

# Prism adaptation enhances decoupling between the default mode network and the attentional networks



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## ABSTRACT

Prism adaptation (PA) is a procedure used for studying visuomotor plasticity in healthy individuals, as well as for alleviating spatial neglect in patients. The adaptation is achieved by performing goal-directed movements while wearing prismatic lenses that induce a lateral displacement of visual information. This results in an initial movement error that is compensated by a recalibration of sensory-motor coordinates; consequently, a lateral bias in both motor and perceptual measurements occurs after prism removal, i.e., after effects. Neuroimaging studies have shown that a brief exposure to a rightward-shifting prism changes the activations in the inferior parietal lobule (IPL) and modulates interhemispheric balance during attention tasks. However, it is yet unknown how PA changes global interplay between cortical networks as evident from task-free resting state connectivity. Thus we compared resting state functional connectivity patterns before ('Pre') and after ('Post') participants performed a session of pointing movements with a rightward-shifting prism (N = 14) or with neutral lenses (as a control condition; N = 12). Global connectivity analysis revealed significant decreases in functional connectivity following PA in two nodes of the Default Mode Network (DMN), and in the left anterior insula. Further analyses of these regions showed specific connectivity decrease between either of the DMN nodes and areas within the attentional networks, including the inferior frontal gyrus, the anterior insula and the right superior temporal sulcus. On the other hand, the anterior insula decreased its connectivity to a large set of areas, all within the boundaries of the DMN. These results demonstrate that a brief exposure to PA enhances the decoupling between the DMN and the attention networks. The change in interplay between those pre-existing networks might be the basis of the rapid and wide-ranged behavioural changes induce by PA in healthy individuals.

## 1. Introduction

Prism adaptation (PA) is a procedure used for studying visuomotor plasticity in healthy individuals, as well as for alleviating unilateral spatial neglect in patients suffering brain lesion. During PA, subjects perform goal-directed movements while wearing prismatic lenses that induce a lateral shift of visual inputs. The shift causes a mismatch between the visual input regarding target position and its physical position, as well as between visual and proprioceptive information regarding hand position. This mismatch results in an initial error in pointing movements, followed by an adaptive correction of movement trajectories (Redding and Wallace, 1996, Rossetti et al. (1998)). A successful adaptation process results in recalibration of sensory-motor coordinates (Redding and Wallace, 1996). Consequently, after removing the prismatic lenses,

participants exhibit pointing errors in the direction opposite to that of the prismatic shift (PA aftereffect). This effect has been reported to last at least 40 min after the prism exposure in healthy individuals (Crottaz-Herbette et al., 2014; Schintu et al., 2014; Tsujimoto et al., 2018) and to have long-term therapeutic effects in neglect patients (Frassinetti et al., 2002; Serino et al., 2009). PA aftereffect is not confined to the motor domain, as PA has been reported to affect also visual perception (Colent et al., 2000; Berberovic and Mattingley, 2003; Dijkerman et al., 2003; Ferber et al., 2003; Sarri et al. 2006, 2011; Nijboer et al., 2010; Striener and Danckert, 2010; Schintu et al. 2014, 2017), auditory perception (Tissieres et al., 2018), and even cognitive domains that do not have explicit spatial properties (e.g., number or letter perception, body representation; for review see Michel, 2015). Taken together, these findings imply that the effect of PA on behaviour is far more extensive than a purely visuomotor recalibration, suggesting an involvement of a wide set

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### Abbreviations

PA	prism adaptation
IPL	inferior parietal lobule
IPS	intraparietal sulcus
STS	superior temporal sulcus
DAN	dorsal attention network
VAN	ventral attention network
DMN	default mode network
ROI	region of interest
MPFC	medial prefrontal cortex
IFG	inferior frontal gyrus

of brain regions, beyond the sensory-motor networks. Nevertheless, despite this vast variety of behavioural outcomes, the PA-induced neural modulations that support these long-lasting behavioural aftereffects are still not fully elucidated.

Imaging studies have singled out several temporo-parietal areas that support the adaptation process in healthy individuals. Activation in left intraparietal sulcus (IPS) was found in the early stages of adaptation (Clower et al., 1996; Danckert et al., 2008; Luauté et al., 2009; Chapman et al., 2010), and in bilateral superior temporal sulcus (STS) during the later stages of the training (Luauté et al., 2009; Werner et al., 2014), suggesting a key role for STS in long term changes induced by PA. Furthermore, PA has been reported to have a long-lasting effect on brain responses: a brief exposure to rightward prism has been shown to change activations in bilateral inferior parietal lobule (IPL) and modulate interhemispheric balance during attention tasks (Crottaz-Herbette et al., 2014; Martín-Arévalo et al., 2016). Yet, PA-induced brain plasticity has so far been mainly assessed while participants were performing specific tasks, thus limiting the findings to brain areas that are responding to the task and confounding the findings with task performance.

Given the variety of behavioural aftereffects induced by PA, measuring spontaneous task-free brain activity can shed light on yet undiscovered cortical plasticity processes that underlie these behavioural changes. A resting state analytic approach is complementary to studies on prism adaptation aftereffect in task-activation, holding two major advantages: the aftereffects can potentially be found anywhere in the brain and are not limited to task-relevant set of regions, and the aftereffects cannot be attributed to changes in task performance. Furthermore, the behavioural shift induced by PA is so abrupt, that it must rely on pre-existing network structures. However, it is still largely unknown whether PA can change general connectivity between cortical networks as highlighted by subsequent task-free resting state connectivity. More specifically, PA might affect connectivity between different nodes within the same network or rather change the interplay between different functional networks that co-exist during rest (Greicius et al., 2003; Fox et al., 2005; Van Den Heuvel and Pol, 2010). A recent study (Tsujiimoto et al., 2018) investigated changes in functional connectivity following PA in a set of pre-defined regions. They reported a temporary PA-induced change in connectivity between different nodes within the right dorsal attention network. However, using a pre-defined set of regions of interest (ROIs) leaves open the possibility of connectivity changes occurring outside these ROIs. In the present work, we used a global, non-ROI-driven, approach for identifying the cortical nodes that modulate their functional connectivity following PA. We hypothesized that PA would modulate pre-existing prominent functional connectivity networks: a) the attentional networks, namely the dorsal (DAN) and the ventral (VAN) attention networks, whose role is to create and sustain spatial representations of the external environment for goal-directed actions (Corbetta and Shulman, 2002; Fox et al., 2006); b) the default mode network (DMN), which is usually deactivated during visuomotor

tasks, and processes intrinsic, self-referential, inputs (Goldberg et al., 2006; Raichle 2010, 2015; Qin and Northoff, 2011; Molnar-Szakacs and Uddin, 2013; Davey et al., 2016; Lockwood et al., 2018).

