motor cortex and the posterior parietal cortex participate during late stages of learning, whereas the cerebellum appears to be involved during early stages. The primary motor cortex is also crucial for long-term retention of new sensorimotor maps. On the other hand, neurophysiological studies carried out in macaques strongly suggest that the formation and persistence of these new sensorimotor maps depend on the flexible remodeling of tuning curves in M1 neurons. Is there evidence that such changes have an impact on the structure of underlying brain circuits?

At a microscopic level, structural plasticity associated with learning a motor skill such as skilled reaching or learning to use a tool is manifested in the generation of new dendritic spines (Xu and others 2009), axon collaterals (Chklovskii and others 2004; Hihara and others 2006), and myelination (Sampaio-Baptista and others 2013). Structural changes associated with skill learning are also detectable at the macroanatomical level through the use of noninvasive MRI techniques. The acquisition of T1 images can provide information regarding gray matter concentration, whereas diffusion-weighted images (DWI) are sensitive to the diffusion of water in the brain. Due to the inhomogeneity imposed by the biological tissue, diffusion in the brain is not isotropic (equal in all directions) but anisotropic. Measures derived from DWI images such as fractional anisotropy (FA) or median diffusivity (MD) can be informative of microscopic details of the underlying tissue architecture such as the integrity of white matter tracts, axon caliber, myelination, or fiber-crossing points. DWI images can also be used to infer brain connectivity based on white matter profiles, a technique known as tractography.

Using DWI we have recently shown that the rate of visuomotor adaptation but not the level of retention is associated with higher fractional anisotropy in regions of the cerebellum that receive information from the cortex and project to M1 via thalamus (Della-Maggiore and others 2009). In other words, faster subjects show stronger level of fractional anisotropy in these areas. Our results suggest that the speed of visuomotor adaptation may be determined partly by brain anatomy. Although this type of cross-sectional studies provide relevant information regarding the putative role of a brain structure/pathway in learning and/or memory, the measure is indirect and may not relate to the level of expertise gained over life but reflect innate or inherited abilities.

