Patients with lesions to the intraparietal cortex show greater proprioceptive realignment after prism adaptation: Evidence from open-loop pointing and manual straight ahead

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Running title: Intraparietal cortex and visual realignment

Word count: 5,551

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Abstract

(249 words)

Reaching toward a target viewed through laterally refracting prisms results in adaptation of both visual and (limb) proprioceptive spatial representations. Common ways to measure adaptation after-effect are to ask a person to point straight ahead with their eyes closed ("manual straight ahead", MSA), or to a seen target using their unseen hand ("open-loop pointing", OLP). MSA measures changes in proprioception only, whereas OLP measures the combined visual and proprioceptive shift. The behavioural and neurological mechanisms of prism adaptation have come under scrutiny following reports of reduced hemispatial neglect in patients following this procedure. We present evidence suggesting that shifts in proprioceptive spatial representations induced by prism adaptation are larger following lesions to the intraparietal cortex – a brain region that integrates retinotopic visual signals with signals of eye position in the orbit and that is activated during prism adaptation. Six healthy participants and six patients with unilateral intraparietal cortex lesions underwent prism adaptation. After-effects were measured with OLP and MSA. After-effects of control participants were larger when measured with OLP than with MSA, consistent with previous research and with the additional contribution of visual shift to OLP after-effects. However, Patients' OLP shifts were not significantly different to their MSA shifts. We conclude that, for the patients, correction of pointing errors during prism adaptation involved proportionally more changes to arm proprioception than for controls. Since lesions to intraparietal cortex led to enhanced realignment of arm proprioceptive representations, our results indirectly suggest that the intraparietal cortex could be key for visual realignment.

Keywords: Prism adaptation; intraparietal cortex; spatial updating; sensory-motor realignment; hemispatial neglect.

Highlights

- Prism adaptation shifted controls' open-loop pointing more than manual straight ahead
- Manual straight ahead shifted more in people with intraparietal cortex lesions than controls
- Shifts in open-loop pointing for the two groups were not different
- Results indicate greater proprioceptive realignment following intraparietal cortex damage
- This could also be indirect evidence of reduced visual realignment

Keywords

"prism adaptation", "hemispatial neglect", "corollary discharge", "optic ataxia", "intraparietal cortex"

1. Introduction

To reach out and touch objects, we need to continuously integrate the location of an object relative to our direction of gaze with the felt location of the head, body, arm, and fingers relative to the object and to each other. Converging evidence suggests that the posterior parietal cortex (PPC) is important for updating visual representations of target locations, integrating these with limb and body position, and realigning them if necessary (Medendorp and Heed, 2019; Sereno and Huang, 2014). Optic ataxia following lesions to the superior parietal lobule (SPL) and cortex surrounding the intraparietal sulcus (IPS) of one or both hemisphere(s) is characterized by reaching errors due to difficulties with aligning arm position information with eye position information (Andersen et al., 2014; Perenin and Vighetto, 1988). Furthermore, problems with on-line correction of eye and arm movements are seen in patients with lesions to the PPC (Duhamel et al., 1992b; Gréa et al., 2002; Heide et al., 1995; Pisella et al., 2011; Van der Stigchel et al., 2013) and neurologically healthy participants who receive transcranial magnetic stimulation (TMS) to cortex bordering the IPS (Desmurget *et al.*, 1999; Morris *et al.*, 2007; Tunik *et al.*, 2005). Indeed, evidence amassed from functional magnetic resonance imaging (fMRI), neuropsychological, and animal studies suggests that within the PPC, the IPS and homologous areas in non-human primates are particularly important in the spatial transformations that occur during goal-directed pointing and reaching (for reviews, see Culham and Kanwisher, 2001; Vingerhoets, 2014).

One way to study the integration of visual and proprioceptive spatial representations is by using prism adaptation. Participants wear goggles or glasses fitted with prismatic lenses that shift the visual image to one side. Since gaze must be rotated to foveate the object, the visual location of the object relative to gaze direction does not correspond to its proprioceptive coordinates relative to the location of the pointing hand and arm. Therefore, if participants reach to touch a visual target, they miss, reaching to where the target appears to be rather than to its true location. With repeated attempts, however, pointing movements shift in the opposite

direction to the visual change and errors are reduced. The reduction in pointing error occurs thought a combination of deliberate mis-pointing ("strategic recalibration") during the early exposure period, and a slower realignment of visual and proprioceptive representations ("adaptive realignment", or "true" adaptation; (Prablanc et al., 2019). When the prisms are removed participants err once again, but this time in the opposite direction to the prismatic shift, and this adaptation "after-effect" is considered to be indicative of the extent of adaptive realignment. With prism adaptation it is possible to study coordination of the visual, proprioceptive, and motor systems when locating and interacting with objects in our environment (Redding and Wallace, 1996; Redding *et al.*, 2005).

Given the converging evidence that intraparietal cortex is involved in spatial transformations during pointing and reaching, it is not surprising that this region has been implicated in prism adaptation. Brain imaging studies have linked anterior intraparietal cortex activity in healthy individuals to strategic recalibration (Chapman et al., 2010; Danckert et al., 2008; Luauté et al., 2009), although one study also implicated anterior intraparietal cortex in adaptive realignment (Chapman et al., 2010). Patients with bilateral lesions to the PPC, including the intraparietal cortex, show adaptation after-effects (Pisella et al., 2004; Striemer et al., 2008; although one patient showed after-effects only when adapting with his right hand and not with his left, Newport and Jackson, 2006), indicating that the IPS is not essential for realignment to occur. Indeed, Pisella and her colleagues (2004) proposed that the PPC was responsible for strategic recalibration, whereas the cerebellum was responsible for adaptive realignment. This division of roles has also been supported by evidence of reduced or no adaptive realignment in patients with cerebellar lesions (Pisella et al., 2005; Weiner et al., 1983), and brain imaging studies linking cerebellar activity with adaptive realignment in healthy controls (Luauté et al., 2009; Striemer et al., 2008; see Panico et al., 2020, for a review).

