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Prismatic Adaptation as a new tool for non-invasive brain modulation: evidence from different neurophysiological techniques.

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COMBINING TDCS WITH PRISMATIC ADAPTATION FOR NON INVASIVE NEUROMODUALTION OF THE MOTOR CORTEX

INTRODUCTION

Non-invasive brain stimulation (NIBS) tools, such as transcranial magnetic stimulation (TMS) and transcranial electric stimulation (tES), have been widely used to modulate brain activity and alter motor and cognitive functions. In the last few years, attention has been raised on a new promising concurrent method in order to change visuospatial attention and motor cortex excitability: prismatic adaptation (PA). PA consists of a protocol which combines a visuo-motor pointing task to a particular kind of goggles that can modulate people's perception of the visual field (for more information read below). Because of the spatial shift induced by prisms, this protocol has been widely applied within the clinical practice in order to rehabilitate neglect patients.

Although the neuroscientific community seems to agree on PA effects on neglect patients' symptoms, but also on normal people, some laboratories have been raising some concerns about its efficacy. These concerns are due to some discrepancies in results when prisms are applied. In fact, whether several evidences of its efficacy exist, not enough is known about its actual effects on brain functions. To this aim, studying how PA actually affects normal brain circuits would be needed. Only a better understanding of how PA works on normal brain would enable us able to better apply this protocol as a rehabilitative tool. Moreover, a few recent results have raised novel and exciting ideas and opportunities about the possibility to use PA as an innovative tool for non-invasive neuromodulation.

The present work inserts itself within the neuroscientific strand of research with the purpose of studying PA neural correlates and, especially, its after-effects. The aim is to shed further light to the neural mechanisms underlying PA by means of the review of the existing literature and of two studies that combine NIBS and neurophysiological techniques. In

particular, the attention will be focused on two of the brain areas identified to be involved by PA after-effects: the posterior parietal cortex (PPC) and the primary motor cortex (M1).

The present work is structured in four chapters. *Chapter I* presents the literature about what, to date, we know regarding PA. In particular, its behavioural effects on patients and normal people are described. Some methodological issues are also presented.

Chapter II reports the studies that have been showing the neural circuits involved and affected by PA. Moreover, a new model is illustrated taking into account the by Striemer and Danckert's (2010a), but integrated with new insights.

Finally, *Chapter III* and *Chapter IV* report two experimental works. The first one (Chapter III) presents the data about PA after-effects on posterior and central EEG signatures. Chapter IV, instead, reports the results of PA after-effect, assessed by single pulse TMS over the M1 either alone or when combined with transcranial direct current stimulation (tDCS).

CHAPTER I

PRISMATIC ADAPTATION: FUNCTIONS AND METHODS

A brief introduction

Prismatic adaptation is based on the preliminary experiments published by Stratton 130 years ago (1896) in which the author used, for the first time, the prismatic goggles in order to change one subject's visual field. PA was, therefore, introduced in clinical studies by Rossetti *et al.* for the very first time in 1998. Indeed, the authors started to use the rightward prism deviation for the treatment of unilateral visuospatial neglect (usually simply called *neglect*), believing it could reduce the severity of patients' symptoms.

Nowadays, a few variants of PA exist. The most common version consists of a visuo-motor pointing task with prisms that displace the visual field either to the right or the left. Thus, when pointing while wearing prismatic goggles, participants initially mispoint toward the direction of the prismatic shift and experience a visuo-proprioceptive mismatch between their movement and the actual position of the target. Following a few trials (10-15), participants are able to adapt their movement to the new visuo-motor contingencies and compensate for the erroneous bias. After this adaptation and with goggles removed, an after-effect is observed which is manifested in pointing movements being biased to the opposite direction of prism deviation (Striemer *et al*., 2016) and that is translated to other visuospatial tasks.

An interesting feature of PA is its long lasting effect. Several studies tested PA after-effect duration with both healthy subjects and patients. Schintu, Pisella, Jacobs, Salemme, Reilly and Farnè (2014) assessed the time-course of the adaptation-induced modifications in a classical perceptual line bisection task with healthy adults and reported that the after-effect become visible after a few minutes following the PA (5-10 minutes) and lasted for 35

minutes. Furthermore, PA after-effect duration has been assessed for also right brain damaged patients and it has been reported that one single session can improve neglect symptoms from two hours (Rossetti *et al.* 1998) to even several days (Farnè, Rossetti, Toniolo, Làdavas, 2002; Pisella, Rode, Farnè, Boisson & Rossetti, 2002). Moreover, two-weeks treatment can produce beneficial effects from one to six months (Frassinetti, Angeli, Meneghello, Avanzi, & Làdavas, 2002; Serino, Bonifazi, Pierfederici, & Làdavas, 2007). Finally, Nijboer, Nys, van der Smagt, van der Stigchel and Dijkerman (2011) reported that a single patient, treated daily for three months, showed the effects even after two years of the prism treatment.

Studies with patients

As already briefly mentioned, PA is widely used in neuropsychological clinical practice to rehabilitate neglect patients. Unilateral visuospatial neglect is a disorder commonly observed following right hemisphere lesions and subsists into the chronic stages in approximately 40-60% of patients (Cassidy, Lewis & Gray, 1998). It is defined as patients' failure to report, respond to and attentionally orient to stimuli presented in the contralateral, personal or extrapersonal hemispace, not caused by either motor (e.g., hemiparesis) or sensory deficits (e.g., hemianopsia) (Heilman & Watson, 1977). Neglect is a complex and multi-composed syndrome with a large variety of symptoms, from a reduced response to a complete lack of awareness of the contralateral space. Although the visual awareness is the most sensory modality studied in neglect patients, this syndrome also affects auditory and tactile modalities in the same way (Brozzoli, Demattè, Pavani, Frassinetti & Farnè, 2006).

Thanks to its visuospatial shift, PA has been proving as an effective rehabilitation procedure in order to reduce neglect symptoms. In this regard, studies about PA with neglects patients can be divided into two groups: studies testing prisms effects on a large

amount of symptoms and studies looking for the most effective and lasting protocol. This section will be focused on the first strand of research.

Classical PA studies with neglect patients assessed and reported beneficial effects of this procedure on visuospatial tasks. Patients' improved performance was reported on several neuropsychological tests, such as line bisection, bell and letter cancellation, copy of a simple figure, draw of a simple figure from memory and visual scanning (Farnè, Rossetti, Toniolo & Làdavas, 2002; Rossetti *et al*., 1998). Moreover, further studies reported PA beneficial effects on more ecological functions linked to the motor component, such as postural control (Nijboer, Olthoff, Van der Stigchel & Visser-Meily, 2014; Tilikete, Rode, Rossetti, Pichon, Li & Boisson, 2001), wheel-chair driving (Jacquin-Courtois, Rode, Pisella, Boisson & Rossetti, 2008), intentional-guided movements (Pisella, Rode, Farnè, Boisson & Rossetti, 2002), but also telephone dialling, and coin and card sorting (Frassinetti, Angeli, Meneghello, Avanzi & Làdavas, 2002), haptic spatial judgements (McIntosh, Rossetti & Milner, 2002), reading (Pisella, Rode, Farnè, Tilikete, & Rossetti, 2006) and writing (Rode, Klos, Courtois-Jacquin, Rossetti & Pisella, 2006), and spatial mental imagery (Rode, Cotton, Revol, Jacquin-Courtois, Rossetti & Bartolomeo, 2010; Rode, Revol, Rossetti, Boisson & Bartolomeo, 2007). In this regard, the results obtained on spatial mental imagery is of high interest. Indeed, Rode and colleagues (Rode, Cotton, Revol, Jacquin-Courtois, Rossetti & Bartolomeo, 2010; Rode, Revol, Rossetti, Boisson & Bartolomeo, 2007) found that, while a strong neglect was observed for mental images, as well as for conventional tests, the mental evocation of left-sided information from an internal image of the map of France was fully recovered following rightward PA. In the same way, Magnani, Oliveri, Mancuso, Galante and Frassinetti (2011) and Oliveri, Magnani, Filipelli, Avanzi, and Frassinetti, (2013) provided evidence about the restoration of neglect patients' time underestimation by means of rightward prisms. The authors explained this effect in terms of a linear representation of time intervals in ascending order from left to right. Namely, short time intervals would be

coded leftward whereas longer time intervals would be represented more rightward. A similar result was reported by Zorzi, Priftis and Umiltà (2002) who found that neglect patients presented a distorted "mental number line", in a similar way as in line bisection, when they had to find the middle between two numbers. This function was restored by prisms directed to the right. These results, taken together, show the complexity of the neglect syndrome, but also and moreover, the massive range of intervention in which PA might be applied (Rossetti, Jacquin-Courtois, Rode, Ota, Michel & Boisson, 2004).

Another interesting result regards PA beneficial effects on auditory modality of neglect patients. As previously mentioned, neglect syndrome consists of symptoms over all sensory modalities (Brozzoli, Demattè, Pavani, Frassinetti & Farnè, 2006). In this regard, Jacquin-Courtois and colleagues (2010) found that PA could improve left auditory extinction. In other, the authors reported that the observed result was specific to the detection asymmetry between the two ears, while it did not affect the total number of responses. The result was interpreted as a specific effect of PA on lateralized processes rather than on general arousal. Moreover, it represents a further evidence about the effects of PA extended to unexposed sensory systems.

Studies with healthy subjects

Although PA effects on neglect patients are the most commonly studied, there are also laboratories that have been trying to test PA with healthy subjects, which is likewise important to better understand its actual mechanism of action. Most of the studies tested PA after-effect only with leftward prisms with the aim to simulate neglect symptoms in healthy people and reduce the so-called *pseudoneglect* usually observed in normal subjects. In brief, pseudoneglect represents healthy people's tendency to misbisect horizontal lines when asked to judge their midpoint during line bisection tasks (Bowers & Heilman, 1980). Their bias is

usually oriented to the contralateral spatial side than neglect patients (Jewell & McCourt, 2000).

Studies using leftward PA on normal subjects found comparable results to the data obtained from right brain damaged patients. Namely, a reduction of pseudoneglect bias and a simulation of neglect symptoms were reported by means of line bisection, greyscales, global/local processing and haptic exploration (Berberovic & Mattingley, 2003; Bultitude & Woods, 2010; Colent, Pisella, Bernieri, Rode, & Rossetti, 2000; Girardi, McIntosh, Michel, Vallar, & Rossetti, 2004; Jackson & Newport, 2001; Loftus, Vijayakumar, & Nicholls, 2009; Michel et al., 2000), but also of reflexive and voluntary reorienting of attention (Striemer, Sablatnig & Danckert, 2006). Moreover, it has been shown that PA, similarly as in neglect patients, can also affect representational spatial attention, such as spatial mapping (Bultitude, Van der Stigchel, & Nijboer, 2013), estimated duration of both visual and auditory stimuli (Magnani, Mangano, Frassinetti & Oliveri, 2013; Magnani, Pavani, & Frassinetti, 2012) and mental alphabet line bisection (Nicholls, Kamer & Loftus, 2008).

Does the procedure matter?

Given these interesting results about PA beneficial effects with neglect symptoms, an important question to deal with is how to make PA more effective and to boost its effects. Indeed, although the above mentioned studies obtained positive results and even long-lasting after-effects, some others found no significant changes of neglect symptoms after PA (Nys, de Haan, Kunneman, de Kort, & Dijkerman, 2008; Rousseaux, Bernati, Saj, & Kozlowski, 2006; Turton, O'Leary, Gabb, Woodward, & Gilchrist, 2009). To this aim, a few laboratories have been looking for the more effective protocols in inducing PA after-effect. For example, Làdavas, Bonifazi, Catena and Serino (2011) compared two PA procedures varying for the amplitudes of visual feedback during the adaptation phase: terminal PA (the last 12 cm of the movement were visible; TPA) and concurrent PA (the second half of the movement was

visible; CPA). They reported that both TPA and CPA treatments induced a greater reduction of neglect symptoms when compared to a control treatment of pointing without prisms. At the same time, the improvement was higher for patients treated with TPA than for those treated with CPA. Fortis *et al.* (2010), in other, obtained better results with a modified PA protocol in which adaptation and after-effect were tested by means of more ecological visuo-motor activities, such as the manipulation of common objects while wearing the prismatic goggles. They also found a better tolerance of this protocol by their patients.

Moreover, Striemer, Russel and Nath (2016), reported that also the magnitude of the shift induced by prisms has an influence on the after-effect. Namely, they showed that the larger was the shift induced (17° than 8.5°) by leftward prisms on healthy subjects the larger was their bias to the right side, measured with the straight-ahead pointing task and a bisection line, but not with the landmark task. The authors explained these data suggesting that larger magnitudes of prism adaptation seem to have a greater influence on tasks that require a response with the adapted hand (i.e., line bisection), compared to tasks that only require a perceptual judgment (i.e., the landmark task).

Finally, a few works have been trying to test whether PA might be combined with NIBS or concurrent tools. To this aim, Làdavas and collegues (2015) submitted three different groups of neglect patients to a 10 days PA session followed by cathodal tDCS over left PPC, anodal tDCS over the damaged PPC and sham tDCS. The authors reported a greater improvement of patients scores on the Behavioral Inattention Test (BIT) only for the a-tDCS condition, than the others. This results suggest a boost of PA effects by means of tDCS. Also Guinet and Mitchel (2015) tried to combine PA with another concurrent tool. In this case they used neck vibration, already used in the clinical practice for the neglect rehabilitation (Karnath, Christ & Hartje, 1993; Schindler, Kerkhoff, Karnath, Keller & Goldenberg, 2002). Differently to Làdavas *et al*. (2015), they found that both of the methods induced a decrease of neglect symptoms, but any evidence of their interaction.

CHAPTER 2

PRISMATIC ADAPTATION AND NEURAL CORRELATES

Neural mechanisms underlying PA

Several studies identified two phases occurring during PA: error correction and spatial realignment (Redding & Wallace, 1993). Namely, error reduction consists of the first phase of PA, when subjects, while wearing prismatic goggles, mispercept the target position. In this stage subjects, after a few trials, anticipate the error and try to correct the movement. Despite the initial bias induced by PA is reduced to zero within the first few trials, a few more repeated pointings are needed for the after-effect (i.e. spatial realignment) to fully develop. In fact, strategic error correction (as measured by the increasing accuracy of early pointing trials) and spatial realignment (as measured by the after-effect) are thought to be correlated, even though being independent (Chapman *et al.*, 2010; Michel *et al.*, 2003; Redding & Wallace, 1993).

The neural circuits underlying the error reduction and the spatial realignment phases are still rather unclear. It has been suggested that the dorsal system would mediate the effects induced by PA. Indeed, the dorsal system is involved into the control of visual guided movement, but also into visuospatial attention (Corbetta & Shulman, 2002). Hence, a big and highly interconnected neural network of brain areas (i.e. the parietal-cerebellar pathway) is involved by this process.

The cerebellum

The cerebellum has well documented evidences to have a role in comparing motor output behaviour (efference) to the visual error of the output (visual afference) (Ramnani,

2006). Because of this role, the cerebellum is thought to be part of PA neural network. In particular, it might be involved during the adaptation phase, while participants are wearing the shifting prisms. Namely, it might make subjects aware of the bias of their pointing movement and induce the error correction. In fact, some lesion studies in both animals (Baizer, Kralj-Hans & Glickstein, 1999) and humans (Block & Bastian, 2012; Pisella *et al.*, 2005) reported that cerebellar disruption makes these subjects slower or even unable to adapt to prims. Following fMRI studies supported the cerebellar-hypothesis. They showed an increased cerebellar BOLD activity during PA, especially within the right posterior cerebellum (Chapman *et al.*, 2010; Luauté *et al.*, 2006).

Although cerebellar involvement during the early stages of PA (error reduction) might be clear and in line with what we know about its functions, an additional interesting result has been showed by Chapman *et al.* (2010). The authors found the the right posterior cerebellar activity increase during the early exposure to PA, but also both right and left cerebellar activation during the later stages (spatial realignment). According to Ramnani (2006), these results could suggest the implication of cerebellar regions in updating its internal models of motor behaviour. Moreover, both cerebellar lesion (Martin, Keating, Goodkin, Bastian & Thach, 1996) and brain stimulation studies (i.e. tDCS) (Panico, Sagliano, Grossi & Trojano, 2016) have also shown the critical role of this region in the development on prism after-effect. In fact, Calzolari and colleagues (Calzolari, Bolognini, Casati, Marzoli & Vallar, 2015) reported a single case of a left cerebellar patient who showed the error reduction during the rightward PA, but also an abnormal shift, ipsilateral to the prisms deviation, as after-effect. Nerveless, the authors were able to restore the normal leftward after-effect by means of cathodal tDCS over the damaged cerebellum. Calzolari *et al*. (2015) explained this result claiming that ctDCS was able to stimulate the spare neurons of the damaged area, restoring the network involved by PA.

