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Behind the Lens
Sensorimotor and Cognitive After-effectsof Prism Adaptation

Gilligan, Therese

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Behind the Lens: Sensorimotor and Cognitive After-effects of Prism Adaptation

Therese M. Gilligan

School of Psychology
Bangor University

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Summary

Over a century of research into prism adaptation (PA) has provided many insights into general sensorimotor functions including plasticity and the role of prediction. More recently, the therapeutic value of PA for conditions relating to right hemisphere dysfunction such as hemispatial neglect, and to body schema related conditions such as complex region pain syndrome, have generated a wealth of new knowledge – and more questions (**Chapter 1**). This thesis examines a cross-section of PA effects: sensorimotor adaptation in healthy participants and cognitive after-effects in a neurological population as well as a group of participants with a virtual lesion. **Chapter 2** reports that PA does not induce an after-effect shift in a visual straight-ahead judgment task, while it does induce after-effects in other tasks which are attributable to a change in state estimates of eye position in the orbit. The results suggest that PA prompts complex changes within ocular proprioception and indicate that the assumption of linear additivity of PA sensorimotor after-effects is a concept requiring re-examination. An increase in priming following both right-shifting and left-shifting PA in patients with a left hemisphere lesion provides a first demonstration of the rehabilitative potential of PA for left hemisphere dysfunctions. Intriguingly, this result also widens the possible candidate mechanisms through which PA facilitates cognitive after-effects (**Chapter 3**). Finally, this thesis explores the potential influence of the cerebellum in the cognitive after-effects of PA (**Chapter 4**). It reports, for the first time, that neurodisruption of the right cerebellar hemisphere increases and left cerebellar stimulation decreases word association priming. The results indicate that the two cerebellar hemispheres conjointly schedule the facilitation and inhibition of associative priming. Taken together, the novel findings reported here suggest that previous theoretical stand-points need to be revised and provide a new framework for understanding the relationship between sensorimotor adaptation, cerebellar function and hemispheric interactions in human cognition.

Glossary of Terms

ACC	anterior cingulate cortex
AVM	arteriovenous malformation
CI	confidence interval
CNS	central nervous system
CT	computerised tomography
DBS	deep brain stimulation
DTI	diffusion tensor imaging
EMP	eye muscle potentiation
EOM	extra ocular muscles
ERP	event related potentials
FAS	forward association strength
fMRI	functional magnetic resonance imaging
IFG	inferior frontal gyrus
IHI	inter-hemispheric inhibition
IPL	inferior parietal lobe
IPS	intra-parietal sulcus
L-PA	left-shifting prism adaptation
L-SOA	long stimulus onset asynchrony
LDT	lexical decision task
LH	left hemisphere
LIPv	ventral lateral intra-parietal
M1	motor cortex
MCA	middle cerebral artery
MIP	medial intra-parietal
OLP	open loop pointing
PA	prism adaptation
PET	positron emission tomography
PICA	posterior inferior cerebellar artery
PMv	ventral pre-motor
PPC	posterior parietal cortex
pSTG	posterior superior temporal gyrus
R-EMP	rightward eye muscle potentiation
R-PA	right-shifting prism adaptation
rCBF	regional cerebral blood flow
RH	right hemisphere
RT	reaction time
rTMS	repetitive transcranial magnetic stimulation
S-SOA	short stimulus onset asynchrony
SA	sham adaptation
SAP	straight ahead pointing
SCA	superior cerebellar artery
SOA	stimulus onset asynchrony
SPL	superior parietal lobule
STG	superior temporal gyrus

STS	superior temporal sulcus
TBS	theta-burst transcranial magnetic stimulation
TPJ	temporo-parietal junction
Vim	ventral intermediate nucleus (thalamic)
VSA	visual straight ahead
WAP	word association priming

Chapter 1
General Introduction

1.1 Prism Adaptation

The signals received by the body's senses come in different formats (e.g., air waves, light waves), from many locations and are subject to different distortions (e.g., retinal curve in vision). These signals are transformed allowing the information they contain to be synthesised, shared, and spatially aligned between the senses allowing functional goal directed behaviour (Newport & Schenk, 2012; Redding & Wallace, 2006). For example, when we hear a sound to our side we know by how much to turn our head and to move our eyes to visually locate that sound.

Prism glasses disrupt this synchronicity. Light passing through wedge -shaped prisms is displaced in a set orientation such that the location of a seen object may appear closer, further away, left, or right of its actual location. The prism wearer's visual experience is similarly moved in the direction on the displacement (Rossetti et al., 1998).

The healthy individual upon first wearing prism goggles is surprised to discover that she cannot accurately point to an object at which she is aiming (Michel et al., 2003). During visually guided pointing the arm is set to function in tandem with the eyes' co-ordinates, but the eye now foveates a location shifted in the direction of the prism and away from the actual location of the object. The prism-shifted vision, thus, results in a pointing action that is also shifted in the direction of the displacement and the target object is missed (Newport & Schenk, 2012).

The initial pointing errors while wearing the prism goggles are called direct-effects of prism adaptation (PA). The healthy individual normally succeeds in touching the object within a few trials (typically <10). However, when the prisms are removed the same movement will result in a pointing error in the opposite direction, the adaptation after-effect (figure 1.1). The adaptation process is conventionally described as consisting of two elements: strategic recalibration and spatial realignment (Newport & Schenk, 2012; Redding & Wallace, 2006).

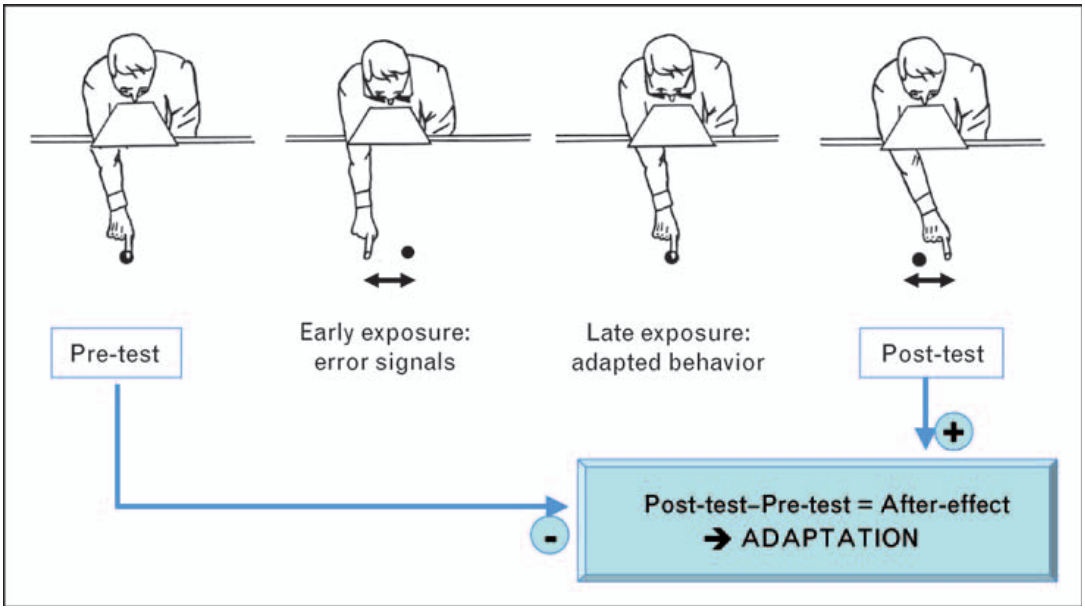


Figure 1.1. Before wearing prisms participants can accurately point to a visual target (pre-test). With the prisms in place, pointing errors are made initially in the direction displacement (early exposure). Repeated pointing results in reducing errors and finally accurate pointing (late exposure). When the prisms are removed, the same pointing action results in a pointing error in the opposite direction (post-test), a sensorimotor after-effect. From "Prism adaptation in the rehabilitation of patients with visuo-spatial disorders", by L. Pisella, G. Rode, A. Farnè, C. Tilkete, Y. Rossetti, 2006, *Current Opinion in Neurology*, *19*, p.536.

Strategic recalibration uses visual feedback of the error. It is partly a conscious effort requiring deliberate reaching in the *wrong* direction i.e., away from the (displaced) location specified by the eyes and toward the actual location. The prism wearer must calculate at each trial how much to 'misreach' or 'side-point' to accurately reach the target. With full visual feedback of the arm trajectory and a sufficiently slow movement the error can be eliminated in one move (Newport & Schenk, 2012; Pisella, Rode, Farnè, Tilikete, & Rossetti, 2006). This deliberate process can be disrupted by adding cognitive load such as solving maths problems (e.g., Redding, Clark, & Wallace, 1985; Redding & Wallace, 1985). While strategic recalibration is a part of the process, it is not the driving one. Adaptation can take place without conscious awareness of any error, such as seen when the prism displacement is gradually and incrementally introduced (Michel, Pisella, Prablanc, Rode, & Rossetti, 2007). Participants who are instructed to adapt by side-pointing cannot sustain this approach and end up making larger errors that reveal that the second process, spatial realignment, is dominant (Mazzoni & Krakauer, 2006).

This second process, spatial realignment, is unconscious and unfolds more gradually. Spatial realignment reflects a reorganisation of the coding or of the relationship between visual, proprioceptive and motor signals that serves to reduce the sensory-motor conflict created by the prism (Newport & Schenk, 2012; Pisella et al., 2006). Given the depth of recoding involved in spatial realignment, at least fifty pointing trials are required to elicit it in healthy adults. At this point, upon removing the prisms and pointing to the same object the person will miss in the opposite direction: the person's spatial co-ordinates are aligned for prism conditions. This is called the indirect or after-effect. These unconscious adjustments, i.e., 'out of sync' interactions becoming 'in sync' as needed, have been characterised as observable neural plasticity (Newport & Schenk, 2012).

The main sensory signal considered to adapt to prism perturbation is proprioception (Redding, Rossetti, & Wallace, 2005). Proprioceptors are specialised sensory receptors that are located within joints, muscles, and tendons. Being sensitive to both tension and length, these receptors relay information concerning muscle dynamics to the central nervous system (CNS). Importantly, for current purposes, they provide information regarding the position of the effector in space. Within the skeletal muscles there are two types of receptors called muscle spindles. Primary muscle spindles send the brain information regarding the speed and size of a muscle length change. Secondary muscle spindles relay a slower signal regarding length information only and, are thus involved with position sense. The receptor within the tendons, golgi tendon organs, are located in tendons near the myotendinous junction. They are attached end to end with extrafusal muscle fibres, the main power producing fibres of the muscles. This description of proprioceptors is relevant for skeletal muscles only.

The proprioceptors of the eye muscles are unusual and somewhat controversial. The uniqueness of ocular non-twitch muscle fibres (a fatigue resistant muscle fibre that does not release action potentials and is not found elsewhere in the human body) and the relatively recent identification of palisade endings (in turn unique to these muscle fibres) have slowed down understanding of their role. Likewise, not only do the extra-ocular muscles lack Golgi tendon organs that have a clearly established proprioceptive role in the rest of the body, but they have their own unique muscle spindles that are found on twitch muscles. The uniqueness of human extra-ocular muscle receptors has created conflicting views around the usefulness of

each type of receptor and even whether they do have a sensory role (e.g., some eye muscle spindles have no innervation). However, the layering and compartmentalisation of the muscle fibres, and the richness of their innervation, suggest a need within the CNS for accurate and detailed afferent feedback (Bruenech & Kjellevold Haugen, 2015; Büttner-Ennever, 2007)

As a result of the change in proprioception provoked by PA, the other signal that gets amended is the motor command. In this case it is information flowing from the brain to the effector(s). If, following adaptation, the brain judges the signals coming from the muscle to relate to a different part of space (e.g., the arm is in objective position A but it is now considered to be in position A - 3°), then the motor command to move the muscle will take that into account (e.g., it is no longer moving from A to B but from A – 3° to B, movement distance is different). Depending on the adaptation paradigm, a motor adaptation or directional motor bias, may occur, this is independent of proprioceptive adaptation *per se*. Nonetheless, an element of motor adaptation may evolve alongside proprioceptive adaptation regardless of the paradigm.

The adaptation after-effect, that is spatial realignment, is conventionally measured using three tests commonly called the visual shift, the proprioceptive shift, and the total shift or negative after-effect. These tests are taken following removal of the prisms. The "visual shift" is commonly measured by asking participants to verbally indicate when an object moving across their visual field is directly in front of their body midline. This visual straight-ahead (VSA) test is understood to capture the induced change/altered perception in the visual system. This shift is in the direction of displacement, i.e., if the prism displaces the image leftwards, the VSA after-effect is to the left. That is, for example, after adapting to rightward refracting prisms, a visual target that is objectively located straight ahead is reported to be to the right of straight ahead. The "proprioceptive shift" is most often tested by asking participants to point with eyes closed or while blindfolded straight ahead of their body midline (in front of their nose). This straight ahead pointing (SAP) test is a measure of a change in limb proprioception i.e., perception of the position of the arm relative to the shoulder/trunk or the head/trunk depending on whether the adaptation paradigm did, or did not, permit movement of the head respectively. SAP captures a shift opposite to the direction of displacement. Finally, the combination of these two changes is understood to be represented by the total shift. This measurement requires the

participant to point to a visual target with their unseen hand, i.e., without visual feedback of their performance. Thus, this open loop pointing (OLP) test, that shows a shift opposite the direction of displacement, is thought to separately capture both the visual and proprioceptive shifts at the same time. All the measures are signed according to the direction of after-effect shift; positive/negative signs indicate a rightward/leftward shift respectively.

That OLP is conventionally understood to capture the total adaptive shift is construed as linear additivity. This states that the change captured by OLP is approximately equal to the sum of the changes of the other two independent tests: OLP = SAP – VSA (Redding & Wallace, 1978, 1988; Wilkinson, 1971). This is the predominant understanding of the sensorimotor changes invoked by PA (Redding et al., 2005). However, it has been criticised as being somewhat simplistic (Facchin, Mornati, Peverelli, Bultitude, & Daini, 2017; Hatada, Rossetti, & Miall, 2006) and indeed some researchers have not always found additivity (Bornschlegl, Fahle, & Redding, 2012; Facchin et al., 2017; Ferber & Murray, 2005; Fortis, Ronchi, Calzolari, Gallucci, & Vallar, 2013; Girardi, McIntosh, Michel, Vallar, & Rossetti, 2004).