Other evidence suggests that the PPC is involved in more than the strategic realignment component of prism adaptation. One reason for the recent interest in prism adaptation is that it has proved to be effective in reducing the symptoms of

hemispatial neglect ("neglect"; Rossetti et al., 1998) – a syndrome that is commonly associated with damage to the right PPC, especially the inferior parietal lobe and temporoparietal cortex (Buxbaum et al., 2004; Mesulam, 1999; Mort et al., 2003; Vallar and Perani, 1986). Neglect reduction following prism adaptation is presumed to result from adaptive realignment (Redding et al., 2005), and is correlated with increased activation of the PPC, amongst other areas (Luauté et al., 2006; Saj et al., 2013; Shiraishi et al., 2008). Streimer and his colleagues (2008) proposed that neglect reduction following prism adaptation were mediated by the SPL, which is typically spared in neglect. They supported this with evidence that a patient with bilateral SPL lesions showed no reduction in their right disengage deficit following prism adaptation (the patient's lesions also involved the anterior IPS). The same procedure reduced disengage deficits in patients with right brain damaged sparing the SPL/IPS (Striemer and Danckert, 2007). In further support of the proposed role of PPC in neglect improvements, Làdavas and her colleagues (2015) found that anodal transcranial direct current stimulation of the right PPC enhanced the reduction of neglect following prism adaptation (although O'Shea et al., 2017, found no such enhancement). So, although the PPC is proposed to be linked to strategic calibration, damage to it can nevertheless cause symptoms that are ameliorated by prism adaptation, and these improvements themselves could be linked to the PPC.

A potential paradox is presented by the fact that lesions to the SPL and intraparietal cortex do not prevent adaptive realignment, but these same brain regions could be critical for neglect reduction following prism adaptation (for which adaptive realignment is presumed key). One possibility is that lesions to these areas do not affect the overall aftereffect, but instead alter the extent to which the aftereffect is achieved by visual compared to limb proprioceptive spatial remapping. Two common ways to measure adaptation after-effects are through "manual straight ahead" (MSA) and "open-loop pointing" (OLP; Harris, 1965; Redding and Wallace, 1992; Wilkinson, 1971). MSA is measured by asking participants to close their eyes and point straight ahead of their mid-sagittal plane, and is thought to mainly indicate realignment of arm muscle proprioception. In OLP, participants point to a visual target while their pointing arm is occluded from sight. OLP after-effects are normally

larger than MSA after-effects and are thought to measure total realignment of both visual spatial representations and limb proprioception together (Prablanc et al., 2019; Redding et al., 2005; Redding and Wallace, 2002). In support of this, Wilkinson (1971; see also Redding and Wallace, 1988; Wallace and Redding, 1979) demonstrated that the shift in OLP is approximately equal to the sum of the absolute MSA shift and the Visual Straight Ahead (VSA) shift, measured by asking participants to indicate when a small point of light viewed in otherwise total darkness is positioned directly in front of their mid-sagittal plane. Thus, MSA and OLP can be used to quantify and compare different components of adaptation after-effect (i.e. limb proprioceptive shift only versus combine visual representations and limb proprioceptive shift). It has been shown that patients with neglect can adapt to rightward-shifting prisms and show the same magnitude of OLP shift (which is presumed to provide a measure of total visual and proprioceptive realignment) as control participants (Aimola et al., 2012; Angeli et al., 2004a, 2004b; Farnè et al., 2002; Maravita et al., 2003; Rossetti et al., 2004; see Sarri et al., 2008, for a review). Thus, parietal lobe damage might lead to different proportions of visual and limb proprioceptive realignment than is seen in neurologically healthy participants, without altering total sensory-motor realignment.

To this end, we measured MSA and OLP errors from patients with chronic lesions to the cortex surrounding the IPS and neurologically healthy control participants before and after prism adaptation. We chose to focus on the intraparietal cortex given its importance for the spatial transformations that occur during goal-directed pointing and reaching (Culham and Kanwisher, 2001; Vingerhoets, 2014). We predicted that control participants would show smaller MSA shifts than OLP shifts consistent with previous evidence (reviewed by Facchin et al., 2019; and Gilligan et al., 2019) and the idea that the former measures only limb proprioceptive shift and the latter measures both visual and limb proprioceptive shifts. If IPS lesions alter the way in which sensory-motor realignment occurs during prism adaptation, then the difference in the magnitude of the MSA versus OLP shifts for the patients would be altered compared to controls. Specifically, if IPS lesions disrupt updating of visual spatial representations, then patients' MSA shifts would be larger (relative to controls') and

more similar to their OLP shifts, reflecting a relatively larger contribution of limb proprioceptive shifts to the OLP error. Conversely, if IPS lesions disrupt updating of limb proprioception, then MSA shifts would be smaller for patients than for controls, reflecting reduced limb proprioceptive shifts.

There is some evidence for hemispheric lateralisation in the neural networks underlying adaptation to different prism directions. Specifically, selective deficits in adaptation to leftward- but not rightward-shifting prisms have been reported following inactivation of the left ventral premotor area in monkeys (Kurata and Hoshi, 1999), and in a patient with a lesion to the left cerebellum (Pisella et al., 2005). People with neglect following right-hemisphere lesions did not adapt to leftward- shifting prisms, although this was not the case for right hemisphere patients without neglect (Luauté et al., 2012). It is therefore possible that IPS lesions may selectively alter the relative amounts of visual and proprioceptive realignment only after adaptation to prisms that shift vision in an ipsilesional direction. To test this possibility, our participants underwent adaptation to shifts of vision in both ipsilesional and contralesional directions.

2. Materials and Methods

2.1. Participants

The participants were six patients with chronic lesions involving the IPS (mean age =61, *SEM*= 7.9; 3 males), and six age-matched control participants (mean age = 63, *SEM*=7.9; 2 males), who were recruited from the North Wales Brain Injury Service where they had been under the neurological care of one of the authors (RR). They were tested at Bangor University and had been regular participants in neuropsychology research overs several years. The clinical details and lesion locations of the patients are summarized in Table 1, Fig. 1 and Supplementary Fig. 1 online. Two of the patients had lesions to the left hemisphere (patients L1 and L2) and four had lesions to the right hemisphere (patients R1 to R4). All participants

gave informed consent to participate in a research protocol that was approved by hospital and university ethics committees according to the Declaration of Helsinki.