The parietal cortex

The posterior parietal cortex is the most widely studied region in terms of neural circuits involved by PA. The interest on the PPC is due to the historical link between this region and visuospatial attention. In this regard, Corbetta and colleagues' neural organization model results rather interesting to understand PA effects on spatial attention (Corbetta, Kincade, Ollinger, McAvoy & Shulman, 2000; Corbetta, Kincade & Shulman, 2002). The authors highlight the presence of neural correlates for distinct functions of spatial attention. Namely, they distinguish the dorsal system, including the inferior parietal sulcus (IPS) and the frontal eyes field (FEF), and the ventral system, including the temporo-parietal junction (TPJ), the supramarginal frontal gyrus (SMG) and the superior temporal sulcus (STS). The former one involves its network bilaterally and has the role in the top-down stimuli selection (i.e. endogenous allocation and maintenance of visual-spatial attention); while the latter is highly lateralized to the right hemisphere and specialized in the detection of relevant stimuli (i.e. detection of unattended stimuli). The top-down attentional control mediated by the dorsal system and the stimulus-driven control operated by the ventral system are highly interconnected. Therefore, several TMS activation studies have reported that, while the ventral system is characterized by the specialization of the right hemisphere, in the dorsal stream, left and right hemispheres are not only interconnected by means of inhibitory connections, but also the right PPC exerts a stronger inhibitory control over the contralateral region (Koch et at., 2011). Thus, it explains the pseudoneglect observed in healthy people (Bowers & Heilman, 1980; Jewell & McCourt, 2000).

Moreover, when this network is disrupted by right PPC lesion, as usually observed in neglect patients, the hypoactivation of the damaged hemisphere is observed concurrently to the hyperctivation of the contralateral hemisphere (Koch *et at*., 2008). Hence, the typical bias to the right side observed in the right damaged patients can be changed "inhibiting" the left PPC or "excitating" the right PPC. Both of this protocols have been reported as efficient,

by means of TMS (Oliveri *et al*., 1999; Oliveri *et al*., 2001) and tDCS (Brem, Unterburger, Speight, & Jäncke, 2014; Sparing, Thimm, Hesse, Kürst, Karbe & Fink, 2009). At this point, rightward PA could be comparable to NIBS methods in reducing neglect symptoms thanks to its action within this disrupted network.

In fact, changes in PPC activation after PA have been reported in both healthy and right damaged subjects. In their pioneering study, Clower and colleagues (Clower, Hoffman, Votaw, Faber, Woods & Alexander, 1996) assessed the variations of the regional cerebral blood flow (rCBF) associated to PA. In their study, the direction of displacement of the prism lenses was reversed every five trials, forcing subjects to correct for the prism-induced errors during all the pointing task duration. Clower *et al.* (1996) reported the activation of the left IPS correlated with the error correction during PA. More recently, in the first fMRI study with rightward PA used with neglect patients, Luauté *et al.* (2006) reported that the decrease of their symptoms was correlated with the increase of activation of the right cerebellum and, in general, of the left cortical hemisphere, concurrently to the decrease of activation of the right PPC. The results by Clower *et al.* (1996) and Luauté *et al.* (2006) were reproduced by further works with both damaged patients (Pisella *et al.* 2006; Pisella *et al.* 2006) and healthy people (Danckert, Ferber & Goodale, 2008; Crottaz-Herbette, Fornari & Clarke, 2014).

Finally, a recent study conducted by Martín-Arévalo and colleagues (Martín-Arévalo, Laube, Koun, Farnè, Reilly & Pisella, 2016) must be considered worthwhile in the present discussion. Indeed, with an electrophysiological study with PA, the authors demonstrated that leftward-deviating PA in healthy subjects can modulate spatial attention (tested by a Posner-like task), simulating the typical attentional patterns observed by neglect patients. In particular, they reported that left PA modulated early stage parietal components, such as the cue-locked N1, known to reflect attentional orienting, and the target locked P1, for invalid cue left-sided, known to reflect attentional disengagement (Herrmann & Knight, 2001; Marzi, Girelli, Natale & Miniussi, 2001).

New insights

Despite the several evidences about the cerebello-parietal network involvement during PA, more recent findings have suggested that even more frontal brain regions are implicated. Danckert, Ferber and Goodale (2008) found the increased activity of regions within the anterior cingulate and primary motor cortex, associated to the early error correction trials. These data suggest the role of the frontal areas during the early stages of PA concurrently to cerebellum and PPC activation. In this regard, few electrophysiological studies measured event-related potentials (ERPs) during the PA (MacLean, Hassall, Ishigami, Krigolson & Eskes, 2015; Vocat, Pourtois & Vuilleumier, 2011). In particular, Vocat *et al.* (2011) reported that the amplitude of the error-related negativity (ERN) was influenced by the magnitude of errors and tended be larger correspondingly to the pointing accuracy increase, revealing a parametric modulation of the medial-frontal areas as monitoring system. On the other hand, MacLean *et al.* (2015) reported that also P300 was concurrently evoked, suggesting that this cortical area would also serve as a system for context updating and learning. The present conclusion has finally been reproduced by Arrighi *et al.* (2016) who measured the modulation of frontal-midline theta (fmθ) activation by means of event-related spectral perturbations (ERSP). The authors found that fmθ increased in the high- but not in the low- error condition. Moreover, during the late trials of PA, the error reduction was observed as associated to the indices of adaptation (i.e., after-effect) suggesting the need to explore if theta oscillations may facilitate learning.

In line with Danckert, Ferber and Goodale's results (2008), there are also the TMS activation studies assessing PA after-effects over the primary motor cortex (Magnani, Caltagirone & Oliveri, 2014; Schintu *et al*., 2016). Namely, Magnani *et al*. (2014), reported the increase of M1 excitability controlaterally to the after-effect induced by prisms directed either to the left and to the right. The authors interpreted the result as an indicator of a more general pattern of hemispheric cortical excitability induced by PA. On the other hand,

Schintu *et al*. (2016), more recently reported significant changes of M1 *per se* after leftward PA, but also a left hemisphere increase and a right hemisphere decrease in the amplitude of motor evoked potentials (MEPs) elicited by paired-pulse TMS (PPC-M1). This study, together with the one by Magnani *et al*. (2014), suggests the influence of PA over M1 depending on the shift induced, but also includes the primary motor cortex within this big fronto-parieto-cerebellar network that has been suggested as involved by PA.

A new possible PA neural model

Taking into account the neural evidences hitherto reported, a new neural model might be outlined (**Fig. 1**). Striemer and Danckert (2010a), but also Chapman *et al*. (2010) and then Clarke and Crottaz-Herbette (*in press*) suggested that the influence of prisms on healthy people and neglect patients can be better understood in terms of its separate effects on the dorsal and ventral streams of visual processing, which mediate "vision for action" and "vision for perception", respectively. They propose that prisms influence acts over the dorsal stream, bypassing the ventral one. In fact, the dorsal system is known to control visually guided motor behaviors (eye and arm movements) and visual attention (Corbetta & Shulman, 2002). The evidences reporting the activation of the circuits in SPL and IPS during PA supports this theory (Clower, Hoffman, Votaw, Faber, Woods & Alexander, 1996; Danckert, Ferber & Goodale, 2008; Luauté *et al.*, 2009). Moreover, it has been reported that the dorsal system is generally undamaged in neglect patients, who usually show lesions rather within the ventral system (IPL and STG) (Coulthard, Parton & Husain, 2006). At the same time, SPL and IPS activation has been positively correlated to the spontaneous recovery from neglect (Corbetta, Kincade, Lewis, Snyder & Sapir, 2005; Luauté *et al.*, 2006).

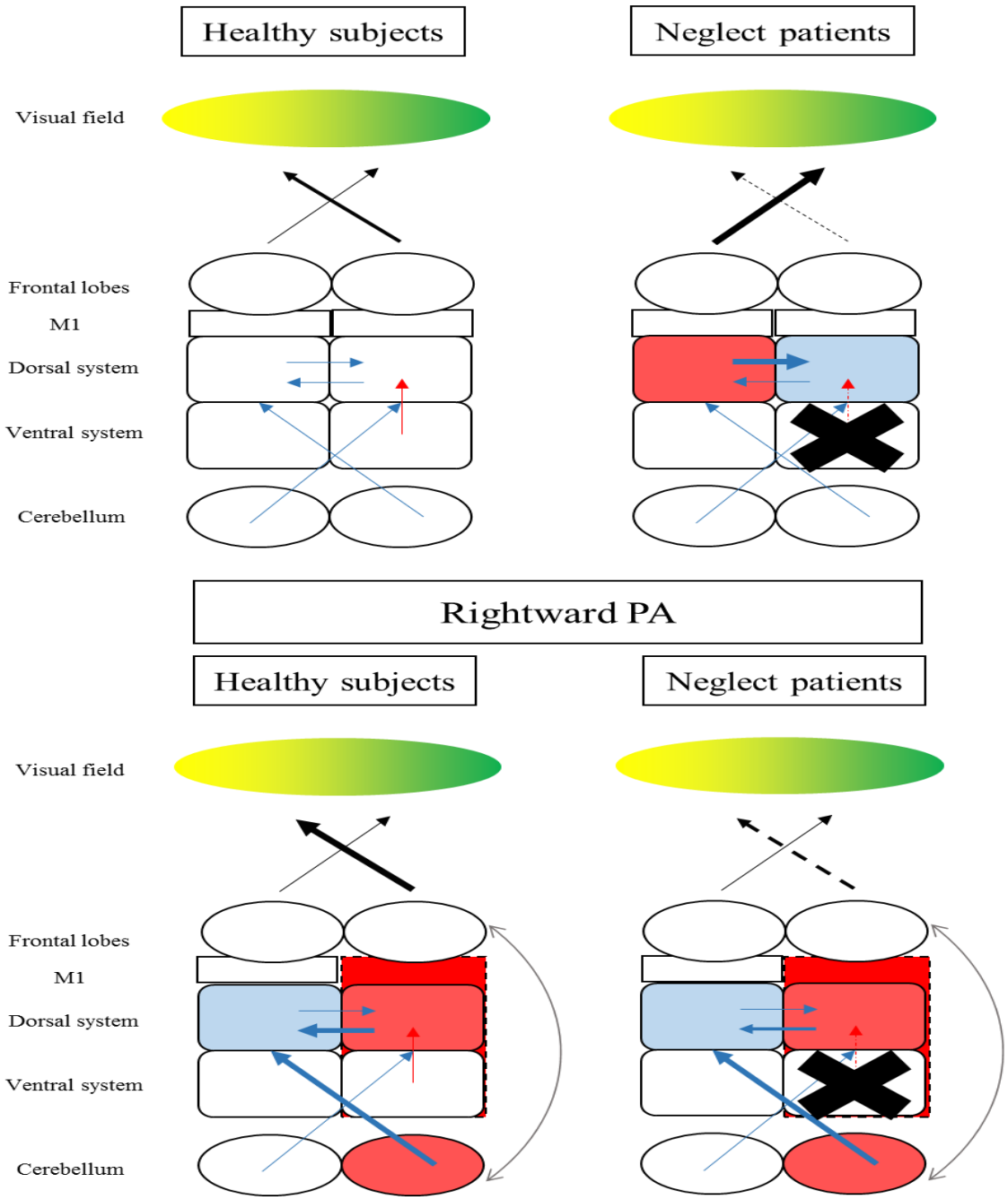

Fig. 1. Schematic rapresentation of the PA neural model. The figure schematically illustrates the brain regions of the network involved by PA: on the left the exemplification of normal subject's (A, C); on the right neglect patient's (B, D). The top of the figure shows a baseline condition for both healthy (A) and right brain damaged (B) subjects, while the bottom the changes induced by rightward PA again for normal people (C) and patients (D). The blue and red arrows represent the brain inhibitory and excitatory connections respectively, while the grey ones are for illustrating the mutual fronto-parieto-cerebellar connection. The black arrows, instead, are to show the attentional direction: slightly shifted to the left for healthy people (pseudoneglect - A); shifted to the right with a neglect for the left visual hemifield for patients (B); significantly shifted to the left for healthy people (C); and restored in neglect patients (D).

Specifically, during the early stages of rightward PA (i.e. error correction), error signals are generated within the frontal-midline circuits (Arrighi *et al.*; 2016; MacLean *et al*., 2015; Vocat *et al*., 2011), concurrently to the SPL/IPL. Although it is not completely clear yet whether the right SPL/IPL or the left SPL/IPL circuit is crucial for PA after-effect, a beneficial role of both of them has been suggested (Striemer & Danckert, 2010a). Namely, the error signals are transmitted to the right cerebellum that generates leftward realignment signals. These are then transferred to the dorsal system in the left hemisphere by means of connections with the dentate nucleus (Dum & Strick, 2003). At this point, by means of trans-callosal connections between each hemisphere, the leftward realignment signals processed in the left SPL are transmitted to the right SPL that is normally responsible for orienting leftwards. Within this network here we are also including the primary motor cortex suggesting, as already done by Magnani, Caltagirone and Oliveri (2014), that it would indicate the general state of activation of the cortical hemisphere modulated by PA.

The present model can explain PA behavioral and physiological effects observed in both healthy subjects and neglect patients. Moreover, on one hand, it is able to explain why a few studies did not observe any significant change in normal people by means of rightward PA (Colent, Pisella, Bernieri, Rode, & Rossetti, 2000; Martín-Arévalo, Laube, Koun, Farnè, Reilly & Pisella, 2016). In fact, the right dorsal system, implicated into the leftward attention, is already prevalent within the normal brain network (Benton & Tranel, 2003; Cavezian, Valadao, Hurwitz, Saoud & Danckert, 2012; Thiebaut de Schotten *et al.*, 2011; Vallar, 1998) and the use of rightward PA might not be able to overtake the normal brain physiological bias. On the other hand, this model could also explain why some other studies found a dissociation between pure visuoattentional and visuo-motor effects (Dijkerman, *et al*., 2003; Farnè, Rossetti, Toniolo & Làdavas, 2002; Ferber & Murray, 2005; Fortis *et al*., 2011; Leigh, Danckert & Eliasmith, 2014; Striemer & Danckert, 2010a; Striemer & Danckert, 2010b; Striemer, Russel & Nath, 2016). Indeed, as above mentioned, the formers are related to the

ventral stream, not involved by PA, whether the latter to the dorsal stream, which, instead, seems to be modulated by prisms.

CHAPTER III

NEURAL CORRELATES OF MOTOR PREPARATION BUT NOT VISUAL ATTENTION ARE MODULATED BY RIGHTWARD PRISMATIC ADAPTATION: AN EEG STUDY

Introduction

Numerous studies reported PA effect in both healthy controls and neglect patients on a number of visuospatial tasks, including line bisection (Pisella, Rode, Farnè, Boisson & Rossetti, 2002; Schintu, Pisella, Jacobs, Salemme, Reilly & Farnè, 2014), visual search (Vangkilde & Habekost, 2010), voluntary orienting of visual attention (Martín-Arévalo, Laube, Koun, Farnè, Reilly & Pisella, 2016; Striemer and Danckert, 2007; Nijboer, McIntosh, Nys, Dijkerman & Milner, 2008; Striemer & Danckert, 2010a), and representational spatial/temporal attention (Bultitude, Van der Stigchel, & Nijboer, 2013; Rode, Cotton, Revol, Jacquin-Courtois, Rossetti & Bartolomeo; Magnani, Mangano, Frassinetti & Oliveri, 2013; Oliveri, Magnani, Filipelli, Avanzi & Frassinetti, 2013). However, while there is a consensus regarding the behavioural effects of PA, the neural mechanisms underlying PA have not been fully elucidated. The most prominent account is that PA results in a recalibration of spatial reference frames underlying visuospatial attentional and visuo-motor functions of the PPC. More specifically, it has been suggested that PA acts on the dorsal stream (Striemer & Danckert, 2010a), which is in line with reports of right and left PPC involvement in PA, with additional cerebellar activation during the error reduction phase of PA (Chapman *et al*., 2010; Clower, Hoffman, Votaw, Faber, Woods & Alexander, 1996; Crottaz-Herbette, Fornari & Clarke, 2014; Danckert Ferber & Goodale, 2008; Luauté, *et al*., 2006, Luauté, *et al*., 2009). More recently, the involvement of the M1 in PA has also been documented, in line with interaction of PA with a cerebello-cortical

network underlying visuo-motor abilities (Koch, 2010). In support of M1 involvement, Magnani, Caltagirone and Oliveri, (2014) reported increased intracortical facilitation in M1 contralateral to the prism-induced compensatory shift. Moreover, using paired-pulse TMS to test PPC-M1 connectivity, Schintu *et al.* (2016) reported enhanced connectivity in the hemisphere contralateral to the compensatory shift, as compared to the ipsilateral hemisphere. Collectively, the existing literature therefore indicates that PA may affect dorsal stream function but it is unclear whether it predominantly affects spatial attention or motor-related dorsal stream processes, or both.

In the present EEG study, the aim was to shed further light on the mechanisms underlying PA by investigating changes in oscillatory electroencephalography EGG activity while healthy participants performed a task which distinguishes between PA-effects on known EEG signatures of dorsal attention versus visuo-motor functions. More specifically, the effects of rightward-deviating prisms on oscillatory activity during a new "double step anticipatory attention/motor preparation" paradigm were examined. This task required participants to first covertly orient to the left or right visual fields (Posner-type task) and then to prepare a visually triggered motor response with either the left or right hand. By analysing the effects of PA on known EEG signatures of lateralized anticipatory attention orienting and motor preparation, namely asymmetric changes in occipito-parietal alpha-activity (Foxe & Snyder, 2011; Thut, Nietzel, Brandt & Pascual-Leone, 2006; Worden, Foxe, Wang & Simpson, 2000) or rolandic mu-/beta-activity (Kilavik, Zaepffel, Brovelli, MacKay & Riehle, 2013; Pfurtscheller & Lopes Da Silva, 1999; Tan, Leuthold & Gross, 2013), the aim was to provide information on the origin of the PA effects.

