Prism Adaptation in M1

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Abstract

■ During prism adaptation (PA), active exposure to an optical shift results in sustained modifications of the sensorimotor system, which have been shown to expand to the cognitive level and serve as a rehabilitation technique for spatial cognition disorders. Several models based on evidence from clinical and neuroimaging studies offered a description of the cognitive and the neural correlates of PA. However, recent findings using noninvasive neurostimulation call for a reexamination of the role of the primary motor cortex (M1) in PA. Specifically, recent studies demonstrated that M1 stimulation reactivates previously vanished sensorimotor changes 1 day after PA, induces after-effect strengthening, and boosts therapeutic effects up to the point of reversing treatment-resistant unilateral neglect. Here, we articulate findings from clinical, neuroimaging, and noninvasive brain stimulation studies to show that M1 contributes to acquiring and storing PA, by means of persisting latent changes after the behavioral training is terminated, consistent with studies on other sensorimotor adaptation procedures. Moreover, we describe the hierarchical organization as well as the timing of PA mechanisms and their anatomical correlates, and identify M1 as an anatomo-functional interface between low- and high-order PA-related mechanisms. ■

THE PRINCIPLE OF PRISM EXPOSURE AND ADAPTATION

Prism adaptation (PA) is an experimental psychology paradigm extensively used since the end of the 19th century to study brain plasticity (Redding, Rossetti, & Wallace, 2005; Welch, 1974). When individuals first look through wedge prisms that optically shift the visual field, typically by 10°–15°, they are unable to report anything else than slight visual distortions and/or color fringes. To their own surprise, when they first attempt to quickly reach for a visual object, they see their hand reaching off the target (active exposure). Actually, their motor system planned their movements toward the *perceived* rather than the *actual* target position (terminal error). Terminal error is gradually reduced within a few trials and reaching accuracy returns to pre-exposure levels (compensation). When pointing movements are repeated for several trials beyond error compensation, the visuomotor system gradually incorporates the visual shift producing a stable and accurate pointing execution toward the target (true adaptation). When prisms are removed, large errors in the opposite direction are typically made (sensorimotor after-effect), thus demonstrating the occurrence of adaptation during prism exposure. Overall, the basic PA procedure involves 1) pre-exposure baseline measurement of performance without visual feedback, 2) active exposure to prismatic displacement with visual feedback, and 3) post-exposure measurement of performance without visual feedback that, compared with pre-exposure measure, provides an index of the after-effect (see Figure 1).

PA has been studied for over a century and appears deceptively simple (Redding et al., 2005), as it has long been considered as a pure sensorimotor plasticity phenomenon. A resurgent interest in PA arose when cognitive effects of PA were described about 20 years ago. In the first report (Rossetti et al., 1998), it was described that unilateral neglect, a spatial cognition disorder characterized by lack of conscious processing of contralesional stimuli, was ameliorated after a few minutes of active exposure to right-shifting wedge prisms. Manifestations of spatial neglect observed in visuomotor tasks such as daisy drawing from memory, copying drawings, cancellation task, and line bisection improved significantly after PA. From this study on, a wave of publications explored the cognitive effects of PA on spatial neglect (Jacquin-Courtois et al., 2013) and assessed whether healthy individuals would exhibit related cognitive effects (Michel, 2016; see Figure 1). Further investigations addressed neural bases of PA and of the expansion of its effects to the high level cognition (Anelli & Frassinetti, 2019; Michel, Bonnet, Podor, Bard, & Poulin-Charronnat, 2019; Schintu, Freedberg, Alam, Shomstein, & Wassermann, 2018; Tissieres, Crottaz-Herbette, & Clarke, 2018).

FUNCTIONAL NEUROANATOMY OF PA

Different processes seem to develop during PA. Traditional conceptualization (Redding et al., 2005; Weiner, Hallett, & Funkenstein, 1983) advocates the presence of at least two