With the aim of identifying sites of plasticity in the motor system induced by visuomotor adaptation, we carried out a longitudinal study that involved relatively intense training (45 min/day) during one continuous week (Landi and others 2011). Figure 7 illustrates the design and main results of the study. T1 and DWI images were obtained before and after training on the same complex visuomotor adaptation paradigm used in our functional study (Della-Maggiore and McIntosh 2005). Given that our previous work showed that 6 days of training in the control group induced no further learning beyond that reached during the baseline nor changes in functional connectivity within the motor network, a control group was not used in the current study (Fig. 7A). On average, adaptation was achieved after 4 days of training. During the second exposure to the perturbation a year later (re-adaptation), subjects adapted within a minute, indicating the presence of strong savings and a long-lasting motor memory (Fig. 7B).
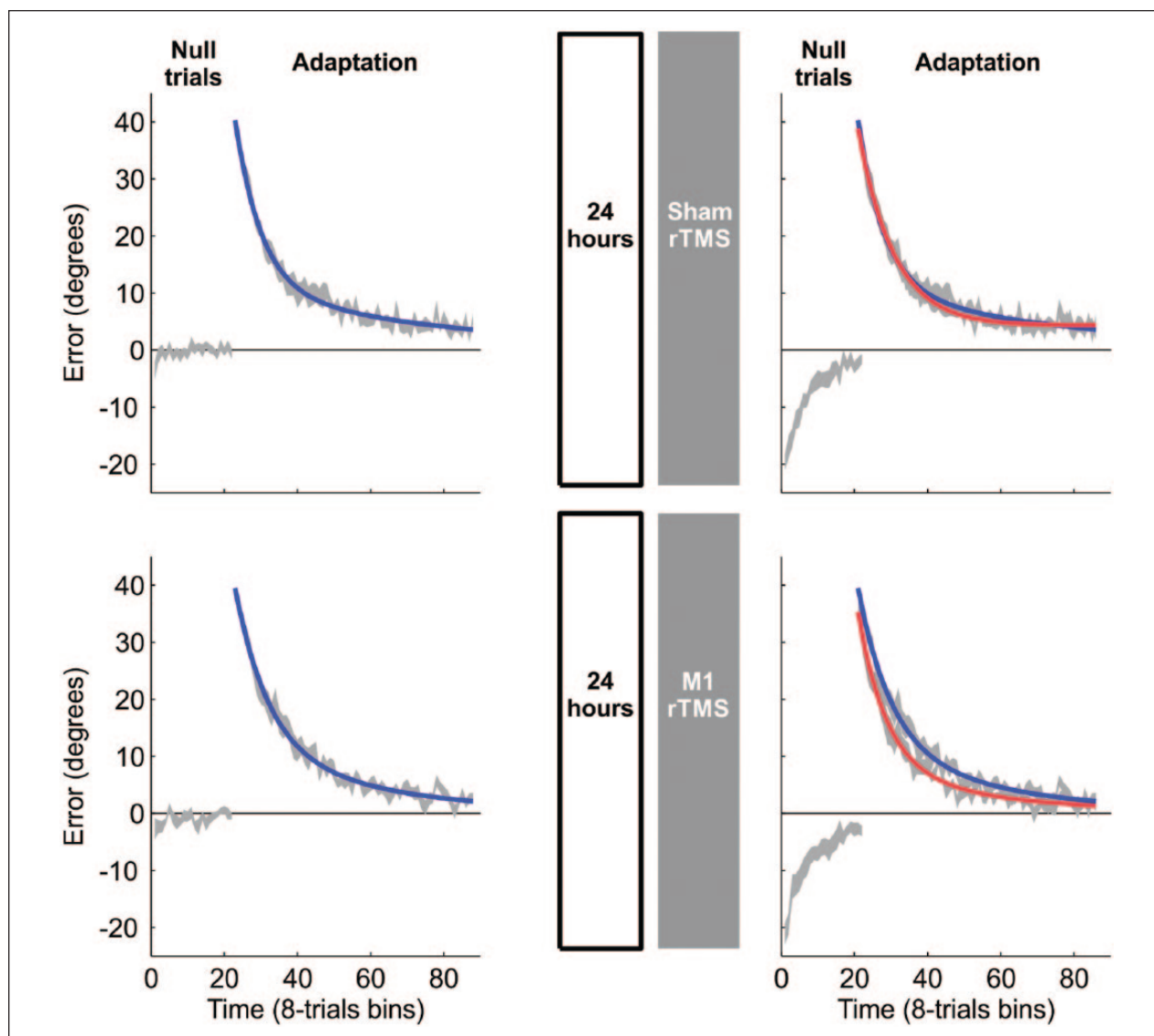
Figure 5. Release from anterograde interference takes place in the primary motor cortex. All subjects adapted to a visuomotor rotation (blue curve) and were washed out 24 hours later immediately before re-adapting to the same perturbation (red curve). Shown is the mean angular visuomotor error ± SE (1 bin = 8 trials) before and after applying 15 minutes of 1-Hz rTMS over the vertex (Sham group, top panel) and the left primary motor cortex (Experimental group, bottom panel) prior to the washout. TMS applied over M1 decreased the level of anterograde interference observed in the Sham group. Redrawn from Villalta and others (2013).

One week of motor training induced an increment in gray matter concentration over the hand area of the contralateral primary motor cortex that correlated positively with improvements in performance a year later (Fig. 7C,i), and an increment in fractional anisotropy of white matter tracts underneath this region that correlated with the speed of learning (Fig. 7C,ii). Tractography confirmed that gray matter and white matter changes were confined to descending pathways including the corticospinal tract (CST), suggesting a functional link between

the mechanisms driving these events (Fig. 7C,iii). We have previously shown that this protocol induces long-lasting learning-related changes in the functional connectivity of a network including M1, PPC, and cerebellum (Della-Maggiore and McIntosh 2005). Our findings are consistent with our previous work, and both the electrophysiological and the TMS/TDCS studies reviewed above, and shed new light on the neural substrates of motor learning. On the one hand, we show that only 1 week of training is associated with topographically
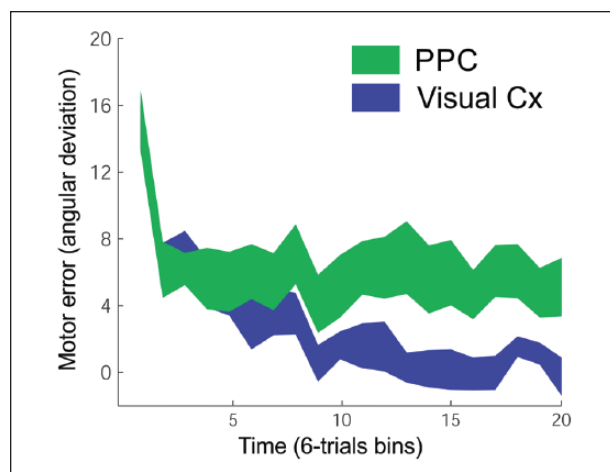
Figure 6. The posterior parietal cortex participates in late stages of adaptation. All subjects performed a force-field adaptation task with their right arm while they were stimulated with single pulses of TMS 40 ms after movement onset. Shown is the mean motor error (averaged every six trials) measured as the initial angular deviation for a Sham group stimulated over the visual cortex and an Experimental group stimulated over the superior bank of the middle intraparietal sulcus (superior parietal lobule) of the left posterior parietal cortex. Although initial learning was similar across groups, middle to late stages of adaptation were significantly affected by TMS in the Experimental group. Redrawn from Della-Maggiore and others (2004).