Material and methods

Participants

Sixteen healthy adults (9 females, 7 males, mean age = 25.62 years, SD = 4.47) volunteered to participate in the experiment. All participants were right handed, had normal or corrected-to-normal vision and reported no history of neurological or psychiatric disease. Participants were financially compensated for taking part in the experiment. Written informed consent was signed by each participant at the beginning of the experiment according to the Declaration of Helsinki. The study was carried out at the Institute of Neuroscience and Psychology, University of Glasgow and was approved by the local ethics committee.

Paradigm, procedure and apparatus

Participants performed a new "double step anticipatory attention/motor preparation" paradigm involving anticipatory attention to lateralized positions (symbolically cued orienting of visual-spatial attention) followed by lateralized motor preparation (with a delayed response component). In this task, a first, attentional cue guided the focus of spatial attention, while a second, motor preparation cue, signaled whether a right or left hand movement had to be prepared. The two post-cue intervals (of 1500ms each) allowed to assess the EEG correlates of anticipatory attention deployment and motor processes towards the left versus right space respectively, namely by analyzing changes in posterior alpha and rolandic alpha/beta oscillations. Because the motor cue was presented at validly cued, attended and invalidly cued, unattended positions, it also served as visual target allowing to assess attentional effects on both post-stimulus EEG and behavioural measures (i.e. visually evoked potentials and behavioural responses to the targets).

All participants took part in one training session and two experimental sessions, each on a separate day. One experimental session involved prism adaptation (using prismatic

lenses), while in the other session, control (neutral) lenses were used. During the training session not involving any EEG recordings, participants were familiarized with the behavioural task. This session also served for target titration. During the experimental sessions, participants were first prepared for EEG recordings. They then performed two blocks of the behavioural task lasting around 8 min each, while EEG was recorded. These two blocks served as baseline. Afterwards, participants underwent prismatic adaptation using prismatic or neutral lenses. At the end of adaptation, EEG was again recorded while participants performed the behavioural task for two further blocks, which served as post-adaptation measurement (**Fig. 2A**). The order of the two experimental sessions was randomized across participants.

Stimuli were presented on a CRT monitor with a 1280 x 1024 pixel resolution, a 100 Hz refresh rate and a grey background using E-Prime (Psychology Software Tools, Pittsburgh, PA).

Attentional/motor task, stimuli and analysis of behavioural data.

Figure 2B illustrates the stimuli and the sequence of events per trial. Each trial began with the presentation of a fixation cross (1.5° visual angle) inscribed into a rhombus (2x2°) located at the centre of the screen. Together with the central rhombus, two lateralized rhombi (3.5x3.5°) serving as placeholders were continuously displayed in the lower left and right visual fields. After 1500ms from trial onset, either the bottom left or the right section of the central rhombus turned green for 30ms, which served as the attentional cue instructing the participants to covertly shift and maintain their attention towards the left or right placeholder, respectively. After another 1500ms, one-half of either placeholder turned black for 40ms (in 80% of trials at validly cued and in 20% of trials at invalidly cued position), serving both as the visual target (to assess attentional effects in both behavioural and EEG data, see below) as well as the motor preparation cue as its form (left or right-pointing triangle) indicated

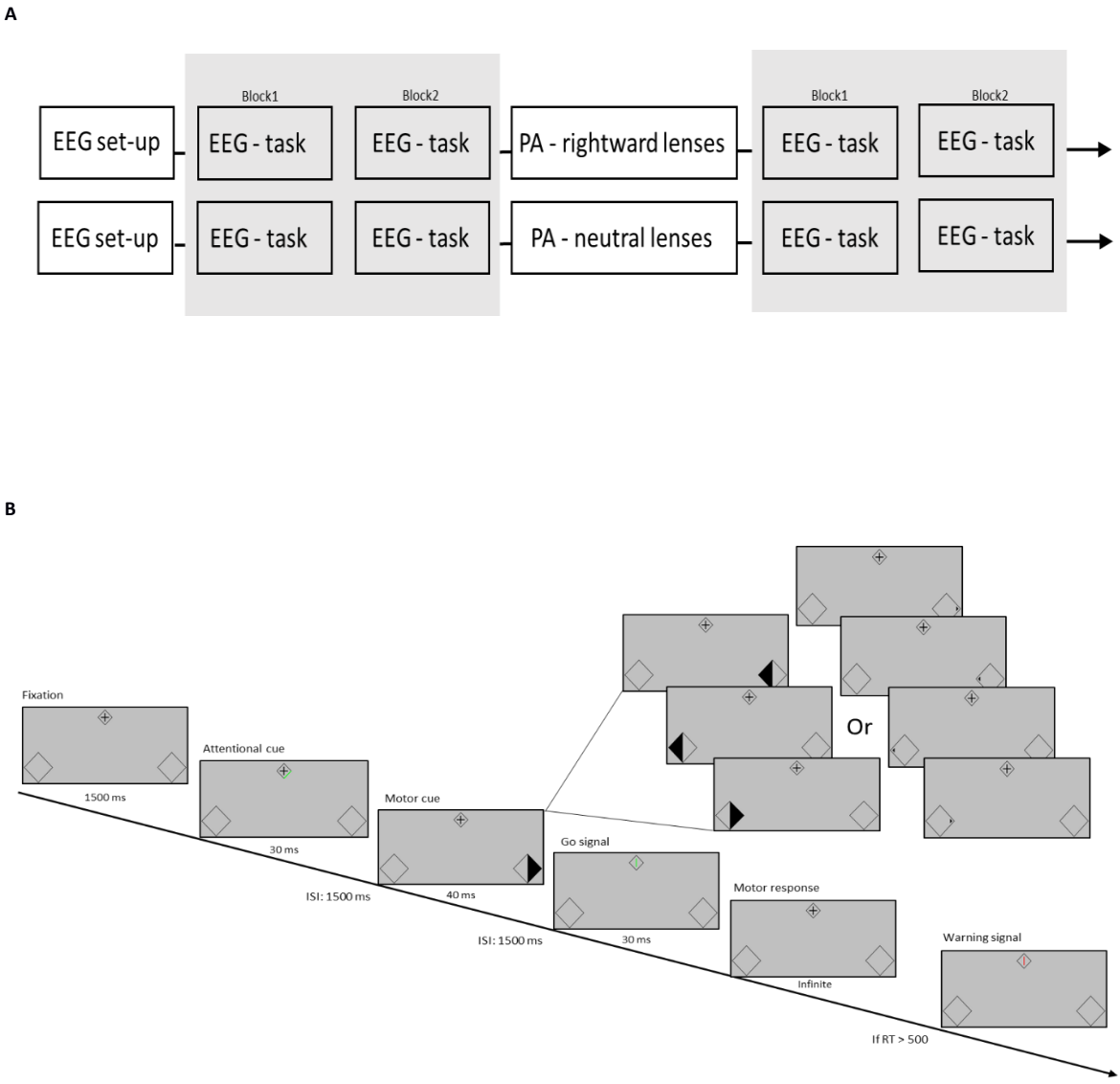

Fig. 2 Experimental setup and paradigm. **A.** Experimental time line. **B.** Experimental paradigm. Each trial started with a fixation cross, followed by an attentional cue (the bottom left or right section of the central rhombus turning green) instructing participants to covertly attend to the left or right lower visual field placeholder. After 1500ms, a second, motor preparation cue (big or small triangle) appeared in the left or right placeholder (80% at attended and 20% at unattended position) pointing either to the left or to the right (probability of 50%). The motor preparation cue indicated which response (left or right hand) the participants needed to prepare. After another 1500ms, a go-signal (green vertical line) instructed participants to perform the prepared action. EEG was analysed in terms of oscillatory alpha- and beta-activity in the two 1500ms post-cue intervals, covering anticipatory attention and preparatory motor processes to the left or right side of space respectively, as well as in terms of visual evoked potentials to the motor cue (also serving as target).

which hand the participants had to use for the upcoming motor response. For motor cueing, the direction of the arrow pointed equally often left and rightward (50% of trials) irrespective of the side of the placeholder the motor cue was presented in. Participants were instructed to prepare a left or right index finger movement according to the arrow direction as soon as this appeared, but were asked to withhold the response for 1500ms, until the fixation cross turned into a green vertical line for 30ms (go signal). To encourage movement preparation before the go-signal, speeded response execution was emphasized and a red vertical line was presented in the central rhombus as a warning signal if no response occurred within the first 500ms after the go-signal, in which case the trial was aborted and a new trial started.

The task consisted of 200 trials divided into 2 blocks of 100 trials each and was presented two times (one before and one after prism adaptation). Since the motor cues were easy to detect, the size of the visual target/motor cue was manipulated in an additional subset of trials (n = 32, added to the 200 trials of salient targets/motor cues described above) in order to ensure via behavioural analysis that participants were actually shifting their attention. These targets/motor cues consisted of smaller left or right segments of the placeholder rhombi turning black, leading to small left or rightward pointing triangles (0.5° visual angle) which were presented in 50% of trials at validly cued and 50% of trials at invalidly cued positions. For these small targets, luminance contrast with the background was titrated during the training session to give rise to perithreshold performance in each participant with a clear behavioural advantage for cued stimuli compared to uncued stimuli (mean detection accuracy valid trials = 0.75; invalid = 0.55)

Participants were seated on a comfortable chair at a distance of 57 cm from the screen. The distance was kept constant throughout the session using a chin rest. Participants were instructed to keep their eyes on the fixation cross throughout the experiment, shift their attention in response to the attentional cue without moving their eyes and to prepare but

withhold the speeded motor response until the go signal appeared. Participants responded with their left or right index finger by a button press on a keyboard, according to the direction indicated by the arrow.

Analysis of behavioural data: Data were analysed separately for "large" and "small" target stimuli. Responses to "large" targets were analysed in terms of accuracy and reaction times for providing (descriptive) information on how well participants prepared for the motor response. Responses to small targets were analysed in terms of accuracy as a function of valid and invalid cueing in order to ensure that participants engaged in the attention task.

Prismatic adaptation (PA) and analysis

PA was applied as previously described (see e.g. Magnani, Caltagirone & Oliveri, 2014; Magnani, Mangano, Frassinetti & Oliveri, 2013; Magnani, Oliveri, Mancuso, Galante & Frassinetti, 2011; Magnani, Oliveri, Mangano & Frassinetti, 2010; Oliveri, Magnani, Filipelli, Avanzi & Frassinetti, 2013). Participants were seated in front of a curved, horizontal plexiglass panel (height: 30 cm, width: 72 cm, depth: 34 cm at the centre and 18 cm at the periphery, participants distance: 57 cm) that was placed on a table top between the participant and the experimenter. The concave side was facing the participant and the convex side the experimenter. The panel was transparent and graded with thin vertical lines per degrees of visual angle (120◦ of visual angle covered), so that the experimenter could readout the participants' pointing accuracy per trial: rightward pointing deviations from a target were scored with positive values, leftward ones with negative values.

During PA, the experimenter placed a visual target (a pen) at the top of the surface of the transparent barrier (tipping the pen on its top edge) in one of three possible positions (randomly determined on each trial): a central position (0°), 11° to the left and 11° to the right of center. At the start of each trial, participants were asked to keep their right hand at the level of the sternum and upon target presentation to position their finger tip on the panel

at target eccentricity, at a fast but comfortable speed. The experimenter recorded spatial accuracy of pointing as distance in degrees of visual angle between the target position and the final position of the participant's finger.

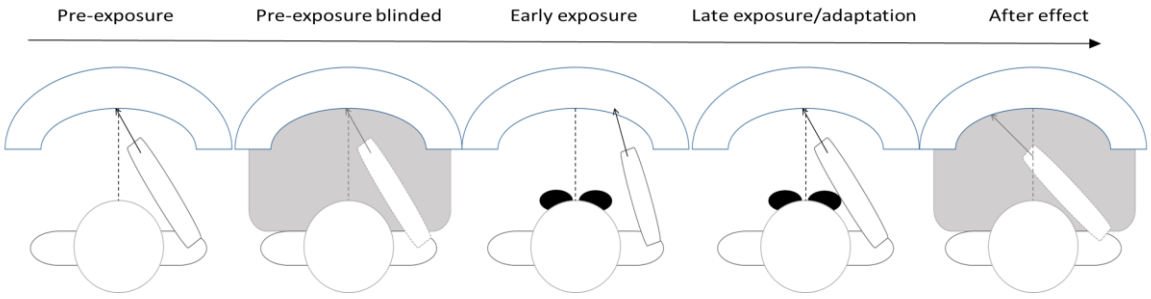

Fig. 3 Prismatic adaptation (PA) setup and time line. Participants point to targets on a curved, transparent panel, with targets presented by the experimenter sitting behind the panel. Pre-exposure (prismatic goggles off) involves pointing in free-viewing conditions (both pointing movements and targets visible) followed by occluded (blinded) pointing to visible targets. Participants were then asked to wear the googles (rightward orientation or neutral lenses) during free-viewing pointing (exposure, goggles on). Adaptation is then tested immediately after exposure with blinded pointing to targets (after-effect).

The pointing task consisted of a total of 180 trials (i.e. 60 trials for each target position) and was subdivided in three stages: pre-exposure, exposure and post-exposure (**Fig 3**). Pre-exposure consisted of 60 trials (20 trials for each pointing position). Participants performed half of the pre-exposure trials (i.e. 30) with visible pointing, and half (i.e. 30) with invisible pointing (pre-exposure blinded). During invisible pointing, the view of the arm movement and panel was occluded by means of a cape that covered the area from neck to the edge of the panel (neither obstructing the pointing movements, nor the visibility of the top edge of the panel or the target position). During exposure, participants performed the task while wearing rightward-deviating prismatic or neutral goggles (see Fig. 3). The prisms induced a 10° shift of the visual field to the right. During exposure, participants could see the trajectory of their movement (visible pointing) and were asked to point 90 times to targets (i.e. 30 trials per position). In the early phases of exposure (early exposure, see Fig. 3),

pointing movements are typically observed to deviate to the right (with rightward-deviating goggles), which is compensated for by adaptation in the late exposure phase (see Fig. 3). In the post-exposure phase, the strength of adaptation was assessed by measuring the after-effects (usually leftward after rightward prisms) during invisible pointing (pointing movements occluded) in 30 trials (10 per target position) (Fig. 3).

Analysis. In order to probe for prismatic adaptation effects, we assessed pointing deviation from the target in visual degrees in the following 5 stages: pre-exposure free-viewing, pre-exposure blinded, early exposure, late exposure, post exposure/after-effects. For exposure, the first and second half of trials were analysed separately, because these are typically associated with differential effects when prismatic lenses are used (early rightward bias with rightward lenses, later compensation for this bias) (e.g. Magnani, Caltagirone & Oliveri, 2014). To statistically test for PA effects with prismatic lenses as compared to neutral lenses, we conducted a 2 x 5 ANOVA with Condition (Prism *vs*. Neutral) and Time (5 PA phases) as within-subjects factor. Simple tests were conducted to break down main effects and interaction where appropriate.

EEG recording and analysis

EEG was continuously recorded during the task with 1000 Hz sampling rate from 62 Ag/AgCl sintered electrodes mounted on an elastic cap according to the International 10-10 system (BrainAmp, Brain Products GmbH, Munich, Germany). An additional electrode was positioned on the outer canthus of the left eye to record eye movements (when referenced to Fp1), while AFz and TP9 served as active reference and ground, respectively. All impedances were kept below 5 kΩ.

EEG data were analysed using BrainVision Analyzer2 (BrainProducts) and FieldTrip toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2011; http://www.ru.nl/fcdonders/fieldtrip/) in Matlab 7 (MatWork, MA). EEG was bandpass

filtered offline from 0.5 to 80 Hz and re-referenced to the average of all channels. A band-stop filter was then used to remove 50 Hz activity. An independent component analysis (ICA) was performed to remove eye blinks and muscle artifacts. EEG data were then segmented into 4000ms epochs, starting 1000ms before and ending 3000ms after the first (attentional) cue (hence spanning 1500ms into the post-motor cue period). Based on visual inspection, trials with further artefacts were rejected. Trials with small motor cues were not included in the EEG analysis. Finally, data sampling rate was reduced to 512 Hz.

Time frequency analyses

For each participant, condition and trial, time-frequency analyses were performed using Fast Fourier transform for all frequencies ranging from 2 to 40Hz, using a Hanning taper with a fixed 500ms sliding time window moving in steps of 20ms. The power was averaged over trials for each block of recording (pre/post Prism, pre/post Neutral). Analysis involved cluster based statistics as well as a calculation of lateralization indices at the frequencies of interest (alpha and beta) that have proven useful for capturing oscillatory changes in anticipatory/preparatory windows (Marshall, O'Shea, Jensen & Bergmann, 2015, see below for details).

Analyses were separated to cover the epochs of anticipatory attention shifts (i.e. –200 to +1500ms from the attentional cue onset) and of motor preparation respectively (i.e. +1300 to +3000ms from attentional cue onset, corresponding to -200 to +1500ms from motor cue onset).