All participants underwent a standard neurological examination (Table 1). Shoulder-joint proprioception was tested by moving one of the participant's outstretched arms to an angle of 10-15º above or below horizontal while their eyes were closed and asking them to match this angle with their other arm. Several trials were performed with each arm and the results established that proprioception was unimpaired in all patients. Results of confrontation testing for visual field deficits, neglect, and extinction were normal for all participants except R3. R3 had initially demonstrated a left inferior visual field quadrantanopia with a Riddoch effect (Riddoch, 1917). At the time of testing, she had recovered the ability to detect targets and to read letters in the quadrant, but reported that they were less clear. She had no difficulty in seeing or pointing toward the visual stimuli used during prism adaptation or while MSA and OLP errors were measured. L2 and R1 had hemispatial neglect early in their illness, but recovery from neglect had been documented by clinicians at the North Wales Brain Injury Service using standard cancellation and drawing tasks. Optic ataxia was assessed in each hand by asking the patient to fixate on the examiner's face while reaching to and grasping a pen presented in the left or right hemifield at the patient's arm's length. Impairments in reach direction and/or hand orientation/scaling consistent with optic ataxia were observed in both left-hemisphere patients (L1 and L2) and one right-hemisphere patient (R1). The control participants were normal on all tests.

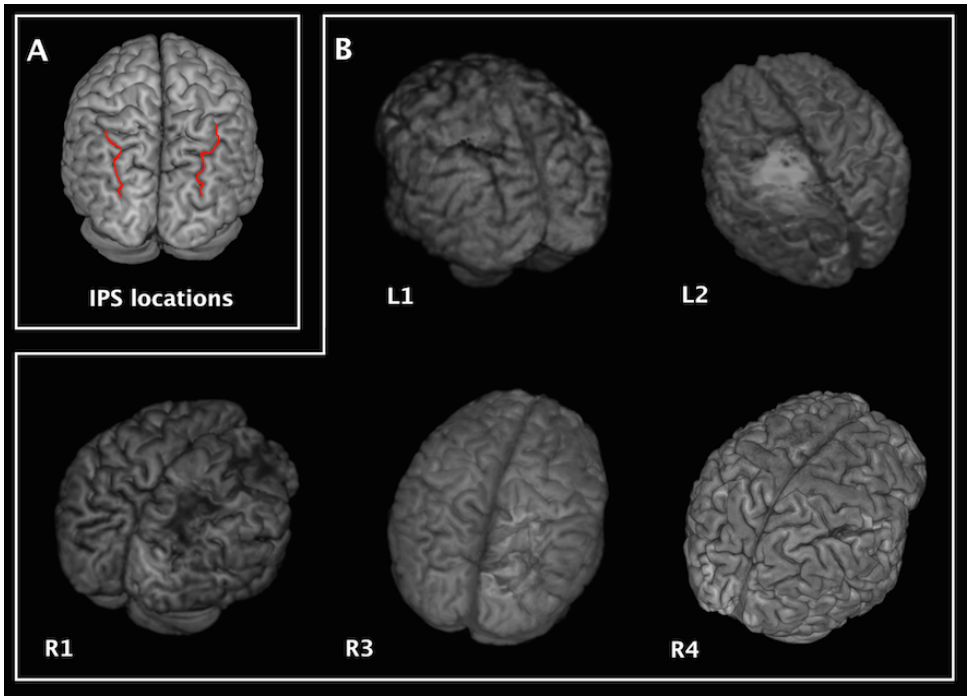

Figure 1. *Lesions of five of the six patients*

Rendered 3-dimensional views of A) a neurologically intact brain with the IPS of each hemisphere indicated in red; and B) individual T1-weighted magnetic resonance images for five of the six patients. The images were constructed using MRIcroN software (Rorden et al., 2007). No MRI scan was available for patient R2, however his lesion is show in axial CT slices, along with axial MR slices for all other patients, in Supplementary Fig. 1 online.

Table 1. Patient clinical details.

Patient	Sex	Age	Weeks post-injury	Handed-ness	Pathology[a]	Lesion information[a]	Neurological deficits at time of testing[b]
L1	M	76	255	R	Intracerebral Haemorrhage	Rostral and medial part of the SPL extending along the horizontal limb of the IPCx posterior to the post-central sulcus. Involves both banks of the rostal IPCx and abuts the post-central sulcus. Extends deep into the white matter to the posterior border of the lateral ventricle. A small component extends laterally into the SMG.	Optic ataxia (left hand: RH-D; Right hand: LH-D, LH-O, RH-D, RH-O)
L2	F	80	171	L	Intracerebral Haemorrhage	LOC, Heschl's gyrus, TPJ including the posterior part of the STG (Wernicke's area 22) and SMG, AG, lateral and medial IPCx and SPL, extending rostrally into the post and pre-central gyri involving M1 and PMd, paracentral lobule (SMA) and caudal part of the SFG. Sparing FEF.	Optic ataxia (Left hand: RH-D); Broca's aphasia; ideomotor apraxia; Hemiplegia of the right lower limb.
R1	F	65	182	R	MCA infarct with gliosis of the right frontal lobe and in the watershed territory of the frontal and parietal lobes	IFG, MFG and SFG including areas 44, 45, 46, 8, 9 and 10 as well as the FEF, M1, premotor cortex, and post-central gyrus. Extends into the SPL along the medial border of the IPS, extends under the IPS into the lateral IPCx. Spares the insula and the basal ganglia.	Optic ataxia (Left hand: RH-O; Right hand: LH-D, LH-O, RH-O).
R2	M	51	170	R	MCA infarct	TPJ including posterior STG and SMG and extending superiorly across the IPCx into the rostral SPL, but sparing post-central gyrus.	None detected
R3	F	27	187	R	Resection of arteriovenous malformation	The lesion damaged much of the precuneus (medial parietal lobe) almost up to the cingulate sulcus and the upper part of the cuneus where it extends almost to the upper bank of calcarine cortex. Extends rostrally along both sides of the IPS damaging IPCx and the SPL up to the border of the post-central sulcus.	Left upper quadrantanopia; Riddoch's Syndrome
R4	M	65	91	R	MCA infarct	Discrete lesion of the cortex posterior to the post-central sulcus involving only the rostral PPC (area 5) along the horizontal segment of the IPS. No involvement of SPL or SMG.	None detected