To test these hypotheses, we compared resting state functional connectivity patterns before ('Pre') and after ('Post') a pointing training with rightward-shifting prism (N = 14) or neutral lenses (as a control condition).

## 2. Materials and methods

### 2.1. Participants

The analyses were performed on resting state fMRI data from two groups of right-handed participants (results from other tasks during the same sessions were published in Crottaz-Herbette et al., 2014): 14 participants were exposed to PA (7 females, mean  $\pm$  STD age  $26.0 \pm 5.0$  years), and 12 other participants performed the same pointing movements without prismatic lenses, i.e., control group (6 females, mean  $\pm$  STD age  $26.0 \pm 5.1$  years). Participants gave written informed consent according to procedures approved by the local ethics committee.

### 2.2. Experimental design

Both groups performed two identical fMRI sessions before and after a 3-min pointing task, which was performed outside the MRI (Fig. 1A).

The prism adaptation training involved pointing with the right index finger to left or right visual targets ( $\sim 150$  trials; see Crottaz-Herbette et al., 2014). The prism adaptation group performed the task while wearing prismatic goggles that shifted their visual field rightward by  $10^\circ$ . The control group performed the same task while wearing plain glasses.

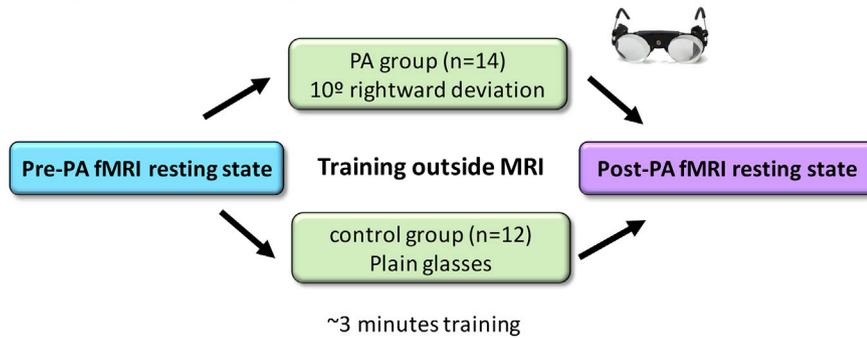
The behavioural aftereffect was assessed similarly in both groups using open loop pointing after the adaptation: After removing the glasses, subjects were asked to look at a target, close their eyes and point to it. The aftereffect corresponded to the lateral distance between the actual pointing position and the target with positive numbers denoting errors to the right and negative numbers denoting errors to the left of the target (in millimeters). Two pointing trials were done towards the left target and two pointing trials towards the right target. Both pointing trials for each target were averaged to produce one value for each target side. A deviation of  $-66 \pm 16$  mm (mean  $\pm$  SD) for left targets and  $-5.6 \pm 1.9$  mm for right targets was found for the PA group, while in the control group the deviation was  $+7 \pm 11$  mm for left targets and  $+6 \pm 8$  mm for right targets.

Each of the two fMRI sessions started with an 8-min resting state acquisition with eyes open (the subjects fixated on a red fixation cross), followed by 3 additional runs of attention or memory tasks. Task-related activation findings are described and reported in Crottaz-Herbette et al. (2014), and will not be discussed in the current paper. The resting-state data reported in the current paper was never before published.

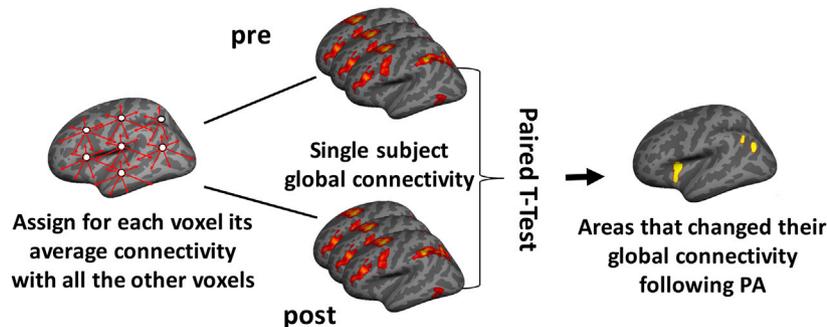
### 2.3. Data acquisition

MRI data was collected with a 3T Siemens Magnetom Trio scanner with a 32-channel head-coil at the Lemanic Biomedical Imaging Centre in the Centre Hospitalier Universitaire Vaudois, Lausanne. Functional MR images were acquired with a single-shot echo planar imaging gradient echo sequence (repetition time 2 s; flip angle  $90^\circ$ ; echo time 30 ms; number of slices 32; voxel size  $3 \times 3 \times 3$  mm; 10% gap). The 32 slices were acquired in a sequential ascending order and covered the whole head volume in the AC-PC plane. A high-resolution T1-weighted 3D gradient-echo sequence was acquired for each participant (160 slices, voxel size  $1 \times 1 \times 1$  mm). To prevent head movements in the coil, we put padding around the participant's head.

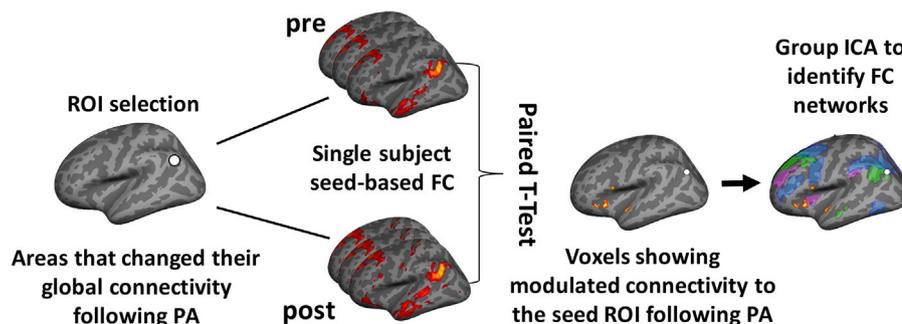
## A. Experimental design



## B. Global connectivity



## C. Seed-based functional connectivity (FC)



### 2.4. Data analysis

#### 2.4.1. fMRI data preprocessing

Data were processed using FSL 5.0.10 ([www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl)), SPM 12 (Wellcome Department of Cognitive Neurology, London, UK), and in-house Matlab code (Mathworks, Natick, MA, USA).