Attentional shift. For each participant, condition and time point, trials were averaged separately for attentional left and attentional right cues and activity between 8-12Hz was examined. This frequency band (in the alpha range) was predefined in line with many previous studies reporting modulation of posterior alpha-activity with spatial attention deployment (for examples see e.g. Foxe & Snyder, 2011; Thut, Nietzel, Brandt & Pascual-

Leone, 2006; Worden, Foxe, Wang & Simpson, 2000). In order to normalize data, a common denominator was created to divide the data by the average over attention left and right trials of all conditions (as in Marshall, O'Shea, Jensen & Bergmann, 2015), here exposure type (Prismatic and Neutral condition) and time (pre and post PA). Data were then interrogated as to differential attentional modulation by contrasting attention right and attention left trials (Power $_{\text{Attention right}}$ - Power $_{\text{Attention left}}$) across conditions (Marshall, O'Shea, Jensen & Bergmann, 2015).

Motor preparation. For each participant, condition and time point, trials were averaged separately for left motor preparation and right motor preparation cues, in analogy to the analysis above. In addition to analysing the alpha/mu band (8-12Hz), we also examined activity between 16-25Hz, as activity within both these frequency bands are known to be modulated by unimanual motor preparation over rolandic sensors (see introduction). Again, a common denominator was calculated in order to normalize data by dividing by the average over motor left and right trials from both conditions (Prism and Neutral) and time points (pre- and post-PA). Data were then analysed in terms of differential motor preparatory signals between left and right hand preparatory trials (Power $_{\text{Right Hand}}$ - Power $_{\text{Left Hand}}$) across conditions.

Statistical analysis. Statistical analysis on power was conducted separately for attentional and motor cue periods and frequency bands of interest (alpha and beta bands). In order to compare conditions (pre *vs.* post, Prism *vs.* Neutral lenses) nonparametric, cluster-based permutation statistics were first computed (Maris & Oostenveld, 2007). Cluster based statistics was performed over the time periods from 200-1000ms for the attentional cue period, and 2000-2700ms for the motor preparatory period in the respective frequency ranges of interest (8-12Hz, 16-25Hz) Dependent-sample *t* tests were then conducted for the contrasts of interest, i.e. either on Post minus Pre Prism *vs*. Post minus Pre Neutral (for exploring the interaction between Condition (Prism *vs*. Neutral) and Time (pre *vs*. post) or

Post Prism *vs*. Pre Prism as well as Post Neutral *vs*. Pre Neutral (for exploring the associated simple effects of Time per Condition when appropriate). Clusters of adjacent data points in space were defined by means of a clustering algorithm using a threshold of $p < .025$ (two-sided *t*-Test). The cluster-level test statistic was defined from the sum of the *t* values of the sensors in a given cluster. Finally, clusters were evaluated in terms of statistical significance against a permutation distribution, obtained by 2500 permutations of randomly shuffling the conditions within all participants.

To further investigate the degree of attentional modulation and motor preparation within each hemisphere, an attentional modulation index (AMI) and a motor preparation index (MPI) were calculated over regions of interest according to the formula: $(Power_{contralateral} - Power_{ipsilateral})$/[Common Denominator] (Marshall, O'Shea, Jensen & Bergmann, 2015). Contralateral and ipsilateral refer to the attentional location with respect to the region of interest within each hemisphere for the AMI, and to the hand participants were instructed to move for the MPI. The Common Denominator refers to the average over contralateral and ipsilateral hemispheres for all conditions, i.e. exposure type (Prismatic and Neutral condition) and time (pre and post PA). AMI and MPI were calculated for electrodes within regions of interest, defined as clusters of electrodes pairs in the left and right hemisphere that showed the strongest average alpha/beta modulation across all sessions (Marshall, O'Shea, Jensen & Bergmann, 2015). AMI and MPI changes were then evaluated by means of a repeated measure ANOVA with factors Condition (Prism *vs*. Neutral), Time (Pre *vs.* Post) and Hemisphere (Left *vs.* Right).

Target-locked ERPs

To investigate if PA effects could manifest as a gain modulation of visual responses (post-stimulus attention effect), rather than in preparatory, pre-stimulus activity, we analysed ERPs locked to the visual motor cues (serving as visual targets). For each participant and

condition, EEG was low-pass filtered at 30 Hz and then segmented in 600ms epochs, from 100ms before to 500ms after target presentation. All epochs were baseline corrected to 100ms pre-stimulus activity and averaged according to block of recording in each condition (pre/post Prism, pre/post Neutral). In line with previous studies (Eimer, 1994; Martín-Arévalo, Laube, Koun, Farnè, Reilly & Pisella, 2016), P1 and N1 peaks were defined over parieto-occipital electrodes (PO7 and PO8) as the most prominent positive and negative peaks within the 70-150ms (P1) and 130-230ms (N1) intervals after target onset respectively, whereas the P3 peak was defined over Cz as the maximum positive voltage between 300-450ms after target onset.

Statistical analysis. For each component of interest (P1, N1 and P3), differences in peak amplitude and latency were analysed through repeated measure ANOVAs testing the factors Condition (Prism vs. Neutral), Time (Pre *vs*. Post), Cueing (Valid *vs*. Invalid), Target position (Left *vs*. Right) and Laterality (Contralateral *vs*. Ipsilateral to the target position).

Results

Prismatic adaptation

Analysis of pointing displacement during PA revealed the expected pattern (**Fig. 4**). When wearing rightward-shifting lenses (solid line), participants showed an initial rightward pointing deviation during early exposure that was compensated for in the late exposure stage. This is explained by adaptation, given that post-exposure pointing was associated with a strong after-effect (leftward overshoot) (Fig 3). No such effects were observed with neutral lenses (dashed line). This was statistically supported by the 2x5 repeated-measures ANOVA revealing significant main effects of Condition [$F(1,15) = 5.75$, $p = .03$, $\eta p2 = .28$] and Time [$F(4,60) = 118.43$, $p < .000$, $\eta p2 = .89$] and a Condition x Time interaction [$F(4,60) = 104.93$, $p < .000$, $\eta p2 = .87$]. Two repeated measures ANOVAs performed separately for each

condition both showed significant main effects of Time (Prism [F(4,60) = 173.45, $p < .000$, ηp2 = .92]; Neutral [F(4,60) = 17.01, $p < .000$, ηp2 = .53], each explained by different

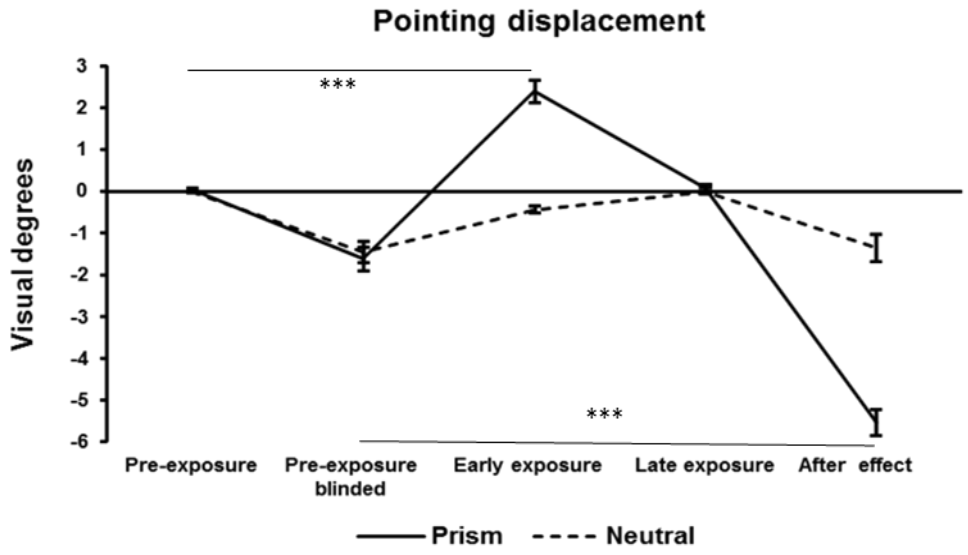

Fig. 4 Mean pointing displacement (expressed in degrees of visual degree) throughout the prism adaptation procedure (pre-exposure free-viewing/pre-exposure blinded, early and late exposure, after-effect) are plotted for each condition. The solid line represents pointing when wearing real (prismatic) lenses (Prismatic goggles), whereas the dotted line represents pointing with neutral lenses (Neutral goggles). Negative values indicate a leftward pointing displacement; positive values a rightward displacement. Error bars represent sem, ***$p <$ .000

changes across PA stages. While wearing prisms, participants significantly pointed more rightward during the early exposure phase as compared to the pre-exposure (free-viewing) baseline ([F(1,15) = 74.72, $p < .000$, ηp2 = .83], .04° *vs.* 2.38°). This bias disappeared during late exposure ([F(1,15) = .04, $p = .83$, $\eta p^2 = .00$], 2.38° *vs.* .07°). In the post-exposure, a significant leftward after-effect was observed in comparison to the pre-exposure blinded baseline ([F(1,15) = 121.35, $p < .000$, ηp2 = .92], -1.62° *vs.* -5.53°). In contrast, when wearing neutral lenses, participants showed a shift to the left in the early-exposure phase ([F(1,15) = 33.84, $p < .000$, ηp2 = .69], .0° *vs.* -.44°), but no significant after-effect post-exposure ([F(1,15) = .09, $p = .76$, $\eta p^2 = .00$], -1.46° *vs.* -1.36°).

Finally, comparing each PA stage between the two conditions revealed no significant

difference in pointing performance during pre-exposure (both free-viewing and blinded) and late exposure (all *p*s > .43), whereas Prismatic lenses induced a rightward shift during early exposure (Prism *vs.* Neutral early exposure: [F(1,15) = 116.77, $p < .000$, ηp2 = .89], 2.38° *vs.* -.44°) and a leftward after-effect (Prism *vs.* Neutral post exposure: [F(1,15) = 158.09, $p < .000$, ηp2 = .91], -5.53° *vs.* -1.36°).

Attentional/motor task

Hit rates to small targets (in delayed responses) were analysed to ensure participants did engage in attentional orienting using a repeated measure ANOVA with the factors Condition (Prism *vs*. Neutral), Time (Pre *vs*. Post exposure), Cueing (Valid *vs.* Invalid) and Target position (Left *vs*. Right). As expected, we found a significant main effect of Cueing [F(1,15) = 63.82, $p < .000$, ηp2 = .81] with more hits at validly cued than invalidly cued positions (0.83±0.03 *vs*. 0.63±0.02) indicating that participants were correctly shifting their attention to the cued location. We also found a significant Time x Cueing [F(1,15) = 39.31, $p < .000$, ηp2 = .72], Condition x Target position [F(1,15) = 4.96, $p = .04$, ηp2 = .25] and Cueing x Target position interaction [F(1,15) = 4.83, $p = .04$, ηp2 = .24]. However, there was no effect in the main interactions of interest (Condition x Time x Cueing: $p > 0.35$) and no 4-way interaction with Target side ($p > 0.35$) suggesting that PA had no effect on target processing depending on the side of attentional orienting.

Hit rates to large targets and reaction times to go-signals were analyzed to ensure that participants engaged well in motor preparation prior to the go signal (presented 1500ms after the motor preparation cue). This was supported by high accuracy (left motor: 0.97±0.2, right: motor: 0.96±0.3) and fast reaction times (left motor: 291±17.8ms, right: motor: 294± 16.7ms). In addition, only in a small proportion of trials (4%) were participants slower than 500ms (the response deadline). Hence, participants were engaging in the motor preparation task. Statistical analysis using repeated-measures ANOVAs on both accuracy and reaction

times to large targets, taking into account condition (Prism *vs.* Neutral), time (Pre *vs*. Post exposure), and hand (Left *vs*. Right) as factors, did not reveal any significant main effect nor interaction (all *p*s > 0.8).

EEG results

Attentional Modulation of alpha activity after prismatic adaptation

The comparison between rightward versus leftward covert attention shifts revealed the well-known alpha-signature of attention orienting. As illustrated by the time-frequency representations (**Figure 5**A), alpha power exhibited a sustained, asymmetric modulation over left versus right occipito-parietal sites (P3/4, P5/6, P7/8, PO3/4, PO7/8 and O1/2) in accordance with the attention focus, starting 200ms after the attentional cue and lasting up to the target, i.e. 1 sec post cue. Note that the mirror-symmetric pattern (see maps in Figure 5A) indicates a decreases in alpha-power contralateral to the attended position and/or an increases ipsilaterally (topographies in Figure 5A reflect $Power_{Attention\ right}$ - $Power_{Attention\ left}$ subtraction maps). Importantly, this signature was observed regardless of condition and time (pre- and post-Prism, pre- and post-Neutral) (compare the four rows in Figure 5A)

To test for potential differences of attention-modulated alpha activity across conditions (pre- and post- Prism and Neutral) a cluster-based permutation test was run (in the 8-12 Hz frequency band from 200 to 1000ms post-cue). The analysis revealed no significant cluster in the main interaction of interest (Condition x Time interaction, see Figure 5B, right middle plot). Therefore, although the attention related alpha modulation seemed to be slightly accentuated post-prism as compared to pre-prism (Figure 5B, see upper left map), this was not statistically different from pre- to post-changes in the neutral condition (Figure 5B, lower left map).

In order to substantiate the absence of differential effects of time (Pre *vs*. Post) on attention-related alpha modulation as a function of Condition (Prism *vs*. Neutral), we

computed an Attentional Modulation Index (i.e. AMI = ($Power_{contralateral}$ – $Power_{ipsilateral}$)/[Common Denominator]) over posterior sites (P3/4, P5/6, P7/8, PO3/4, PO7/8 and O1/02). Figure 4C illustrates this index across conditions per hemisphere. The ANOVA testing the factors Condition (Prism *vs*. Neutral), Exposure (Pre *vs*. Post) and Hemisphere (Left *vs*. Right) confirmed the results of the cluster analysis, showing no significant main effects or interactions (all *p*s > .12).

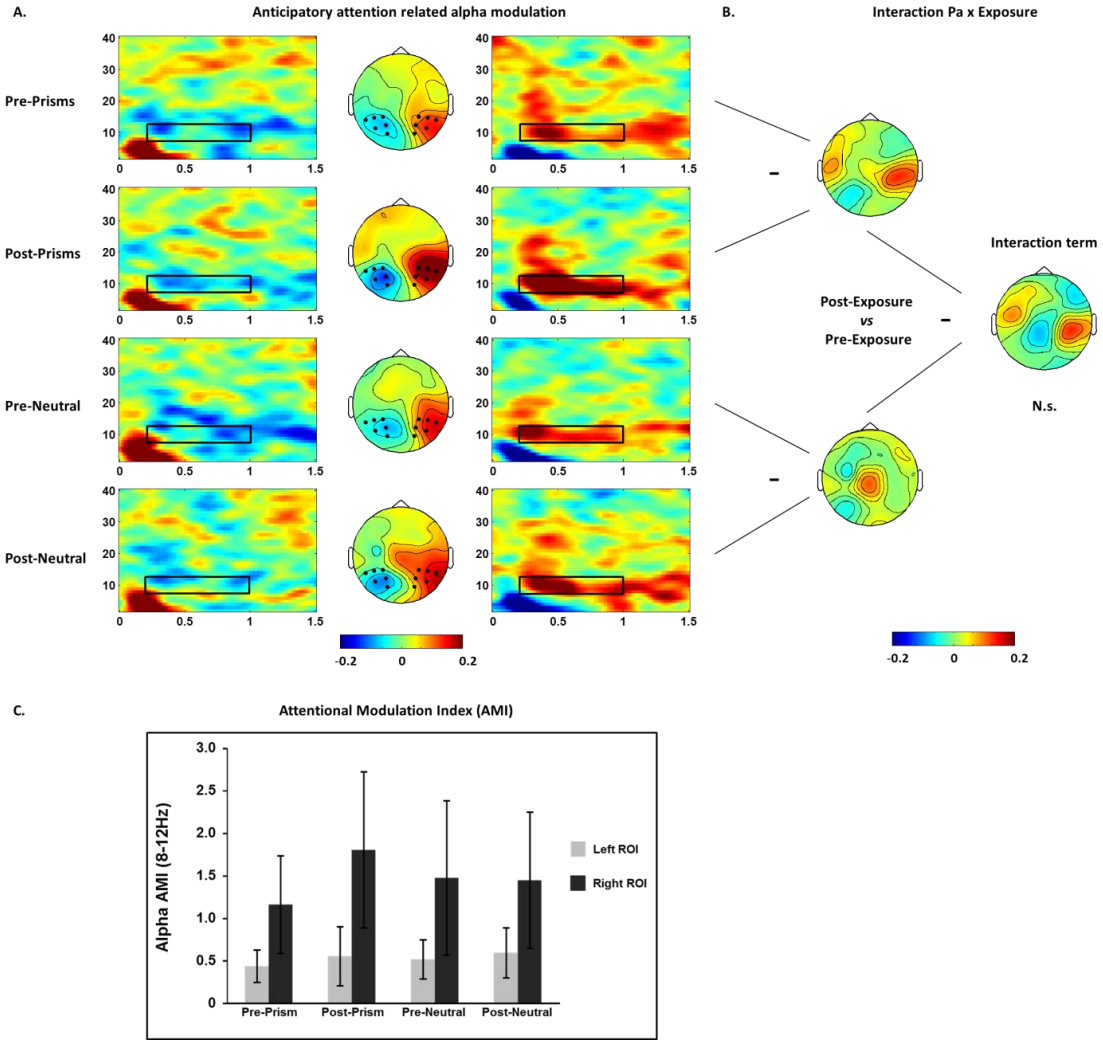

Fig. 5 Alpha modulation by attention orienting. **A.** Time-frequency representations (TRF) of the anticipatory attention related alpha modulation are shown separately across rows for each PA conditions (pre/post Prism, pre/post Neutral) for two posterior ROIs (left and right columns) after contrasting attention right and attention left trials ($Power_{Attention\ right}$ - $Power_{Attention\ left}$). The electrodes included in the left and right ROIs are indicated by black dots (P3/4, P5/6, P7/8, PO3/4, PO7/8 and O1/2). The middle column represents the alpha topography (8-12) Hz between 200 and 1000ms after the attentional cue onset (at zero). **B.** Differential maps of alpha power (8-12) from 200 to 1000ms post-cue. Raw effects are shown for each condition (Pre- *vs.* Post- prism exposure; Pre- *vs.* Post- neutral exposure) on the left and for the Exposure x PA interaction. No significant cluster was identified ($p > .05$). **C.** ROIs analysis: Attentional modulation index [AMI = ($Power_{Attention\ Contra}$ - $Power_{Attention\ Ipsi}$)/ average over all attention and PA conditions]) in the alpha band (8-12 Hz, 0.2-1sec) over posterior sites (P3/4, P5/6, P7/8, PO3/4, PO7/8, O1/2). Statistical analysis revealed no significant 2x2 interactions. Error bars: sem.