[a]AG = angular gyrus; FEF = frontal eye field; IFG = inferior frontal gyrus; IPCx = intraparietal cortex; IPS = intraparietal sulcus; LOC = lateral occipital cortex; MCA = middle cerebral artery; MFG = middle frontal gyrus; PMd = dorsal premotor cortex; PPC = posterior parietal cortex; SFG

= superior frontal gyrus; SMA=supplementary motor area SMG = supramarginal gyrus; SPL = superior parietal lobe; STG = superior temporal gyrus; TPJ = temporo-parietal junction.

[b]Optic ataxia assessment notes. LH-D = impairment in reach direction when reaching into the left hemifield; LH-O = impairment in hand orientation/scaling when reaching into the left hemifield; RH-D = impairment in reach direction when reaching into the right hemifield; RH-O = impairment in hand orientation/scaling when reaching into the right hemifield.

2.2. Apparatus

Participants sat at a 90cm deep x 90cm wide prism adaptation box. The box had 86 cm high walls on the left, right and rear sides. The side that was facing the participant was open. The bottom surface of the box and all three walls were painted black. A moveable white vertical panel was placed within the box, parallel to both the participant's body and the back wall and at a depth that was slightly less than reaching distance from the participant. This panel served as a backboard to which all pointing movements were directed. Three vertical black lines were drawn on the panel: one in the centre of the panel, and the others 15 cm (approximately 15º) to the left and right. These lines were the targets for prism adaptation and for pre- and post-adaptation OLP (see Procedure section). During MSA and OLP a second panel was placed horizontally 30cm above the base of the box. Participants rested their chin lightly on this panel during MSA and OLP to ensure head stability, and the panel also occluded vision of the arm during OLP. Finally, there was a 1cm x 1cm tactile marker on the bottom surface of the box, approximately 2cm from the front edge, which served as the starting position for all pointing movements.

Pre- and post-adaptation pointing errors were recorded using a MiniBIRD electromagnetic motion tracker (Ascension Technologies Corporation Inc.) that was operated via a Dell computer using custom software. The position of the participant's pointing hand was recorded using an 8mm x 8mm x 18mm sensor that was attached to the tip of their index finger using medical tape.

Prism adaptation was performed using optician's trial frames that were fitted with adjustable Risley biprisms set to induce a 15º leftward or rightward shift in the visual image. The construction of the prism goggles was such that when participants pointed to a visual target, only the second half of their pointing movement was visible to them ("concurrent" feedback).

2.3. Design and Procedure

The experiment had a repeated-measures design. The MSA and OLP errors of each participant were recorded before and after adaptation to leftward- and rightward-shifting prisms, with every participant undergoing both directions of prism adaptation in separate sessions on different days. Patients used their contralesional hand for all pointing movements. Control participants used the same hand as the patient to whom they were matched.

An overview of the procedure for each research session is represented in Fig 2. At the beginning of each session four calibration trials were performed in which the transmitter was held at the starting position and against each of the three target lines and these locations were recorded to use as reference points for the calculation of pointing errors. The transmitter was then attached to the participant's finger. In each session participants completed two blocks of each type of pointing before and after prism adaptation (i.e., eight blocks per session). The order of pointing type was counterbalanced between participants in an ABBA manner. Participants first performed all four pre-adaptation blocks. They then performed one block of prism adaptation immediately before each of the post-adaptation blocks, totalling four prism adaptation blocks per session. Repeating prism adaptation in this way was done to ensure that the adaptation after-effect was maximally present for all four post-adaptation blocks (see Bultitude et al., 2013a, 2013b; Schindler et al., 2009 for similar designs). Breaks were provided as required with the exception that prism adaptation was always followed immediately by the relevant post-adaptation pointing block.

Pre-adaptation				Post-adaptation							
MSA	OLP	OLP	MSA	PA	MSA	PA	OLP	PA	OLP	PA	MSA

Figure 2. An example order of events for a single research session. Order of MSA and OLP was counterbalanced between participants in an ABBA manner. MSA=manual straight ahead; OLP=open loop pointing; PA=prism adaptation.

2.3.1. Manual straight ahead

Participants performed 12 trials of MSA judgments in which they kept their eyes closed and their chins resting on the horizontal occluding panel. The instructions were to "point directly ahead of the line that runs down the middle of your body, through your nose and your belly-button, cutting your body in half". Before the beginning of each trial participants placed the index finger of their adapting arm on the starting position. The experimenter confirmed that the participant was correctly positioned before initiating each trial. Each trial began with a 500ms tone of 500Hz. Upon hearing the tone, the participant reached out to touch the backboard immediately in front of their perceived mid-sagittal plane. They held their finger in this position until the experimenter instructed them to return their finger to the starting position in preparation for the next trial.

2.3.2. Open-loop pointing

With their eyes open, participants were instructed to point to one of the three target vertical lines (left, centre or right) that were drawn on the backboard. The horizontal occluding panel hid the participant's arm and the lower portion of the three target lines from their view. The upper portion of the target lines could be seen extending above the panel. At the beginning of each trial the experimenter instructed the participant which line they should point to before triggering the trial in the same way as described for MSA judgements. Each block consisted of four trials per location in pseudorandom order (12 trials in total).