Two processes difficult to disentangle from the output of spatial realignment, and thus described as "hidden" within it, are: Use-dependent plasticity and operant reinforcement. Use-dependent plasticity characterises the phenomenon whereby repetition of an action results in future movements being directionally biased towards that action, whereas, operant reinforcement refers to an association of the adapted movement with successful (error-free) behaviour (Huang, Haith, Mazzoni, & Krakauer, 2011; McDougle, Ivry, & Taylor, 2016). These processes may lie behind over-additivity (when OLP > SAP – VSA). Over-additivity has previously been attributed to use of a single target location (in contrast to procedures that vary the location of the target from trial to trial) during prism exposure and during OLP testing. Over-additivity due to a single target during exposure has been labelled as a motor learning, whereas over-additivity due to a single target during both exposure and OLP has been labelled as a cognitive cue (Redding & Wallace, 1978).

In summary, prismatic shifts in the perceived location of a visual target disrupt the smooth coordination between the eye and hand that is essential for effective behaviour. The direct effect of this disruption is observable through pointing errors under exposure to prisms. Prism adaptation describes the process that returns

harmony to the eye-hand system. It commences with a partly conscious error-correction step, or side-pointing, and evolves into a second unconscious mechanism that reorganises the coding of visual, proprioceptive and motor reference frames. The first step is known as strategic recalibration and the latter as spatial realignment. After removal of the prisms, adaptation is measured with after-effect tests, most commonly, the visual straight-ahead (VSA), straight-ahead pointing (SAP), and open loop pointing (OLP) tasks. The concept of linear additivity in PA is defined as OLP = SAP – VSA.

1.2 Cognitive After-effects of Prism Adaptation

Interest in prism adaptation (PA) has grown following the seminal finding that it may have rehabilitative value for those suffering from left neglect, a common debilitating syndrome caused by right hemisphere lesions (Rossetti et al., 1998). Subsequent to that study researchers reported PA-invoked improvements, described as spatial cognitive after-effects, in a variety of neglect symptoms including: postural stability (Tilikete et al., 2001); wheelchair navigation (Jacquin-Courtois, Rode, Pisella, Boisson, & Rossetti, 2008); visual search (Saevarsson, Kristjánsson, Hildebrandt, & Halsband, 2009; Vangkilde & Habekost, 2010); leftward ocular exploration (Angeli, Benassi, & Làdavas, 2004; Serino, Angeli, Frassinetti, & Làdavas, 2006); and left directed voluntary attention (Nijboer, McIntosh, Nys, Dijkerman, & Milner, 2008). The same PA procedure produces after-effects that spread to other sensory domains e.g., touch (Maravita et al., 2003), pressure sensitivity (Dijkerman, Webeling, Ter Wal, Groet, & Van Zandvoort, 2004), and audition (Jacquin-Courtois et al., 2010); to mental imagery (Rode, Rossetti, & Boisson, 2001); and to tasks that do not utilise lateralised spatial cognition (Bultitude, Rafal, & List, 2009). Intriguingly, PA can produce cognitive after-effects in healthy people that simulate neglect-like behaviour (Bultitude & Woods, 2010; Colent, Pisella, Rossetti, Bernieri, & Rode, 2000; Loftus, Vijayakumar, & Nicholls, 2009; Michel et al., 2003).

Although the understanding of PA's mechanism of operation is incomplete, its use as a research tool is helping to enhance knowledge of various syndromes - predominantly neglect (Newport & Schenk, 2012; Pisella et al., 2006), but also complex regional pain (Bultitude & Rafal, 2010; Torta, Legrain, Rossetti, & Mouraux, 2016), bodily awareness and physiological processes (Calzolari, Gallace, Moseley, & Vallar, 2016); autism (Carmody, Kaplan, & Gaydos, 2001; Gidley

Larson, Bastian, Donchin, Shadmehr, & Mostofsky, 2008); developmental disorders (Brookes, Nicolson, & Fawcett, 2007; Krab et al., 2011); schizophrenia (Bigelow et al., 2006) and gait initiation in Parkinson's disease (Bultitude, Rafal, & Tinker, 2012).

1.3 Internal Models: Sensorimotor Integration and Adaptation

Cognitive after-effects, while interesting and important, are knock-on effects of PA. The immediate function of adaptation is to produce behaviour that is adaptive to a change in sensorimotor contingencies and which achieves smooth and effortless, effective and useful behaviour. That is, it is aiming to reproduce the everyday skill of coordination, between the senses and between the senses and action, that allows frequent tasks, such as visually guided reaching, to appear seamless and automatic. An internal model is a concept that describes the predictive processes underlying everyday actions that support such automatic behaviour. Prism exposure creates the trigger for the formulation of a new internal model or guide to interacting with the world.

The aim of internal models is a perfect mapping between what is desired (a movement goal) and what is achieved (the sensory feedback of that goal). Discordance between what is expected and what is achieved creates the necessary condition for the learning of a new internal model (Huang et al., 2011).

Within internal models, the sensorimotor loop governing behaviour employs three main elements: A specification of the actions required to achieve a goal given the state and context, a specification of the changes in the state given those actions, and finally a prediction of the sensory feedback expected upon completion of the goal (Wolpert & Ghahramani, 2000). That is, the inverse model, the forward dynamic model and the forward sensory model respectively, i.e., different types of internal models. In time terms it is: before, during, and after an action. State refers to such things as the position and speed of the limb (i.e., the activations of its muscle groups), which change continuously over time, whereas context, which usually changes more slowly, refers to elements such as the object being acted upon or the mass of the limb (Wolpert & Ghahramani, 2000).

These models provide advantages such as: 1) overcoming the problem of delays in receiving sensory feedback: the outcome is already predicted; 2) affording ownership of action: the motor outflow (efference copy) is used to cancel out sensory effects of the action (reafference); 3) supporting learning and action selection: the

difference between the actual and desired sensory outcome of a movement can be inputted as an error in the motor command thus providing an update/learning signal. Likewise, simulation of the action and its predicted outcome affords better decision making between actions; and 4) improving accuracy of state estimation: Through combining the predicted state with reafferent sensory correction (Wolpert, Ghahramani, & Jordan, 1995).

The Bayesian probability computations, used as a framework to investigate these models, incorporate and compare uncertainty relating to noise in sensory and motor signals, knowledge from experience (the prior), and the sensory and motor feedback (the likelihood) (Körding & Wolpert, 2006). Notably, from the perspective of PA, that the central nervous system may approach adaptive problems in this way assumes that multiple predictive models work in parallel to test a set of context driven hypotheses.

Using all available sensory signals is always optimal because their total variance or error will be less than taking a signal in isolation (Ernst & Bülthoff, 2004; Wolpert, 2007). However, how information from the different modalities is integrated is determined by probabilities relating to the reliabilities of each of the various available signals in that moment. Increasing noise or uncertainty will down-weight the reliability of one signal compared to another or of the feedback to the prior. For example, removing prescription glasses or wearing gloves will down-weight the reliability given to vision and touch respectively. The difference in after-effects elicited dependent on the type of feedback available during PA also illustrates this point. When the last half of the arm movement is visible (concurrent feedback), limb proprioception (SAP test) adapts more than vision (VSA test). Notably though, when visual information is rendered less reliable, through restricting visual feedback to the tip of the finger at the completion of the movement (terminal feedback), it tends to adapt more than limb proprioception (Herlihey, Black, & Ferber, 2012).

The likelihood and priors are combined in a dynamic manner to make an optimal estimate and to minimise cost or maximise utility and desirability. In terms of movement this is often defined as precision or accuracy in achieving the desired goal (Körding & Wolpert, 2006). A key feature of this optimal feedback control is that errors are selectively corrected or ignored depending on whether they will influence outcome – the minimum intervention principle (Scott, 2004).

McGuire & Sabes (2009) proposed that, in order to optimally use sensory information it is transformed into multiple reference frames, with the choice of one reference frame for action made on the relative reliabilities. This fits with the neurophysiological evidence of a variety of mixed spatial representations in the reach planning network, a more retinotopic version in the parietal cortex and a more hand or body centred one in the frontal cortex. (Others, however, have argued that it is transformed and combined into a single common reference frame (e.g., Cohen & Andersen, 2002).) Alongside this is new evidence that, in the face of goal uncertainty or the possibility of several action options, multiple competing sensorimotor control policies (forward models) are generated prior to implementing just one of them (Gallivan, Logan, Wolpert, & Flanagan, 2016). The additional processing that this requires may, in part, explain the initial hesitation that is commonly observed when people start pointing during early prism exposure – in the face of uncertainty multiple possible responses are produced and compared.

For sensory signals to be integrated, it must be clear to the system that they relate to the same event, i.e., that there is no, or at least little, temporal or spatial discrepancy. In cases where the discrepancy is too large and falls outside of a tolerance limit for integration, a discrepant source may be discounted instead of integrated (Banks & Backus, 1998; Ernst & Bülthoff, 2004). If the discrepancy is within a tolerance limit, an adaptation or recalibration[1] will occur to resolve the conflict. Notably, for this to occur, the system has to keep access to the individual (i.e., non-integrated) estimates (Ernst & Bülthoff, 2004).

That is, up or down weighting a signal, based on its reliability, to achieve sensorimotor integration is not the same as sensory recalibration (spatial realignment). See figure 1.2. However, both recalibration and a change in signal reliability weighting may take place in adaptation. In support of this is the finding that the senses are never actually aligned, and that everyday integration is based on the optimal use of unaligned sensory information. This explains the observed systematic drift in pointing to objects with the unseen hand (Smeets, van den Dobbelsteen, de Grave, van Beers, & Brenner, 2006).

[1] Confusingly, in the sensorimotor literature the term recalibration is equivalent to spatial realignment in the PA literature.

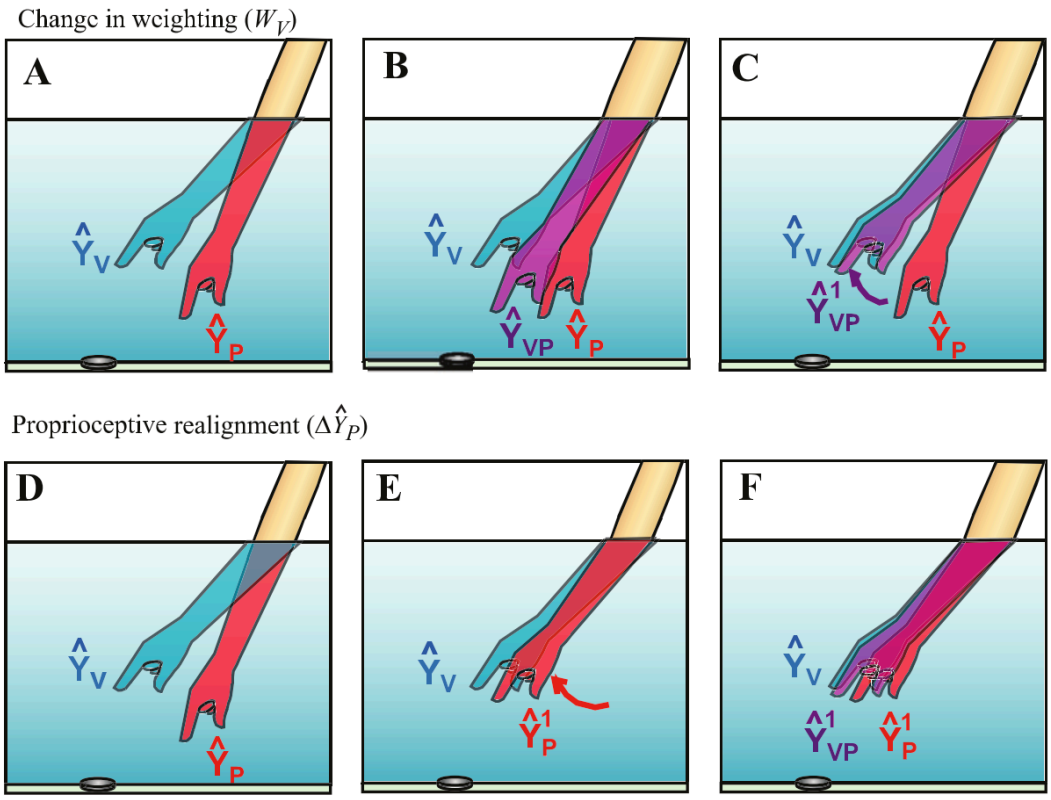


Figure 1.2. A) & D) Looking through water to pick up a coin, the water refracts the light such that the hand looks (Y_v) and feels (Y_p) in two different places. The top row describes adaptation achieved through reweighting alone during sensorimotor integration. B) Weighting and integrating theses estimates as they are (Y_{vp}) will result in missing the coin. C) Up-weighting the visual estimate will result in a more accurate movement (Y^1_{vp}). Alternatively the brain can adapt through re-alignment, E) the brain could re-align proprioception brining it closer to vision (Y^1_p). F) When these estimates are then integrated accurate reaching is achieved (Y^1_{vp}). From "Sensory weighting and realignment: independent compensatory processes" by H.J. Block & A.J. Bastian, 2011, Journal of Neurophysiology, 106, p.60.

Block & Bastian (2011) provided evidence that while sensory integration and realignment both make use of signal reliability, they are independent processes, either of which can be used solely or in combination to compensate for sensory discrepancies. In a study where the prisms were introduced so gradually that the participants did not notice, it had previously been shown that spatial realignment can take place without the sensory recalibration step (Michel et al., 2007). However, the Block & Bastian (2011) study demonstrated the independence of the two processes by showing that realignment may take place independently of weighting (i.e., the lowest weighted may not necessarily realign the most). This was found by comparing the results of two scenarios: one where a visual-proprioceptive conflict was introduced

but endpoint feedback was given such that the participant would regard vision as most reliable, and another scenario where no feedback was given. Re-weighting in sensory integration has the advantage of speed while the slower process of realignment has the advantage of preserving information from each signal. Therefore, context is important. The availability of two separate biological processes provides behavioural flexibility.

While the processes are independent, optimally, spatial realignment (sensorimotor recalibration) will make use of reliability signals. It is known that proprioception is more reliable for depth judgements and vision for (lateral) direction judgements. van Beers, Wolpert, & Haggard, (2002) elegantly demonstrated that the modality weighted most adapts the least. Their paradigms consisted of adaptation to a gradually increased displacement in either depth (forward) or direction (leftward) in different sessions. Before and after each adaptation type participants were asked to make independent proprioceptive and visual judgements. The researchers showed that following lateral adaptation a smaller visual adaptation (after-effect) was apparent compared to a limb proprioception after-effect. The opposite was true when the perceptual judgements were conducted following depth adaptation. Then, limb proprioception after-effects were smaller than visual after-effects.