Functional data were analyzed using FMRIB's expert analysis tool (FEAT, version 6). The following pre-statistics processing was applied to the data of each participant: motion correction using FMRIB's Linear Image Registration Tool (MCFLIRT) (Jenkinson et al., 2002); brain extraction using BET (Smith et al., 2004); high-pass temporal filtering with a cut-off frequency of 0.01 Hz; removal of the first 2 vol from each functional run, and 4 mm Gaussian spatial smoothing. Functional images were aligned with high-resolution anatomical volumes initially using linear registration (FLIRT), then optimized using Boundary-Based Registration (Greve and Fischl, 2009). Structural images were then transformed into standard MNI space using non-linear registration tool (FNIRT), and the resulting warp parameters were applied to the functional images as well. All the functional images were resampled to  $2 \times 2 \times 2 \text{ mm}^3$  standard space, and therefore all further analyses were

**Fig. 1.** Design and analysis. (A) experimental design: participants underwent two identical fMRI sessions before and after a training period outside the MRI. During training participants performed pointing movements to visual targets while wearing either prismatic goggles or plain glasses (control group). (B) A global connectivity of all gray matter voxels was performed and contrasted between pre- and post-resting state. (C) ROIs were selected according to regions that changed their average connectivity following PA. Group ICA was based on the pre-training runs of both control and PA groups combined. PA = Prism adaptation; ROI = region of interest. ICA = independent component analysis.

performed in standard MNI space.

A scrubbing procedure was applied for censoring motion-contaminated frames using the framewise displacement (FD) and the DVARS measures (Power et al., 2014).

Then regressing out of signals from the white matter and ventricles was performed as follows: The white matter and ventricles of each participant were automatically defined using FSL's FAST (Zhang et al., 2001), and eroded to avoid boundaries between tissues (Hahamy et al., 2015). The non-neuronal contributions to the BOLD signal were removed by linear regression of motion parameters, ventricle and white matter timecourses for each participant (Fox et al., 2009), while no global signal regression was performed (Weissenbacher et al., 2009; Hahamy et al., 2014; Murphy and Fox, 2017).

#### 2.4.2. Global connectivity analysis

The global connectivity map was computed for each subject individually. All the gray matter voxels were considered for the analysis. Each voxel's timecourse was correlated with the timecourses of all the other voxels in the gray matter, and an index of the mean correlation value was computed. This index was then assigned to the voxel's position

(Salomon et al., 2011). This produced a map of the mean connectivity of each voxel with all the other voxels, in which voxels with higher values are on average more ‘functionally connected’ with other cortical voxels. This procedure was performed separately for the pre-PA resting state and for the post-PA resting state, resulting in two (pre- and post-) maps of global connectivity for each subject (Fig. 1B). These maps were then Fisher’s  $z$  transformed and the pre-PA and post-PA conditions were contrasted using voxel-wise paired  $t$ -test in SPM. This contrast produced a map displaying changes in global connectivity between pre-PA and post-PA (i.e., voxels that on average changed their connectivity following PA). The map was then thresholded at  $p < 0.005$ , and family-wise error (FWER) corrected for multiple comparisons using cluster thresholding. The same analysis was performed separately for the PA group and for the control group. For display purposes, the maps were overlaid on the common FreeSurfer template surface (fsaverage; Dale et al., 1999), while all statistical analyses were performed in the volume MNI space.

#### 2.4.3. Seed-based functional connectivity analysis

Three regions of interest (ROIs) were taken as seeds for functional connectivity analysis. The ROIs were selected according to the global connectivity contrast map as areas that showed modulated global connectivity following PA. Spherical ROIs were defined around the peak voxels in the three clusters: left inferior parietal lobule ( $-47, -66, 38$ ; IPL), medial prefrontal cortex ( $2, 46, -10$ ; MPFC), and an area next to the left anterior insula ( $-48, 22, -4$ ; aInsula).

After ROI definition, a similar analysis procedure was applied for the PA group and for the control group. Functional connectivity maps were calculated separately for each subject and each ROI, for the pre- and post-PA runs. The maps were then Fisher’s  $z$  normalized and taken for second-level analysis (described in Fig. 1C): namely, voxel-wise paired  $t$ -tests were performed to compare within each subject the pre- and post-connectivity to the seed ROI. Then a threshold at  $p < 0.001$  was used at the voxel level and a cluster threshold correction of 100 voxels (which exceeds the number of voxels that serve as FWER threshold in SPM) was applied. Each ROI map was then overlaid on the common FreeSurfer template.

#### 2.4.4. Group independent component analysis (ICA)

To identify the relevant functional connectivity networks in our group of participants, all the pre-training runs from both the PA group and the control group were pooled together (these baseline runs are on principle similar between the groups). Then a dual regression group-ICA was performed using FSL’s MELODIC with 15 components. The resulting components were then labeled according to, and were found in agreement with, the different networks in the FIND lab network atlas ([http://findlab.stanford.edu/functional\\_ROIs.html](http://findlab.stanford.edu/functional_ROIs.html); Shirer et al., 2012). Specifically, three networks of interest were defined: the default mode network (DMN), the dorsal attention network (DAN; also termed ‘visuospatial network’; Beauchamp et al., 2001, and also shows overlap with the ‘frontoparietal network’, Dixon et al., 2018), and the ventral attention network (VAN; also termed ‘the salience network’; Uddin, 2015). These networks were overlaid on the inflated surface to facilitate interpretation of the functional connectivity results (Fig. 1C; right).

### 2.5. Data and code sharing

The data that support the findings of this study are available from the corresponding author, M.W., upon reasonable request.

All the custom codes are publicly available at the following link:

[https://osf.io/awf5t/?view\\_only=11e5187b34cb4c2d8f726c47cf595f1d](https://osf.io/awf5t/?view_only=11e5187b34cb4c2d8f726c47cf595f1d).

## 3. Results

First, the connectivity modulations induced by rightward shifting prism adaptation training (PA) were assessed by calculating a global