2.3.3. Prism adaptation

The occluding panel was removed and participants were fitted with the prism goggles. Participants pointed alternately with their index finger to the left and right target line at shoulder height, returning their hand to the starting position between each pointing movement. They made 50 pointing movements in time with a metronome set to 60Hz. Cognitive impairments prevented the use of the metronome for two of the patients (L2 and R1) who were instead guided through rapid target pointing by the experimenter on a trial-by-trial basis. Participants were

instructed to keep their head still throughout prism adaptation and head position was monitored by the experimenter. After the last pointing movement participants rested their hand on the table and closed their eyes while the experimenter removed the prism goggles and replaced the horizontal occluding panel for the next MSA or OLP block.

3. Results

Horizontal pointing errors relative to the true target location were calculated for each trial in degrees of visual angle (º). The following transformations were performed to enable meaningful combination of the data from left and right hemisphere lesioned patients and controls. For the patients, the direction of prismatic shift was coded relative to the lesioned hemisphere (ipsilesionally-shifting or contralesionally-shifting). For each control participant, the direction of prismatic shift was similarly coded relative to the lesioned hemisphere of the patient to whom they were matched. To meaningfully compare the magnitudes of after-effects for the different prism directions, errors were expressed with regards to the expected after-effect direction, with positive numbers indicating an error in the direction of the expected after-effect, and negative numbers indicating an error in the opposite direction of the expected after-effect (i.e., the direction of the prismatic shift). Of the 2304 total trials, 49 (2.1%) were discarded due to a participant failing to follow task instructions (e.g., failing to touch the back-board) or were missing due to equipment failure or experimenter error. For each participant, boxplots were constructed for each individual condition to identify potential outliers (defined as >1.5 times the interquartile range larger than quartile 3, or <1.5 times the interquartile range below quartile 1). Because adaptation after-effects are typically largest in the first post-adaptation pointing trial and then decay, some of these values could represent valid pointing errors. Therefore, the outliers from the boxplots were further investigated by visually inspecting plots of the endpoint errors for the twelve trials in the relevant pointing block. Of 40 potential outliers, 14 were identified as being initial large error trials or as otherwise fitting with the overall pattern of the endpoint errors for that

block, and were retained. The remaining 26 outliers were removed (1.1% of total trials) .

Analyses were performed with R software (R Core Team, 2015) using linear mixed models regression with bootstrapping procedures wherein 1000 bootstrap samples were generated for each analysis. The combination of linear mixed models and bootstrapping addressed potential problems that could arise due to missing data and differences in the variances for the patients and the control groups. It also enabled the evaluation of the effects of the experimental conditions on the trial-to-trial variability in endpoint errors while factoring out the intra-participant variability, whereas a more traditional repeated measures approach was not feasible due to the small number of participants. A variable made a significant contribution to predicting the outcome variable when the 95% confidence interval (CI) around the regression coefficient (B) did not include zero.

We first conducted an omnibus analysis in which we entered Group (controls, patients), Session (pre, post), Pointing Type (MSA, OLP), and Prism Direction (contralesional, ipsilesional) using dummy variable coding into the analyses of the endpoint error, along with all possible two-, three-way, and four-way interaction terms. The results indicated that the four-way Group x Session x Pointing Type x Prism Direction interaction term significantly contributed to the prediction of pointing error (*B*=2.2, *95% CI* = [-4.0, -0.2]). We therefore ran separate analyses for the contralesional and ipsilesional Prism Directions. These analyses included the terms Group (controls, patients), Session (post, pre), and Pointing Type (MSA, OLP), along with all possible two-way interaction terms, and the three-way interaction term Group x Session x Pointing Type.

Table 2
The results of separate bootstrapped (*N* = 1000) linear mixed models regression analyses of endpoint errors made when adapting to contralesionally and ipsilesionally shifting prisms.

	Contralesional prismatic shift			Ipsilesional prismatic shift		
Effect	Coefficient estimate	Lower *CI*	Upper *CI*	Coefficient estimate	Lower *CI*	Upper *CI*
Intercept	1.6*	1.0	2.2	5.1*	4.7	5.6
Group (*controls = 0*)	1.5*	0.2	2.9	4.1*	3.1	5.0
Session (*post = 0*)	-3.1*	-3.9	-2.4	-5.0*	-5.8	-4.2
Pointing Condition (*MSA = 0*)	5.7*	4.5	7.4	0.7	-0.6	2.0
Group x Session	-3.4*	-5.1	-1.9	-3.4*	-4.7	-2.1
Group x Pointing Condition	-1.6	-4.0	0.5	-4.1*	-5.6	-2.5
Session x Pointing Condition	-3.8*	-5.5	-2.5	-2.1*	-3.6	-0.5
Group x Pointing Condition x Session	3.3*	0.7	6.1	3.6*	1.7	5.5

Notes: * = Significant predictor of endpoint error (95% *CI* around the coefficient estimate does not include 0). Reference terms for dummy variable coding are indicated in brackets next to the main effect terms.

In both analyses, Group (*control vs patient*) was a significant predictor of endpoint error (see Table 2). Compared to the controls, the patients' endpoint errors were on average 1.6º (*95% CI* = [1.0, 2.2]) larger when adapting to contralesionally-shifting prisms and 5.1º (*95% CI* = [4.7, 5.6]) larger when adapting to ipsilesionally-shifting prisms. Session (*post vs pre*) was also a significant predictor in both analyses, indicating that overall the participants' endpoint errors were smaller before than after adaptation (pre-minus-post difference = -3.1º, *95% CI* = [-3.9,-2.4] for contralesionally- and -5.0º, *95% CI* = [-5.8, -4.2] for ipsilesionally-shifting prisms). Pointing Condition (*MSA vs OLP*) also significantly contributed to the prediction of endpoint error when participants adapted to contralesionally-shifting prisms, with endpoint errors for OLP larger by an average of 5.7º (*95% CI* = [4.5, 7.4]). However, on average, Pointing Condition did not significantly predict pointing error when participants adapted to ipsilesionally-shifting prisms (the 95% CI around the regression coefficient included zero: -0.6, 2.0).