Motor preparatory signals after prismatic adaptation

Figure 6 and **7** show time-frequency representations of the EEG activity recorded in the motor preparatory window (motor cue at: 1.5s, go signal at: 3s) over sensors close to the hand motor areas (C3/Cp3, C4/Cp4) as difference between right and left hand movement preparation. In line with previous research (e.g, Pfurtscheller and Lopes Da Silva, 1999), alpha activity (Figure 6A) and beta activity (Figure 7A) showed a sustained, asymmetric modulation over the two hemispheres in accordance with the to-be-moved hand starting 500ms (2s mark) after the motor preparation cue and lasting up to the go-signal (3s mark). The mirror symmetric pattern for both alpha and beta activity (see maps in Figures 6A and 7A) indicates that activity in these frequency bands decreased contralateral and or increased ipsilateral to the planned movement (as topographies in Figure 6A and 7A illustrate $Power_{Right\ Hand}$ - $Power_{Left\ Hand}$ subtraction maps).

As for attentional modulation, we ran cluster-based permutation tests (8-12 and 16-25Hz frequency bands from 2-2.7s) and analyses of lateralization indices, here motor preparation index (MPI = ($Power_{contralateral\ Hand}$ - $Power_{ipsilateral\ Hand}$)/[Common Denominator]) over electrode pairs C3/4 and Cp3/4, to examine effects of prims adaptation on this motor related activity. For the alpha band, we did not find any significant effect, neither in terms of significant clusters in the interaction of interest (Condition x Time, see right middle right map in Figure 6B) nor in the analysis of the MPI (Figure 6C), as the corresponding ANOVA testing the factors Condition (Prism *vs*. Neutral), Time (Pre *vs*. Post) and Hemisphere (Left *vs*. Right) revealed no significant main effects or interactions (all *p*s > .14; Figure 6C). When considering the beta band (see Figure 7), the cluster based permutation tests showed a significant Condition x Time interaction for a cluster of central electrodes (Figure 7B, right middle map, black dots illustrate the significant interaction cluster on top of the difference map, raw data) ($p < .03$). To further test this interaction, we run two separate follow-up cluster-based permutation tests to compare effects of time (Pre *vs*. Post) for Prismatic and

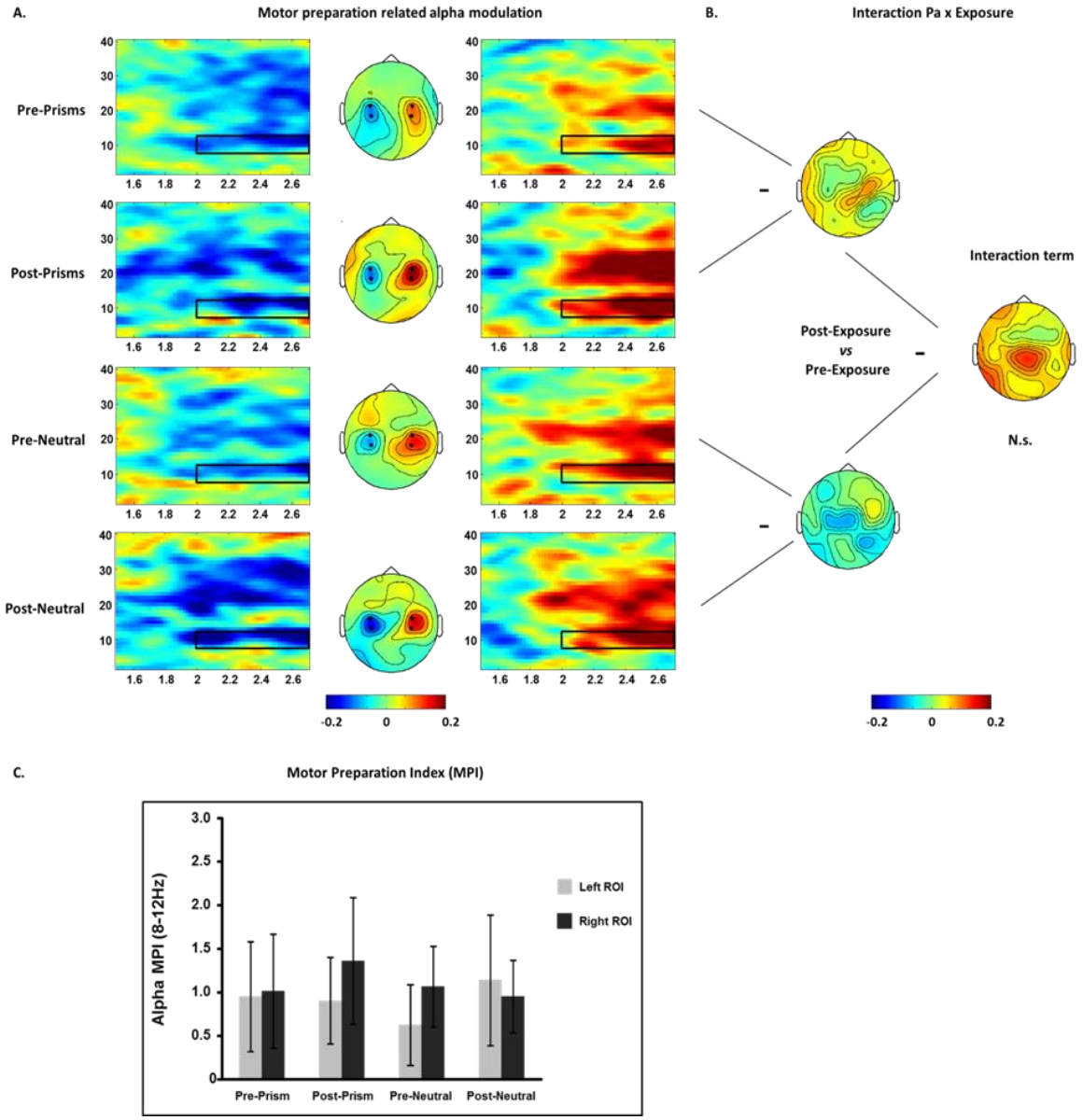

Fig. 6 Alpha/mu modulation by motor preparation. **A.** Time-frequency representations (TRF) of the motor preparation related alpha/mu modulation are shown separately across rows for each PA conditions (pre/post Prism, pre/post Neutral) for two central ROIs (left and right columns) by contrasting right and left hand motor preparation (*Power* $_{\text{Right Hand}}$ - *Power* $_{\text{Left Hand}}$). The middle column represents the alpha-band topography (8-12 Hz) between 2000 and 2700ms after the cue (target/go interval) and depicts the ROIs (electrodes C3/4, CP3/4, see black dots). **B.** Differential maps of alpha/mu power (8-12) from 2 to 2.7s post-cue. Raw effects are shown for each condition (Pre- *vs.* Post- prism exposure; Pre- *vs.* Post- neutral exposure) on the left and for the Exposure x PA interaction. No significant cluster was identified ($p > .05$). **C.** ROIs analysis: Motor preparation index [MPI = (Power $_{\text{Hand Contra}}$ – Power$_{\text{Hand Ipsi}}$)/ average over all attention and PA conditions] in the mu band (8-12 Hz, 2.0-2.7sec) over central sites (C3/4, CP3/4). Statistical analysis revealed no significant 2x2 interactions. Error bars: sem.

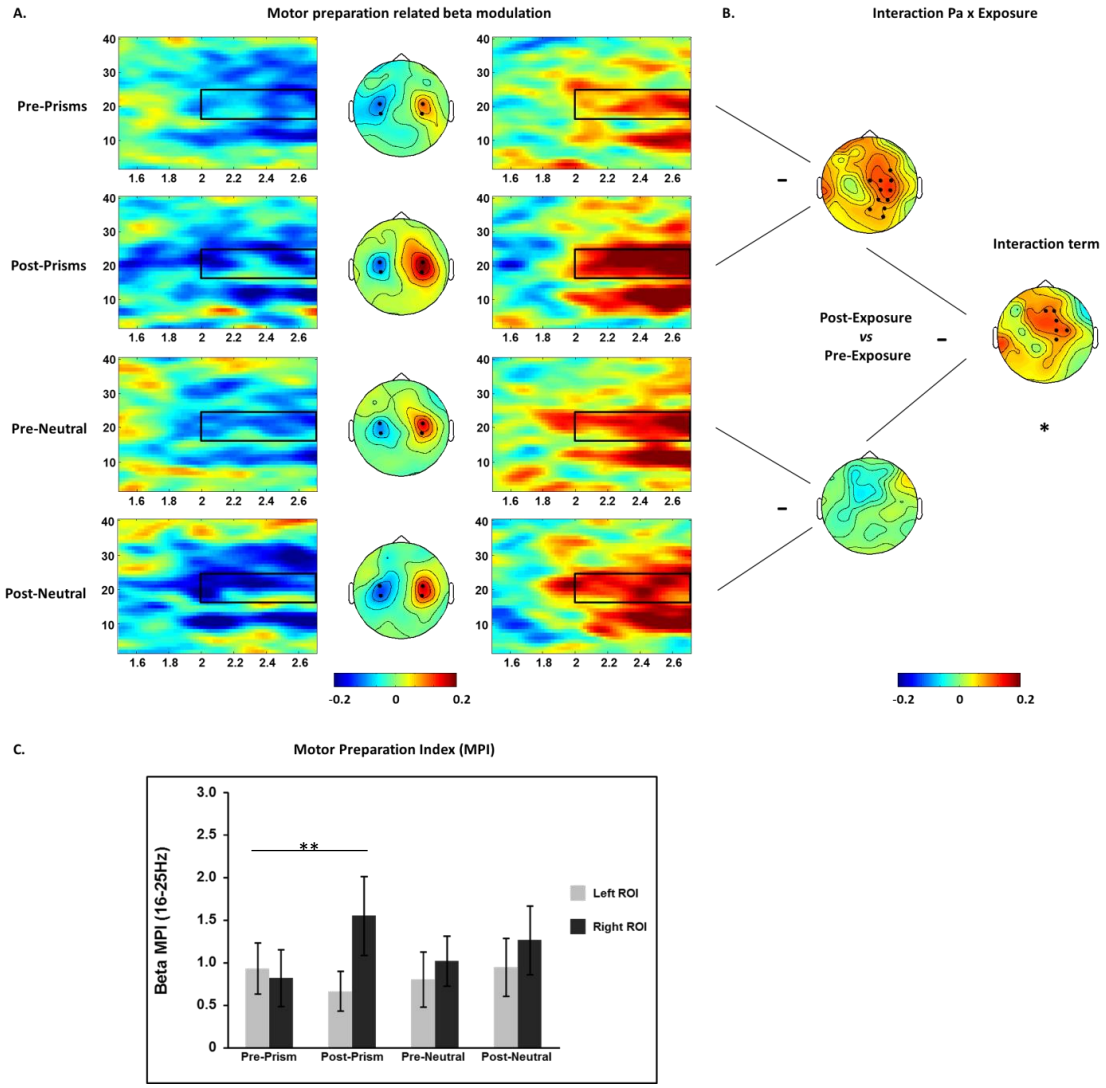

Fig. 7 Beta modulation by motor preparation**. A.** Time-frequency representations (TRF) of the motor preparation related beta modulation are shown for left and right ROIs separately (left and right columns) and for each PA conditions (rows). The middle column represents the beta-band topography (16-25 Hz) between 2000 and 2700ms after the cue (target/go interval) and depicts the ROIs (electrodes C3/4, CP3/4, see black dots). **B.** Differential maps of alpha/mu power (16-25) from 2 to 2.7s post-cue. Raw effects are shown for each condition (Pre- *vs.* Post- prism exposure; Pre- *vs.* Post- neutral exposure) on the left and for the Exposure x PA interaction revealing a significant cluster ($p < .03$, see black dots in right interaction map). Follow-up simple tests revealed a significant cluster ($p = .008$) when contrasting Pre versus Post Prism PA but not when contrasting Pre versus Post for neutral lenses (see left maps). **C.** ROIs analysis: Motor preparation index [MPI = ($Power_{Hand\ Contra} - Power_{Hand\ Ipsi}$)/ average over all attention and PA conditions] in the beta band (16-25Hz, 2-2.7sec) over central sites (C3/4, CP3/4). Statistical analysis revealed significant interaction of Condition x time x hemisphere. MPI over the right hemisphere increased after rightward Prism adaptation ($p = .01$). Error bars: sem.

Neutral lenses separately. The analysis revealed a significant increase of beta power after Prism use over a centro-parietal cluster of electrodes (p = .008) (Figure 7B, upper left map), whereas no clusters significantly differentiated pre and post Neutral measurements (p = 1) (Figure 7B, lower left map).

This was confirmed by the analysis of MPI (Figure 7C), as the corresponding ANOVA showed a significant Condition x Time x Hemisphere interaction [F(1,15) = 4.53, p =.05, ηp2 = .23]. Breaking down the interaction revealed a significant Time x Hemisphere interaction for the prism condition [F(1,15) = 5.49, p = .03, ηp2 = .40], due to an increase of MPI over the right hemisphere after PA [F(1,15 = 4.28, p = .015, ηp2 = .33], whereas no significant effects emerged for the left hemisphere (p > .29). No main effects or interaction were found for the Neutral condition (p > .48; Figure 7C).

Event-related potentials

Separate repeated measures ANOVAs were conducted for peak amplitude and latency of each component of interest (P1, N1 and P3) with Condition (Prism vs. Neutral), Time (Pre vs. Post), Cueing (Valid *vs*. Invalid), Target position (Left *vs*. Right) and Laterality (Contralateral *vs*. Ipsilateral hemisphere to the target position) as factors.

P1. In line with previous studies (Eimer 1994; Martín-Arévalo, Laube, Koun, Farnè, Reilly & Pisella, 2016), ANOVAs on P1 amplitude and latency revealed a main effect of Cueing. P1 peak amplitude was maximal on the invalid trials (F(1,15) = 6.29, p = .02, ηp2 = .28; 3.02 *vs*. 3.43 µV), but peaked earlier on the valid trials ([F(1,15) = 5.38, p = .03, ηp2 = .30]; 119.9 *vs*. 124.3ms). Moreover, a significant Cueing x Laterality interaction emerged for P1 latency, indicating a longer latency within the hemisphere contralateral to the target position for the invalid compared to valid trials (Cueing x Laterality [F(1,15) = 134.76, p < .000, ηp2 = .90]; 108.2 *vs*. 142.5ms), and an opposite pattern for the hemisphere ipsilateral to the target position ([F(1,15) = 50.99, p < .000, ηp2 = .78]; valid= 131.70 *vs*. invalid=

106.00ms). A significant Time x Cueing x Target position interaction [F(1,15) = 4.69, *p* = .04, ηp2 = .24] revealed a higher peak amplitude for the uncued targets presented on the left hemispace during the post blocks regardless of the PA condition ([F(1,15) = 6.87, *p* = .02, ηp2 = .31] 2.86 *vs*. 3.39 V). No other significant main effects or interaction was found either for amplitude or latency (all *p*s > .69; **Figure 8**).

N1. A similar pattern of result was found for N1 component. Its amplitude was indeed maximal for uncued targets (main effect of Cueing: F(1,15) = 8.10, *p* = .01, ηp2 = .35; -4.35 *vs*. -4.98 µV), but peaked earlier on the cued targets (main effect of Cueing [F(1,15) = 14.59, *p* = .001, ηp2 = .49]; 194.1 *vs*. 202.5ms). A significant Cueing x Laterality interaction pointed to higher amplitude for uncued compared to cued targets within the ipsilateral hemisphere ([F(1,15) = 28.33, *p* < .000, ηp2 = .65]; -4.69 vs. -5.28µV). No other significant main effects or interaction were found either for amplitude or latency (all *p*s > .08, Figure 8).