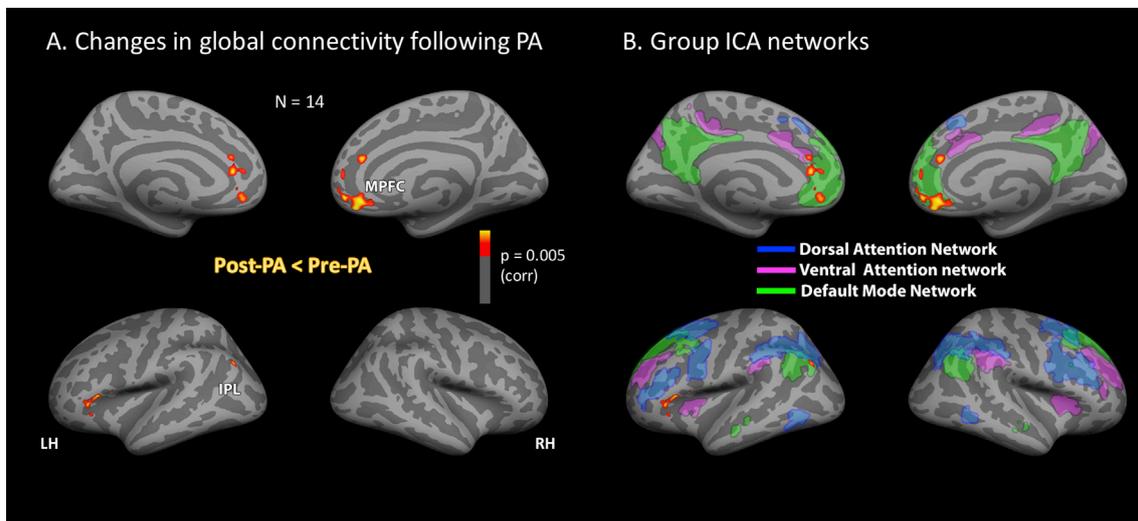
connectivity measure for each voxel pre- and post- PA training. This was achieved by performing an ROI-independent analysis that takes into account the differences in average connectivity between pre- and post-training runs in all the voxels in the cortex (‘global connectivity analysis’; see methods and Fig. 1B). In the PA-group, we found a set of areas that decreased their global connectivity following PA (Fig. 2A). These regions were located in the left anterior insula, left inferior parietal lobule (IPL), and medial prefrontal cortex (MPFC). No area showed an increase in overall connectivity following PA, suggesting that PA induces an overall decrease in cortical connectivity. Next, we overlaid the three prominent functional connectivity networks, as emerged from our ICA analysis of the baseline (pre-training) runs (Fig. 2B). This revealed that both the clusters in the IPL and in the MPFC were confined in different nodes of the DMN, while the cluster next to the anterior insula was in close proximity to a node of the VAN. The control group showed no such modulation pattern, and in fact only an increase in connectivity in primary visual cortex was found following visuomotor training with plain glasses (Fig. S1).

Based on the findings of the global connectivity analyses we studied in detail the pattern of PA-induced connectivity modulations for each of the ROIs that significantly changed their global connectivity following PA (as depicted in the map in Fig. 2). Specifically, we tested whether the connectivity decrease was confined within functional connectivity networks, or rather spanned between functional networks. For each ROI, we calculated the seed-based functional connectivity map before and after the PA training and then performed voxel-wise  $t$ -tests on the normalized correlation values (see methods and Fig. 1C for details). Using this analysis, we were able to single out voxels that significantly changed their connectivity to the seed ROI after the PA training. In accordance with the global connectivity results, all the ROIs significantly reduced their connectivity to other cortical voxels following PA, while no increase in functional connectivity was found following PA training.

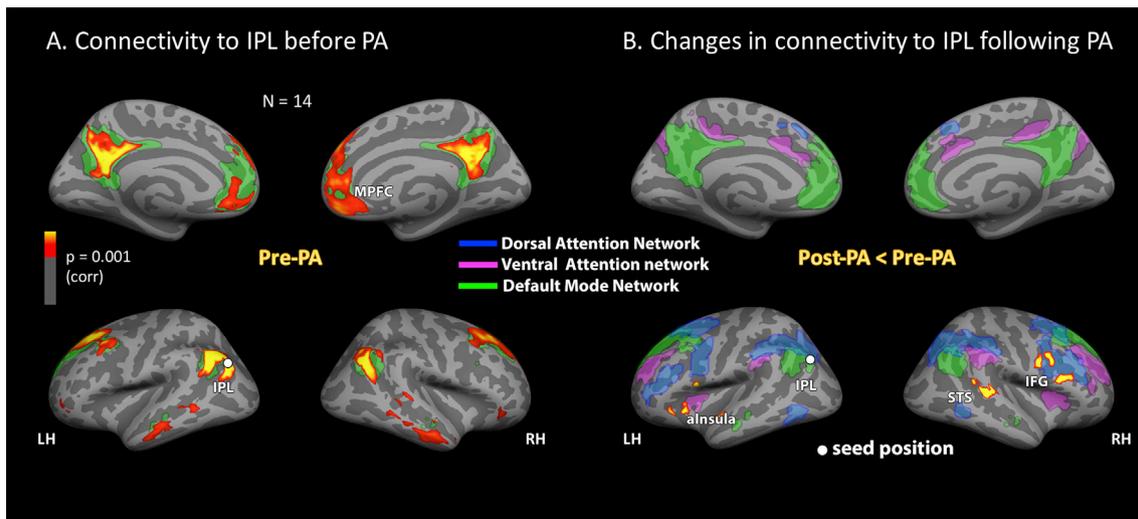
When measuring functional connectivity from the ROI in the left IPL in the pre-PA resting state, we found that it was connected to default mode network (DMN) nodes. Together with the ICA results, this confirmed this IPL region is part of the DMN (Fig. 3A). Importantly, when we assessed the changes in connectivity to the IPL region following PA, we found that it reduced its correlation to a set of areas that were all outside the DMN (green contour). These included clusters in the right inferior frontal gyrus (IFG) that fall within the DAN, the left anterior insula that is part of the VAN, as well as the right STS (Fig. 2), an area that had been shown to activate during the late stages of PA (Luauté et al., 2009; Werner et al., 2014). In the control group, which trained with plain glasses, no significant changes in connectivity to the IPL seed were found.

Similarly, a ROI in the medial prefrontal cortex (MPFC; defined around the peak voxel in the right hemisphere), which is also part of the DMN, showed high functional connectivity with other DMN regions in the pre-PA rest (Fig. 4A), and decreased its correlation with a set of areas outside the DMN following PA training (Fig. 4B). These included areas in the left parietal and frontal cortex that are either part of the DAN or considered motor and ‘dorsal stream’ areas, as well as a region near the left anterior insula that is part of the VAN. In the right hemisphere, the areas that decreased their connectivity to the MPFC seed were similar to those who decreased connectivity to the IPL, namely right IFG and right STS. Again, no significant changes in connectivity were found in the control group.

When we tested the ROI in the ventral attentional network, i.e., near the left anterior insula, we found that in the pre-PA resting state it was functionally connected with bilateral STS, bilateral anterior insula, and bilateral anterior cingulate, most of which are part of the VAN (Fig. 5A). However, following PA, anterior insula decreased its connectivity to areas outside the VAN. Specifically, it reduced connectivity to an extensive set of areas that included left precuneus, right MPFC, and left IPL, which together constitute the main nodes of the DMN (Fig. 5B). The control group showed no changes in connectivity to the seed following training.