Multiple two-way interactions were significant in both regression analyses (see Table 2), however these were superseded by significant three-way Group x Pointing Condition x Session interactions. The estimated marginal means for these interactions are provided in Table 3. We followed up on the three-way interactions for both analyses by calculating bootstrapped (N=1000) 95% confidence intervals around the estimated pairwise differences between pre and post adaptation pointing errors (Figure 3). For both Prism Directions, the upper boundary of the 95% confidence interval for MSA shifts of the control participants were lower than the lower boundaries for the OLP shifts. In contrast, for both Prism Directions, the patient's 95% CIs for MSA shifts overlapped the 95% Cis for the OLP shifts. Furthermore, for both Prism Directions the 95% confidence intervals for the OLP shifts for patients and controls overlapped, whereas the upper boundary of the 95% confidence interval for the MSA shifts of the control participants were lower than the lower boundary for the MSA shifts of the patients.

Table 3. Estimated marginal means (EMMs) with bootstrapped (N=1000) confidence intervals (Cis) for endpoint errors (º) for manual straight ahead (MSA) and open-loop (OLP) pointing of control and patient participants before and after adaptation to contralesionally- and ipsilesionally-shifting prisms. Positive numbers indicate errors in the direction of the expected after-effect (i.e. the direction opposite to that of the prismatic shift).

	Contralesional shift			Ipsilesional shift		
Condition	EMM	Lower *CI*	Upper *CI*	EMM	Lower *CI*	Upper *CI*
Controls – Manual straight ahead						
Pre	-1.48	-4.16	1.20	0.13	-2.4	2.6
Post	1.62	-1.06	4.30	5.13*	2.64	7.62
Controls - Open-loop pointing						
Pre	0.44	-2.24	3.12	-1.23	-3.72	1.26
Post	7.35*	4.67	10.03	5.87*	3.38	8.36
Patients – Manual straight ahead						
Pre	-3.43*	-6.11	-0.74	0.79	-1.71	3.28
Post	3.09*	0.41	5.78	9.23*	6.73	11.73
Patients - Open-loop pointing						
Pre	0.11	-2.57	2.80	-1.05	-3.54	1.43
Post	7.17*	4.49	9.85	5.90*	3.41	8.39

* = 95% *CI* around the estimated marginal mean does not include 0.

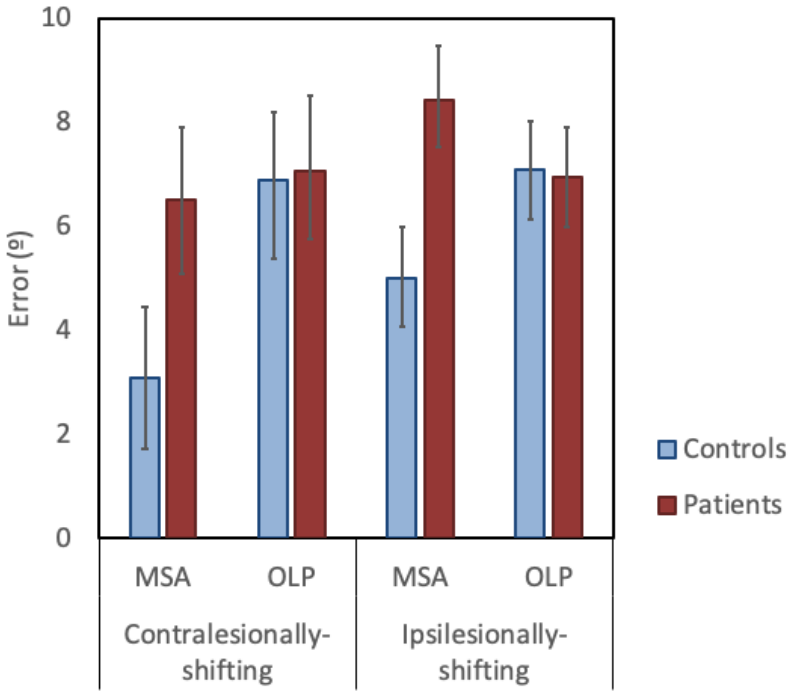

Figure 3. Estimated pairwise differences between pre- and post-adaptation endpoint errors (º) of control and patient participants for manual straight ahead (MSA) and open-loop pointing (OLP), separated by Prism Direction. Positive numbers indicate errors in the direction of the expected after-effect. Error bars indicate bootstrapped (N=1000) 95% confidence intervals.

At the suggestion of a reviewer, we investigated the trial-by-trial changes in pointing errors at the individual level to gain insights into whether the findings from our main analysis could be explained by differences in the rate of decay in after-effects, and to examine for differences across patients. We first collapsed the data across prism direction and plotted post-adaptation OLP and MSA errors by trial number for each participant. We then constructed linear fits (f(x)=ax + b) around the data (Figures 4 and 5). Each participant showed decreases in errors across trial number for both OLP and MSA. Such decays, even in the absence of visual feedback, have been taken to reflect the extent of consolidation of the after-effect (O'Shea et al., 2017). There were no significant group differences in the slopes (a) for either OLP (U = 15, Z = -.48, p = .63) or MSA (U = 15.5, Z = -.4, p = .69) errors, suggesting no differences in rates of decay of after-effects. For the constants (b), there were no significant group

differences for OLP (U = 13, Z = -.8, p = .42). For MSA, the constant was significantly larger for the patients (U = 5, Z = -2.1, p = .037), however this was no longer the case when we excluded one patient who had a particularly large MSA constant (L1; U = 5, Z = -1.8, p = .068).