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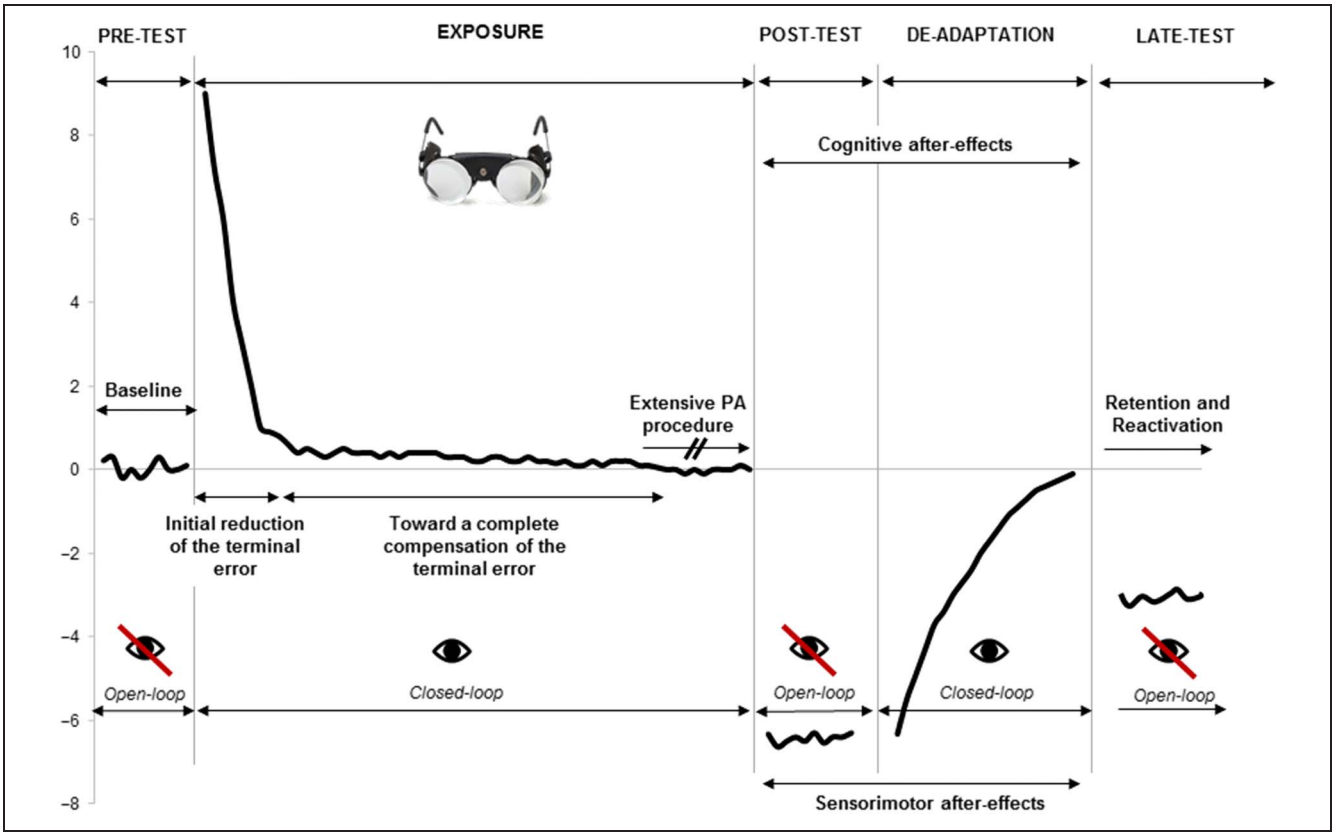


Figure 1. Timeline of PA procedure. The classical PA procedure involves three distinct phases. The present figure depicts the evolution of pointing performance across the PA procedure. Performance refers to the lateral errors between the aimed target and the terminal position of the finger. PRE-TEST enables the measurement of baseline performance (i.e., before any exposure to the prismatic shift) without visual feedback (open-loop pointing). During EXPOSURE, participants are actively exposed to the prismatic shift with visual feedback (closed-loop pointing). They initially experience errors in the direction of the prismatic shift, which are rapidly reduced during the first trials. The following trials allow to reduce completely the lateral errors and to regain baseline accuracy. POST-TEST allows to measure performance upon prism removal, that is, after-effects. Post-test is performed in the same conditions than pre-test, that is, without visual feedback. After-effects are oriented in the direction opposite to the prismatic shift. When participants perform movements with visual feedback after EXPOSURE, they de-adapt: performance is initially biased toward the direction opposite to the prismatic shift (after-effects), and then gradually regains baseline levels. The classical procedure of PA entails PRE-TEST, EXPOSURE and POST-TEST. Assessment of cognitive after-effects could be ensured during post-test. Assessment of retention and reactivation represents late tests, which are realized after a substantial delay. Notably, all measurements during post-test are necessarily also assessed during pre-test to obtain baseline performance.

processes: i) a fast strategic process ("recalibration") would permit a rapid compensation of the pointing behavior (terminal error), and ii) a slower automatic process ("realignment") would be responsible for true adaptation and after-effect development (Prablanc et al., 2020; Redding & Wallace, 2006a, 2006b). Recalibration would entail strategic adjustments of motor plans based on previous terminal errors. Realignment would be triggered by sensory prediction errors (Gaveau et al., 2018) and would adjust the coordination between visual and proprioceptive sensory maps that has been disrupted by the visual shift (Petitet, O'Reilly, and O'Shea, 2018; Redding et al., 2005). This conceptualization in PA parallels the two-state computational model accounting for a range of behaviors in the force field adaptation tasks, in which individuals adapt their reaching movements to force field perturbations induced by a robotic device (Smith, Ghazizadeh, & Shadmehr, 2006). The two-state model postulates two distinct processes in motor adaptation, one that would respond strongly to error but with poor retention and another that would respond weakly to error but with better retention (see Appendix).