specific changes in the structure of the primary motor cortex. The colocalization of gray and white matter clusters to the same pathways reinforces the anatomical specificity of our results. In addition, the fact that increments in GMC of the motor cortex predicted the level of savings *1 year* later points to this region as a key node of a network where motor memories for new visuomotor maps are stored. Ours is the first demonstration that early structural changes induced by adaptation may have an impact on behavior after such a long period in the absence of training. Our findings therefore underscore the relevance of structural plasticity both in the formation and persistence of new sensorimotor maps.

What do the MRI changes detected in our study reflect in terms of microscopical changes? The correspondence between structural plasticity and macroscopic alterations detected with MRI has only recently begun to unveil. Work from rodents indicates that skilled reaching and rotarod learning induce new dendritic spines in M1, a minimal portion of which persist up to 3 months (Xu and others 2009). Synaptogenesis is thought to result from long-lasting Hebbian plasticity (e.g., LTP; Engert and Bonhoeffer 1999) and is also accompanied by glial changes. Astrocyte surface increases following LTP induction (Wenzel and others 1991), whereas glial

hypertrophy is induced by motor skill learning (Kleim and others 2007). A number of recent studies examining learning-related changes in brain structure through the combination of histological and imaging tools open the possibility to map plastic changes occurring at the microscopic level into corresponding changes at the systems level using MRI (Lerch and others 2011; Sagi and others 2012; Sampaio-Baptista and others 2013). For example, Sagi and others (2012) have reported that learning a spatial task induces DWI changes in the hippocampus and parahippocampus of both humans and rats after only 2 hours of training. Histological examination of this region suggests that MRI changes correlate with an increment in the number/size of synapses and with glial hypertrophy, the latter of which is likely to explain the changes detected in such a short time scale given the low spatial resolution of MRI. Given the time scale of training chosen in our study, it is likely that longitudinal alterations in GMC resulted from (a) an increment in spine density triggered by the strengthening of cortico-cortical connections (LTP) during directional tuning and/or (b) glial hypertrophy induced by LTP.

As for the biological basis of macroscopical alterations in white matter, several factors could have led to longitudinal changes in FA. Myelination, axonal packing density, and axon diameter have been proposed to influence fractional anisotropy (Beaulieu 2002). The colocalization of WM and GM clusters to descending pathways including the corticospinal tract opens the possibility that functional changes in the efficacy of motor circuits—such as LTP—may have led to axonal remodeling and/or myelination. Whereas the former may be triggered by the occurrence of new synaptic spines (Chklovskii and others 2004; Hihara and others 2006), the latter could result from increased neuronal activity (Demerens and others 1996). A recent optogenetic study carried out in rats showing that stimulation of neurons in layer V of premotor cortex induces oligodendrogenesis, thickening of the myelin sheath, and improvements in motor performance provides evidence supporting the latter possibility (Gibson and others 2014).