**Fig. 2.** Global connectivity modulations following prism adaptation. (A) The map depicts areas that significantly decreased their global connectivity following PA (N = 14, paired *t*-test, FWER corrected). (B) The same map overlaid with contours depicting the DMN, DAN and VAN, as emerged from a group ICA on pooling together all pre-training resting state of both PA and control groups. The map and contours are overlaid on an inflated MNI fsaverage Freesurfer surface. MPFC = medial prefrontal cortex; IPL = inferior parietal lobule.



**Fig. 3.** Areas showing decreased connectivity to left IPL following prism adaptation. (A) The map in yellow depicts functional connectivity to the seed area in the inferior parietal lobule (IPL) during the pre-PA resting state (B) The map in yellow depicts voxels that significantly reduced their connectivity to the seed region in the left IPL following PA (n = 14, paired *t*-test, FWER corrected). Other specification same as in Fig. 2 aInsula = anterior insula; STS = superior temporal sulcus; IFG = inferior frontal gyrus.

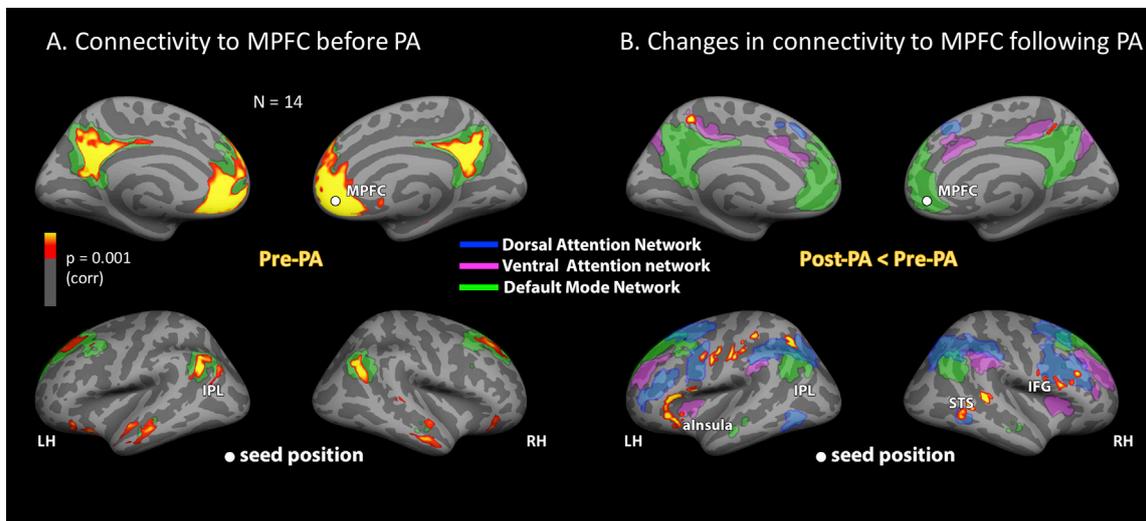
Interestingly, the present data-driven results on changes in resting state connectivity were closely linked to task-related changes in functional activation after PA. We found high correspondence between the set of areas that modulated their connectivity following PA with a set of areas that have been previously shown to modulate their response to a visual attention task following PA (Crottaz-Herbette et al., 2014). Indeed, the same IPL, aInsula, and IFG regions emerged from the present analysis and from activation data reported in (Crottaz-Herbette et al., 2014; Fig. 6).

In a similar vein, an alternative approach for ROI selection is to use prior knowledge instead of the first-step global connectivity analysis. To test this approach, we replicated the ROI seed-based analysis (Fig. 1C), with the exception of now taking as ROIs regions that were reported to modulate their response to an attentional task following prism adaptation (Crottaz-Herbette et al., 2014, Fig. 7A). As there is a large overlap between these previously reported regions and the results of our global

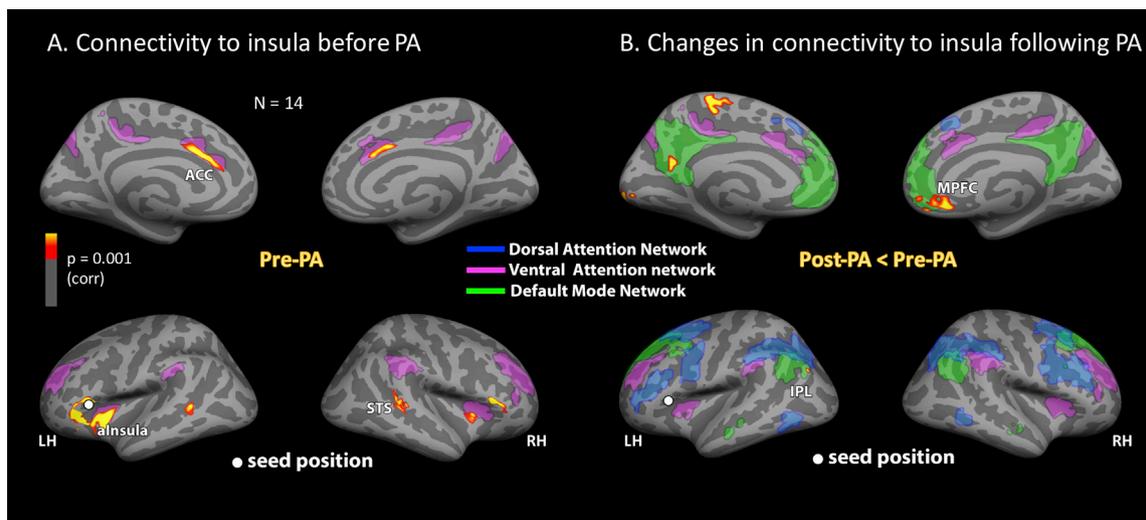
connectivity (see Fig. 6), we found comparable results and thus reach the same conclusion of enhanced decoupling between DMN and attentional networks. When sampling the task-based left IPL, we again find decreased connectivity to attentional areas STS and IFG on the right hemisphere, and IFG and anterior insula on the left hemisphere following PA (Fig. 7B). On the other hand, when taking the task-based right IFG as seed, we found reduction in connectivity in bilateral MPFC and precuneus, and left IPL, all within the boundaries of the DMN (Fig. 7C). Lastly, when taking the task-based left anterior insula as seed, we found connectivity reductions in bilateral MPFC, within the DMN (Fig. 7D), thus replicating the results of the global connectivity-based approach.

#### 4. Discussion

In the current work, we found that a brief PA training induced specific changes in functional connectivity between nodes of the DMN and the



**Fig. 4.** Areas showing decreased connectivity to right MPFC following prism adaptation. (A) The map depicts functional connectivity to the seed area in the medial prefrontal cortex (MPFC) during the pre-PA resting state (B) The map depicts voxels that significantly reduced their connectivity to the seed region in the right MPFC following PA ( $n = 14$ , paired  $t$ -test, FWER corrected). Other specification same as in Fig. 2. STS = superior temporal sulcus; IFG = inferior frontal gyrus.