The use of reliability signals during adaptation has also been demonstrated in other modalities. Burge, Girshick, & Banks (2010) used an adaptation paradigm that created a conflict between vision and haptics through manipulating the perceived slant of an object's surface. Importantly, at baseline, an estimate was made of each participant's visual and haptic reliabilities. After-effects revealed that when vision was more reliable haptics adapted to match vision, and when vision was less reliable vision adapted to match haptics. These vision/proprioception and vision/haptics examples support the contention that access to the individual (un-integrated and unaligned) estimates are retained following adaptation (Ernst & Bülthoff, 2004).

The final element of PA, and of internal models, is the motor command. This is also called reach adaptation or motor learning and refers to the tendency of the effector to continue to be influenced directionally by the adapted movement (Redding & Wallace, 2006). The source of this adaptation is the error signal that arises due to the mismatch between the desired and achieved movement in terms of goal outcome (e.g., hitting a target). It has been shown that reach adaptation occurs independently of proprioceptive realignment and that the errors detected within one system are used or

made available to the other system. Therefore both signals may independently spur adaptation (Cressman & Henriques, 2015). Within PA literature the limited focus that has been given to the motor element has been discussed in terms of the arm, adaptation of oculomotor commands has received even less attention to date. Nonetheless, there is a broad literature on saccadic adaptation (Pélisson, Alahyane, Panouillères, & Tilikete, 2010).

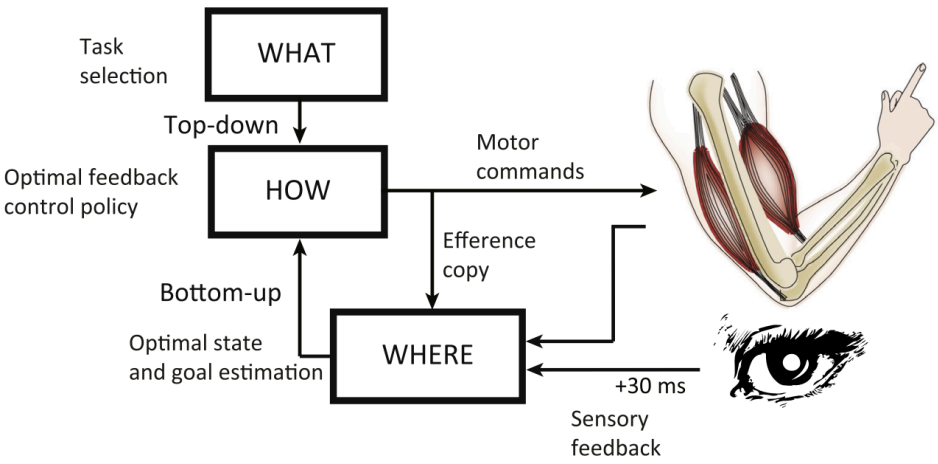


Figure 1.3 The CNS combines afferent information (cutaneous, proprioceptive, visual) with a copy of the motor command to make an estimate of a motor effector's (limb) position in space. This information is combined with the goal instruction to produce a successful movement. From " A functional taxonomy of bottom-up sensory feedback processing for motor actions", by S.H. Scott, 2016, *Trends in Neuroscience, 39*, p. 514.

To sum up, prism adaptation is achieved through the formulation of new internal models, or predictive processes, that code the relationship between visual and proprioceptive inputs; between those inputs and motor outputs; and between motor output and sensory feedback (see Figure 1.3). This data-heavy cycle requires access to the trustworthiness and reliability of the different pieces of information in order for them to be usefully combined. Some of this information comes from interaction with the current environment and context (sensory and motor feedback), and some of it is stored knowledge that has built up over time (e.g., signal delays). In cases of sensory perturbation, the most trustworthy and most reliable information is the most useful, and is therefore most likely to be incorporated into a new prediction with the least amount of change and vice versa. Trustworthiness may be understood as the relative availability of information, e.g., the difference between the proportion of visual information supplied during concurrent feedback (most of arm trajectory is visible)

compared to during terminal feedback (only the finger is visible at end of movement). Reliability refers to the general performance or usefulness of a sensory signal under different conditions (e.g., vision is less reliable than audition in the dark).

1.4 Neural Correlates of Internal Models and Sensorimotor Integration

Much research attention has focused on the neural substrates of internal models. This work points to the vital role played by the cerebellum in generating and updating predictions about on-going motor and sensory interactions (Baumann et al., 2015). The relatively uniform neuronal circuits throughout the cerebellum facilitate a unique type of synaptic plasticity called long-term depression (a type of memory learning). An error signal, e.g., a discrepancy between an actual and intended movement, arrives at a Purkinje cell of the cerebellum via a climbing fibre. This signal produces complex spikes. Long-term depression of those complex spikes is achieved through repeated behavioural attempts at minimising the error. This cerebellar synaptic learning or memory formation is the key to internal models and in turn the ability to adapt. Ultimately an internal model assists the brain in performing a movement precisely without the need to refer to dynamic feedback from the moving body part, i.e., to perform skilfully and seemingly intuitively (Ito, 2000, 2008).

The structures that send the command signals for a movement and receive the sensory feedback of it are cortical and sub-cortical. Many of these areas form closed loops with the cerebellum, and indeed closed loop circuits have been deemed the major functional unit of cerebro-cerebellar circuitry (Middleton & Strick, 1998). Visually guided reaching is an everyday activity that requires sensorimotor integration and is thought to involve the medial intraparietal sulcus, the dorsal premotor cortex and the medial occipito-parietal junctions (Culham & Valyear, 2006). The ventral portion of the cerebellar dentate nucleus has been posited to deal with cognitive and visuospatial functions and is connected to the prefrontal and parietal cortices whereas primary motor and premotor cortices form a loop with the dorsal dentate nucleus (Dum & Strick, 2003). See figure 1.4 for an example of the richness of the cerebellar network (it does not show network loops).

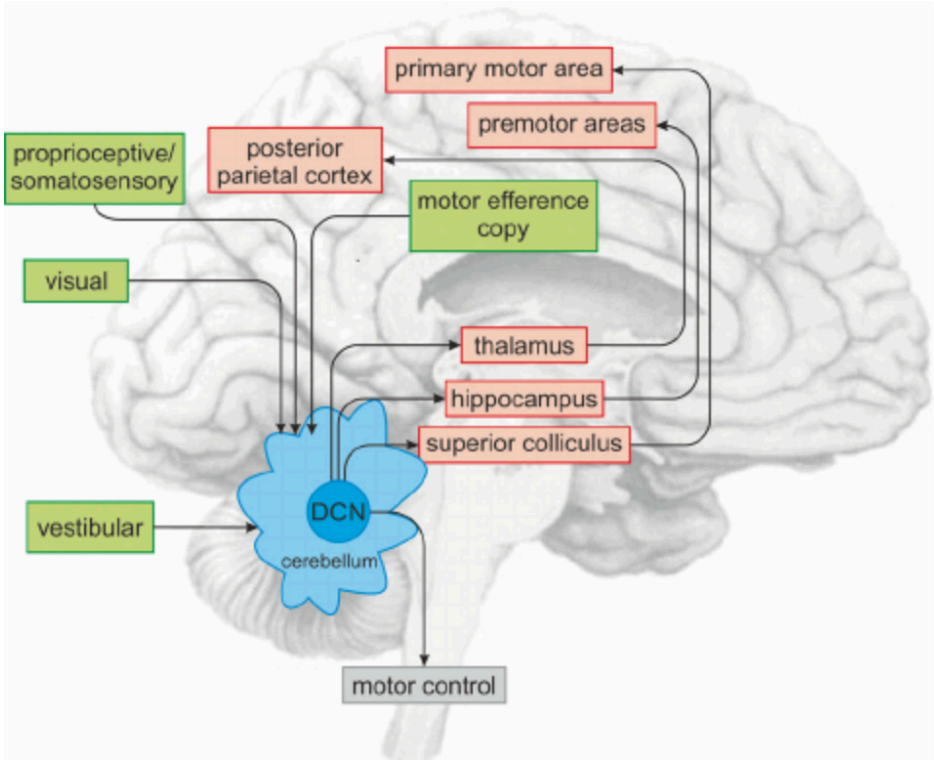


Figure 1.4. Multiple sensory system information (e.g., green boxes) and copies of the motor command (motor efference) is integrated by the cerebellum. Ascending projections of cerebellar output neurons connect with the thalamus, hippocampus, and superior colliculus, which in turn connect to numerous cortical areas. From "Consensus paper: The role of the cerebellum in perceptual processes", by O. Baumann et al., 2016, Cerebellum, 14, p.207.

Therefore, internal models constitute a general framework for understanding information integration; system monitoring; learning; prediction, and behavioural adaptability. PA is a particular instance of an internal model and will thus invoke its own particular pattern of neural processes. More accurately, each particular paradigm of PA and the specific context within which it takes place will have its own neural footprint. The next sections review the neural correlates of early and late PA, evidence from neuropsychological studies, and recent evidence of the neural consequences of PA i.e., the cognitive after-effects.

1.5 Neuroanatomy of Prism Adaptation

Investigating the neural mechanisms of PA with scanning methods presents challenges related to conducting the adaptation in a confined space, and minimising head movements. Additionally, whereas strategic recalibration, or error correction, is

said to precede spatial realignment, they can interfere with each other and overlap. It takes a long time, at least 50 pointing movements, for spatial realignment to be established and this presents a challenge specific to scanning studies. Overall, the challenges have hindered the neural investigation of PA in terms of number of studies and the control of those studies (Bultitude et al., 2016). The result is that the imaging findings presented below are subject to the "first-look" limitations which often accompany pioneering studies.

1.5.1 Neural Correlates of Strategic Error Correction

Clower et al. (1996), in a positron emission tomography (PET) design, localised activation to the lateral intra-parietal sulcus (IPS), in the meeting area of the superior parietal lobule (SPL) and the inferior parietal lobule (IPL) contralateral to the pointing limb. This area is understood to contain intra-modal and inter-modal visual and somatosensory maps, suggesting that this area works under PA to re-coordinate vision and proprioception.

In an fMRI design using left-shifting prisms and the right hand, Luauté et al. (2009) found activation deemed to reflect strategic adaptation in the left supero-anterior bank of the parieto-occipital sulcus that increased as error-correction continued to improve. Correspondingly, activation in the left anterior IPS was correlated with error detection: as the size of the error decreased activity in the area decreased. Activity was also noted in the right SPL extending to the IPS. Activity localised in the right cerebellar lobules IV and V was ascribed to emerging realignment given its evolution.

Also employing a left-shifting prism and the right hand, Chapman et al. (2010) in an fMRI design found activity in the left posterior cerebellar, and right anterior cerebellar, right SPL and IPL (specifically the supramarginal gyrus along the anterior IPS). They found no PA related activity in the left cortex.

Kuper et al. 2014, exclusively investigating cerebellar contributions, identified activity that was exclusive to early phase or strategic correction in the right cerebellar cortex (lobules VIII and IX) and the ventro-caudal dentate nucleus. The ventro-caudal dentate nucleus is connected to the prefrontal and posterior parietal cortex (PPC) while lobule VIII receives mossy fibre input from the PPC. This led to the interpretation of a closed cerebellar-parietal loop for early stage error correction.

Event related potential (ERP) designs have localised early stage PA activity to the anterior cingulate cortex (ACC). These findings were interpreted as reflecting an unconscious internal online monitoring of the action command, and dopaminergic activity that may hold a specific value (related to error size) that guides behaviour toward accuracy (MacLean, Hassall, Ishigami, Krigolson, & Eskes, 2015; Vocat, Pourtois, & Vuilleumier, 2011). Interestingly, Arrighi et al. (2016) found theta activity that was only invoked by larger errors and tentatively implicated the ACC and the precuneus. They suggested that the frontal executive system (ACC/medial prefrontal cortex), becomes involved in error processing when a certain threshold is exceeded and that its involvement may be triggered by the cerebellum.

Given the relatively small number of studies, it is worth noting that similar patterns of activity have been observed in visuomotor rotation adaptation studies. In an fMRI study (Graydon, Friston, Thomas, Brooks, & Menon, 2005), the authors ascribed early bilateral parietal cortex activations that decreased over time to the acquisition of visuo-motor transformation, while increasing cerebellar and putamen activation was posited to reflect an emerging new internal model. A PET study (Inoue et al., 2000) likewise identified bilateral parietal areas (right SPL and IPL, left posterior SPL) and bilateral pre-motor cortex under early phase adaptation.

Thus, in the scanning studies, early stage activity accorded to recalibration has been isolated to the PPC (unilaterally by two research groups and bilaterally by another two) and to the cerebellum; whereas early stage activity accorded to emerging realignment was localised to cerebellar activity by three groups. The feasibility of early involvement of the cerebellum in *both* recalibration and realignment has since been demonstrated with evidence that both processes were slowed by inhibitory direct current stimulation of the cerebellum (Panico, Sagliano, Grossi, & Trojano, 2016). As for ERP studies, they have localised early stage activity to the ACC and precuneus that may reflect either monitoring of the sensorimotor process (the strategic correction element) or early indications that a realignment process needs to be, or is being, triggered.

1.5.2 Neural Correlates of Spatial Realignment

In their fMRI study, Luauté et al. (2009) noted activity bilaterally in the superior temporal sulcus (STS) extending into the superior temporal gyrus (STG) that they understood to be underpinned by sustained activity in the cerebellum. Given its

association with multi-modal input and cross-modal integration, the authors suggested a role in the STS and STG for both realignment and possibly for the spatio-cognitive after-effects of PA. Chapman et al. (2010), with left-shifting PA and right hand pointing paradigm, isolated realignment phase activity in the right posterior cerebellum and right IPL during fMRI. They suggested that the parietal areas are involved in the updating of cerebellar internal models.

Nagao, Honda, & Yamazaki (2013) used a memory trace model they developed to account for learning in visual reflexes and applied it to PA. Their model suggests that short-term memories created as adaptation progresses (30-40 trials) are formed at parallel fibre – Purkinje cell synapses in the cerebellar cortex and that the speed of memory formation may be due to the *parallel* involvement of cerebellar areas and cerebello-cortico loops (Nagao et al., 2013).