In PA, a third ultraslow process has been recently proposed (Inoue et al., 2015) to account for the behavioral performance after prolonged prism exposure (150–500 trials) complementing Smith et al.'s (2006) findings. This three-state model in PA (Inoue et al., 2015) would account for a reduced speed of decay and increased retention as the number of exposure trials increases. For instance, McIntosh, Brown, and Young (2019) found that prolonged prism exposure (more than 250 movements) and high prism powers (15°) produced most robust and reliable cognitive after-effects. Finally, a recent neuro-computational account on PA (Petitet et al., 2018) proposed an algorithmic explanation of the computations and operations that drive behavior during PA, and offered means to generate and test behavioral predictions. However, a detailed description of such computational account is beyond the purposes of this paper, which has been conceptualized within the traditional PA framework.

Within this theoretical background, neuroimaging and neurostimulation studies have attempted to unravel the neural correlates of PA (Panico, Rossetti, & Trojano, 2020). On the one hand neuroimaging studies converged in identifying several regions in the parietal cortex involved in the processes of error compensation (Chapman et al., 2010; Luauté et al., 2009; Danckert, Ferber, & Goodale, 2008; Clower et al., 1996), whereas the cerebellum would be involved in realignment and after-effect development (Küper et al., 2014; Chapman et al., 2010; Luauté et al., 2009); parietal, temporal, and prefrontal regions would contribute to PA expansion on the cognitive level (Crottaz-Herbette et al., 2017; Crottaz-Herbette, Fornari, & Clarke, 2014; Saj, Cojan, Vocat, Luauté, & Vuilleumier, 2013). On the other hand, stimulation studies confirmed the causal role of the cerebellum in the process of realignment and after-effect development (Panico, Sagliano, Nozzolillo, Trojano, & Rossetti, 2018; Panico, Sagliano, Grossi, & Trojano, 2016), consistent with early lesion studies (Weiner et al., 1983).

Most interestingly, recent neurostimulation studies revealed that appropriate stimulation of motor cortex could produce after-effect reactivation in healthy participants (Panico et al., 2017) and boost retention of after-effects and PA outcomes in neglect patients (O'Shea et al., 2017). From a theoretical perspective, these neurostimulation findings are highly informative. Indeed, they seem to suggest that, after PA, some plastic dormant activity is stored within intact sensorimotor circuits and could be triggered to reactivate PA after-effects and, if appropriately manipulated, to drive recovery in neuropsychological rehabilitation.

MOTOR MEMORY FORMATION, RETENTION, AND CONSOLIDATION IN M1

Several studies in the psychophysiological, neuroimaging, and neurostimulation fields seem to suggest a role of M1 in the acquisition, consolidation, and retention of motor memory. Within the electrophysiological field, it has been demonstrated (Pollok, Latz, Krause, Butz, & Schnitzler, 2014) that acquisition and early consolidation of a motor sequence were associated with a stepwise decline of alpha-band event-related desynchronization in M1; moreover, the improvement in RTs was linearly associated with the amount of beta power suppression. A relevant role of alpha-band during learning in M1 was reported also by Sauseng, Klimesch, Gerloff, and Hummel (2009) who found that the higher the alpha amplitude, the lower the excitation level in M1. Recently, Amo et al. (2017) observed a significant increase in gamma-band activity at the end of a task involving hand movements with respect to earlier stages of the task.

These electrophysiological studies seem to be in line with the idea that electrophysiological activity in M1 changes as a function of motor learning. Neurostimulation studies further confirmed this assumption. Bütefisch, Khurana, Kopylev, and Cohen (2004) found that TMS applied to the motor cortex contralateral to the hand used in a motor-task-enhanced acquisition of motor memory, whereas TMS applied to the motor cortex ipsilateral to the training hand reduced it. Moreover, stimulation of the contralateral motor cortex enhanced the training effects when applied in synchrony with the training motions (up to 60-min retention). Similarly, Hamel, Trempe, and Bernier (2017) demonstrated that TMS disruption of M1 activity selectively impaired consolidation of motor memories (assessed 24 hr later) whereas it did not influence performance in a visuomotor adaptation paradigm. This effect was specific when TMS was delivered during the hold phase of adaptation and for the M1 area, as TMS delivered in late adaptation or over adjacent dorsal premotor cortex had no significant effect. The role of M1 in motor learning and retention has been also demonstrated by two tDCS studies using different motor tasks. Galea, Vazquez, Pasricha, Orban de Xivry, and Celnik (2011) showed that anodal tDCS over M1 resulted in a marked increase in retention of a newly learnt visuomotor transformation in a rotation adaptation task. Karok, Fletcher, and Witney (2017) demonstrated that excitatory anodal tDCS over M1 reduced average completion time in a manual dexterity task, and this effect was maintained after 1 week. Moreover, in this latter study, tDCS over M1 enhanced consolidation over training sessions in two tasks of visuomotor adaptation with a long-term (1-month) retention.