**Fig. 5.** Areas showing decreased connectivity to left anterior insula following prism adaptation. (A) The map depicts functional connectivity to the seed area near the anterior insula (ainsula) during the pre-PA resting state (B) The map depicts voxels that significantly reduced their connectivity to the seed region next to the left ainsula following PA ( $n = 14$ , paired  $t$ -test, FWER corrected). Other specifications same as in Fig. 2. ACC = anterior cingulate cortex.

attentional networks, both VAN and DAN. All changes were characterized by a reduction of connectivity, and none of them was present in a control group exposed to the same motor training without prismatic lenses. Specifically, after PA, right inferior frontal areas in the DAN, left anterior insula region in the VAN and right STS reduced their connectivity to the left IPL and the MPFC, which are part of the DMN. Thus, areas related to goal directed attention and action, being part of the VAN and DAN, reduced their connectivity to key nodes of the DMN, being mainly involved in self-referential processing.

#### 4.1. Decoupling between DMN and attention networks in healthy individuals

The DMN and the attentional networks are normally uncorrelated or even anticorrelated during rest (Dixon et al., 2017a). Our data show that PA actually caused an enhancement of this pre-existing decoupling. It has been suggested that the DMN serves as a “self-centred predictive model of the world” (Raichle, 2015), while the DAN and VAN have been related

with orienting attention to stimuli in the external environment for goal-directed actions (Corbetta and Shulman, 2002). Studies on task-based activations found that the DMN became more deactivated as the external task became more engaging and subjects “loose themselves in the action” (Goldberg et al., 2006), but not when equally engaging tasks were self-oriented, i.e., autobiographical memory (Spreng and Grady, 2010). Therefore, a possible interpretation of our findings of enhanced decoupling between the DMN and the attention networks is that PA-related decoupling is linked to the balance between intrinsic signals and inputs from the external environment. This notion is in line with the fact that participants need to dissociate between intrinsic self-centred proprioceptive inputs of hand position and the visual inputs related to the hand and targets in order to execute suitable actions and achieve successful adaptation.

Another possible, though somewhat speculative, interpretation relates to the hetero-modal nature of DAN and DMN. In a series of recent studies, Dixon et al., examined the interplay between the DAN and the frontoparietal network, also with respect to the DMN (Dixon et al.,

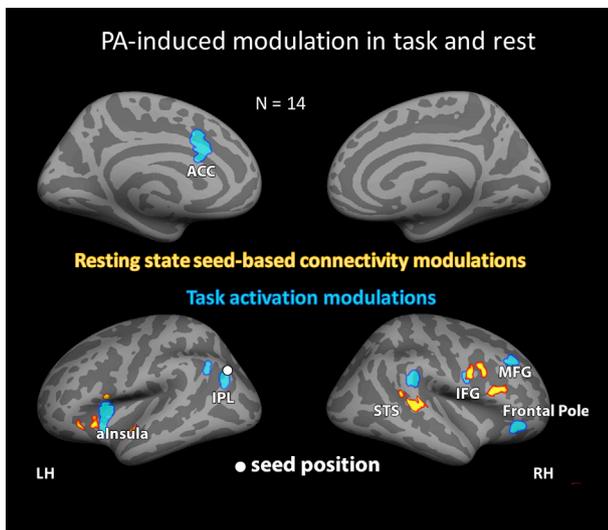


Fig. 6. Overlap between ROIs that modulated their responses to a visual attention task (Crottaz-Herbette et al., 2014), and regions that reduced their connectivity to left IPL following PA (same map as in Fig. 3B notice the overlap in the IFG, IPL, and aInsula areas. MFG = middle frontal gyrus.

2017a, 2017b, 2018). They conclude that the DAN and frontoparietal networks mediate goal-congruent behaviour by top-down control over sensorimotor regions that execute the actions (Dixon et al., 2017b). In other words, these areas allocate attentional resources to a task that requires a response, without being constrained by the specific modality of the task at hand. Similarly, the DMN is considered a heteromodal network that allows mental simulations that are detached from a specific sensory stimulus. Correspondingly, this network is the most physically remote from primary sensorimotor cortices (Margulies et al., 2016).

In the current work, we found an area in the right inferior frontal junction (IFJ) that modulated its connectivity to the left IPL following prism adaptation (Fig. 3). The IFJ has been previously shown to be decoupled from DMN regions when there is a need for external attention

(Dixon et al., 2018). Furthermore, Baldauf and Desimone (2014) found that IFJ drives object-based attention in a top-down manner in a visual task, therefore it can influence sensory processing in an object-based manner. A recent study concluded that “attention allocation is controlled through interhemispheric competition within the frontoparietal network, while an imbalanced network is likely to lead to attention biases” (Kim and Kastner, 2019). Taken together, these notions could suggest that enhanced decoupling of the right IFJ from the DMN region causes an attentional bias towards the left side of space. This bias might be reflected in the processing of any extrinsic stimulus that has spatial features, such as the stimuli in which PA aftereffects are found, regardless of specific modality or stimulus features.

#### 4.2. DMN and attentional networks decoupling in neuropathology

Changes in the coupling between the DMN and attentional networks after PA might have a key value from a clinical standpoint. PA is considered one of the more effective approaches for neglect rehabilitation (Barrett et al., 2012; Jacquin-Courtois et al., 2013, but see Rousseaux et al., 2006; Nys et al., 2008; Turton et al., 2010). A recent study with neglect patients showed that the recovery of decoupling between DAN and DMN within each hemisphere (both damaged and intact) was positively correlated with behavioural recovery from neglect symptoms (Ramsey et al., 2016). Thus, it is possible that one of the cortical mechanisms underlying neglect rehabilitation with PA lies in enhancing the decoupling between DMN and attentional networks.