It is again worthwhile to consider results from the related field of rotational visuomotor adaptation. Tanaka, Sejnowski, & Krakauer (2009) conducted population-coding computational analysis to replicate psychophysical results and thus uncover the neuronal mechanisms underlying visuomotor adaptation. They concluded that adaptation is underpinned by changes in synaptic weights between sensory and motor areas. Their model identified narrow sensory directional tuning which, alongside clinical and imaging results, reduced the possible anatomical candidates to the PPC. Specifically, it was a match for the visually selective cells in area 7a of the PPC. The authors proposed that the originating signal for adaptation comes from a prediction error generated by the cerebellum. This signal is relayed to area 7a, and in turn its synaptic weights with neurons in the motor cortex are modified to reduce the prediction error, thus leading to a remapping between the reach trajectory in visual space and movement direction in hand space. The change in signal connection strength is manifest as increased neuronal activity in the motor and/or premotor cortex. In this account the forward model trains the inverse model (Tanaka et al., 2009).

In the Graydon et al. (2005) fMRI study of visuomotor rotation adaptation, ongoing cerebellar involvement was noted and a late increase in activation in the fusiform and superior temporal gyri was also observed. The temporal activity was proposed to reflect a reliance on higher level visual and visuo-spatial processing as participants refined their performance.

Overall, these results from studies on healthy people and modelling reflect the dynamic nature of visuo-spatial learning and a network-wide recruitment of multiple loops (cortico-cortico, cortico-cerebellar and cortico-basal) over time. While the cerebellum has been proposed to be critical for realignment/true adaptation (see below), a parallel involvement of cerebellar areas and cerebello-cortico loops seems to be emerging as studies accumulate.

1.6 Neuropsychological Insights into the Neuroanatomy of PA

Martin, Keating, Goodkin, Bastian, & Thach (1996) tested patients with a variety of cerebellar related pathology and deficits with a clay-throwing left-shifting prism adaptation paradigm. Instead of pointing to targets, this paradigm involves throwing clay balls at a target on a wall. The clay leaves a mark allowing the distance of its location from the target, the error, to be measured. Overall, they found a significant tendency for performance (baseline) and adaptation deficits to be dissociated. Those found with impaired or absent adaptation had generalised cerebellar atrophy, inferior olive hypertrophy, or focal infarcts in the distribution of the posterior inferior cerebellar artery (PICA), in the ipsilateral inferior peduncle, in the contralateral basal pons or in the ipsilateral middle cerebellar peduncle. Ipsi- here refers to the adapting arm. The authors noted that PICA territory lesions were traditionally considered not to produce recognisable cerebellar-deficit signs but that the area had been associated with cognitive activities such as mental timing and learning word associations (Martin et al., 1996). It has also been found that damage to the PICA area in monkeys impairs PA (Baizer, Kralj-Hans, & Glickstein, 1999; Norris, Hathaway, Taylor, & Thach, 2011).

Pisella et al. (2004) tested a patient with bilateral optic ataxia with a view to testing the dissociation between strategic error correction associated with the PPC and true adaptation driven by the cerebellum. They put forward that the two aspects work in tandem and when one operation is disturbed it will be reflected in the results of the other operation. For example, a damaged PPC would result in a deficit in error correction but intact and perhaps magnified after-effects. They further posited that the unbalanced PPC-cerebellum relationship seen in neglect patients accounts for their larger after-effects and wide generalisation or spread of effects. This account was reflected in the results. A relatively symmetrical bilateral PPC lesion did not affect

true adaptation but did diminish strategic error correction. The lesion was located symmetrically in Brodmann areas 19, 18, and the posterior part of the IPS, and areas 7 and 39 (SPL) suggesting their involvement in strategic error correction. The results could not, therefore, rule out contributions of the supramarginal gyrus nor of the anterior IPS in spatial realignment.

Newport & Jackson (2006) worked with another patient with optic ataxia, this time with asymmetrical bilateral damage to the PPC and underlying white matter tracts. The dissociations that emerged in the behavioural results led the authors to speculate that while on-line correction and side-pointing are supported by the parietal lobes they appear to be unnecessary for true adaptation (the appearance of after-effects). They suggested instead that the cerebellar-ventral premotor (PMv) loop is essential and responsible for spatial realignment, and quoted evidence for the ability of PMv neurons to specify target direction irrespective of limb or eye position. In terms of the parietal cortex, they suggested that the parieto-cerebellar loop is required for online control and the parieto-PMv loop for strategic control (Newport & Jackson, 2006).

Pisella et al., (2005) studied a patient with left anterior cerebellar stroke damage. The patient performed accurately *during* exposure, regardless of hand use or prism shift, but a lack of after-effect was reported only with ipsilesional shifting prisms. They concluded that the anterior cerebellum computes the ipsilateral visual error signal. Without access to visual reafferance the visuo-spatial reference frame cannot be integrated with the motor efference copy (thought to rely on activity in the posterior cerebellum, PICA territory) necessary for successful sensorimotor behaviour. The authors referred to the non-human primate findings of Kurata & Hoshi (1999) that PMv inactivation produces PA deficits only when the visual image is prismatically shifted contra-lesionally. Taken together they suggested that PA requires a lateralised cerebro-cerebellar network for the computation and integration of directional visual error.

Chen, Hua, Smith, Lenz, & Shadmehr (2006) collaborated with essential tremor patients with therapeutic deep brain stimulation (DBS) electrodes placed in the ventral intermediate nucleus (Vim) and the posterior aspect of the ventrolateral thalamus. Overall, they found that abnormal oscillatory activity in the inferior olive-

cerebellum neural network, that then propagates to the motor cortex by the cerebello-thalamo-cortical circuit results in reduced adaptation to force. Vim DBS or thalamotomy, while relieving essential tremor, further deteriorates adaptation ability thus revealing a thalamic role in force field adaptation (Chen et al., 2006). Basal ganglia involvement in the realignment aspect of PA has also been shown by patient studies (Fernández-Ruiz et al., 2003).

In summary, the neuropsychological findings are broadly reflective of the studies of healthy people. They suggest a role of the posterior parietal cortex (particularly the SPL and IPS) in the strategic error correction of early phase adaptation and, an anterior cerebellar role in visual realignment and posterior cerebellar role in the motor efference aspect both of which rely on sub-cortical structures to connect with the parietal and motor cortices.

1.7 Neural Correlates of Cognitive After-effects

Although much is yet to be understood regarding the neural correlates during PA, the rehabilitative potential of the process has prompted recent investigations into the change in neural behaviour subsequent to PA. It has been proposed that PA spatial cognitive after-effects are due to an initial inhibition of the PPC contralateral to the prismatic shift, that is followed by a modulation of inter-hemispheric balance (Pisella et al., 2006). This is reflected in a growing body of evidence converging on the idea that a rebalancing of inter-hemispheric rivalry underpins the cognitive after-effects of PA.

Crottaz-Herbette, Fornari, & Clarke (2014) investigated, via fMRI, neural changes on a visual detection task following 10° right-shifting PA with the right arm. Participants had to detect on-screen stimuli appearing for 500ms mid-sagittally, or 20° to the left or right of centre. Following PA, activation in the left angular gyrus increased for all visual field stimuli while activation decreased in the right supramarginal gyrus for ipsilateral and central stimuli. The authors interpreted the findings as a PA-induced reversal of hemispheric dominance for spatial attention and target detection (so-called ventral attentional system), away from the right inferior parietal network toward a latent ipsilateral field space representation in the left parietal cortex, and suggested that this is the mechanism underlying its therapeutic

value in neglect patients (Crottaz-Herbette et al., 2014).

Knowing that PA can influence the perception of time, Magnani, Mangano, Frassinetti, & Oliveri (2013), in a mixed group design, applied neuro-disruptive repetitive transcranial magnetic stimulation (rTMS) to the PPC prior to adaptation, to see if it would interfere with the effects of PA on a time reproduction task. Across two experiments, they investigated both left- and right- shifting prisms, use of the dominant right or the left hand, and stimulation of the left or right PPC. In baseline conditions they replicated the effects of PA on time, i.e., time underestimation following right- and time overestimation following left- shifting PA. When the dominant right hand was employed, rTMS of the left PPC abolished the effects of both directions of PA on time reproduction (with no interference of PA after-effects). With non-dominant left handed pointing, rTMS of the left PPC abolished a right-shifting PA induced time underestimation. The authors concluded that regardless of motor process or lateralisation, the left PPC is involved in transferring the spatial after-effects of PA onto spatial cognition.

In a paired-pulse trancranial magnetic stimulation (TMS) study investigating motor cortex (M1) excitability following PA, Magnani, Caltagirone, & Oliveri (2014) found an increase in M1 intra-cortical facilitation ipsilateral to the prism shift. By using this TMS paradigm, both prism directions and stimulating both hemispheres but only employing right-handed pointing, they were able to rule out influence of spino-cortical and transcallosal effects on the results. Providing direct evidence that the PA after-effect involves increased M1 excitability, the authors proposed that PA influences cognition through changing the inter-hemispheric rivalry for healthy people or restores it in the case of brain-damaged patients.

An ERP study (Martín-Arévalo et al., 2016) reported left-shifting, but not right-shifting, PA-induced changes in attentional allocation that had previously gone undetected in behavioural studies. Using an endogenous version of the Posner task, left-shifting PA created an asymmetry in cue-locked N1 interpreted to reflect a reduced efficiency to direct spatial attention towards left lateralised cues. Additionally, there was a significant bi-hemispheric amplitude decrease in the target-locked P1 for invalidly cued left- compared to right- sided targets, interpreted as a

difficulty disengaging from right-lateralised cues in order to orient to left-lateralised targets.

The neural generator of the cue-locked N1, thought to facilitate further perceptual processing, has been localised to the IPS and the SPL. While the P1 has been localized more generically to the parietal lobe, the authors qualify that they found no modulation of the P3 that is thought to measure right temporo-parietal junction's involvement in attentional disengagement. The report concluded that PA after-effects are subsequent to initial inhibition of the parietal cortex contralateral to the prism-shift, followed by a further modulation of the attentional balance via inter-hemispheric interactions of the parietal cortices (Martín-Arévalo et al., 2016).

Luauté et al. (2006) used PET to measure regional cerebral blood flow (rCBF) in neglect patients following one session of right-shifting PA. Activity increases in the right cerebellum (dentate nucleus and lobule V), the left thalamus, left temporo-occipital, and activation decreases in left medial temporal cortex and the right PPC were correlated with improved performance on measures of neglect. Another study (Shiraishi, Yamakawa, Itou, Muraki, & Asada, 2008) looked at a course of PA treatment for left neglect patients with approximately four PA sessions a week for eight weeks. The patients showed a significant increase in rCBF in the left parietal lobe suggesting that the intact opposite homologue region was compensating for right hemisphere damage. Striemer et al. (2008) in a neuropsychological case, studying an individual with bilateral SPL damage and optic ataxia, attributed a lack of beneficial spatial after-effects in a covert-orienting-of-attention task to the damaged left SPL. Elsewhere, a correlation between increased bilateral activation in the posterior parietal, superior/middle frontal and occipital cortices following right-shifting PA and improved performance in spatial cognitive tasks in a group of left neglect patients has been observed (Saj, Cojan, Vocat, Luauté, & Vuilleumier, 2013). A different imaging study has linked the beneficial effects of PA on left neglect to the integrity of the right medial temporal and subcortical regions; a more liberal interpretation also implicated the right medial temporal gyrus, the superior temporal area, the anterior transverse temporal area, and the inferior longitudinal fasciculus. Notably, those neglect patients whose lesions included damage to the frontal lobes benefited significantly more from the PA treatment compared to those with posterior only lesions (Chen, Goedert, Priyanka, Foundas, & Barrett, 2014).

Finally, it should be remembered that without spatial realignment (i.e. 'true' adaptation) there are no after-effects - sensorimotor or cognitive. No after-effects have been found in some neglect patients following right-shifting PA (Frassinetti, Angeli, Meneghello, Avanzi, & Làdavas, 2002) and left-shifting PA did not evoke any after-effects in a group of neglect patients (Luauté et al., 2012). This lack of after-effects in patients without cerebellar damage should not be taken as evidence minimising the importance of the cerebellum in successful spatial realignment. Rather, it is more likely a reflection of a parallel involvement of cerebellar areas and cerebello-cortico loops (e.g., lobule VIII receives mossy fibre input from the PPC). Indeed, there is evidence that the ability to correct pointing errors during prism exposure may better predict rehabilitative outcome from neglect (Serino, Bonifazi, Pierfederici, & Làdavas, 2007), and, that such benefits have been found not to correlate with after-effects in terms of magnitude (Sarri et al., 2008; Serino et al., 2006) or duration (Frassinetti et al., 2002).

Taken together, the results from healthy and brain-damaged people suggest that spatial cognitive after-effects recruit a wide range of bi-hemispheric areas. The bilateral PPC, possibly the SPL in particular, and motor cortices seem to be key in neurologically unimpaired individuals. Patient studies have implicated a wider network of brain areas in the cognitive after-effects encompassing frontal, temporal, parietal, subcortical and cerebellar structures. Broadly speaking, the network of bi-hemispheric areas recruited in both populations is supportive of the premise that a modulation of inter-hemispheric balance underlies the cognitive after-effects. Crucially, this activity is underpinned by cerebellar driven spatial realignment.

1.8 Thesis outline

The relative ease with which a person can adapt to prism-altered vision belies the complexity of the processes that underlie that adaptation. This complexity cuts across disentangling the strategic error correction and spatial realignment steps as well as the balance of visual, proprioceptive, and motor elements within those steps. Likewise, the neural correlates and mechanisms that support not just spatial realignment but also its cognitive after-effects are intricate and intriguing and much remains to be understood.

The current thesis set out to investigate three distinct areas of PA: the role of ocular proprioception in spatial realignment; a hemispheric balance account of cognitive after-effects; and a cerebellar account of cognitive after-effects.

The first empirical chapter (Chapter 2) aims to provide a better understanding of the sensorimotor after-effects of PA, specifically the shift in visual straight-ahead. Through use of multiple after-effect tests, an eye muscle potentiation contrast condition, and eye-tracking methodology, an attempt was made to isolate an assumed but under-investigated role of ocular proprioception in spatial realignment.

Chapter three takes a neuropsychological approach to investigating a hemispheric balance account of PA. In a radical departure from visuospatial cognition, the experiment's premise was that an inter-hemispheric balance restoration account of PA should extend to left hemisphere functions. The study looked at PA effects on language priming in a group of left hemisphere stroke patients.