Importantly, visuomotor rotation (VR) adaptation and PA present several similarities that allow to draw parallels concerning the potential involvement of M1 in processes at work, although methodological differences might account for divergent processes contribution (see Appendix).

PA IN M1

Notwithstanding the above-mentioned studies demonstrating M1 contribution in several motor tasks, the role of M1 in PA literature seems to be strongly underestimated. This can be partially because of the high level of complexity in PA, which represents at the same time a task to assess motor learning and a tool to affect the highest levels of cognition. Only recently, two studies in the neurostimulation field challenged the traditional conceptualization of the neural mechanisms and adaptive processes during PA and addressed the contribution of M1 in sensorimotor (O'Shea et al., 2017; Panico et al., 2017) and cognitive after-effects of PA (O'Shea et al., 2017).

Role of M1 in Sensorimotor After-Effect

Panico et al. (2017) assessed the possibility of affecting consolidation of PA and possibly reactivating adaptation circuits by means of anodal (excitatory) tDCS over the left M1 during exposure to 10° right-shifting prisms. The results demonstrated that promoting activation of M1 by tDCS reactivated the sensorimotor after-effect 24 hr after PA (with no need of repeating PA). Moreover, the reactivated after-effect was still present 24 hr later. Similarly, O'Shea

et al. (2017) stimulated M1 by anodal tDCS while healthy participants and patients with neglect adapted to 10° right-shifting prism glasses by making rapid pointing movements toward visual targets. The results demonstrated that tDCS increased the magnitude of sensorimotor after-effect during adaptation and enhanced after-effect persistence in the washout and retention phases. These findings showed that a single session of tDCS enhanced consolidation of PA, stabilizing sensorimotor after-effects.

A mechanism of repetition-dependent plasticity is likely involved in sustaining M1 contribution to PA, as in other sensorimotor tasks (Hamel et al., 2017). In force field adaptation, M1 disruption by TMS is able to impair performance when the same motor commands are activated repeatedly, that is, during late exposure when the performance reaches a plateau, but not during the early error reduction process, in which motor commands are progressively updated (Orban de Xivry, Criscimagna-Hemminger, & Shadmehr, 2011). Similarly, extensive repetition of movements with prismatic lenses on would prompt M1 consolidating long-term memory, even if the contribution of other brain areas outside M1 needs to be investigated as well (Herzfeld, Pastor, et al., 2014; Herzfeld, Vaswani, Marko, & Shadmehr, 2014). Moreover, in line with Orban de Xivry et al. (2011), M1 contribution should be assessed in PA experimental procedures inducing gradual or abrupt perturbations of the visual field (e.g., by using the multiple-step or single-step PA procedures as in Prablanc et al., 2020; Michel, Pisella, Prablanc, Rode, & Rossetti, 2007) and in experimental settings allowing to dissect motor learning components during visuomotor adaptation (for a review, see Spampinato & Celnik, 2020).

The neurobiological and molecular mechanisms sustaining reactivation of sensorimotor after-effect after adaptation would parallel those sustaining motor learning (Bütefisch et al., 2004). Indeed, any kind of motor training leads to encoding and storing durable traces (Shadmehr & Brashers-Krug, 1997). Sustained motor training would leave a memory trace in M1, likely reflecting the kinematic details of the practiced movements (Classen, Liepert, Wise, Hallett, & Cohen, 1998). This would mean that it is possible to enhance this plastic process by synchronous stimulation to the motor cortex engaged in the training motions, consistent with the Hebbian principle that synaptic potentiation occurs when its pre- and postsynaptic elements are simultaneously active (Hebb, 1949). When inputs converge onto a target neural structure in temporal synchrony, they can enhance cortical plasticity (Iriki, Pavlides, Keller, & Asanuma, 1989; Baranyi & Szente, 1987; Baranyi & Feher, 1981). It is worth mentioning at this point that, in Panico et al. (2017), PA in the first day of investigation was coupled with active stimulation of M1, to maximize the temporal synchrony between motor training and synaptic potentiation. The above-mentioned studies could suggest that noninvasive brain stimulation targeting pyramidal tract neurons (Rothwell, 1997), when M1 is engaged in a training, would enhance motor plasticity.

Role of M1 in Cognitive After-Effects

As far as expansion to cognition is concerned, the study by O'Shea et al. (2017) also showed that M1 stimulation coupled with PA determined persistent improvements of neglect on standard paper-and-pencil tests such as star cancellation, line bisection, and copy drawing (up to 18 and 46 days after the intervention). Thus, these findings suggested that motor cortex stimulation can enhance cognitive after-effect as well.