Closing Remarks

The aim of this work was to review the most relevant literature on visuomotor and force-field adaptation pointing to putative substrates of neural plasticity associated with this type of learning. Convergent experimental evidence from neurophysiological, transcranial stimulation and imaging studies point to the primary motor cortex as a major player in the formation and persistence of long-term memories. These plastic changes likely involve synaptic and axonal remodeling associated with persistent changes in the tuning curves of M1 neurons. On the other
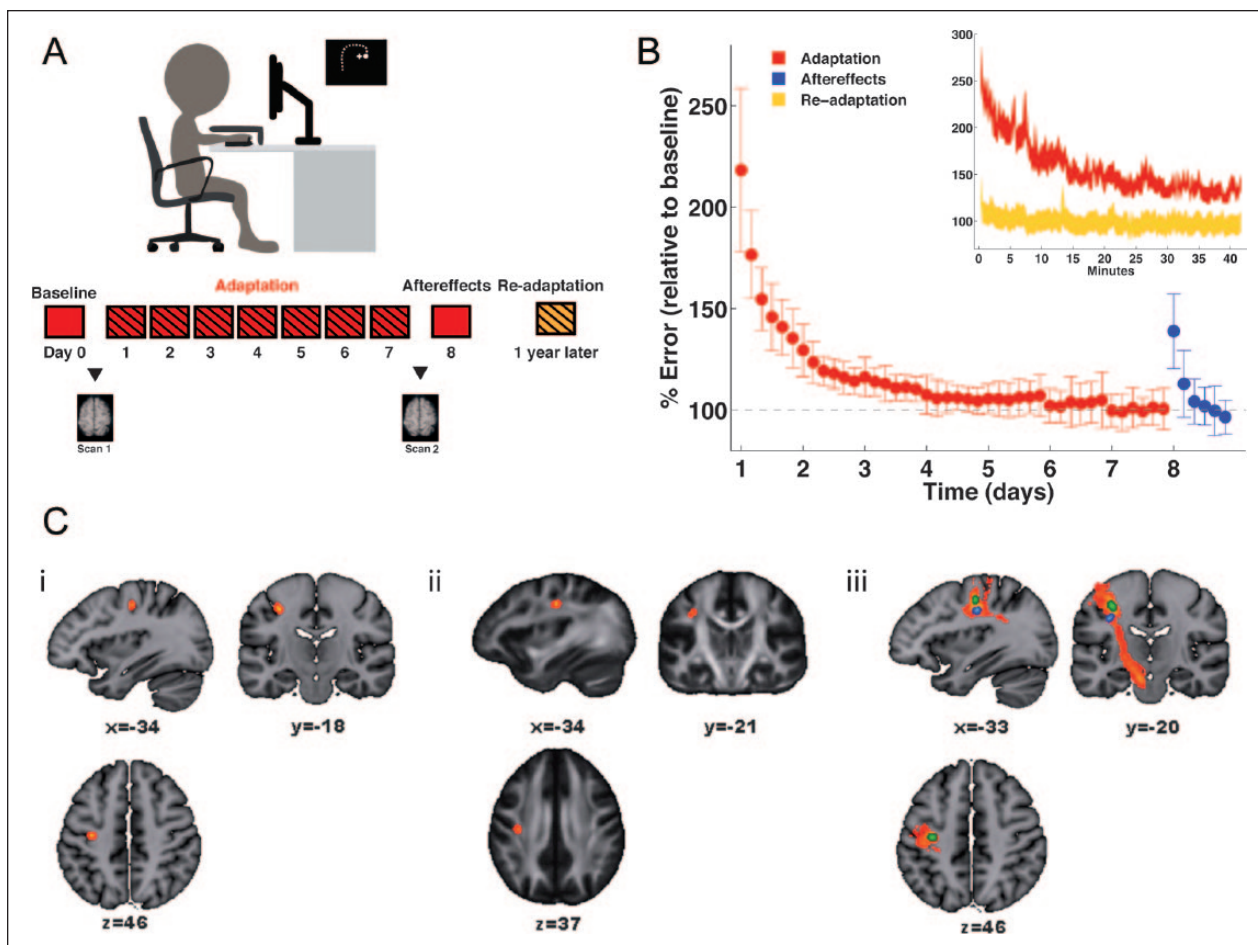
Figure 7. Structural plasticity associated with visuomotor adaptation. (A) Experimental paradigm and design. Subjects performed the same task as in Figure 3 but for seven consecutive days (~45 min/day). T1 and DWI images were acquired on days 1 and 7 before and after training. Aftereffects were measured on day 8, and retention was measured 1 year later during re-adaptation. (B) Time course of the mean visuomotor error (distance between target and cursor) ± SE of each 7-minute block throughout the experiment. The inset shows the time course of decay in the level of visuomotor error during the first session of adaptation (red) and during the session of re-adaptation 1 year later (yellow). Note the differences in retention and the rate of learning. (C) One week of adaptation induced increments in gray matter concentration in the left primary motor cortex (i) and an increment in fractional anisotropy in white-matter fibers underlying that cortical region (ii). Tractography connects these two clusters as part of the descending fibers that include the corticospinal tract (iii). (B) and (C) were redrawn from Landi and others (2011).

hand, the posterior parietal cortex, presumably involved in movement planning and state estimation, appears to be crucial during late phases of adaptation and memory retention immediately after training. Yet further work is required to evaluate whether this region is only necessary to acquire a new sensorimotor map in combination with M1 through the recalibration of reference frames or whether it is also involved in the formation and persistence of sensorimotor memories. In contrast, most work on the cerebellum point to a key role of this structure during early stages of adaptation, probably to successfully counter the perturbation through sensory prediction error. Altogether, the studies reviewed here suggest a temporal order of involvement within this network, with the cerebellum involved in acquisition and the PPC and M1 in the consolidation (or fixation) of new sensorimotor maps.

Declaration of Conflicting Interests

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