The final empirical investigation (Chapter four) utilised a non-invasive neuro-disruptive method, transcranial magnetic stimulation, to examine a cerebellar contribution to language priming. The idea being that if PA can effect language priming the origin of that effect is likely to be cerebellar driven.

In chapter five, the findings are briefly summarised, their implications are discussed, and directions for future research are proposed.

Chapter 2

The Visual Straight-Ahead After-Effect

Abstract

Eye-tracking methodology and novel tasks were used to investigate the prism adaptation (PA) induced visual shift, in particular whether it had an ocular proprioceptive component. A comparison condition of eye muscle potentiation (EMP), in which participants pointed toward a prism-refracted visual target without error feedback, was employed to perturb state estimation of eye position independent of any adaptation. Following PA the often-observed visual straight-ahead shift was not found whereas a predicted shift in straight-ahead pointing (SAP) and a larger shift measured by open loop pointing (OLP) were. Thus, additivity as conventionally measured was not observed. Nonetheless, there was evidence for a shift in state estimation of eye position indirectly from the larger OLP relative to SAP shifts following PA. It was observed that following PA people continued to be able to correctly look straight ahead but, when with eyes open they pointed to subjective straight-ahead with the unseen hand, an incorrect ocular signal was employed. This presents a potential paradox. Different interpretations are discussed. One being a return to the primary eye position but a change in the interpretation of that position signal by the brain, it is tentatively suggested that this situation could be supported by different ocular muscle fibres and their associated proprioceptive receptors. Alternatively, the results could represent a dissociation between oculomotor commands and ocular proprioception.

2.1 Introduction

The experiment in this chapter set out to explore the visual after-effect induced by prism adaptation. To set the scene, the introduction recaps and expands upon some of the sensorimotor aspects of prism adaptation.

Wearing prisms while pointing creates a conflict between the signals received from the eye and the arm, and thus, a discrepancy between predicted and expected sensory feedback. Adaptation is the process of restoring harmony to that relationship in order for behaviour to be coherent and effective. This, mostly unconscious, process includes an assessment of the trustworthiness of the context in which the conflict is occurring; an evaluation of the reliability of each of the sensory signals (thought to be predominantly proprioceptive) involved; a change in the relationship, in particular the spatial coding, between the sensory signals involved; and, given this new relationship, a change in motor commands to the relevant effectors (eye and arm).

2.1.1 Tests of the Sensorimotor After-Effects of Prism Adaptation

Prism adaptation is assessed using standard sensorimotor tests: visual straight-ahead (VSA), straight-ahead pointing (SAP), and open loop pointing (OLP). VSA involves verbally indicating visual subjective straight-ahead, usually saying when to stop a moving light or target. The VSA after-effect, that is the change that occurs following prism adaptation, is *in* the direction of the prismatic displacement. That is, after adapting to right refracting prims, a stimulus that is straight ahead is perceived to be to the right of straight ahead. This after-effect, often called the visual shift, is conventionally assumed to reflect a change in ocular proprioception. However, it is an under-investigated after-effect and it is unclear whether the measure is confounded with any motor, retinal, or other component. SAP involves actively pointing with eyes closed to the point in space that is subjectively in front of the body midline. SAP errors reflect a limb proprioceptive after-effect. However, because it is an active movement, the measure is confounded with the motor adaptation; and as such it is in the direction *opposite* the prismatic displacement. OLP involves pointing with the unseen hand to visual targets and is considered the combined after-effect (limb and ocular proprioception and motor adaptation). This sensorimotor after-effect is in the direction *opposite* the prismatic displacement. That OLP represents the combined effect is reflected in the concept of linear additivity of the sensorimotor after-effects (i.e., OLP = SAP – VSA) (for a review see, Redding, Rossetti, & Wallace, 2005).

It is now understood that there were weaknesses in past investigations of the sensorimotor after-effects of prism adaptation. Importantly, these methodological weaknesses could have led to an inaccurate picture of the role different sensory signals play in adaptation. Currently accepted best practice requires inclusion of multiple symmetrically placed targets during the adaptation exposure (to minimise motor learning cue and to minimise any muscle potentiation effects), and that after-effects tests, specifically OLP, should be as different as possible from the prism exposure set-up (to minimise any spatial or cognitive cues) (Huang et al., 2011; Redding et al., 2005). Many studies that form the basis of the current understanding of the interplay between the sensorimotor after-effects did not follow one or both of these practices (Choe & Welch, 1974; Craske & Crawshaw, 1974; Redding & Wallace, 1987, 1988, 1993, 1998, 2000, 2001, 2004; Welch, Choe, & Heinrich, 1974; Wilkinson, 1971).

Furthermore, many of the papers which are cited as key evidence for the phenomenon of linear additivity of the sensorimotor after-effects (i.e., OLP = SAP – VSA) have other potential problems, e.g., a lack of after-effect tests (Templeton, Howard, & Wilkinson, 1974); measures taken only during exposure (McLaughlin & Webster, 1967); no explicit statistical testing of additivity (Hay & Pick, 1966); no individual after-effect measures or measures taken with prism still being worn (Mikaelian, 1970, 1972). An objective overview of the literature suggests that analysis to check for statistically significant differences between the after-effect tests, particularly OLP and SAP, have not been routinely employed. Indeed, the concept of simple linear additivity is thrown into question by studies that have not presented perfect additivity (e.g., Bornschlegl, Fahle, & Redding, 2012; Facchin, Mornati, Peverelli, Bultitude, & Daini, 2017; Ferber & Murray, 2005; Fortis, Ronchi, Calzolari, Gallucci, & Vallar, 2013; Girardi, McIntosh, Michel, Vallar, & Rossetti, 2004).

The SAP test presents an additional problem. The use of active pointing may confound motor signals and proprioceptive ones. Thus, a straight comparison of SAP to VSA for relative changes in limb and ocular proprioception is not without problems. Additionally, there is now an accumulation of studies that report no visual after-effect in healthy people (Bornschlegl et al., 2012; Choe & Welch, 1974; Harris, 1963; Herlihey & Rushton, 2012; Michel, Gaveau, Pozzo, & Papaxanthis, 2013; Morton & Bastian, 2004; Newport, Preston, Pearce, & Holton, 2009). Importantly,

those investigations differed from each other across a number of factors: different and yet commonly employed shift magnitudes (9°, 11.4°, 15°, 17°); use of both left and right refracting prisms, different number of exposure targets (1, 3, and multiple), and different lengths of exposure trials (20, 30, 80, 90, and 100). Thus, allowing those factors to be discounted in broad terms as explanatory for the absence of a VSA test after-effect. Indeed, some investigators have reported no VSA and nonetheless a larger OLP compared to SAP (e.g., Michel et al., 2013), others have found OLP to be larger than SAP following a full decay of VSA (Hatada et al., 2006), and others have observed OLP to be greater than VSA and SAP combined (e.g., Welch et al., 1974). In sum, some studies report no visual shift, some report no direct but at same time indirect evidence for a visual shift, others report evidence suggestive of a temporal evolution of the visual shift, and others report deviations from linear additivity.

The conflicting findings regarding the visual shift raise important questions. It speaks to concerns about the concept of linear additivity being too simplistic (Hatada et al., 2006). It raises doubts about the adequacy of the visual after-effect measure. It also questions the role of an oculomotor adaptation in the efficacy of prism adaptation treatment for neglect (Newport et al., 2009; Sarri et al., 2008; Serino et al., 2006, 2007).

2.1.2 Understanding of the Visual Shift

In the notes section of their papers Redding and Wallace, experts in the sensorimotor aspects of prism adaptation, explained "The term visual shift designates adaptive change in the eye-head system that has phenomenal consequences for visual perception. The basic nature of such change may be realignment of either retinal local sign or direction of gaze (e.g., Crawshaw & Craske, 1974; Harris, 1980). Current theory development does not permit one to compare those two possible accounts of visual change…"(Redding & Wallace, 1987, 1988, 1993, 1998, 2000, 2001, 2004). In a more recent paper, they asserted that the "visual shift test involves coordination of both retinal and oculomotor components" but did not expand on those terms or explicitly define them operationally. (Redding, Rossetti, & Wallace, 2005, p.441). This is broadly representative of the current state of understanding of the visual shift following PA. It thus seems reasonable to suggest that the visual shift is somewhat conceptually under-specified.

Evidence in support of a prism adaptation induced visual shift.

Two studies used a method of repeated photography of eye position, and both reported a shift in eye position in the direction of prism displacement. Kalil & Freedman (1966), who investigated after-effects following 60 trials of left- and right-shifting PA, explained the shift in eye position as a persisting "unconscious" lateral rotation of the eye. McLaughlin & Webster (1967) studied eye position *during* left-shifting PA and reported the shift as rising from 32% to 66% of the displacement (20 dioptre) from trial 1 to trial 15. They proposed that the shift took place in a parametric adjustment centre that combined unchanged efference signals with changed signals that included "tonus of the individual muscles, position of the eye, and the metabolic state of the organism" (p.43). Effectively both sets of authors identify ocular proprioception as an underlying cause of the shift in visual straight ahead judgements without making an explicit claim.

Craske & Crawshaw (1974) studied PA effects on eye position in the orbit using 10° base-out prisms. A base-out setting creates a reduction of apparent distance during exposure and results in a distance over-estimation after-effect. To adapt, participants inspected their stationary feet for 3 minutes. In a control condition, participants fixated a disc simulated to be in the same position as their feet. Before and after adaptation, and in a dark room, participants, using pen and paper and their unseen hand, recorded their judgements of the location of light targets that were within arm's length. Following the experimental condition, participants: 1) estimated the target lights to be further away than their objective position (an overestimation of distance) as judged binocularly, and 2) estimated the targets to be shifted laterally in opposite directions for each eye as judged monocularly. There were no changes in the control condition. The authors concluded that, given the change in both distance and direction and the lack of arm involvement during exposure, the shifts were due to an adaptation in registered eye position. Taken together with the two photography studies, the results provide direct evidence of a visual after-effect, and are supportive of an ocular proprioceptive adaptation.

Evidence for an eye muscle potentiation account of the visual shift.

Muscle potentiation is a continuation of muscle innervation in the presence of attempted relaxation or removal of the innervation-causing stimulus following a period of sustained activation of that muscle. Plainly put, the muscle retains a

preference to remain in a certain position following continuous exercise in that same position, e.g., sustained gaze. The proponents of the eye muscle potentiation account found that the visual after-effects of sustained ocular deviation and prism adaptation were in the same direction. Thus, they asserted that evidence of a realignment of the visual system following PA is exaggerated by the incidental presence of eye muscle potentiation (Ebenholtz & Wolfson, 1975).

In a series of experiments Ebenholtz & Wolfson (1975), focusing on sustained convergence (distance fixation), demonstrated that the potentiation effect is present in the extra-ocular muscles. Sustained convergence produced a pattern of open loop pointing (OLP) aftereffects similar to those induced by base-out prism adaptation (OLP errors increased with increasing exposure time and increasing deviation magnitude); and the pattern of results varied with the pattern of innervation (muscle positions/degree of deviation held). Their results led the authors to ascertain that eye muscle potentiation drives prism adaptation after-effects. Paap & Ebenholtz (1976) reasserted the claim following examinations of visual straight-ahead (VSA) subsequent to sustained lateral eye deviation, and of the decay rate of right shifting PA. In summary, they proposed that their findings justified a downgrading of support for the notion of recalibration of the visual system evoked by PA (Paap & Ebenholtz, 1977).

Recently, Newport, Preston, Pearce, & Holton (2009) included both an eye muscle potentiation and a prism adaptation condition in the same experiment. They were investigating whether eye rotation, measured as shift in VSA, contributed to straight-ahead pointing (SAP) following prism adaptation. The authors were interested in whether ocular rotation/VSA shift was influential in neglect recovery following PA therapy and concluded it was not. Using a system of real-time video feedback that could be manipulated, one condition shifted the perceived position of the hand laterally with 0 dioptre Fresnel prisms (hand only adaptation); another condition used 20 dioptre Fresnel prisms (standard PA); and a third condition used the 20 dioptre prism to produce ocular deviation but manipulated the visual feedback to cancel the attendant error (eye muscle potentiation condition, EMP). Neither PA nor the hand-only adaptation produced a visual shift, but both produced a change in SAP. However, in the EMP condition only a visual shift, in the leftward direction of the displacement, was reported.

Current status.

It has been shown that prism adaptation can take place in the absence of eye muscle potentiation (Craske & Crawshaw, 1978). Thus, the prevailing account is that the prism adaptation visual after-effect incorporates eye muscle potentiation to some extent (Redding et al., 2005). However, the Newport, Preston, Pearce, & Holton (2009) study threw this into question: they reported a visual straight-ahead shift following an eye muscle potentiation condition but not following prism adaptation. Thus, the role of eye muscle potentiation within prism adaptation is unclear. It may be a separable part of the visual after-effect and/or a process that is manipulated by prism adaptation.

Elsewhere, there are reports both of the presence and of the absence of a visual shift following prism adaptation. There has also been an advance in the understanding of how best to conduct the prism exposure itself, and to measure the sensorimotor after-effects of prism adaptation, since the first demonstration of an eye position shift and the proposal of the linear additivity of those after-effects. Additionally, there has been an increase in the use of prism adaptation as a therapy for unilateral left neglect but a relative dearth in the understanding of why it is a useful treatment, and whether the visual shift has a role in identifying those who may benefit from it (Newport et al., 2009; Sarri et al., 2008; Serino et al., 2006, 2007). Taken together, there is a need to further examine the visual after-effect of prism adaptation.

2.1.3 The Current Experiment

Knowledge of its sensorimotor foundations can benefit the advancement and appropriate application of prism adaptation as a rehabilitation tool. The current experiment set out to expand understanding of the visual after-effect of right-shifting prism adaptation (R-PA). This under-investigated shift has been assumed, without experimental validation, to represent a change in ocular proprioception. Understanding of the visual shift is further complicated by the fact that the effect has not always been found. Additionally, confounding factors in past studies of PA sensorimotor after-effects that may have obscured appreciation of the visual shift.

Three design interventions are particular to this study. The first is use of eye tracking throughout the experiment, including during prism exposure, and the custom build of a frame to facilitate that process. The use of eye tracking equipment

permitted proxy measurement of changes in state estimates of eye position in the orbit.