The mechanism by which M1 might contribute to expansion of PA effects to the cognitive domain is not clearly understood. Presumably, M1 represents an interface between sensorimotor and cognitive after-effects in PA. Indeed M1 activation during PA contributes to develop a bias opposite to the prism displacement within its adapting circuits and then might trigger cognitive expansion, that is, cognitive and therapeutic PA effects (O'Shea et al., 2017; Michel, 2016; Jacquin-Courtois et al., 2013). Anatomo-functional connections between motor cortex, middle temporal gyrus, tempo-occipital regions, and prefrontal areas could participate in the expansion mechanism involved in triggering PA cognitive after-effects (Crottaz-Herbette et al., 2014, 2017; Saj et al., 2013; Luauté et al., 2006, 2009).

Taken together, evidence from these studies paves the way for updating the traditional neuro-anatomical models of PA, which focused solely on the contribution of the parietal and cerebellar regions, and the cognitive models of PA, which did not mention a system devoted to the consolidation, retention, and possibly reactivation of the PA after-effect.

EMBEDDING M1 IN PA MODELS

In the last 20 years, several cognitive models addressed the effects of PA in healthy individuals and in brain-damaged patients, with particular attention to spatial neglect, after the first study by Rossetti et al. (1998).

Redding and Wallace (2006b) conceptualized neglect as a deficit in positioning and sizing the region of space appropriated for the current task. On this basis, the authors proposed that PA could ameliorate the dysfunctional positioning (but not sizing) of the workspace relevant for fulfillment of a task, thanks to an improved positioning of spatial attention (although with a narrowed focus). This model did not provide strict description of the brain areas sustaining PA effects but referred to classic neuropsychological evidence that the ability to adapt to the prismatic displacement is spared in patients with intact cerebellum and damaged posterior parietal cortex (PPC; Pisella, Rode, Farnè, Tilikete, & Rossetti, 2006; Pisella et al., 2004), whereas it is lost in patients with damaged cerebellum, and intact PPC (Baizer, Kralj-Hans, & Glickstein, 1999; Martin, Keating, Goodkin, Bastian, & Thach, 1996; Weiner et al., 1983).

Within the interhemispheric balance framework positing that right-neglect patients exhibit a bias to the left side, Pisella et al. (2006) proposed that PA is able to restore balance between the two hemispheres. PA would act at the

cerebellar level, ipsilateral to the prismatic deviation, and would indirectly inhibit the left hemisphere, thus restoring (or at least improving) the hemispheric balance. Serino, Angeli, Frassinetti, and Làdavas (2006) too ascribed neglect amelioration after PA to resetting of oculo-motor system and proposed that the occipital lobe has a significant role in modulating PA and neglect recovery.

As far as the level of complexity of PA effects is concerned, several studies reported PA effects on higher cognitive functions (Anelli & Frassinetti, 2019; Michel et al., 2003, 2019; Schintu et al., 2018; Tissieres, Fornari, Clarke, & Crottaz-Herbette, 2018; Michel, 2016). Danckert and Ferber (2006) and Striemer and Danckert (2010) proposed that PA alters computations carried out by the dorsal visual stream in the PPC, but not information processing within the ventral stream in the temporal cortex. For this reason, PA would only affect attention, particularly the disengagement process, and motor control. The observed dissociation between effects on tasks requiring a motor response and those requiring pure perceptive judgments after PA has been accounted for also by a recent computational model by Leigh, Danckert, and Eliasmith (2015). In their model, authors simulated line bisection behavior in neglect using the neural engineering framework and supported that prisms primarily influence the behaviors normally thought to be controlled by the dorsal stream (Leigh et al., 2015).

Moreover, several recent studies provided further cues for comprehending the neural correlates underlying PA effects on visuospatial processing. Saj et al. (2013) reported a bilateral recruitment of frontoparietal network mediating the cognitive and rehabilitative effects of PA on spatial attention, in line with Pisella et al. (2006). Similarly, Clarke and Crottaz-Herbette (2016), starting from findings showing that rightward PA is able to shift hemispheric dominance in the ventral attentional system, proposed a model providing explanation for the effect of rightward PA. According to this model, the dorsal attentional system and the ventral attentional system contribute to visual reorienting with a functional specialization. While the dorsal attentional system would be mainly in charge of endogenous allocation and maintenance of visuospatial attention, the ventral attentional system would be primarily implicated in detecting stimuli appearing at unattended locations. The dorsal and ventral attentional systems would interact closely, the left and right dorsal attentional systems would be interconnected, but the right and not left dorsal attentional system would exert an inhibitory contralateral effect. In hemispatial neglect, the inhibition that the right dorsal attentional system exerts on the left one is disrupted by the lesion, resulting in an overactive left dorsal attentional system and a subsequent attentional bias toward the right side. PA would restore right-to-left inhibition, by changing hemispheric dominance in the ventral attentional system and restoring ventral attentional system inputs to the dorsal attentional system, thus explaining neglect amelioration.