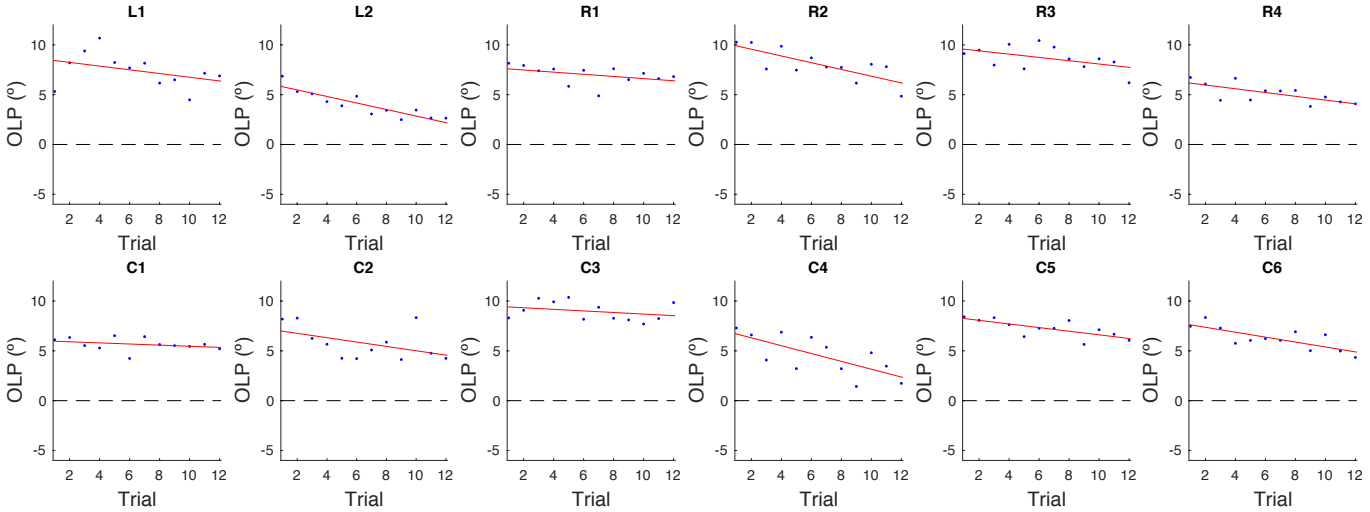

Figure 4. Linear plots of post-adaptation OLP errors for individual patients (top row) and controls (bottom row)

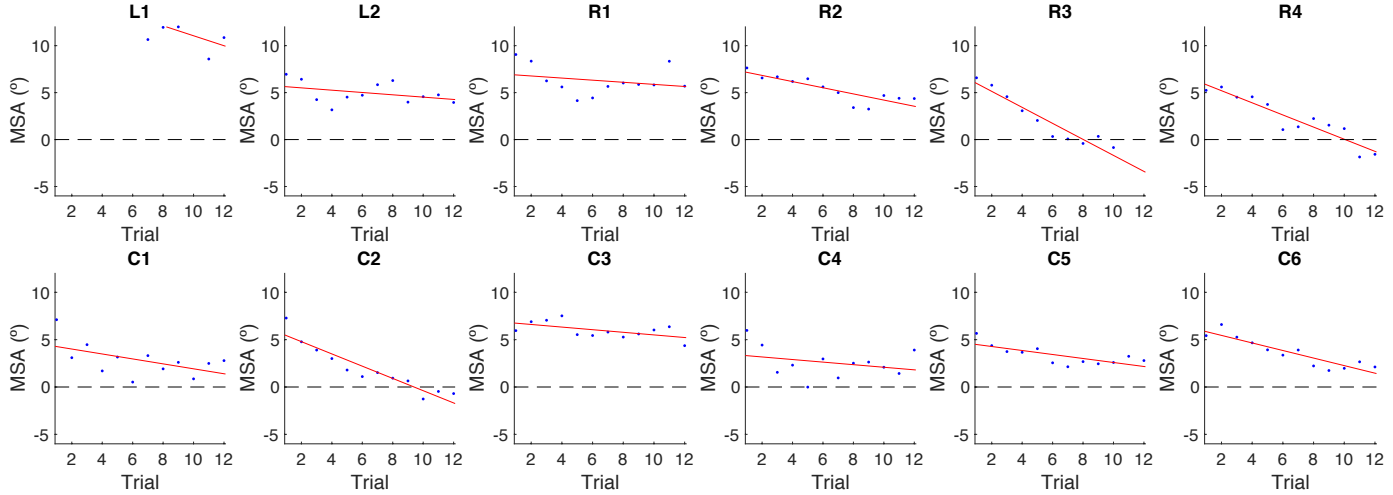

Figure 5. Linear plots of post-adaptation MSA errors for individual patients (top row) and controls (bottom row). For patient R3, the errors for trials 11 and 12 are visible outliers, and are based on only 2 and 1 trials, respectively, due to missing data. These were excluded from the linear fit.

4. Discussion

The aim of the present study was to examine the effects of IPS lesions on MSA and OLP after-effects following prism adaptation. Regardless of the direction of the prismatic shift, neurologically healthy participants showed smaller shifts in MSA compared to OLP in agreement with Wilkinson's (1971) additive model and previous research (Redding and Wallace, 2001, 2000, 1993; Sarri et al., 2008). At a group level, OLP shifts were not different between controls and patients, consistent with previous studies of OLP after-effects in patients with unilateral parietal lobe lesions (Weiner et al., 1983). In contrast, the MSA shifts of the patients were larger relative to those for the controls, and not different from patients' OLP shifts, suggesting that patients had enhanced proprioceptive adaptation. Slopes of the trial-by-trial decay in MSA and OLP after-effects were not different between the groups, consistent with previous evidence that the PPC is not important for after-effect consolidation (O'Shea et al., 2017).

The normal magnitude of patients' OLP shifts, combined with larger-than-normal MSA shifts, could mean that when the intraparietal cortex is unavailable, sensory-motor discrepancy is resolved through greater than normal realignment of limb proprioceptive relative to visual reference frames. We speculate that visual realignment involves the cortex surrounding the IPS, but that the mechanisms that update realignment of limb proprioceptive reference frames occurs through other brain regions (which were presumably undamaged in the patients in our study). Interestingly, Rode and his colleagues (2015) found that neglect reduction following a mild prism adaptation protocol was predicted by VSA, not MSA. This, along with the proposal that intraparietal cortex is important for neglect amelioration following prism adaptation (Striemer et al., 2008), suggests that the therapeutic benefit of prism adaptation could stem from visual realignment.