The second design feature is the comparison condition, right-shifting eye muscle potentiation (R-EMP). Eye muscle potentiation was achieved by having the participant point, without vision of the adapting hand, while looking through a right-shifting prism. In this way, their eyes sustained the directional deviation imposed by the prismatic displacement, but adaptation did not take place because the mismatch between arm and eye signals went undetected. The after-effects of the R-PA and R-EMP conditions were compared in order to isolate and ascertain whether EMP, is a part of, or is manipulated by PA.

The final feature is the mix of conventional and novel after-effect tests that were conducted; some provided direct measures of the visual after-effect while others assessed the interaction between the visual after-effect and the limb after-effect. The conventional tasks were the straight-ahead pointing, visual straight-ahead, and open loop pointing tasks; the novel tasks were variations of them. As far as is known, this is the first time that lateral-shifting PA and EMP induced effects have been compared within participants on a battery of after-effect tasks.

2.2 Methods

The current experiment set out to expand understanding of the visual after-effect of right-shifting prism adaptation (R-PA). In a within-subject design each condition (R-PA, R-EMP) was conducted a minimum of a week apart. Within each session there was a sham exposure and a prism exposure task, both followed by after-effect tasks. Responses were captured through a mix of touch position on a touchscreen, verbal responses, positioning items on screen with a cursor, and eye tracking. Responses were translated from pixels to visual angles. The dependent variable for each task was the error from the objective position of the relevant target.

2.2.1 Participants

Twenty-three self-declared neurologically intact participants were recruited from the University community. Recruitment was based on right-handedness and normal or corrected-to-normal vision. Testing was terminated early for five participants due to problems tracking their eyes and/or with recording touch due to arm length. Of the 18 participants included in the analysis mean age was 24.9 years

(SD = 5.2, range 20-40), gender mix was M/F = 6/12 (33.3/66.6%). Mean right-handed was -0.77 (Oldfield, 1971) as measured for 15 people; eye dominance was 50/50 left/right as measured for 16 people.
Informed consent was sought in line with university ethics committee approved guidelines and the 1964 Declaration of Helsinki. Participants received £12 or course credits for a c3.5 hour testing period across two sessions/weeks. Following completion of the second session (the second week) participants received a verbal debrief.

2.2.2 Apparatus

All tasks took place at the same desk in a dark room. The participant sat in a height-adjustable computer chair, with their head fully stabilised and their viewing restricted to forwards, and responded to the various tasks by looking, pointing and touching, and/or verbally replying.

In order to track the eyes during adaptation it was necessary to place the eye-tracker between the prism lens and the eyes. In place of conventional prism goggles, a large square (30 x 30 cm) 40 dioptre (21.8°) Fresnel prism lens (RHK Japan Inc) was used. The sham "lens" was the same size and made of clear Perspex. The lens was fitted 22cm from the eyes and 31cm from the touchscreen. A tower-mounted eye-tracker (Eyelink 1000) was placed between the prism lens and the face. A forehead rest and chin rest kept the head stabilised and side-blinkers restricted viewing to forwards/through the lens. A custom designed mounting frame (130 x 60 x 35 cm) accommodated the set-up, while also allowing unrestricted access and movement of the arms underneath the frame (figures 2.1 – 2.3). The frame also held a retractable arm occluder and a fitment for the lens. The limb occluder was made of matt black reinforced cardboard. It attached to the top of the frame, and spanned the horizontal distance between the participant and the touchscreen, or 4 cm short of it upon retraction. The last piece of the custom build was a removable hand-board. This Perspex-covered black painted board (55 cm wide x 41 cm deep) was attachable to the frame in front of the screen and a height-adjustable support (max height 25 cm) sat underneath it towards the participant. A similar sized piece of cardboard, in an upside-down T shape, was placed on top of the board. The surfaces of both materials facilitated a free gliding movement making it easy to move the participant's relaxed passive arm from side to side.

Stimuli were presented on, and some task responses recorded from, a flat-screen landscape LCD touchscreen monitor (HannsG model HT271HPB, 1920 x 1080 resolution, 59 Hz). This was positioned off-centre by 0.5 cm to the participant's objective straight-ahead. An offset matt black frame covered some of the display leaving 44.5 x 24.5 cm visible while also overhanging the edges of the monitor by 23 cm to the right and 23.5 cm to the left. These adjustments were designed to minimise contextual spatial information while encouraging judgements based on participant body position (see figures 2.3-2.4). The screen was positioned 53 cm from the participant on a stand. A 44.5 x 24.5 cm portion of the display was visible and a 59 x 8 cm portion was out of sight below the arm occluder.

All tasks were programmed and executed, and behavioural responses were recorded, using Matlab (R2014a). The software ran on a windows 64-bit operating system on a Windows 7 Stone PC-1210. Stimuli were custom created for the experiment. All visual stimuli were white (R = 255 G= 255 B = 255) presented on a black background (R = 0 G= 0 B = 0). All auditory stimuli were tonal beeps played from the touchscreen in-built speakers. A touchpad (Logitech T650, 13.5 x 12.8 cm), strapped to participant's chest, responded to touch commands to either start a trial or record a response depending on the task. A dim backlit keyboard, (Trust 17365-03), designed for use in the dark, was used by experimenter as necessary; any verbal responses were recorded on it. The room was in darkness apart from light from the monitors, they either had a black background or were set on dim.

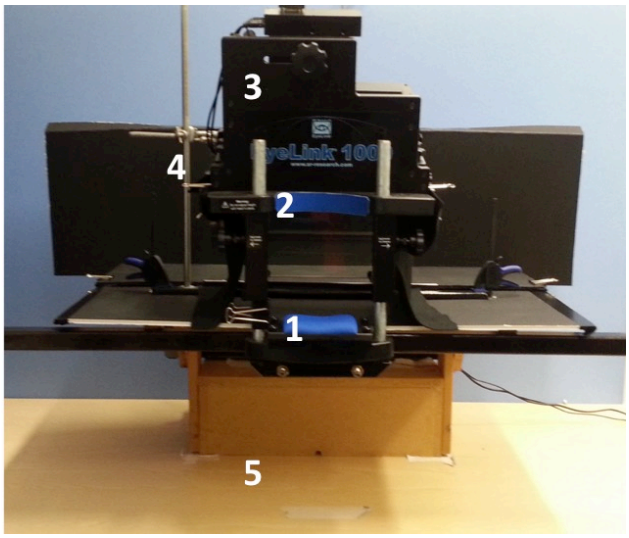


Figure 2.1: Apparatus front view.
1) Chin rest,
2) forehead rest,
3) tower-mounted eye-tracker,
4) arm to hold lens in place,
5) space for uninterrupted movement of arm (a handboard was placed in this space for the finger location task).

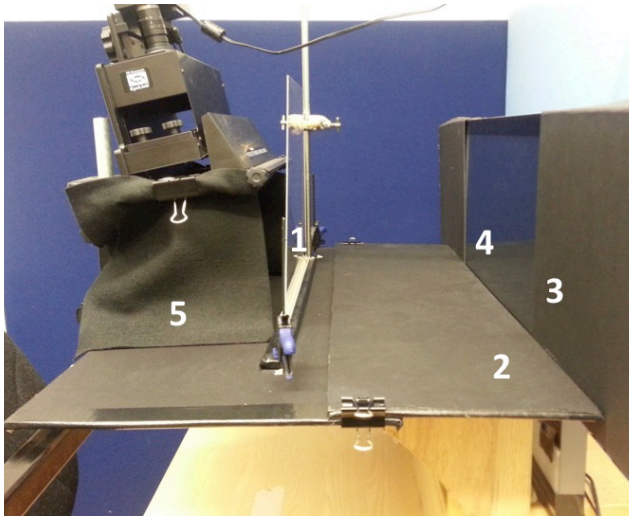


Figure 2.2: Apparatus side view.
1) The sham lens,
2) the limb occluder abutting the screen,
3) touchscreen frame extender,
4) touchscreen, bottom portion below the occluder,
5) side blinkers to prevent non-prism deviated vision

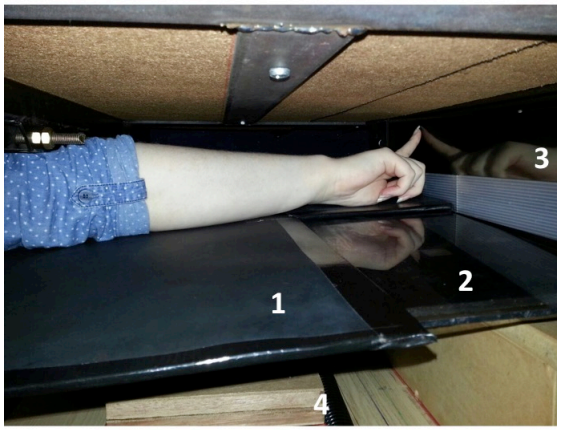


Figure 2.3: Apparatus underside view with handboard in place for finger location task.
1) Movable top handboard,
2) perspex covered bottom board attachable to main frame,
3) touchscreen,
4) partial view of height-adjustable support (under handboard)
Note: photo is for illustrative purposes, the hand and fingers were relaxed during experimental task.

2.2.3 Tasks

The sham-exposure and prism-exposure tasks.

In the sham-exposure tasks the clear, flat Perspex panel was used. In the prism-exposure tasks the Fresnel prism was used. The aim of the prism-exposure tasks was to produce prism adaptation or eye muscle potentiation in the R-PA and R-EMP conditions respectively. The aim of the sham exposures was to provide a baseline measurement of exposure pointing in both conditions. For the R-PA condition this meant pointing with visual feedback of the end of the finger only (terminal pointing). For the R-EMP condition it meant pointing without any visual feedback of pointing accuracy. The sham exposures also ensured that the baseline (i.e., post sham exposure) sensorimotor tasks were preceded by a physical pointing exercise, similar to the prism-exposure sensorimotor after-effect tasks.

After-effect testing is used to assess whether the manipulations have been successful. However, the direct effects of the manipulations can be assessed by

measurement of pointing errors. The response for each trial was recorded as the first touch on the touchscreen. In the R-PA condition it was expected that the initial rightward pointing errors would decrease toward baseline with continuing exposure. In the R-EMP exposure it was expected that rightward pointing errors would be stable such that they would remain uncorrected throughout exposure.

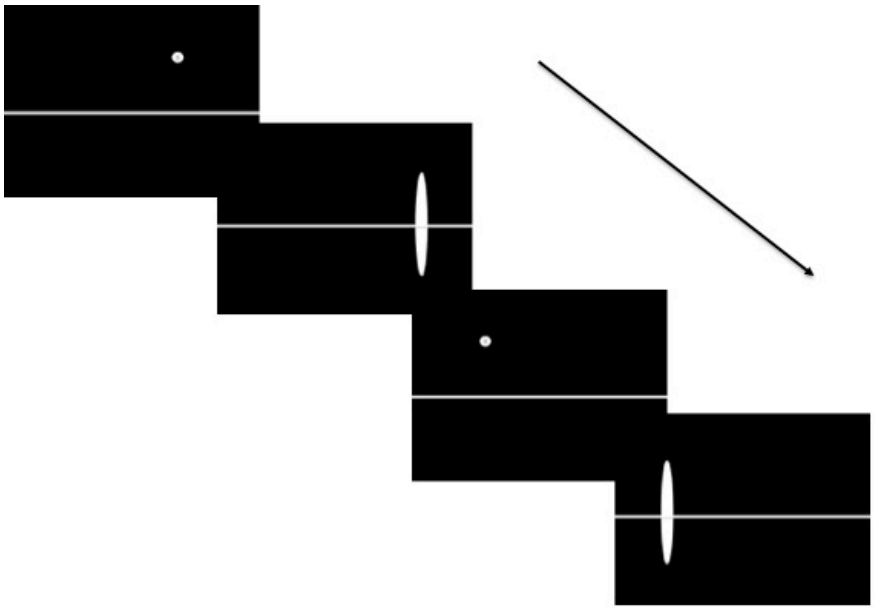


Figure 2.4: Two trials from the sham/exposure task. The horizontal line represents the level of the matt black arm occluder. In the R-EMP condition, the occluder abutted the touchscreen thus hiding the pointing arm. In the R-PA condition, there was gap between the occluder and the touchscreen allowing the top of the finger to be seen when pointing. This held regardless of whether it was the sham-exposure or prism-exposure task.

See figure 2.4 for a schematic of the task. A fixation annulus (0.6° x 0.6° with an inner hole of 0.2° x 0.2°) appeared on the screen, the participant was instructed to use their right index finger and to swipe the trackpad (strapped to their chest) while looking at the annulus. Upon swiping the annulus disappeared and in a nearby location (within 5.4° s to the l/r) a stretched spherical shape (1° pixels wide x 10° pixels high) appeared, half of the shape was above the occluder level. Still using their right index finger, the participant was required to make a swift and continuous movement from the trackpad to touch the shape on the screen and to return their hand to the chest trackpad. Upon touching the screen the spherical shape disappeared and

was replaced by a new fixation annulus. This was repeated 96 times for the main exposure tasks and 30 times in two subsequent exposure top-ups. The spherical shape appeared in an equally numbered but pseudo-random order in three positions: centre screen, 12° to left and 12° to right of centre. The use of multiple positions presented in random order aimed to limit any motor adaptation independent of a motor response to proprioceptive adaptation.

The stimuli during the exposure tasks (and for its related calibration) were presented 6.7° to the left of the centre. This step was taken in order to ensure that the pointing errors (and after-effects) caused by the lateral displacement would fall within an area that could still be captured by the touchscreen.

Prior to R-PA prism-exposure task participants were advised that they would be likely to miss the target and that they should try to resist the temptation of correcting themselves on the first few trials in order that errors could be recorded. They were also advised that they would then 'naturally' get better as the task continued.

Visual straight ahead (VSA).

The different elements of this task aimed to measure changes in perceptual VSA (stopping a bar, with the unseen non-adapting hand, when it is judged to be straight ahead) and in the position of the eye as it looked straight ahead (before the bar appeared on screen and as the bar was positioned straight-ahead). For both the R-PA and R-EMP conditions, all these after-effects were expected to be in the rightward direction, and to predominantly represent a change in ocular proprioceptive signals of what constitutes visual straight ahead.