In the above-mentioned models, the contribution of the motor cortex in the adaptive and cognitive effects of PA has not been discussed, thus leaving out some recent findings that could be of high relevance for enhancing comprehension of M1 functional properties and in the contest of neuropsychological rehabilitation. Indeed, recent evidence from the neurostimulation field (for a review, see Panico et al., 2020) supported the idea that PA is mediated by a brain network including the cerebellum, parietal, temporal, and frontal regions. Such areas would contribute to the processes of recalibration and realignment, that is, the adaptive mechanisms responsible for the sensorimotor and cognitive effects of PA, making possible the phenomena of generalization, transfer, and expansion.

Here, we provide a chiseled description of the time flow and the hierarchy of PA-related plasticity phenomena based on the complete set of neuropsychological, functional neuroimaging, and neurostimulations data available so far (Figure 2). In very early stages of exposure to prismatic glasses, the cerebellar cortex and deep cerebellar nuclei

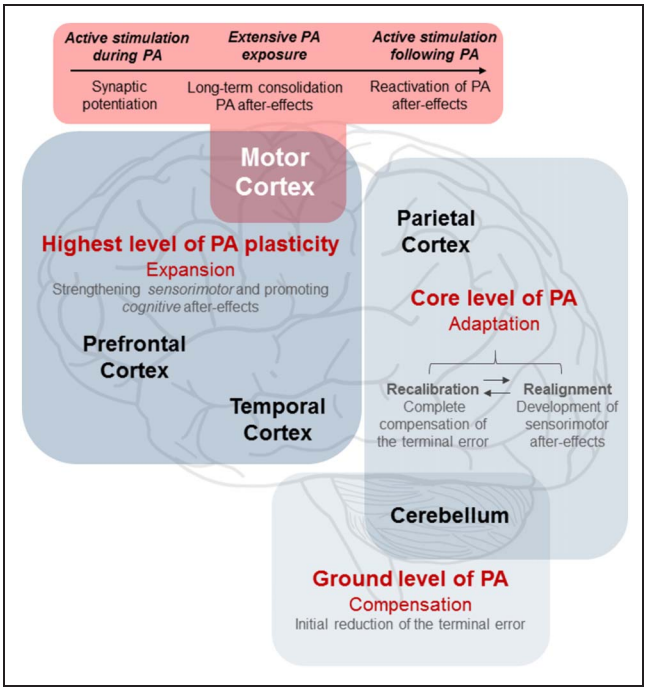


Figure 2. Hierarchical organization of PA mechanisms. PA mechanisms can be considered as organized in a hierarchical architecture (here depicted as squares in different blue color shades): at the ground level of PA, the cerebellum and subcortical nuclei are involved in initial transient compensation of the terminal error; distinct anatomical regions in the parietal cortex and the cerebellum contribute to the core level, fulfilling adaptive processes of PA (recalibration and realignment), and generating its sensorimotor effects; the highest level of PA-related plasticity is responsible for storage and consolidation of the newly acquired visuomotor transformation in the primary motor cortex, and triggers cognitive after-effects through connections with the temporal cortex and prefrontal areas. The primary motor cortex is involved in several processes during PA (in light red): synchronous stimulation over the motor cortex engaged in the training motions is able to boost long-term consolidation of the motor memory and strengthen PA after-effects by synaptic potentiation; the newly acquired visuomotor transformation leaves a trace in the motor cortex, which can be triggered to reactivate PA after-effects and drive recovery in neuropsychological rehabilitation.

are engaged in initial compensation of terminal error and on-line motor control (Panico et al., 2018). This would represent the ground level for adaptation. Then, the cerebellum would assume a crucial role in generating the sensorimotor effects of PA, allowing fulfillment of recalibration and realignment. As suggested by some recent findings (Panico et al., 2016, 2018; Küper et al., 2014; Chapman et al., 2010; Luauté et al., 2009) within the cerebellar and the parietal regions, likely distinct anatomical areas would participate to the recalibration and realignment processes with a further involvement of the superior temporal gyrus and superior temporal sulcus in realignment (Luauté et al., 2009). This would represent the core level of PA. Cerebellofrontal connections would be responsible for the storage of the newly acquired visuomotor transformation in M1, making possible PA consolidation. Indeed, indirect connections between the cerebellum and the motor cortex (Bostan, Dum, & Strick, 2018; Schlerf, Galea, Spampinato, & Celnik, 2015; Kishore, Meunier, & Popa, 2014) would exert a modulatory effect (Ates, Alaydin, & Cengiz, 2018). Connectivity changes between the cerebellum and M1 have been also demonstrated by using the cerebellar inhibition paradigm before and after visuomotor learning (Spampinato & Celnik, 2020). One clinical study showed that both cerebellar inhibition paradigm and PA are affected in patients with essential tremor (Hanajima et al., 2016), but no study yet addressed changes in connectivity between the cerebellum and M1 during PA in healthy or brain-damaged participants. Consolidation of sensorimotor after-effect in M1 would prompt a mechanism of cognitive expansion, thus triggering cognitive after-effects through anatomo-functional connections with the middle temporal gyrus and temporo-occipital regions, and of prefrontal areas. This would represent the highest level of PA-related plasticity. The cognitive after-effects of PA would be mediated by the development of realignment through bottom–up connections between the middle temporal gyrus and temporo-occipital regions, and prefrontal areas (Crottaz-Herbette et al., 2014, 2017; Saj et al., 2013; Luauté et al., 2006, 2009). At this level, the changes in hemispheric dominance in the ventral attentional system induced by sustained prism exposure would affect hemispheric balance and the ventral attentional system inputs to the dorsal attentional system, thus exerting PA effects on healthy and brain-damaged individuals.