A leading theory of brain functional pathology leading to neglect is an imbalance in interhemispheric connectivity (Corbetta et al., 2005; He et al., 2007; Lunven et al., 2015; Lunven and Bartolomeo, 2017; Bartolomeo, 2019). In line with this notion, Ramsey et al. (2016) reported that the increase in interhemispheric connectivity correlates with spontaneous recovery from neglect. However, in our results with healthy subjects we did not find any change in interhemispheric connectivity following PA. A possible reason is that in healthy participants, the interhemispheric balance is already at the optimal level, therefore PA cannot further increase it. Rather different results can be expected in brain damaged patients, with pathologically reduced interhemispheric balance: in this case, the use of PA might increase and normalize

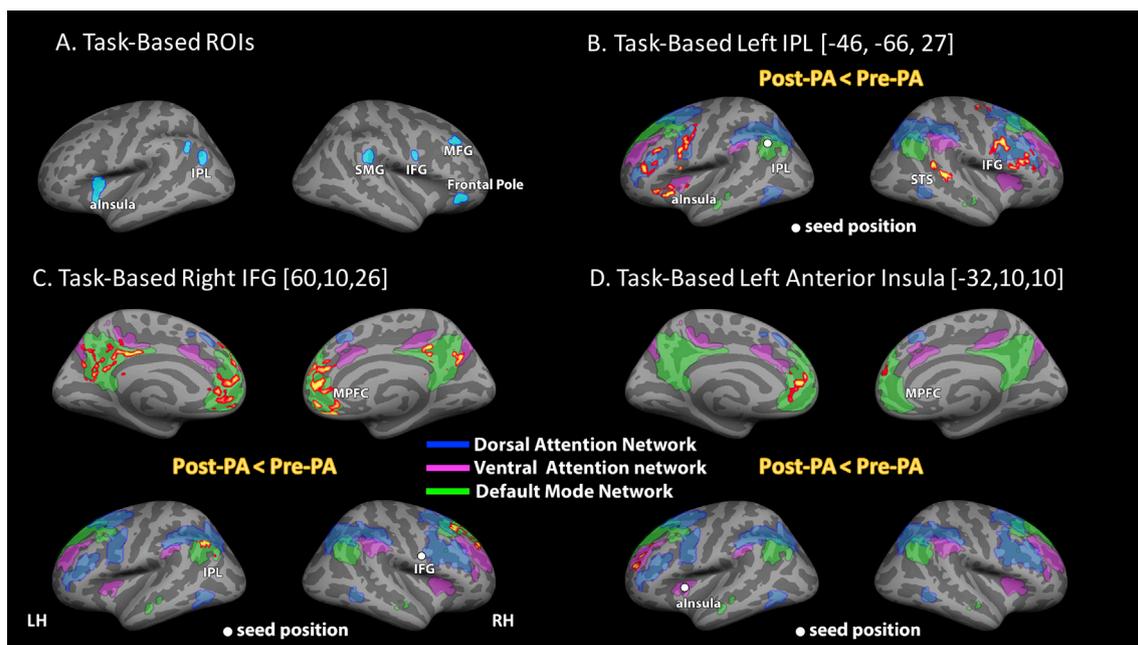


Fig. 7. PA-induced connectivity modulations to task-based ROIs. (A) Areas that changed their response to a visual attention task following PA (adapted from Crottaz-Herbette et al., 2014) were selected as seed ROIs. (B–D) voxels that significantly reduced their connectivity to the seed region in the (B) left IPL (C) right IFG (D) left anterior insula. The numbers in the brackets denote the MNI coordinates of the seed centre of mass. Other specifications same as in Fig. 2.

interhemispheric connectivity, in those cases where the relevant callosal tracts are preserved (Lunven et al., 2019).

Furthermore, the involvement of the DMN might be a more general mechanism explaining cognitive recovery after stroke, as similar changes in DMN were found also for aphasic patients who underwent linguistic therapy (Marcotte et al., 2013). Post-therapy, a deactivation in DMN regions and a positive correlation between anterior insula activation and recovery from symptoms were shown (Geranmayeh et al., 2014).

#### 4.3. DMN and task behaviour

The involvement of the DMN and attentional network in the PA-induced connectivity modulations is in line with the accumulating evidence of versatile and non-task-specific behavioural aftereffects of PA (Colent et al., 2000; Schintu et al., 2014; Michel, 2015; Tissieres et al., 2018). The DMN has been shown to be deactivated in a wide range of sensory tasks (McKiernan et al., 2003; Raichle, 2015), while attentional networks are not modality specific. Thus, a change in the interplay between the self-oriented DMN and extrinsic, task-based, attentional networks could account for a variety of behavioural changes demonstrated after PA (Michel, 2015). A recent study by Cassady et al. (2018) shows that connectivity patterns can predict the rate of adaptation to visuomotor rotation and savings (the speed in which participants adapt again in a subsequent session). In particular, connectivity within the DMN was found to be predictive of long-lasting effects of adaptation savings, while higher global connectivity to anterior insula was predictive of faster initial adaptation. Linking these data and our current results, we can propose that similar regions that are necessary for successful adaptation are also the ones undergoing connectivity modulations following adaptation training.

#### 4.4. STS has a unique role during prism adaptation

Another important finding of the present study is the reduced connectivity between the IPL and MPFC nodes of the DMN and the right STS. The STS is an area that had been found to be active during the last stages of adaptation training, once the error has been fully corrected (Luauté et al., 2009; Werner et al., 2014), and the phase of sensorimotor recalibration, consolidating the visuomotor correction, is in place. Thus, its disconnection from the DMN following PA is compatible with the notion that this area has a role in preserving the long-lasting behavioural effects of PA. Indeed, the posterior STS/STG region, in particular on the right hemisphere, has been linked to spatial awareness; it has been suggested to integrate egocentric and object-centred reference frames, and damage to it can lead to hemispatial neglect (Karnath, 2001).

#### 4.5. First-person perspective in action observation

Our study is the first to examine the effect of PA on global functional connectivity. Our data-driven approach was effective in discovering the most significant connectivity modulations, without limiting the findings to a specific set of ROIs. A recent paper by Tsujimoto et al. (2018) found decreased connectivity between parietal and frontal areas of the DAN following PA. However, their strict ROI-based approach did not focus on the central role of the DMN in PA-induced connectivity modulations. In our analysis pipeline, we performed two steps of analysis on the data - first detecting the global changes, and then focusing on the resulting ROIs to reveal the sources of those changes. It is important to point out that the second level analysis serves as a post-hoc test aimed at revealing the sources that drive the global connectivity effect and their robustness across subjects, and not for re-testing the statistical validity of the pre-detected ROIs (the so-called “double-dipping”, Kriegeskorte et al., 2009). Namely, using the post-hoc second level connectivity analysis provides us not with statistical power, but with explanatory power for understanding our effects. Moreover, using an alternative approach of selecting the ROIs according to task activations, we found similar results

and reached the same conclusion (Fig. 7). As the two approaches for ROI selection are in agreement, our results could not be attributed the specific ROI selection process.

Using global connectivity analysis, we found that areas in the left IPL, MPFC and the left anterior insula modulated their overall connectivity following PA. MPFC has been found to be related to self-referential actions and ownership sensation (Salomon et al., 2009; Lockwood et al., 2018). Furthermore, IPL and MPFC areas show less DMN deactivation when subjects view first-person self-referential actions (David et al., 2006; Bischoff et al., 2012), which might point on a connection between the increased decoupling we find and a change in perspective imposed by the prism.