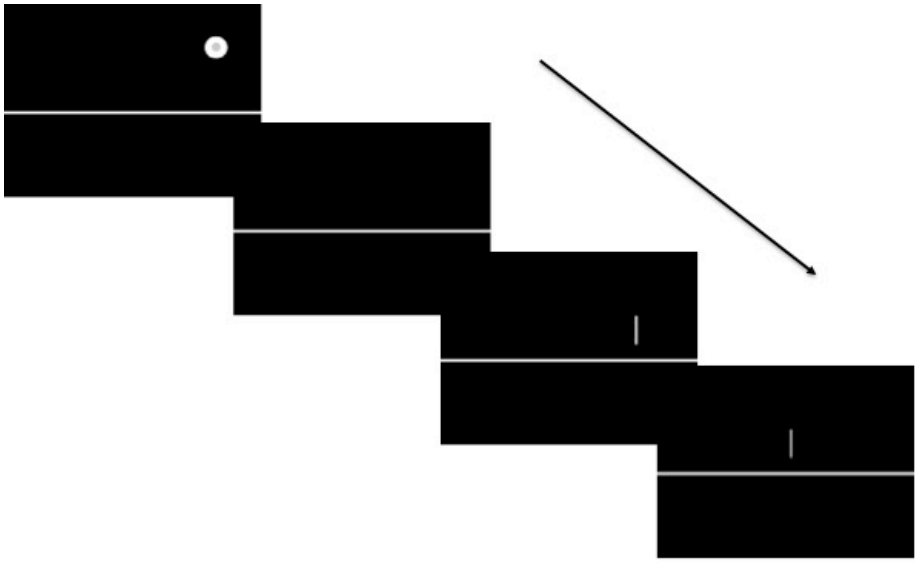


Figure 2.5: One trial from the VSA task. The horizontal line represents where the matt black arm occluder touches the screen. The final screen represents an example perceptual response.

See figure 2.5 for a schematic of the task. Participants were required to fixate an annulus. It disappeared upon verification of accurate fixation as assessed by the experimenter at the eye-tracker monitor. It was judged accurate if the representation of the eye overlapped the position of the stimulus.

The participant was then required to look straight ahead and to use their left index finger to swipe the chest trackpad to indicate such, thus allowing their eye position to be recorded at that instant.

Following that swipe a vertical line (.34° width) appeared at the same location as the annulus, while staying looking straight ahead, the participant had to use their left hand to scroll across the chest trackpad to move the bar to where they were looking, i.e., keeping their eyes still the bar was to be moved to meet their straight ahead gaze. The participant knocked on the table to indicate completion of the trial and the experimenter recorded the response via keypress. The task consisted of 24 trials, split equally between a starting point that varied between 9.4° and 12.7° either on the left or right of centre screen and presented in a pseudorandom order.

The eye positions selected for analysis were the last fixations of that element of the task: For the VSA-with-no-screen-stimuli element that consisted of the last fixation after the disappearance of the annulus/before the appearance of the bar stimuli. For eye position while looking at bar in the subjective VSA position that was

the last fixation with the bar in position. If no fixation was recorded during an element of a trial, the last saccade was taken. The perceptual response was recorded as the final position of the bar on the touchscreen.

Straight ahead pointing (SAP) – eyes closed.

The rationale for inclusion of this and *the remaining sensorimotor after-effect tasks* was to facilitate interpretation of any exposure driven eye-position and visual perception changes in the context of other sensorimotor after-effects.

This one-element task aimed to measure the changes in active SAP. Following prism adaptation this measure may confound limb proprioceptive changes with any motor adaptation that has taken place independently of the adaptation (although, note that steps were taken in the prism exposure design to minimise that happening). It was predicted that the R-PA after-effect would be leftward in direction, that is, the motor response takes into account that the limb proprioceptive signal has shifted rightward and thus 'over-compensates' by moving the arm too far leftwards to reach straight-ahead. It was predicted that there would be no change in SAP following R-EMP (because there was no adaptation nor sustained limb posture).

With the eyes closed the participant was required to point straight ahead and touch the touchscreen with the right hand (i.e. the hand used during sham and exposure tasks). Participants were instructed to hold their index finger in front of the trackpad and keep their elbow elevated and then, following a beep, to reach out straight ahead of them and touch the touchscreen at that point and then return their finger to swipe the trackpad to end the trial. There were eight trials. The beep was presented at jittered intervals of 2-5 s to help minimise any rote answering. The response was recorded as the first touch on the touchscreen.

Straight ahead pointing (SAP) – eyes open.

To the best of my knowledge, a SAP eyes open task has not been run before. This task involves pointing with the unseen hand and looking straight ahead in the absence of a target. The task represents a step between conventional SAP with no visual or ocular involvement, and OLP that involves both (unseen) hand and eye aiming at a visual target. It was not clear whether following the manipulations, *and* in the absence of a visual target, the hand and eye would act in a coupled or uncoupled manner, i.e., whether the effectors would effectively interact in a spatially coherent

manner or would act independently of each other. This led to two different predictions as set out in table 2.1.

Table 2.1: Predictions of the straight-head pointing (SAP) eyes open task

Task	Position Measure	Shift	After-effect direction
SAP eyes open, pre pointing	Eye	R-PA	Left if aligned and interacting with limb/right if adapted but not interacting with limb
		R-EMP	Straight-ahead if guided by limb/ right if eyes not interacting with limb
SAP eyes open, eyes open	Point	R-PA	left
		R-EMP	Straight-ahead if guided by limb / Right if limb interacting with eyes
SAP eyes open, upon pointing	Eye	R-PA	Left if aligned and interacting with limb/right if adapted but not interacting with limb
		R-EMP	Straight-ahead if guided by limb/ right if eyes not interacting with limb

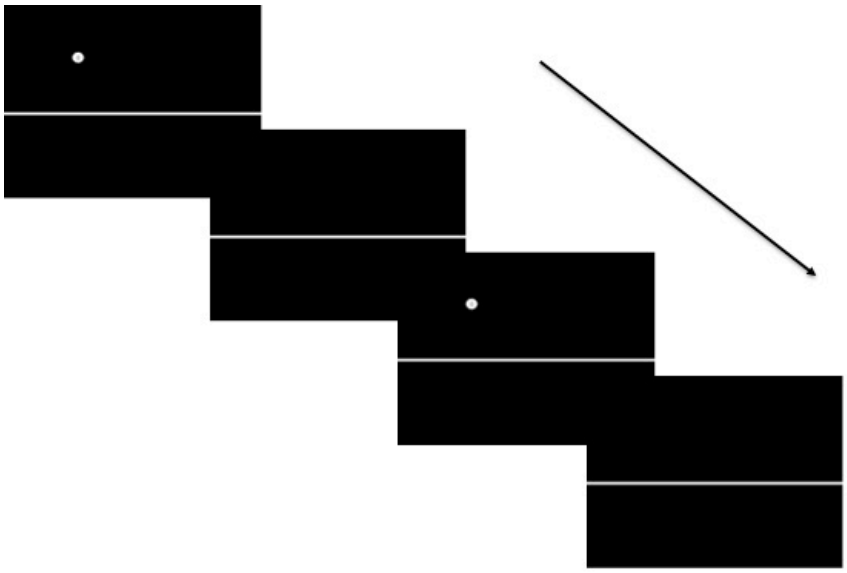


Figure 2.6: One trial from the straight-ahead pointing with eyes open task. The horizontal line represents where the matt black arm occluder touches the screen.

Participants were required to fixate an annulus, it disappeared upon verification of accurate fixation by the experimenter and the participant was then required to look straight ahead. A second annulus appeared, upon verification of accurate fixation it disappeared, and the participant was required to both look straight ahead and to touch the screen straight ahead (with elbow elevated, moving the right hand from chest to screen) and to return their finger to swipe the trackpad to end the trial. There were eight trials (see figure 2.6).

Eye position measures were taken before and upon SAP. The pre-SAP eye position measure was selected as the last fixation after the disappearance of the annulus/before SAP. The upon-SAP eye-position was selected as the last fixation of a trial (touching the touchscreen ended the trial). The pointing response was recorded as the first position pointed at on the touchscreen.

Open loop pointing (OLP).

The purpose of this task was to build up from the previous tasks by adding visual stimuli. Here, the participant was asked to point with the occluded exposed hand at visual targets presented on the touchscreen. (Only pointing responses are reported from this task; see the section on calibration for further details.)

This task contains a motor response, and therefore, like the straight-ahead pointing after-effect, it was predicted that the R-PA after-effect would be leftward in direction. However, consistent with the linear additivity concept, it should be larger than SAP with the difference accounted for by the visual shift, i.e. OLP = SAP – VSA. Thus, OLP should represent the combination of two erroneous proprioceptive responses (eye and limb) to a visual target compared to a uni-sensory response (limb proprioceptive only in SAP eyes closed) (Redding et al, 2005).

For the R-EMP condition, it was predicted that after-effect would be a rightward error, and that it would not be significantly different from the rightward eye-position error recorded in the VSA task (or the SAP eyes open task if present there). This was predicted because due to the lack of feedback during the exposure task, the CNS would not register the drift in eye position caused by EMP nor the subsequent the misalignment between the eye and hand – therefore in the absence of knowing the eye position signal was unreliable the hand would aim for the location the eye was registered as gazing at.

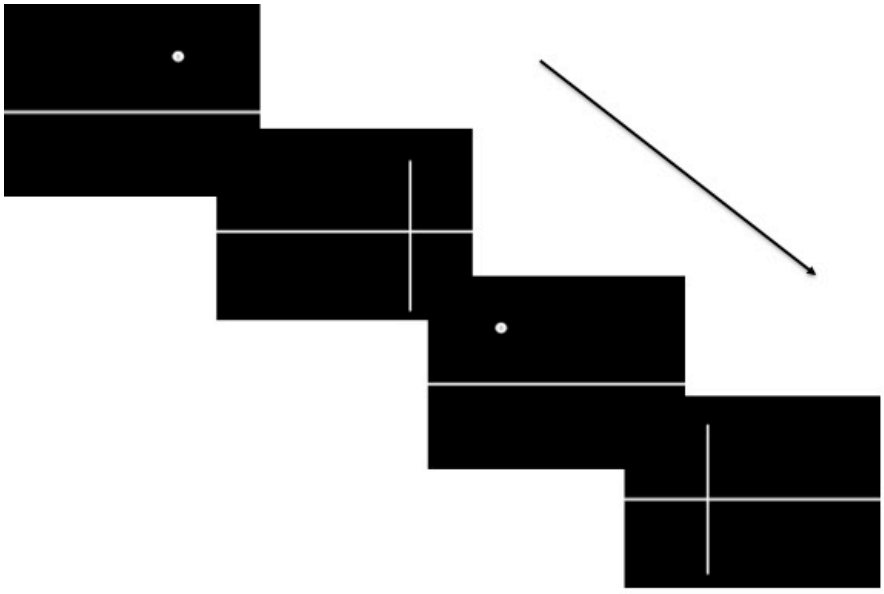


Figure 2.7: Two trials from the open loop pointing task. The horizontal line represents where the mat black arm occluder touches the screen.

See figure 2.7 for a schematic of the task. Participants were required to fixate an annulus, upon experimenter verification of accurate fixation, the annulus disappeared and a vertical line (0.34° width) appeared that ran vertically down the touchscreen and out of view below the cardboard. Participants were instructed to touch the line as accurately as possible with their right unseen exposed hand and to return their finger to swipe the chest trackpad to end the trial. There were 36 trials. Lines were presented across the width of the screen at 36 individual locations in a random order. Eighteen locations were presented left of screen centre and the remaining lines were presented in mirror positions to the right of centre. The behavioural point response was recorded as the position touched on the touchscreen.

Finger localisation.

Here, the participant's unseen hand was moved by the experimenter to different lateral positions, and the participant was asked to look to the location on the touchscreen that corresponded to the horizontal position of their unseen middle finger.

This task was run first for the right (exposed) hand and then following another calibration for the unexposed left hand. The purpose of this task was: 1) to investigate after-effects on passive limb proprioception of the exposed right hand and 2) to isolate an ocular after-effect through visual localisation of the passive non-exposed left hand.

To the best of my knowledge, visual location of the unseen hand(s) has not been tested following EMP. However, the R-EMP prediction was for a rightward after-effect for both hands that should be similar in size. This is consistent with the OLP prediction – a shift in displacement direction with respect to a target.

Different tests for shifts in the unexposed hand following PA have been used and have resulted in different findings. Using an OLP measure, Taub & Goldberg (1973) concluded that the observed shift resulted from a transfer of learning. Redding & Wallace (2008) using SAP, OLP, and VSA measures found a transfer in limb proprioception from the dominant exposed right hand to the left hand, but only when the right hand was tested for after-effects first. Scarpina, Van Der Stigchel, Nijboer, & Dijkerman (2013) reported a shift in passive proprioception in both hands as judged with eyes open, but only when the left hand was exposed to left shifting prisms. In the visuomotor rotation adaptation literature, a transfer of adaptation to the non-exposed hand has been attributed to a learning process (Block & Celnik, 2013). This has been further clarified with the assertion that only motor learning transfers from the dominant (right) trained hand to the non-dominant hand, and that there is no transfer of felt position (Mostafa, Salomonczyk, Cressman, & Henriques, 2014).

Here, a rightward after-effect in the localisation of the left unexposed hand following both R-PA and R-EMP was predicted with the presence of an after-effect in both conditions indicative of an ocular mechanism being responsible. In addition, there should be a larger rightward R-PA after-effect for the exposed compared to the unexposed hand, with the difference attributable to a shift in limb proprioception of the exposed hand.