The newly acquired visuomotor transformation related to sustained prism exposure would leave a trace in M1 in a temporal window after the behavioral training; such traces would be responsible for late or off-line PA effect (O'Shea et al., 2017; Panico et al., 2017). The neurobiological and molecular mechanisms sustaining these effects in M1 would probably follow the Hebbian principles of synaptic potentiation that occur in any kind of learning (Hamel et al., 2017; Herzfeld, Vaswani, et al., 2014; Hebb, 1949).

In the clinical context, the above presented model predicts a crucial role of M1 contralateral to brain damage in deploying rehabilitative effects of PA. This claim is supported by neuropsychological studies showing that frontal lesions may moderate response to PA treatment (Goedert, Chen, Foundas, & Barrett, 2020) and that the contralesional left hemisphere might contribute to neglect amelioration exploiting sensorimotor and cognitive circuits in the frontal lobe (Lunven et al., 2019).

DISCUSSION AND FUTURE DIRECTIONS

More than 20 years have elapsed from the first clinical application of PA (Rossetti et al., 1998), and hundreds of publications have been produced, but the mechanisms of PA have not been entirely understood yet. The available models on PA functioning mainly relied on evidence from the clinical and neuroimaging fields. In this paper, we provided a more comprehensive model including findings from the neurostimulation context.

The model presented here could prompt future experimental studies aimed at understanding the exact neurobiological and molecular mechanisms sustaining PA effects in M1 as the behavioral training takes place. The possibility to study dynamic changes associated with PA is challenging and difficult to assess by the traditional neuroimaging techniques such as MRI and PET. These limitations are mainly related to the need of adjusting the PA setting to the neuroimaging setting.

A closer investigation of the timing of M1 involvement in consolidating sensorimotor after-effect and triggering expansion to cognitive after-effects warrants further studies combining highly time-resolved electrophysiological recordings and neurostimulation methods. This combination of electrophysiological and stimulation techniques seems to be even more relevant as recent studies did not report consistent behavioral effects of tDCS on visuomotor adaptation, raising the issue of the effectiveness of noninvasive brain stimulation within clinical contexts (Jalali, Miall, & Galea, 2017).

It is worth underlining that the main purpose of this paper was to revise evidence on the role of the motor cortex in PA and its possible applications in the clinical setting. However, the sensory mechanisms of PA and their relationship with somatosensory brain areas deserve attention in future studies. Indeed, PA involves visual, motor, and proprioceptive components contributing to error reduction and after-effects (Welch, Widawski, Harrington, & Warren, 1979; Welch, 1974; Welch, Choe, & Heinrich, 1974; Harris, 1963). PA is thought to imply a change in the felt position of the arm relative to the body (Harris, 1963), a change in the felt direction of gaze (Kalil & Freedman, 1966) and an assimilated corrective response that adds to the proprioceptive and visual changes to produce the after-effect (Welch et al., 1974). The possibility that M1 is also involved in integrating multisensory information by means of its connections with associative premotor and parietal cortices (Isayama et al., 2019) should be addressed. Indeed, an instance of the interplay between M1 and other somatosensory and parietal areas (Isayama et al., 2019) comes from literature on the rubber hand illusion (for a review, see Butler,

Héroux, & Gandevia, 2017), in which the ability to solve the discrepancy between motor, visual, and proprioceptive information seems to be related with M1 excitability (Munoz-Rubke, Mirdamadi, Lynch, & Block, 2017; Della Gatta et al., 2016). The possible role of somatosensory cortex in PA is suggested by a study on healthy individuals in which somatosensory suppression by means of TMS affected proprioceptive and visual prisms' after-effects in a PA paradigm in which only terminal visual feedback was provided (Yoon, Lee, Huh, Lee, & Lee, 2014). Analogously, in the context of force-field adaptation, animal studies demonstrated that inhibition of somatosensory cortex could abolish the ability to update subsequent motor commands (Mathis, Mathis, & Uchida, 2017), and studies on healthy humans showed that TMS inducing a suppression of somatosensory cortex affected motor memory consolidation (Kumar, Manning, & Ostry, 2019).