We considered, and ruled out, the possibility that the greater MSA shifts we observed could be attributed to the presence of residual neglect. Changes in OLP

errors shown by neglect patients tend to be within the normal range (Angeli et al., 2004a, 2004b; Bultitude et al., 2017; Facchin et al., 2020; Farnè et al., 2002; Frassinetti et al., 2002; Maravita et al., 2003; Rossetti et al., 2004). However, when neglect patients adapt to rightward- (i.e. ipsilesionally-)shifting prisms, the leftward shifts in MSA are frequently larger than those shown by control participants (Ferber et al., 2003; Pisella et al., 2002; Rode et al., 2001; Rossetti et al., 1998), and even larger than their OLP errors (Sarri et al., 2008; although see Rode et al., 2015). Since one manifestation of neglect is an ipsilesional deviation in MSA at baseline, the MSA shifts of neglect patients following prism adaptation are likely to reflect a combination of both the adaptation after-effect and neglect amelioration. In contrast, neglect does not impact baseline OLP accuracy (see Sarri *et al.*, 2008 for a comprehensive treatment of this topic). There are several reasons, however, that the larger-than-normal MSA shifts reported here could not be due to similar effects. First, neurological examination revealed no clinical signs of neglect or extinction in any of the patients in this study. Second, baseline MSA errors of the patients deviated from zero only in the contralesionally-shifting prism condition. This baseline deviation was in a contralesional direction (e.g. leftward deviation for a right-hemisphere lesioned patient) rather than the ipsilesional MSA bias that is typical of hemispatial neglect. Third, the patients showed an MSA shift for both Prism Direction conditions. Previous studies suggest that although patients with left neglect show larger-than-normal leftward shifts in MSA after adaptation to rightward-, ipsilesionally-shifting prisms, their MSA errors are unaltered by adaption to leftward, contralesional shifts (Luauté et al., 2012; Rossetti et al., 1998). We therefore conclude the larger-than-normal MSA shifts shown by our patients cannot be attributed to residual neglect.

The specific mechanism through which visual representations of space are updated, and that might be disrupted by damage to the IPS, is unclear. One possibility is that this could be to do with the way in which signals from the orbital muscles are used to encode and updated gaze direction information. Locating visual objects requires information about the position of the eyes within the orbit which, during dynamically shifting gaze, is gained primarily from corollary discharge (Guthrie *et al.*,

1983; Sommer and Wurtz, 2004; Wurtz and Sommer, 2004; see reviews Sommer and Wurtz, 2006, 2008a, 2008b; Wurtz, 2008). The neural mechanism of corollary discharge seems to be the presaccadic updating of receptive fields of eye movement neurons in the Frontal Eye Field (FEF; Sommer and Wurtz, 2004, 2006, 2008b; Wurtz and Sommer, 2004). It is thought that corollary discharge is maintained as a true representation of the position of the eyes in their orbits through on-going calibration against proprioceptive signals from the orbital muscles (Guthrie et al., 1983; Poletti et al., 2013; Steinbach, 1986). Wang and colleagues (2007) identified ocular proprioception neurons in area 3a of monkey somatosensory cortex. Although the precise neural mechanism of the calibration of corollary discharge from ocular proprioceptive signals is not known, they suggested that the calibration of corollary discharge might result from updating of parietal lobe signals based on information from these somatosensory neurons. The IPS is a likely area for the calibration of corollary discharge. Like the FEF, presaccadic spatial updating is also seen in monkey lateral intraparietal cortex (LIP), an area that is directly connected to the FEF, plays a role in selecting saccades towards salient stimuli (Duhamel et al., 1992a), and is thought to be homologous to the mid-posterior region of the human IPS (Culham and Kanwisher, 2001; Müri et al., 1996). One possibility is that lesions to the IPS could disrupt the calibration of corollary discharge, preventing any adjustment in visual reference frames that would normally occur during prism exposure. However, previous research has disputed the role of felt eye position in visual realignment during prism adaptation (Gilligan et al., 2019; Newport et al., 2009).

Our omnibus analysis suggested that there were differences in pointing error according to the direction of prismatic shift (i.e. the four-way Group by Session by Pointing Type by Prism Direction interaction term was significant). However, qualitatively, the direction of prismatic shift did not appear to make a difference to the patterns of MSA and OLP shifts for patients versus controls (Figure 3). Therefore, our results do not provide further support for hemispheric lateralisation of neural networks underlying adaptation to different prism directions.

A limitation of our study is that we did not directly measure the visual component of the after-effect, for example by recording VSA judgements. We only inferred the relative extents of visual and limb proprioceptive realignment by comparing MSA shifts to OLP shifts. Some prism adaptation studies in which all three measurements were recorded have not found that OLP shifts equate to the sum of VSA and MSA shifts (e.g. Facchin et al., 2020; Ferber and Murray, 2005; Gilligan et al., 2019; Girardi et al., 2004), which could call into question the validity of inferring visual shift from MSA and OLP shifts. However, these failures to fit with the additive model could also be due to inconsistencies in how VSA was measured. The larger MSA errors shown by patients in our study can be interpreted as evidence of greater proprioceptive realignment. However, without a direct measure of visual shift, our interpretation of our findings as also being related to a decrease in visual shift can only be tentative. Future research could improve on our study by measuring VSA, MSA, and OLP in people with IPS lesions before and after prism adaptation.

The cortex neighbouring the IPS is often spared in patients with neglect, and has been put forward as potentially critical area for the therapeutic effects of prism adaptation (Sarri et al., 2008; Striemer et al., 2008). The results of the present study demonstrate that when patients with IPS lesions adapt to prisms, the resulting shifts in MSA (a measure of limb proprioceptive shifts only) are not significantly different to the shifts in OLP (a measure of the total shift in both visual and limb proprioceptive references). This suggests that lesions to the IPS lead to enhanced realignment of proprioceptive representations, and realignment of visual representations might be impaired.

Data Statement

The data are available for download from the Mendeley Data repository.

Acknowledgements

We thank Dr Robert McIntosh for providing the custom MiniBIRD software, Muriel Panouilléres for her comments on an earlier version of this paper, and the patients and control participants who generously volunteered their time. JHB received financial support from the British Federation of Women Graduates

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