P300. The P3 mean peak amplitude revealed only a main effect of Cueing, with higher peaks and latency for uncued compared to cued target ([F(1,15) = 28.82, *p* < .000, ηp2 = .67] 3.69 *vs*. 5.25µV).When testing for latency modulations we also found a significant Time x Cueing interaction [F(1,15) = 6.20, *p* = .02, ηp2 = .29]. No significant Condition x Exposure interaction were found (*p* > .28, Figure 8).

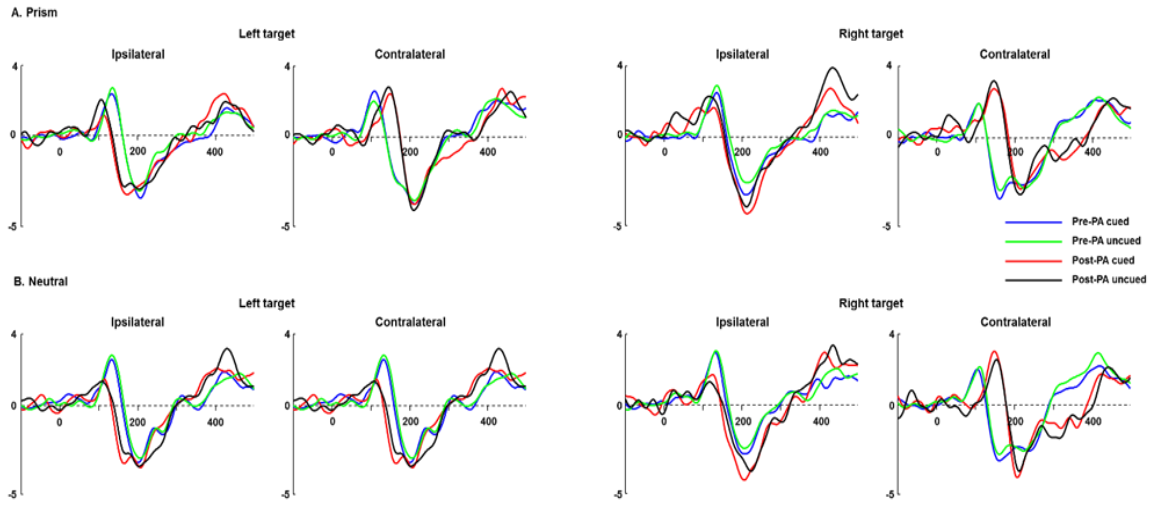

Fig 7 Target-locked ERP before and after PA (A: Prism and B: Neutral) are shown separately for hemispheres (ipsilateral and contralateral to the target position), validity (valid and invalid conditions), and target position (left and right). Electrodes: PO7/8.

Discussion

The aim of the present study was to characterize neural mechanisms underlying rightward PA, with a new protocol allowing us to evaluate whether PA predominantly affects spatial attention or motor-related processes, or both. Therefore, we focused on PA induced change on well-known EEG signature of attentional and motor processes; anticipatory parieto-occipital alpha for attention and rolandic alpha/mu and beta bands for motor preparation. Our result is twofold: on one hand we could not report any attentional effects on oscillatory activity or with the behavioral task RTs or with ERPs; on the other, we found a significant modulation of rolandic beta-activity after rightward PA, but none of alpha band. Taken together, our results suggest that rightward prisms were able to modulate motor but not attentional processes. To the best of our knowledge, this is the first EEG study to test PA after-effects on brain oscillations. However, our results can be compared with the existing literature.

PA is known to modulate spatial attention with several evidences, on neglect patients and healthy subjects (Bultitude, Van der Stigchel, & Nijboer, 2013; Magnani, Mangano,

Frassinetti & Oliveri, 2013; Nijboer, McIntosh, Nys, Dijkerman & Milner, 2008; Oliveri *et al.* 2013; Pisella, Rode, Farnè, Boisson & Rossetti, 2002.; Rode, Cotton, Revol, Jacquin-Courtois, Rossetti& Bartolomeo, 2010; Schintu, Pisella, Jacobs, Salemme, Reilly & Farnè, 2014; Striemer & Danckert, 2007; Striemer & Danckert, 2010a; Vangkilde & Habekost, 2010), but, when tested on the latter ones, its effects are more usually reported with leftward rather than rightward prims (Colent, Pisella, Bernieri, Rode, & Rossetti, 2000). Moreover, although these successful demonstrations about leftward PA modulatory effects on normal people, there is also a lack of results that report behavioral changes by means of RTs alteration (Bultitude, List & Aimola, 2013; Morris, Kritikos, Berberovic, Pisella, Chambers & Mattingleyet, 2004). This is in agreement with our behavioral data. While we found a cueing effect on the Posner-like participants' performance proving that they were correctly shifting their attention accordingly to the attentional cue, we did not find any change induced by prisms. This discrepancy on RTs behavioral results between neglect and normal people, has been suggested as consequences of the severity of right brain damaged symptoms. Neglects patients would be more affected by prisms than normal people due to their severe attentional deficits (Martín-Arévalo, Laube, Koun, Farnè, Reilly & Pisella, 2016). However, our EEG findings confirmed that rightward prisms did not affect visuospatial attention. As expected, we found asymmetric changes of the occipito-parietal alpha-activity as a value of lateralized anticipatory attentional shift (Thut et al., 2006), but any modulation induced by prisms. Thus, our results are again in line with previous behavioral studies reporting no attentional changes with rightward PA (Colent, Pisella, Bernieri, Rode, & Rossetti, 2000; Schintu, Pisella, Jacobs, Salemme, Reilly & Farnè, 2014).

To further investigate the attentional processes involved by PA, we analysed also the ERPs locked to the visuo-motor cues. In particular, we tested whether PA, rather than the anticipatory attentional activity, affected early stages visual components that have been linked to attentional processes and that are also known to be impaired in neglect patients:

N1 linked to the allocation and the maintenance of attentional resources facilitating perception of stimuli, P1 representing the "attentional cost" due to the shift of the attention and P3 used to measure the allocation of attention and suggested as a tool for assessing high-level visual impairments (Herrmann & Knight, 2001; Marzi, Girelli, Natale & Miniussi, 2001; Saevarsson, Kristjánsson, Bach & Heinrich, 2012). This analysis allowed us to replicate Martín-Arévalo and colleagues study (Martín-Arévalo, Laube, Koun, Farnè, Reilly & Pisella, 2016) reporting that leftward but not rightward PA is able to modulate these electrophysiological markers.

In the present study, we found also the involvement of rolandic alpha/mu and beta rhythms during the motor preparation phase of the task. As widely described in literature, our data show a significant decrease of alpha/beta-activity contralateral to the hand to be prepared (Kilavik, Zaepffel, Brovelli, MacKay & Riehle, 2013; Pfurtscheller & Lopes Da Silva, 1999; Tan, Leuthold & Gross, 2013). Interestingly, we found that rightward PA modulated beta- but not alpha-activity. Namely, our data showed an increased modulation of beta rhythm power after PA within the right hemisphere with a higher power when subjects were moving the ipsilateral hand (see the cluster-based analysis) and *vice versa*. The difference between alpha and beta results can be explained considering the different role of these two rhythms within the central areas. Because of their topographical distribution, more sensorimotor for beta and more widespread and including also parietal cortices for alpha (Vukelić, Bauer, Naros, Naros, Braun & Gharabaghi, 2014), they have been proposed to reflect different functions. In particular, alpha has been reported to reflect more the general state of the motor cortex under resting condition (Veniero, Brignani, Thut & Miniussi, 2011) and to be involved on the selection of task-relevant areas (Pineda, 2005; Vukelić, Bauer, Naros, Naros, Braun & Gharabaghi, 2014) and the inhibition of task irrelevant areas (Jensen & Mazaheri, 2010; Vukelić, Bauer, Naros, Naros, Braun & Gharabaghi, 2014), both activity been related to the attention (Klimesch, 2012). On the other hand, rolandic beta rhythm has

been suggested to be strictly related to motor functions, such as cortical control and monitoring of the muscular descending pathways (Baker, 2007; Kilavik, Zaepffel, Brovelli, MacKay & Riehle, 2013; Veniero, Brignani, Thut & Miniussi, 2011; Vukelić, Bauer, Naros, Naros, Braun & Gharabaghi, 2014). To our opinion, the modulation of only beta signatures is a further evidence that rightward PA affected motor but non attentional processes.

Although a few studies found a correlation between attentional and motor after-effects (Sarri, Greenwood, Kalra, Papps, Husain & Driveret, 2000), many others found a dissociation between them (Dijkerman, *et al*., 2003; Farnè, Rossetti, Toniolo & Làdavas, 2002; Ferber & Murray, 2005; Fortis *et al*., 2011). Moreover, a likewise amount of works failed to report any prisms after-effect beyond the straight-ahead pointing task. In fact, numerous studies have been reporting more related to motor than pure attentional functions PA effects on either healthy and right brain damaged people (Leigh, Danckert & Eliasmith, 2014; Striemer & Danckert, 2010a; Striemer & Danckert, 2010b; Striemer, Russel & Nath, 2016). A clear example has been given by Striemer and Danckert (2010b) who reported that, after PA neglect patients showed the after-effect only for straight-ahead and line bisection task, but not for the landmark task. Thus, PA may have a larger influence on tasks requiring motor active responses (i.e. line bisection), rather than judgements (i.e. landmark). More recently, Striemer *et al*. (2016) also found a similar pattern of result in healthy participants, but in their case the dissociated effect between the tasks vanished increasing the prismatic deviation (8.5° *vs*. 17°).

Collectively, the existing literature and our results seems to suggest that rightward PA, at least on healthy people and with a 10° of prismatic deviation, can affect only the motor but not the attentional areas. One possible explanation could be the right hemisphere dominance for spatial attention well documented with normal people (Cavezian, Valadao, Hurwitz, Saoud & Danckert, 2012; Thiebaut de Schotten *et al*., 2011) and neglect patients (Benton & Tranel, 2003; Vallar, 1998). This right parietal dominance, causing also the

known pseudoneglect phenomenon in healthy subjects, may be compensated by means of leftward PA. Conversely, the use of rightward PA might not be able to force the physiological leftward shift of normal people. Differently to the PPC, the motor cortex may be directly activated thanks to its cerebellar connection (Koch, 2010; Magnani, Mangano, Frassinetti & Oliveri, 2013) known to be involved by PA (Chapman *et al*., 2010; Luauté *et al*., 2006, Luauté *et al*., 2009).

By analysing central and posterior signature during an attentional/motor task we provided the first evidence of PA is able to modulate brain oscillatory activity. Moreover, it allowed us to show PA after-effects that usually remain hidden (i.e. motor effects and rightward PA after-effects on normal people, in general). The limitation of the present study is the absence of leftward PA condition. Future research should probe leftward PA modulation on brain oscillation and also the effects induced by rightward prims on patients.

CHAPTER IV

COMBINING TDCS WITH PRISMATIC ADAPTATION FOR NON INVASIVE NEUROMODUALTION OF THE MOTOR CORTEX

Introduction

Modulation of excitability of the human primary motor cortex is an emerging field in the literature, especially for its potential clinical applications for recovery from stroke and other neurological diseases. Several studies showed that M1 activity could be modulated by non-invasive brain stimulation methods, such as tDCS and TMS (Di Lazzaro, Ziemann & Lemon, 2008; Pascual-Leone, Tormos, Keenan, Tarazona, Cañete & Catalá, 1998; Stagg & Nitsche, 2011). Although NIBS can induce selective excitatory or inhibitory effects over the target brain region, the question of the best combination of excitation and inhibition for potentiation of plastic changes in the motor cortex is still unresolved.

A limit for selective neuromodulatory effects of NIBS is the inter- and intra-individual variability of brain excitability. In fact, in response to extrinsic stimulation neurons can change and adapt the strength of their connections or synapses. Hebbian plasticity, including long-term potentiation (LTP) and long-term depression (LTD) is the most known form of activity-dependent adaptation of synaptic plasticity (Collindgidge, Isaac, Wang, 2004; Feldman, 2009; Malenka & Bear, 2004; Turrigiano & Nelson, 2000). However, in order to prevent neural networks from reaching extremes of excitation and inhibition, a homeostatic negative feedback regulation constrains neural activity levels and maintains network stability (i.e. homeostatic plasticity) (Davis & Bezprozvanny, 2001; Karabanov *et al*., 2015; Pozo & Goda, 2010; Yin & Yuan, 2015). Homeostatic plasticity has been tested in NIBS studies, reporting that differences in the recent history of neuronal activity contribute to the marked inter-individual variability of corticospinal excitability

following NIBS (Ilić, Milanović, Krstić, Bajec, Grajić & Ilić, 2011; Karabanov *et al*., 2015).

Lang and *et al*. (2004) and Siebner *et al*. (2004) showed that preconditioning motor cortical excitability using tDCS modulates the direction of effects induced by subsequent repetitive TMS. Further studies reported an analogous homeostatic pattern by associating tDCS with rTMS protocols (Cosentino *et al*., 2012), tDCS with paired associative stimulation (PAS) (Pötter-Nerger *et al*., 2009) and PAS-LTP with PAS-LTD (Müller, Orekhov, Liu & Ziemann, 2007). More recently, homeostatic plasticity has been tested by using a behavioral stimulation as a preconditioning tool of cortical excitability, with sensory adaptation, priming or music stimulation applied before NIBS (Cattaneo, Rota, Vecchi & Silvanto, 2008; Picazio, Granata, Caltagirone & Oliveri, 2015; Silvanto, Silvanto, Muggleton, Cowey & Walsh, 2007). Moreover, the interaction of individual baseline characteristic (i.e. performance in a task) and tDCS outcome has been reported (Benwell, Learmonth, Miniussi, Harvey & Thut, 2015). PA is a behavioral method potentially useful for neuromodulation. Several findings suggest that PA affects not only low-level sensory-motor processes, but also high-level cognitive functions, such as visuospatial attention (Schintu, Pisella, Jacobs, Salemme, Reilly & Farnè, 2014; Vangkilde & Habekost, 2010), time perception (Magnani, Mangano, Frassinetti & Oliveri, 2013; Magnani, Oliveri, Mancuso, Galante & Frassinetti, 2011; Magnani, Oliveri, Mangano & Frassinetti, 2010; Oliveri, Magnani, Filipelli, Avanzi & Frassinetti, 2013), number processing (Loftus, Nicholls, Mattingley & Bradshaw, 2008; Nicholls, Kamer & Loftus, 2008). Although a number of studies investigated the effects of PA in cognitive functions, its influence on the neural mechanisms subserving these functions has been less explored. Magnani, Caltagirone and Oliveri (2014) adopted a paired-pulse TMS protocol over M1 to assess short-interval intracortical-inhibition (SICI) and intracortical-facilitation (ICF) before and after PA. They reported that PA-related leftward after-effects increased ICF in the right M1 and PA-related rightward after-effects increased ICF in the left M1, while no effects were found on the M1

ipsilateral to the side of after-effect. These findings indicate the potential of PA to modulate excitatory neurotransmission at motor cortical level.

The aim of the present study was to further investigate the power of PA to modulate brain excitability. We combined tDCS with PA in order to induce state-dependent effects over M1 circuits. Specifically, we combined two protocols known to increase right M1 excitability: right anodal tDCS (Di Lazzaro *et al*., 2013; Kim, Kim, Kim, Chun, Kim & Park, 2012; Sugawara *et al*., 2015; Zhang, Woolley, Swinnen, Feys, Meesen & Wenderoth, 2014) and PA with a leftward after-effect (Magnani, Caltagirone & Oliveri, 2014). We assessed any changes of corticospinal excitability induced by the two protocols, either as alone or combined, by measuring the motor threshold (MT) for inducing motor evoked potentials (MEPs) of 1 mV (S1MT), the amplitude of motor potentials (MEPs) evoked by single pulse TMS and the input-output (IO) curve, known to measure the neurophysiological strength of intracortical and corticospinal connections (Carroll, Riek & Cassidy, 2011; Devanne, Lavoie & Capaday, 1997; Liu & Au-Yeung, 2014). The main predictions were the following: PA with a leftward after-effect increases the excitability of the right M1 (Magnani *et al.*, 2014) similarly to anodal tDCS of the right M1; excitatory preconditioning of the right M1 with either PA or anodal tDCS induces homeostatic plasticity of the targeted region, thus reducing its excitability when the other method (anodal tDCS or PA) is subsequently applied.

Material and methods

Participants

Twenty-four healthy adults (mean age: 24.4 ± 2.9 years) participated in the experiments. Written informed consent was obtained from each participant. All participants were volunteers naive to the experimental hypothesis being tested. They were right handed, had normal or corrected-to-normal vision and reported no history of neurological or

psychiatric disorder or any other contraindication for tDCS or TMS. Exclusion criteria were head trauma, past neurosurgical intervention, pregnancy, presence of cardiac pacemakers and intracranial metallic plates and family or personal history of epilepsy.

Participants were randomly divided in three groups, each associated with a different experimental condition.

Experimental design

Experiment 1. The experiment was designed to explore the effects of PA shifting attention to the left space on right M1 excitability. Eight participants (mean age: 24.8 ± 1.6 years) received PA with a leftward after-effect (G1).