On the other hand, the region in the left anterior insula has been previously reported to be active during movement observation (Hamzei et al., 2003), but also in action inhibition tasks (Wager et al., 2005). The insula is considered part of the salience network, aimed at mediating switching between areas responsible for executive functions and DMN (Menon and Uddin, 2010; Uddin, 2015). The reduced connectivity of the insula with DMN, but not to other ‘extrinsic’ regions following PA, might imply that such adaptation induces a decoupling from the self-referential signals in favour of coupling with networks driven by external inputs.

#### 4.6. Functional connectivity changes are linked to task-evoked activity changes

All the connectivity changes we found following PA training were characterized by a decrease in connectivity, while following sham training in the control group we found only a slight increase in visual cortex connectivity. However, the connectivity reduction effect was not a general phenomenon in the entire cortex, but was limited to a few cortical areas. Importantly, these regions corresponded to areas of PA-induced modulations during task, as they well overlap with regions whose activity changed during an attentional task following PA (Crottaz-Herbette et al., 2014). This suggests a link between changes in functional connectivity and attention-related cortical processing due to PA.

Interestingly, the more prominent decrease in global connectivity was in the left hemisphere, suggesting that the rightward shifting prisms tilted the balance between the two hemispheres. This is in line with the results of Crottaz-Herbette et al. (2014), which reported strongest activity changes in the left hemisphere following rightward PA. In contrast to our global connectivity findings, our results of the ROI-based analyses did not show a clear lateralization to either hemisphere (except for a slightly higher modulation in the right hemisphere seen in Fig. 3). This seems at odds with the task-related findings previously reported by Crottaz-Herbette et al. (2014). However, this difference might be due to the fact that functional connectivity networks tend to be more symmetrical than task-induced activations, which can exhibit more lateralized activity maps due to the stimulus properties (Hahamy et al., 2015).

#### 4.7. DMN deactivation in relation to task difficulty

An alternative, although not mutually exclusive, explanation can be proposed for the present findings. It might be the case that the difficulty of the adaptation task caused more deactivation of the DMN during the PA training itself, thus farther detaching it from the extrinsic, action-related, attention networks. It was previously reported that DMN areas progressively de-activate as a function of task difficulty, while, in contrast, attention and action related areas increase their activity (McKiernan et al., 2003; McKiernan et al., 2006). In this view, one might suggest that adaptation causes a decrease of the DMN activity and an increase in activity in attention/action areas, explaining their reduced connectivity. While the latter effect is compatible with other imaging studies investigating the neural correlates of PA (Luauté et al., 2009), no evidence is currently available on changes in the DMN during the adaptation phase of PA. On the other hand, it is also currently conceived

that PA relies on two complementary, only partially overlapping, processes, implying different levels of task difficulty. The early phase of PA engages a strategic recalibration mechanism, consisting in higher pointing error, error detection and a resources-consuming process of error correction. The later phase consists of the so-called realignment mechanism, which is a more implicit and less demanding process of long-lasting correction of proprioceptive and visual coordinates (Redding and Wallace, 2002). Thus, an explanation based on task-difficulty for the reduced coupling between DMN and attention networks found in the present study would fit with the first phase of PA, but less with the second phase. As subjects usually complete the initial, more challenging, stage of adaptation within 5–10 trials, most of the training session contains a non-demanding task. Our data focus on post-training effects and thus less likely relate to early changes due to task difficulty.

Finally, a recent study that measured the effect of movement error on resting state connectivity found that primary visual and motor areas and area V5/MT showed connectivity modulation corresponding to the amount of motor error (Bernardi et al., 2018). No changes were reported in the areas where we found PA-related connectivity modulations and that could potentially reflect error detection, e.g., insula and DMN nodes. Thus, the present results seem specifically linked to changes in functional connectivity due to PA training rather than to experiencing movement errors. Nevertheless, more data are needed on the DMN deactivation during the different phases of the PA training in order to determine whether the current PA-induced changes in functional connectivity are better explained in terms of adaptation-related task difficulty, changes in the interplay between intrinsic vs. extrinsic processing, or both processes.

#### 4.8. Study considerations

In the current study, we chose to have an independent control group with naïve participants, instead of using the subjects of the PA group after de-adaptation as control (as in e.g., Tsujimoto et al., 2018). This approach has several benefits: first, the current design controls for test-retest effects: the post training rest had identical parameters between the two groups in terms of timing in the session and past sensory experience (besides the adaptation). Second, adaptation has long-term behavioural aftereffects in healthy subjects - pointing errors are observed for more than 40 min past adaptation (Schintu et al., 2014), can induce changes on brain activity even in the absence of measurable behavioural aftereffects (Martín-Arévalo et al., 2016), and even after active de-adaptation subjects still exhibit motor savings (Cassady et al., 2018). Third, in healthy subjects, functional connectivity networks are relatively stable across subjects (Damoiseaux et al., 2006). Given that subjects were randomly assigned to either the PA or the control group, inter-individual differences should not be the cause of a systematic difference between the two groups. For these reasons, the independent control group allows us to isolate the effect of the prism adaptation without being confounded by long-term behavioural aftereffects or differences in experimental parameters.

It might be argued that the fact that the participants were fixating on a visual target during the resting state affected the results. However, a recent study found that following PA, there was no bias in gaze direction while subjects are looking straight ahead or fixating (Gilligan et al., 2019). As the control group had also performed fixation during resting state, and also performed pointing movements towards stimuli presented in the same sectors of space, the differences in brain modulations between the two groups are not likely to stem from differences in fixating. Future studies using rest with eyes closed would help shed light on this notion.

A potential limitation of the study is a relatively small sample size. While statistically significant results with a medium sample size might indicate a larger effect size (Friston, 2012), some studies show the potential limitations of using small samples (Lindquist et al., 2013). However, in the current prism adaptation paradigm, detecting significant effects in a medium sized sample is of particular importance, as a similar

paradigm could then be transferred to studying neglect patients, where collecting fMRI data with large sample size is extremely difficult.

## 5. Conclusion

To conclude, our data show for the first time an involvement of the DMN in PA-related plasticity. We found that the PA-induced functional connectivity modulation was not limited within specific networks, but was rather characterized by an enhancement of the decoupling between prominent cortical networks, namely, the DMN and VAN/DAN. Since the balance between these networks has been proposed to determine the interplay between self-referential and extrinsic sensory stimuli, changes to this balance could account for the broad variety of behavioural effects that are induced by PA and might underlie the therapeutic effect of PA in neglect patients.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neuroimage.2019.06.050>.

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