Taken together, these findings suggest a contribution of somatosensory areas in PA and, at the same time, an effect of PA on somatosensory processing, paving the way for a new field of investigation. It is also important to mention at this point the possibility that previous tDCS findings on the role of M1 in after-effect consolidation, retention, and reactivation (O'Shea et al., 2017; Panico et al., 2017) could have been partially affected by weak widespread stimulation of surrounding somatosensory areas, in addition to the targeted M1. To this purpose, future studies are needed to disentangle the specific contribution of sensorimotor areas to PA, by using high-definition tDCS paradigms (To, Hart, De Ridder, & Vanneste, 2016) and TMS.

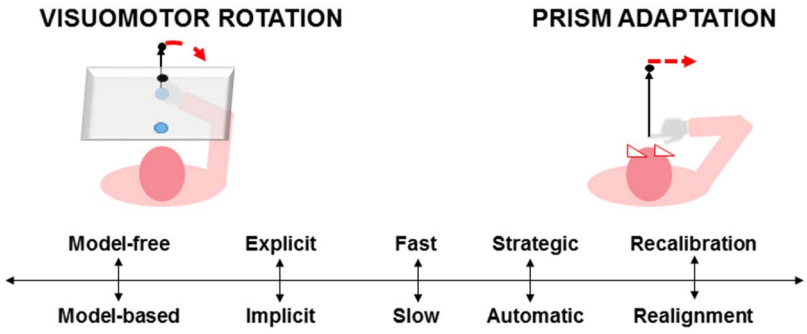
APPENDIX. VR AND PA: UNIFYING VISUOMOTOR ADAPTATION?

The field of sensorimotor adaptation suffers a lack of consensus concerning the terms used to describe processes at work (Prablanc et al., 2020). Here, we highlight the different terminologies adopted in two related fields, PA and VR, both taping visuomotor learning. PA is described in this paper, whereas in VR, a cursor represents the position of the moving hand, and participants do not have direct vision of their limb (Krakauer, 2009). Therefore, in VR, rotations can be applied to the cursor and the mapping between motor commands and desired outcomes can be manipulated. In both prism and VRs paradigms, a visuomotor perturbation is applied and participants experience large initial errors that are gradually reduced until regaining baseline performance. In both paradigms, when the perturbation is removed, after-effects can be observed, that is, errors in the direction opposite to initial errors.

Both paradigms are thought to involve two error-based correction mechanisms: a fast process and a slow process (Smith et al., 2006), but various terms are used to define these processes in the two paradigms. The terms *recalibration* and *realignment* are very specific to the prism literature. Recalibration refers to the process allowing the rapid reduction of initial errors by means of strategic adjustment of motor plans (Redding et al., 2005), but note that recalibration in other fields refers to a broader definition, that is, the general modification of a previously learned movement in response to perturbations (as in Spampinato & Celnik, 2020). In PA literature, recalibration is related to the strategic, the fast, or the explicit process described in VR literature, and might be considered parallel to the so-called model-free process, that is, to the ability to compensate for the perturbation without any change in internal models, according to Haith and Krakauer (2013). Realignment in PA literature would instead correspond to the automatic, the slow, or the implicit process described in VR literature, and to the model-based processes driven by sensory prediction errors to update internal models when facing a visuomotor perturbations according to Haith and Krakauer (2013).

Differences in terminology are related to different historic and cultural perspectives, but one must keep in mind that they also differ by crucial methodological aspects. As an instance, the nature of sensory reafferences varies considerably in the two sensorimotor paradigms: Whereas PA allows the direct view of the moving hand, VR involves a virtual representation of the hand, that is, a moving cursor on the screen. Moreover, PA provides expansion of after-effects toward high-level cognitive functions, whereas this has not been fully explored in VR.

These differences might influence the respective contribution of the above-mentioned processes during sensorimotor adaptation and must be considered when comparing results arising from different fields (Fleury,



Prablanc, & Priot, 2019). Nonetheless, attempts at using uniform terminology might reveal useful for favoring exchanges and comparisons among different fields.

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Diversity in Citation Practices

A retrospective analysis of the citations in every article published in this journal from 2010 to 2020 has revealed a persistent pattern of gender imbalance: Although the proportions of authorship teams (categorized by estimated gender identification of first author/last author) publishing in the *Journal of Cognitive Neuroscience (JoCN)* during this period were M(an)/M = .408, W(oman)/M = .335, M/W = .108, and W/W = .149, the comparable proportions for the articles that these authorship teams cited were M/M = .579, W/M = .243, M/W = .102, and W/W = .076 (Fulvio et al., *JoCN*, 33:1, pp. 3–7). Consequently, *JoCN* encourages all authors to consider gender balance explicitly when selecting which articles to cite and gives them the opportunity to report their article's gender citation balance.

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