Experiment 2. The experiment was designed to test the effects of anodal tDCS on right M1 excitability. Eight participants (mean age: 25 ± 4.1 years) received a 20 minutes anodal tDCS over the right M1 (G2).

Experiment 3. The experiment was designed to investigate the effects of anodal tDCS of the right M1 applied before or immediately following PA with a leftward after-effect. Eight participants (mean age: 23.4 ± 2.8 years) received anodal tDCS and PA with leftward after-effect, randomly combined (i.e. tDCS followed by PA and vice-versa; G3).

In all experiments, MEPs amplitude and the slope of TMS IO curve were used as a method to measure cortical excitability before and after the conditioning methods (PA, anodal tDCS, PA+ anodal tDCS).

Prismatic adaptation (PA) procedure

PA was applied as described in literature (Magnani, Caltagirone & Oliveri, 2014;

Magnani, Mangano, Frassinetti & Oliveri, 2013; Magnani, Oliveri, Mancuso, Galante & Frassinetti, 2011; Magnani, Oliveri, Mangano & Frassinetti, 2010; Oliveri, Magnani, Filipelli, Avanzi & Frassinetti, 2013 – for more details see also Chapter III). Subjects were seated at a table in front of a box (height: 30 cm, width: 72 cm, depth: 34 cm at the centre and 18 cm at the periphery, participant distance: 57cm) that was opened on the side facing the participant and on the opposite side, facing the experimenter. A transparent curved plexiglass barrier was placed between the participant and the experimenter. The concave side was facing the participant and the convex side the experimenter. The transparent barrier was graduated with thin vertical lines in degrees of visual angle (120° of visual angle covered), so that the experimenter could measure participants' pointing accuracy: rightward pointing deviations from the target were scored with positive values, leftward ones with negative values.

The experimenter placed a visual target (a pen) at the distal edge of the top surface of the box, in one of three possible positions (randomly determined on each trial): a central position (0°), 21° to the left of the center, and 21° to the right of the center. Participants were asked to keep right hand at the level of the sternum (hand starting position), to point with the index finger toward the pen, at a fast but comfortable speed and then to return their hand to the starting position. The experimenter recorded participants' pointing spatial accuracy in degrees of visual angles as the distance between the target position and the final position of their finger.

The pointing task, lasting about 15 minutes, consisted of a total of 180 target positions (i.e. 60 trials for each position). Namely, PA was performed in three experimental stages: pre-exposure, exposure and post-exposure. The pre-exposure phase consisted of 20 trials. Participants performed half of the pre-exposure trials (i.e. 10) with *visible* pointing, and half (i.e. 10) with *invisible* pointing (pre-exposure blinded). During the invisible pointing, the view of the arm movement was occluded by means of a black cape cape that covered the

area from neck to the edge of the panel (neither obstructing the pointing movements, nor the visibility of the top edge of the panel or the target position).

In the exposure stage participants performed the task while wearing prismatic goggles that induced a 20° shift of the visual field to the right. Participants were asked to point 30 targets at visible pointing way (i.e. 30 trials).

In the post-exposure phase, immediately after removal of the prisms, participants were required to make their pointing movements for 10 trials and their finger was not visible at any stage (invisible pointing).

tDCS procedure

Twenty minutes anodal tDCS was delivered over the right motor cortex through a battery-driven constant current stimulator (BrainStim, EMS, Bologna Italy) using 5x5 cm surface electrodes (placed in saline-dampened sponges). Stimulation was applied with an intensity of 1.0 mA for 20 min (45 fade-in/out). The anode was placed on the right scalp over the area representing the first dorsal interosseus (FDI) muscle, as identified by a single-pulse TMS; the cathode was placed above the ipsilateral deltoid muscle (Im, Park, Shim, Chang & Kim, 2012; Priori, Berardelli, Rona, Accornero & Manfredi, 1998; Vandermeeren, Jamart & Ossemann, 2010).

TMS procedure

A MagStim Super Rapid 2 biphasic magnetic stimulator (Magstim Company, Whitland, Wales, UK), connected with a 70 mm figure-of-eight coil was used to apply single-pulse TMS over a scalp site corresponding to the right M1. The stimulating coil was placed tangential to the scalp at the optimal position (hot spot) for eliciting MEPs in the contralateral FDI muscle. The coil handle pointed backwards and 45° away from the midline, approximately perpendicular to the line of the central sulcus. So, the induced current in the

M1 flowed in an anterior-posterior direction.

At the beginning of the experiment, the stimulus intensity required to evoke an MEP of 1 mV peak-to-peak amplitude was set (S1 mV). Ten MEPs were then recorded with stimulus intensities of 100%, 110%, 130% and 150% of S1 mV. The order in which the individual intensities were acquired was randomized. MEPs to single-pulse TMS were recorded from the contralateral resting FDI via surface Ag/AgCl electrodes with a belly-tendon montage.

Data analysis

Prismatic Adaptation parameters. In order to test for adaptation to prisms in the different experimental groups, we measured visual degrees of pointing deviation in pre-exposure *vs*. exposure trials. We compared mean pointing deviation during trials of the pre-exposure condition with pointing deviation of the first three and the last three trials of the exposure condition. A difference between the pre-exposure condition and the first three trials of the exposure condition was expected due to the rightward deviation induced by prisms. Instead, no differences between pre-exposure condition and the last three trials of the exposure condition were expected, due to the participants' capability to correct for the prisms-induced bias. On the other hand, in order to verify the induction of after-effect by PA, we compared visual degrees of pointing deviation during blinded pointing in pre-exposure vs. post-exposure conditions. A leftward after-effect was expected following rightward PA. Finally, PA sessions were compared using repeated measure ANOVA with LSD *post-hoc* tests where needed. The level of significance was set at $p < .05$.

Physiological measures. Participants' S1MT was taken as a M1 cortical excitability measure. Namely, the minimum intensity required to elicit 1mV MEP, at the beginning of all the three sessions, was used as value.

A two-steps MEP analysis was conducted. Means of MEPs per stimulus intensities were normalized to the first intensity (100%) in all three conditions. To further explore the effects of the modulation on MEPs, the IO curve was used as an index of cortical excitability. In order to calculate the IO curve slopes of each participant, a linear regression between average peak-to-peak MEP amplitude and TMS intensity, excluding values of the plateau phase of MEP amplitudes, was conducted (Devanne et al., 1997; Liu et al., 2014). B value was taken as a measure of the slope curve. R^2 values were also calculated in order to assess the fit of the linear slope to the curve.

The normal distribution of all the physiological measures was tested by applying the Kolmogorov–Smirnov test.

PA sessions, S1MTs, MEPs and IO curve comparisons were conducted using separate repeated measures ANOVA with LSD *post-hoc* tests where needed. The level of significance was set at $p < .05$.

Correlational analysis. The relationship between the effect of modulation over M1 and PA parameters was tested by mean of Pearson correlation analysis. Namely, as value of cortical excitably, the percentage of change in steepness of the IO curve slope both for PA and PA+tDCS was taken (i.e *post*PA – *pre*PA; *post*PA+tDCS – *pre*PA+tDCS). As a measure of error reduction during PA, the difference between the mean pointing displacement in the first three trials and the mean pointing displacement in the last three trials in the exposure condition was computed. On the other hand, as a measure of after-effect, the difference between the mean pointing displacement in pre-exposure condition blinded and in the post-exposure condition. The level of significance was set at $p < .05$.

All the analyses were conducted using STATISTICA 8.

Results

Prismatic adaptation

A 2 x 5 ANOVA was conducted, with Group (G1 = PA; G3 = PA + tDCS) as a between-subjects and Session (pre-exposure *vs*. pre-exposure blinded *vs*. exposure-condition-first three trials vs. exposure-condition-last three trials *vs*. post-exposure) as within-subjects factor.

The interaction Group x Session was not significant [F (4,56) = .66; p = .62], whereas the main effect for Session was significant [F (4,56) = 57.64; p = .000; ηp^2 = .80] (**Figure 8**).

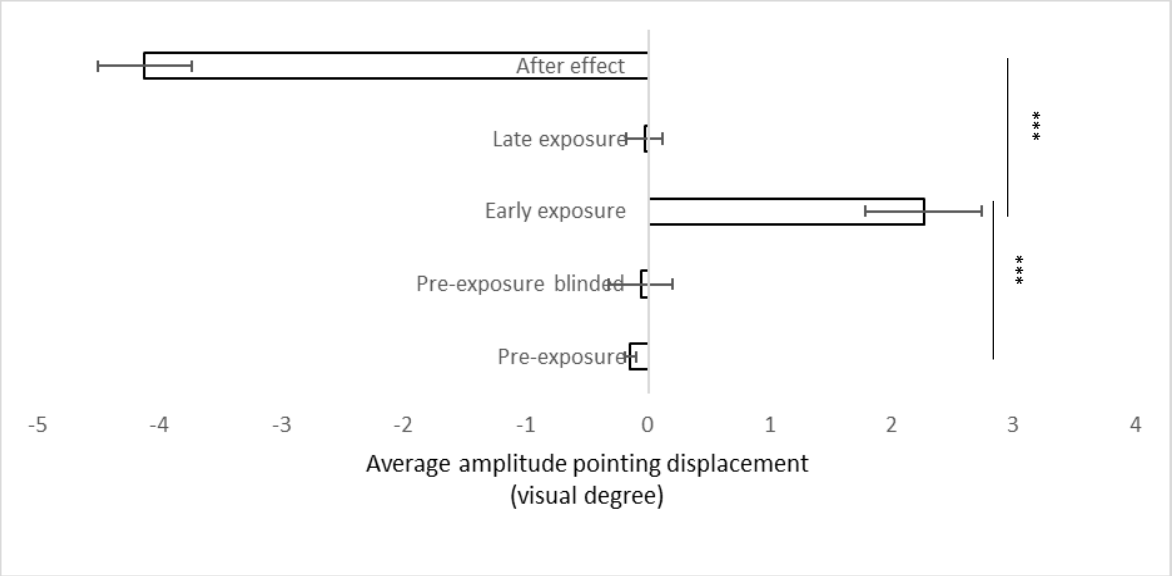

Fig. 8. Mean pointing displacement (expressed in degrees of visual degree) throughout the prism adaptation procedure (pre-exposure free-viewing/pre-exposure blinded, early and late exposure, after-effect) are plotted. Negative values indicate a leftward pointing displacement; positive values a rightward displacement. Error bars: sem. ***p < .000

Post-hoc comparisons for the main effect showed that pointing displacement in the pre-exposure session was significantly different from the exposure-condition-first three trials (- .14 *vs*. 2.25; p < .000), but not from exposure-condition-last three trials (- .14 *vs*. - .03, p = .78). This shows that participants' pointing task was affected by prims, with a shift

to the right side and a following adaptation at the end of the protocol. On the other hand, pre-exposure blinded session was significantly different when compared with post-exposure (- .07 *vs* -4.13; $p < .000$) revealing an after-effect, with a participants' bias to the left side.

Motor Threshold

A 3 x 2 ANOVA was conducted, with Group (G1 = PA; G2 = anodal tDCS; G3 = PA + anodal tDCS) as a between-subjects and Session (baseline vs. post-manipulation – tDCS or PA or PA + tDCS) as a within-subjects factor. This analysis revealed no significant main effects (Group [$F(2,21) = 2.48$; $p = .10$], Condition [$F(1.21) = 1.13$; $p = .30$], or interaction (Group x Time [$F(2.21) = 3.17$; $p = .063$)]. **Figure 9** shows, however, that, whereas G1 and G2's S1MTs where stable over time, in G3 S1MT tended to increase.

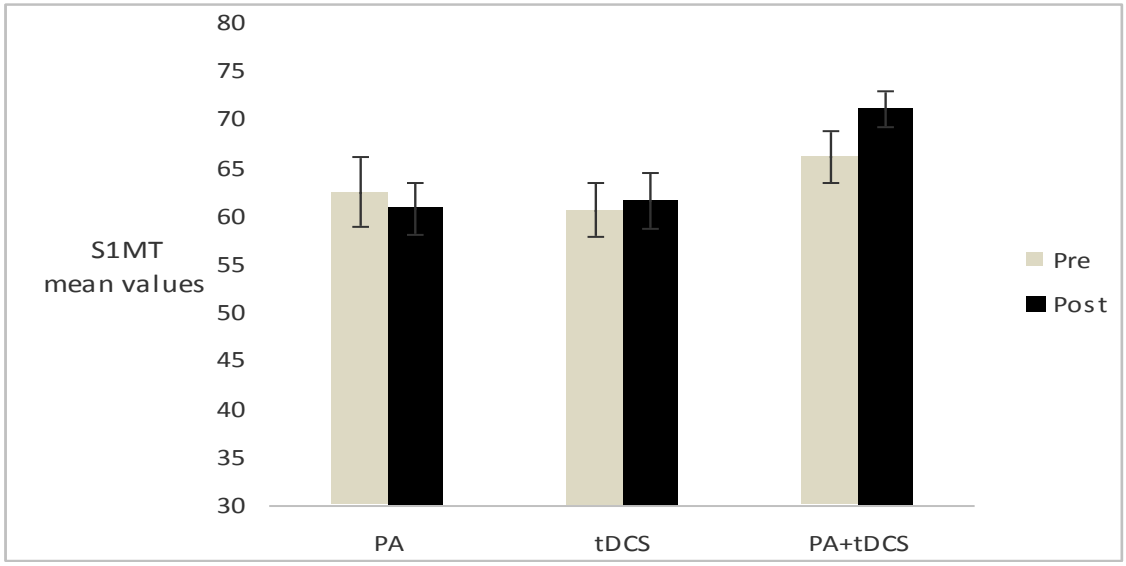

Fig 9. S1 Motor Threshold, between-groups, before and after modulation. Resting Motor Thresholds as minimum TMS intensity required to elicit a MEP of 1mV, before and after each modulation (PA, atDCS, PA+atDCS). No significant result, but a trend that after PA+tDCS modulation right S1MT increased. Error bars: sem. $p > .05$

Motor evoked potentials

Figure 10 shows the results of MEPs analysis. A 3 x 2 x 3 ANOVA on the normalized-first-intensity MEPs for the pre/post time for each group (Group [G1 = PA; G2

= anodal tDCS; G3 = PA + anodal tDCS] *vs*. Time [pre *vs*. post] *vs*. Intensity [110, 130, 150]) was conducted.

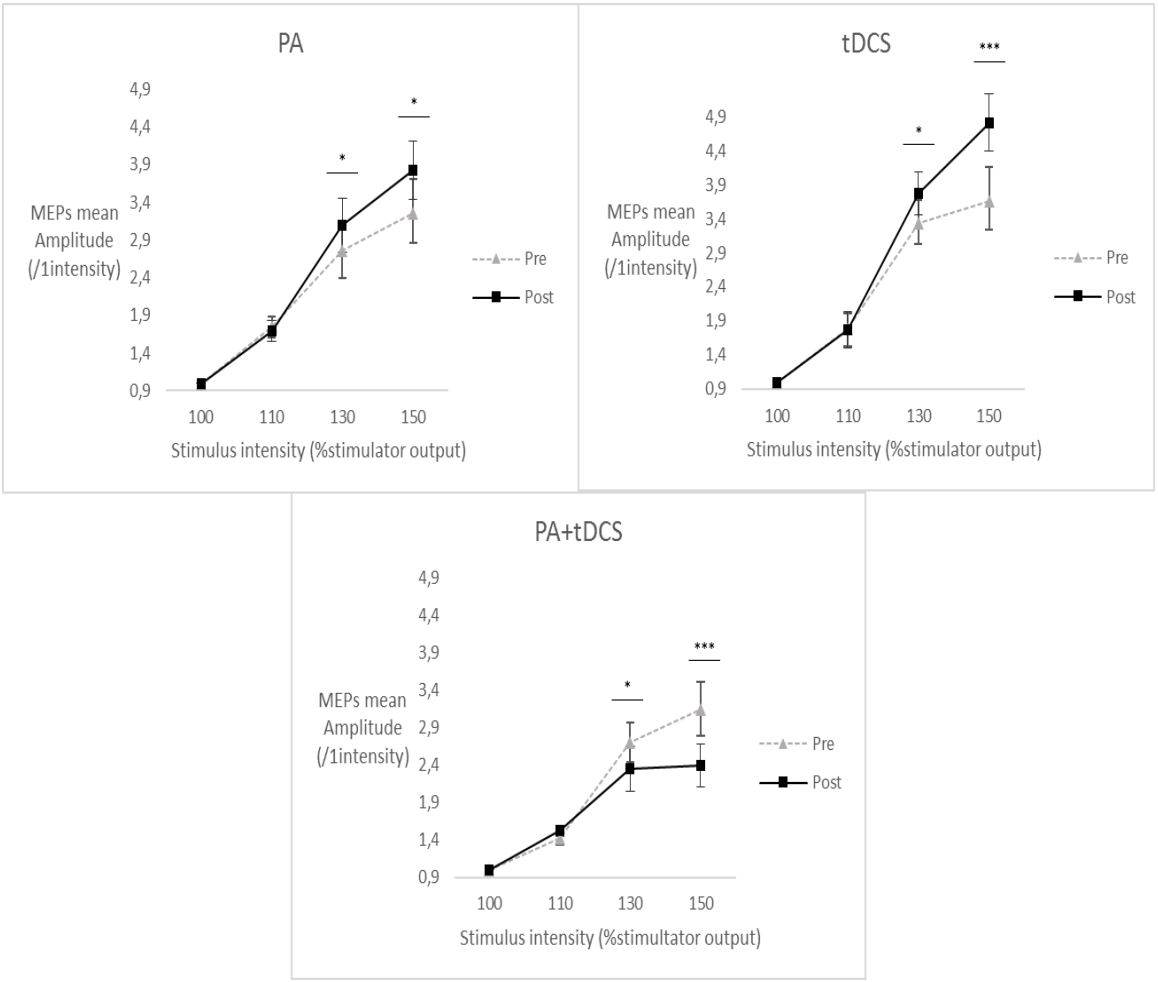

Fig. 10. MEPs mean amplitudes, between-groups, before and after modulation. Participants' mean MEPs amplitude, normalized to the first block, across the four stimulus intensities (100%, 110%, 130%, 150%) of S1 1mV, in the three sessions. (PA, tDCS, PA+tDCS. After PA (A) and tDCS (B) modulations, right M1 MEPs from 130% and 150% stimulator output increased, while after PA+tDCS (C) decreased. Error bars: ES. ***p < .000; **p < .01; *p < .05

The analysis revealed no Group and Time main effects (Group [F(2,21) = 1.72; p = .2], Time [F(1,21) = .1; p = .75]), but a significant Intensity main effect [F(2,42) = 38.64; p < .000; ηp^2 = .66]. The rm-ANOVA revealed also no significant Group x Time [F(2,21) = 3.07; p = .07], Group x Intensity [F(4,42) = 1.95; p = .12] and Time x Intensity [F(2,42) =. 80; p = .45] interactions, while a Group x Time x Intensity interaction was significant [F(4,42

= 4.91; p = .002; ηp^2 = .41]. *Post-hoc* comparisons between pre and post MEPs amplitude revealed no significant differences for the intensity of 110% in all the three groups (G1: 1.79 *vs.* 1.69, p = .48; G2: 1.78 *vs.*1.77, p = .92; G3: 1.41 *vs.* 1.52, p = .47); significant differences for the intensity of 130% in G1 (2.76 *vs.* 3.92, p = .04) and G2 (3.34 *vs.* 3.77, p = .007) groups, with an increase of MEPs amplitude after both PA and anodal tDCS, and also G3 (2.69 *vs.* 2.35, p = .03) group, with a decrease of MEPs amplitude when PA and tDCS were combined; significant differences for intensity 150% in G1 (3.26 *vs.* 3.82, p < .000) and G2 (3.66 *vs.* 4.81, p = .01) groups, with an increase of MEPs amplitude after PA and tDCS, and in G3 (3.14 *vs.* 2.41, p < .000) group, with a significant decrease of MEPs amplitude when PA and tDCS were combined.

Input-output curve

Repeated measure ANOVA was conducted, with Group (G1 = PA; G2 = anodal tDCS; G3 = PA + anodal tDCS) as a between-subjects and Session (baseline vs. post-manipulation – tDCS or PA or PA + tDCS) as a within-subjects factor.

ANOVA showed no Group significant main effect [F (2.21) = 0.35; p = .70], a Session main effect [F (1.21) = 7.79; p = .01; ηp^2 = .27] and a significant Group x Session interaction [F (2.21) = 20.31; p < .000; ηp^2 = .65]. *Post-hoc* analyses showed that in G1 (PA) group the IO curve slopes significantly increased in the right M1 after PA compared with baseline (.96 *vs.* 1.40, p = .002). Similarly, in G2 (anodal tDCS) group the IO curve slopes significantly increased in the right M1 after-tDCS compared with baseline (1.02 *vs.* 1.63, p < .000). On the other hand, in G3 (PA + tDCS) group the IO curve slopes significantly decreased in the right M1 after PA + tDCS compared with baseline (1.27 *vs.* .83, p = .002) (**Figure 11**). There were not significant differences among the three baseline conditions.

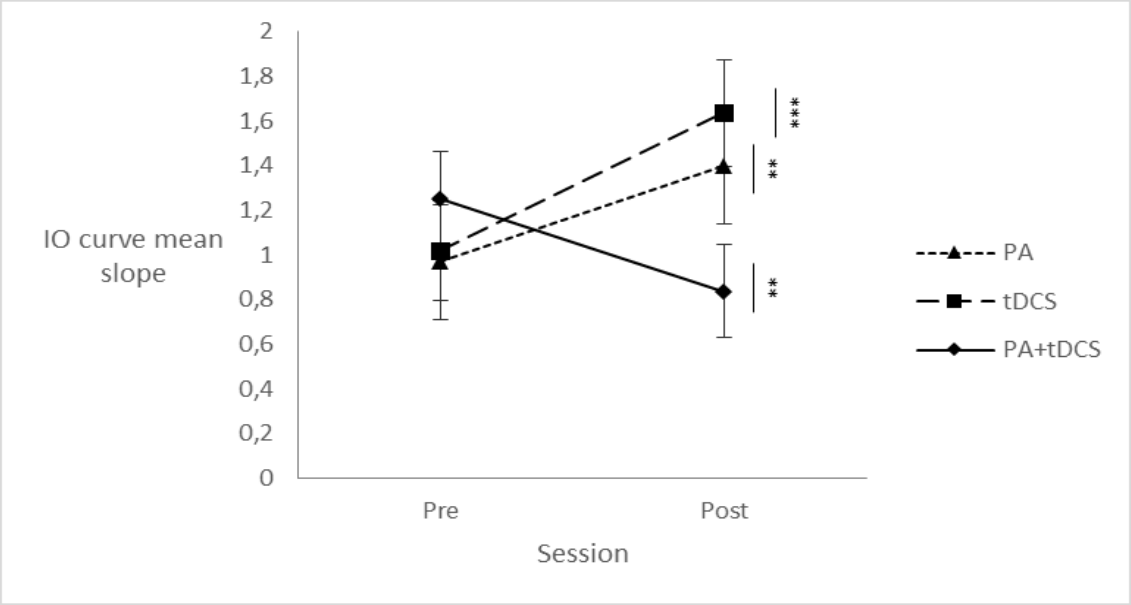

Fig. 11. IO curves mean slope, between-groups, before and after modulation. Participants' IO curves mean slope, in the three sessions. After PA and tDCS modulation right M1 IO curve slopes significantly increased. After PA+tDCS modulation right M1 IO curve slopes significantly decreased. Error bars: ES. ***p < .000; ***p* < .01; **p* < .05

Correlations

The analysis revealed no significant correlations. Motor cortex excitability did not correlate with either PA error reduction or after-effect for both G1 (r = - .45, p = .25; r = .38, p = .35) and G2 (r = .35, p = .40; r = - .33, p = .42). Finally, also PA parameters were no significantly correlated each other (r = - .24, p = .57).

Discussion

The aim of the present study was twofold: to test whether prismatic goggles can modulate motor cortical excitability similarly as anodal tDCS does; to test whether neuromodulatory effects induced by tDCS and prismatic goggles could interact between each other and induce homeostatic changes in brain excitability. To this aim, we analysed the effects on M1 excitability of anodal tDCS and rightward PA with leftward after-effect,

either when applied as alone or in combination. Changes of M1 excitability were measured by analysing MEPs amplitude and the steepness of IO curves following single-pulse TMS at increasing intensities.

The main results showed that, while no significant differences were found for the S1MTs, significant changes in MEPs amplitude and IO curve were found. Namely, the MEPs mean amplitudes for the last two output stimulation intensities were higher and the slope of the IO curves was significantly steeper in the participants submitted to either anodal tDCS or PA compared with a baseline condition where no prior modulation of M1 excitability was applied. On the other hand, the MEPs mean amplitude for the last output stimulation intensity was lower and the slope of the IO curves was significantly less steep in the participants submitted to both anodal tDCS and PA consecutively delivered, compared with a condition where only one tool was applied.

These findings suggest that modulation of spatial attention with prismatic goggles can be a powerful and non-invasive method to neuromodulate cortical excitability, with effects comparable to those of excitatory non-invasive brain stimulation tools. In addition, our findings suggest that by providing an excitatory input to the motor cortex with PA or anodal tDCS while its excitability level is increased by respectively anodal tDCS or PA may be a highly effective means for inducing homeostatic plasticity.

In the present study no correlations were found between MEP values of IO curves and measures of spatial after-effect induced by PA in PA and PA+tDCS groups. Similarly, one could have expected that anodal tDCS changed basic parameters of PA, i.e. error reduction and after-effect, as compared with PA when applied alone. On the other hand, results showed that both error reduction and after-effect were similarly modulated by PA and PA + tDCS. These findings could suggest that the observed effect of PA on brain excitability is rather independent on the visual-spatial attentional modulation. By contrast, in Magnani, Caltagirone and Oliveri's work (2014), the extant of intracortical facilitation by

paired-TMS and of the after-effect were correlated to each other. This discrepancy suggests that the lack of correlation between PA parameters and measures of brain excitability in the present study could depend on the sample size of each experimental group. Further studies in larger groups of participants could better investigate the relations between spatial attentional parameters and measures of brain excitability.

The finding of increased slope of IO curves of MEPs following anodal tDCS is in accord with the well-documented excitatory effect of this brain stimulation method (Di Lazzaro *et al*., 2013; Kim, Kim, Kim, Chun, Kim & Park, 2012; Sugawara *et al*., 2015; Zhang, Woolley, Swinnen, Feys, Meesen & Wenderoth, 2014), probably linked to increased glutamatergic activity (Clark, Coffman, Trumbo & Gasparovic, 2011; Di Lazzaro *et al*., 2003; Hunter, Coffman, Gasparovic, Calhoun, Trumbo & Clark., 2015; Nitsche *et al*., 2005; Stagg *et al*., 2011; Stagg & Nitsche, 2011). The finding that modulation of spatial attentional mechanisms via PA induces similar excitatory effects over the M1 contralateral to the side of space where attention is shifted is a novelest finding. While several studies reported that PA could affect activation of the posterior parietal cortex (Magnani, Mangano, Frassinetti & Oliveri, 2013; Magnani, Oliveri, Mancuso, Galante & Frassinetti, 2011; Magnani, Oliveri, Mangano & Frassinetti, 2010; Oliveri, Magnani, Filipelli, Avanzi & Frassinetti, 2013), to date, the involvement of M1 following PA has not been intensively studied. Magnani, Caltagirone and Oliveri (2014), using a short-interval paired-TMS protocol, reported an increased facilitation of intracortical excitatory mechanisms of the M1 contralateral to the side of the after-effect induced by PA. Although the exact mechanisms of intracortical facilitation induced by paired-TMS with long interstimulus intervals are still unclear, some studies suggest that it is related with excitatory neurotrasmission by glutamate NMDA receptors (Paulus *et al*., 2008; Schwenkreis *et al*., 1999). The slope of the MEP IO curves is an index of excitability within a wider region of the motor cortex, with steeper slopes reflecting increased cortical excitability.

Interestingly, a significant relationship between MEP IO curve slope and glutamate within M1 was recently reported, suggesting that glutamate is an important indicator of motor cortical excitability (Bestmann, de Berker & Bonaiuto, 2015; Di Lazzaro *et al*., 2003). Therefore, different TMS measures (paired-TMS and IO TMS curve) support the hypothesis that PA could increase glutamatergic levels in motor cortices. On the other hand, Schintu *et al*. (2016) recently reported no significant changes in IO curve slope after leftward PA, but a left hemisphere increase and a right hemisphere decrease in the amplitude of MEPs elicited by paired (PPC-M1) and single pulses TMS. The differences in the results could be due by different methodologies used. Although the different results in IO curve changes than the present study, Schintu *et al*.'s work represent a further support to the idea that PA can elicit changes in M1 excitability.

A growing amount of works suggests that PA activates both ventral and dorsal visual streams, known to control visually guided motor behaviors (eye and arm movements) (Striemer & Danckert, 2010a). Recruitment of different brain areas, such as dorsal and ventral premotor cortices, supplementary motor area (Inoue *et al*., 2000; Kurata & Hoshi, 1999; Lee & van Donkelaar, 2006) and cerebellum (Baizer, Kralj-Hans & Glickstein 1999; Pisella *et al*., 2005), has been widely reported during PA. If brain regions anatomically and functionally linked with M1 are recruited by PA, it is reasonable to hypothesize that the primary motor cortex might be affected as well. As a support to our findings, it is known that stroke can affect interhemispheric balance (Di Lazzaro *et al*., 2010; Koch *et al*., 2008) and that hemineglect following right hemispheric injuries is related with interhemispheric excitability changes (Corbetta & Shulman, 2002; Umarova *et al*., 2013). Prismatic lenses with after-effect toward the neglected side of space force subjects to re-modulate their visuospatial/motor maps, thus decreasing the severity of neglect (Frassinetti, Angeli, Meneghello, Avanzi, & Làdavas, 2002; Vangkilde & Habekost, 2010). Interestingly, reduction of interhemispheric bias in neglect patients is also associated with modulation of

cortical excitability in both affected and unaffected hemispheres (Koch *et al*., 2012; Koch *et al*., 2008; Oliveri *et al*., 2000; Oliveri et al., 1999).

The second main finding of the present study is that random combination of anodal tDCS and PA with leftward after-effect significantly reduces M1 cortical excitability. We suggest that the suppressive effect on cortical excitability could be interpreted in terms of the state-dependency of the cerebral cortex to the effects of different modulations. Indeed, the observed shift of cortical excitability may be due to homeostatic plasticity regulations. Homeostatic plasticity plays an important role in activity-dependent synaptic plasticity, such as LTP and LTD. For example, when inducing LTP, synapses are more excitable and the same connections have a reduced threshold for undergoing further LTP, with a propensity for runaway excitation. In order to prevent neural networks from reaching such extremes, a homeostatic negative feedback regulation constraining activity levels becomes critical for maintaining network stability. In this view, a reduction in postsynaptic activity would lead to a reduction in the modification threshold, favoring the induction of LTP. On the contrary, an increase in postsynaptic activity would increase the modification threshold, favoring the induction of LTD (Silvanto & Pascual-Leone, 2008). In the present study, the application of either PA or tDCS, both eliciting an increase of cortical activity, could have induced a spread of cortical excitation that had to be balanced in order to prevent the risk of uncontrolled increase of synaptic effectiveness. Although our study is not the first that combined PA and tDCS (Calzolari, Bolognini, Casati, Marzoli & Vallar, 2015; Làdavas *et al*., 2015), this is the first work that shows this kind of results. Làdavas *et al*. (2015) delivered these two tools combined in different ways in four different conditions. They reported that the combination of rightward PA with anodal tDCS over the affected posterior parietal cortex, strongly improved attentional performances in patients with left spatial neglect. The difference between our results and those of Ladavas *et al*. may depend on the different sample of examined subjects. In fact, in contrast to healthy people, stroke patients present with pre-

existing excitatory/inhibitory cortical alterations. It is widely known that stroke produces a cortical excitability unbalance characterized by a decrease of excitability of the affected hemisphere and an increase of excitability of the unaffected one (Koch *et al*., 2008; 2012; Oliveri *et al*., 2011). Therefore, by delivering anodal tDCS over the damaged hemisphere Làdavas *et al*. presumably stimulated a cortical area with a recent history of reduced cortical excitability. Their result could be in agreement with studies that report a significant and strong enhancement of cortical excitability when brain cortex is stimulated by high frequency TMS after an inhibitory prime (Lang *et al*., 2004; Nitsche *et al*. 2004).

In conclusion, the present findings suggest that PA could be a useful tool for excitatory neuromodulation and for testing state-dependency of the motor cortices. Prismatic goggles influence cortical excitability and their modulating power could be transferred in clinical practice. Indeed, although PA is widely used for treatment of hemispatial neglect, the present results suggest the possibility of using PA also for treatment of patients with motor symptoms different from neglect.

CONCLUSION

PA has been raising the attention of the scientific community thanks to its beneficial effects on neglect patients. Furthermore, the recent findings have been suggesting even more uses of this tool, until its capability on modulating brain activity.

The present work reports the effects of rightward PA over the normal brain. The studies used two different neuropshysiological ways to test cortical brain activity. The first one probed PA neural correlates of visuospatial attention and motor preparation by analysing their well-known EEG signatures. On the other hand, the second study assessed the solely primary motor cortex excitability changes induced by PA, either alone or when combined with tDCS, by means of a single-pulse TMS protocol. Although the differences due to the diverse methods used, both of the studies reported rightward PA capability on modulating normal brain motor cortex excitability, selectively to the hemisphere contralateral to the spatial shift induced, which is in line with the existing literature. Moreover, these studies have some more implications each. First of all, to the best of our knowledge, the EEG study reported for the first time that PA modulates brain oscillations. Second, it was able to dissociate PA attentional and motor effects that had, previously, reported only with behavioral measures. And last but not least, the TMS study was able to report that PA can, not only modulate cortical excitability, but also induce cortical homeostatic plasticity.

Aware that further research is needed to better elucidate the mechanisms of PA, the present work provides evidences about its neural correlates. Future research should further examine neurophysiological effects of both rightward and leftward PA on normal brain and also start to the assessment of its modulatory effects also on brain damaged patients. However, the general implication of the present work is twofold: it allows to enhance a little more our knowledge about PA and give us some insights about how to further improve the protocols used within the clinical practice.

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