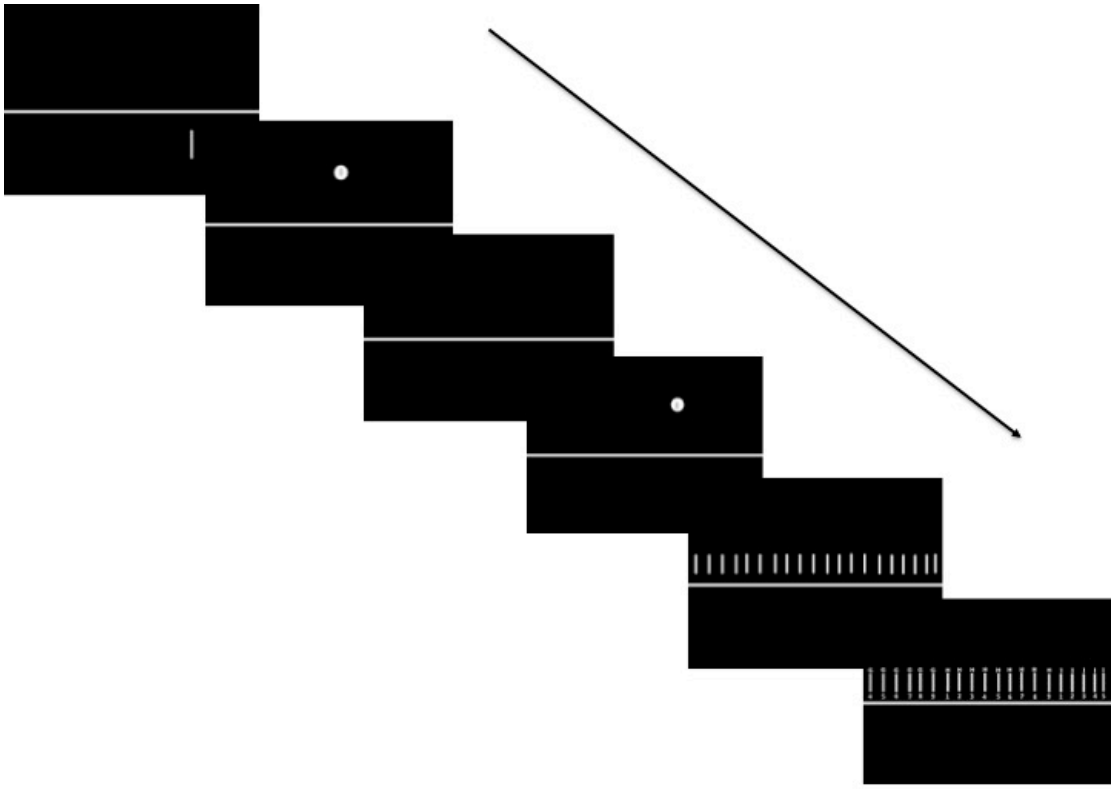


Figure 2.8: One trial from the finger location task. The horizontal line represents where the matt black arm occluder touches the screen. The last screen shows scale identifiers above and below each scale marking.

See figure 2.8 for a schematic of the task. Underneath the occluder a target line on the touchscreen indicated to the experimenter the position to slide the participant's hand to, once there the participant's middle finger was lightly touched as a cue. The trial began. The participant was required to fixate an annulus, upon verification of accurate fixation by the experimenter it disappeared, and the participant had to look to a location on screen that was above their middle finger. A second annulus appeared and required experimenter-verified fixation, upon its disappearance a horizontal scale, without labels, appeared for 4 s across the width of the screen. The participant was required to look at the location on the scale that was directly above their middle finger. After 4 s the labels appeared and the participant was asked to say which point on the scale matched their finger location. The experimenter entered the response by keyboard. There were eight trials with pre-determined positions, four trials had positions on the same side as the arm and four had positions that were across the body midline, presentation was random.

The scale ran the length of the screen with scale-points 0.5° apart. In order to maximise the number of possible responses a two-level scale was employed: there was a letter on the upper part of the scale and one digit numbers on the lower part to correspond to each letter used, e.g. B7. The allocation of letters to the scale was randomised in order to minimise any use of strategy and to focus the participant on providing body-centred responses.

Eye position measurements were taken at three points: 1) Blank screen: the last fixation following the disappearance of the annulus, 2) The un-numbered scale: the last fixation, 3) Numbered-scale: the last fixation. For the behavioural response, the scale co-ordinate was verbally supplied to, and key-press recorded by, the experimenter.

Calibration.

A 5-point eye-tracker calibration procedure preceded each task (except SAP eyes closed). The position of the calibration targets on the vertical plane varied according to the subsequent task; VSA targets were above centre, finger localisation were below centre, and for all other tasks they were centralised to the visible display. For the exposure tasks the calibration points were shifted by 6.7° to the left of horizontal centre - this step was taken to be in line with the subsequent exposure task (see above). Finally, the positions of the calibration points were horizontally jittered in order to ensure they were spatially non-informative.

Ensuring the eye-tracker can make an accurate assessment of each individual's eye position provides confidence in the measurement, and is, in reality, the only way a measurement of eye position can be obtained. However, the necessary repeats of calibration given the multi-step nature of the experiment greatly diminish the opportunity to capture a *change in eye-position over time.* This is because the calibration is not a data output source; it only ensures accurate measurement in the task that follows it. Because following calibration the tracker can accurately reproduce *the current* eye-position, then, by definition it overwrites any change in eye position in orbit from one task to the next. There is no way to compare the calibration points themselves across time.

For calibrated tasks where the participant was *not* required to look at a visual stimulus a change from post sham to post exposure can be still be captured, the participant is calibrated but is free to "choose" the location at which to look. The

same is true for tasks where the participant can select from a choice of on-screen stimuli.

However, for calibrated tasks with single (no choice) on-screen visual stimuli the ability to detect *change* is limited and to make interpretations is complicated. Therefore, eye position data for the OLP task and for the sham/exposure tasks are not presented.

2.2.4 Procedure

Each participant completed a series of 18 tasks, broken into two halves, in a pre-determined order (figure 2.9). The R-EMP condition was always completed in the first week in order to preserve naivety regarding prism effects going into the R-PA condition.

With six after-effect tasks it was deemed unfeasible to effectively counter-balance them, rather it was decided to include top-ups of the sham/exposure task after every two after-effect tasks to ensure that there was no loss of exposure effect throughout the course of the experiment. A 10 min break halfway through (after baseline testing) was included to allow the participant refresh their eyes in lighted conditions outside the testing room.

Participants were advised not to over-think any tasks, that SAP required pointing straight ahead of the line formed between the nose and belly-button and that VSA was letting the eyes rest in a natural forward position (i.e., it did not require judgements of peri-personal space but judgements arising from their own body). In order to avoid spatial decisions being influenced by room layout participants were led into the testing room with eyes closed and kept their eyes closed until the equipment was adjusted to achieve a comfortable seating position. The participants' eyes were closed between all tasks.

Task	No. of trials
Sham Task	96
↓	
Visual Straight Ahead	24
↓	
Straight Ahead Pointing (eyes closed)	8
↓	
Sham Top-Up	30
↓	
Straight Ahead Pointing (eyes open)	8
↓	
Open Loop Pointing	36
↓	
Sham Top-Up	30
↓	
Finger Localisation (R hand)	8
↓	
Finger Localisation (L hand)	8
↓	
Break	10 minutes
↓	
Exposure Task	use prism lens & then repeat subsequent tasks

Figure 2.9: The flow of tasks. Sham tasks used the Perspex lens, exposure tasks used the Fresnel lens.

2.2.5 Hypothesis Summary

The predictions for each task were provided within each task description above, a summary is provided in table 2.2. However, relative after-effect magnitudes were not considered. It was expected that any pointing after-effects would be larger in magnitude for R-PA than for R-EMP due to the involvement of a limb proprioceptive after-effect in R-PA only. For the same reason, R-PA after-effects would be larger than R-EMP for the exposed arm in the passive proprioceptive test.

In terms of eye position after-effect magnitude it is less clear. On the one hand, the R-EMP condition exposes the eye to the full extent of sustained gaze toward

the prismatically refracted visual target for the entire exposure period, while for the R-PA condition the error feedback allows the eye the opportunity to move against the prism deviation (towards the adapting hand). This would result in a larger R-EMP eye position after-effect compared to R-PA. On the other hand, R-PA is an adaptation condition and the magnitude and time point at which a shift in eye position would take place relative to a sustained eye deviation shift is unclear. The purpose here was to ascertain whether the presence and pattern of after-effects indicate a change in the visual system either directly through eye position or in how the eye position signals are interpreted following PA, and whether EMP may be part of that change, not the magnitude of that involvement.

Table 2.2: After-effect predictions. Tasks and task sub-parts are blocked by colour.

	Task	Position Measure	Shift	After-effect direction
1.1	VSA pre bar	Eye	R-PA REMP	right
1.2	VSA	Bar	R-PA REMP	right
1.3	Upon VSA bar	Eye	R-PA REMP	right
2.1	SAP eyes closed	Point	R-PA	left
			R-EMP	No after-effect (straight ahead)
3.1	SAP eyes open, pre pointing	Eye	R-PA	Left if aligned and interacting with limb/right if adapted but not interacting with limb
			R-EMP	Straight-ahead if guided by limb/ right if eyes not interacting with limb
3.2	SAP eyes open, eyes open	Point	R-PA	left
			R-EMP	Straight-ahead if guided by limb / Right if limb interacting with eyes
3.3	SAP eyes open, upon pointing	Eye	R-PA	Left if aligned and interacting with limb/right if adapted but not interacting with limb
			R-EMP	Straight-ahead if guided by limb/ right if eyes not interacting with limb
4	OLP	Point	R-PA	left
			R-EMP	right
5.1-5.3	Finger exposed hand	Eye	R-PA R-EMP	right (R-PA > R-EMP)
5.4		Verbal	R-PA REMP	right (R-PA > R-EMP)
6.1-6.3	Finger unexposed hand	Eye	R-PA R-EMP	right
6.4		Verbal	R-PA R-EMP	right

2.3 Analysis

2.3.1 Data Preparation

A negligible number of problematic trials, noted as such by the experimenter during experimental sessions, were removed in the first instance (Appendix A). R basic package (R Core Team, 2016) and *dpylr* package (Wickham, Francois, Henry, & Müller, 2017) were used to prepare the data.

2.3.2 Data Measurement

The dependent variables were captured in pixels, and calculated as the difference, or error, between the objective target and the participant's response. The after-effect was calculated by subtracting the baseline (post-sham) scores from the post-manipulation scores. Negative values denote leftward, and positive values dente rightward after-effects. Pixels were converted to visual angles (10 pixels = 0.335°).

2.3.3 Data Analysis

A mixed effects linear modelling approach was chosen. An important advantage of this approach compared to repeated-measures ANVOA is that it facilitates the inclusion of all data. With all trials included (i.e., participant data are not aggregated) the data variability and hence the signal-to-noise ratio is maximised. This approach can also cope with missing data.

R (R Core Team, 2016) and *nlme* (Pinheiro, Bates, DebRoy, Sarkar, & Team, 2017) was used to compute the linear mixed effects analysis with a maximum likelihood method. Following proposed guidelines (Barr, Levy, Scheepers, & Tily, 2013), a maximal random effects structure was chosen based on the experimental design. The aim of this approach is to maximise the generalizability of the results and minimise type 1 error.

In the current analysis this meant that a random intercept for participant and random slopes for Time (post-sham, post-shift) and Shift (R-EMP, R-PA) and their interaction were set in all cases. The random intercept accounts for the non-independence of responses from the same participant whereas the random slopes, by allowing for variation in the sensitivity of each participant to those factors, improve the model's generalizability.

A control predictor of Position (annulus/stimuli appearing left, right, and sometimes objective straight ahead depending on the task) was included when present

in the task, however, a corresponding random effect was not included (Barr et al., 2013).

A model containing only the random effects and the control predictor served as a baseline against which a model containing the predictors of interest was compared via an ANOVA with p-values obtained by χ square test.

In all cases the predictors of interest were Time (post-sham, post-shift), Shift (R-EMP, R-PA) and their interaction. These two-level categorical predictors were centred to decrease correlations among the residuals. Centring also has the benefit of producing a value for the intercept-change per predictor. However, unlike a contrast-based approach, it requires further tests to clarify any significant interactions. These tests were conducted via a least squared means test analysis based on a general linear model, specified as above, where the predictors were not centred to accommodate the analysis. The R packages *lsmeans* (Lenth, 2016) and *multcomp* (Hothorn, Bretz, & Westfall, 2008) supported that analysis.

The r-squared value was computed using the *sjstats* package for R (Lüdecke, 2017) and represents the correlation between the fitted and observed values. Checks on homoscedasticity and normality of the model residuals were done through visual inspection of residual plots. Outliers that were over 3 S.D.s from the residual mean, and where further inspection revealed no underlying cause of interest other than a suspected behavioural anomaly, were removed (Appendix A). Such removals did not change the significance or interpretation of the results but did improve the fit of the model.

Descriptive statistics were extracted on observed (unfitted) data using the *pastecs* package for R (Grosjean, Ibanez, & Etienne, 2014) and graphs, based on said data, were developed with the *ggplot2* package (Wickham, 2009). Unfitted data were chosen for descriptions and graphs in order to provide a rich overview of the data alongside the analytical technique employed.

2.4 Results

This section opens with a results overview and some limited interpretation. The remainder of this chapter section consists of: graphs of the after-effects grouped for comparison purposes, descriptive data for the various tasks; details of statistical analyses per task and any comparison analyses, and finally, a summary results table.

2.4.1 Results Overview

Errors during exposure.

As expected the rightward pointing errors created by the prism declined rapidly during the initial R-PA exposure. Unexpectedly, given the large number of trials, these errors stabilised but did not return to baseline by the end of that first exposure period. The initial rightward pointing errors in the two subsequent top-ups showed signs of some loss of adaptation. However, these errors rapidly decreased and a return to baseline errors was observed at the end of each of the top-up periods. These direct errors, while not a measure of adaptation *per se*, suggest that participants may not have been fully adapted when they undertook the first two after-effect tasks but were fully adapted for the later tasks (section 2.4.2, fig 2.10, table 2.3). As predicted, the rightward pointing errors during the R-EMP remained constant throughout all three exposure-periods (section 2.4.2, fig 2.11, table 2.4).

After-effect errors.

Contrary to predictions of a rightward after-effect, all three measures, two eye-position and one perceptual, taken during the visual straight-ahead (VSA) task revealed no significant change in either the R-PA or R-EMP condition. This suggests that, following 96 exposure trials, neither manipulation had any effect on any extra-retinal signals. However, graphically there is an indication in the R-EMP condition that an expected rightward after-effect was emerging by the end of the task (section 2.4.2, figs 2.12 & 2.13, tables 2.5 & 2.6).

Consistent with predictions, there was a significant leftward after-effect in the R-PA condition in the straight-ahead pointing (SAP) eyes closed task, indicative of an adaptive leftward motor response to a rightward shift in the proprioceptive estimate of arm position. As predicted there was no change in SAP following R-EMP – due to the lack of feedback during the exposure, no conflict between ocular and limb proprioceptive spatial coding was registered and therefore no adaptation took place (although note that, in any case, the results of the VSA task suggest that no significant eye position change had taken place in order to create a conflict). (section 2.4.2, fig 2.13, table 2.6)

In contrast with predictions of a rightward after-effect, following R-PA there was no change in either of the two eye-position measures taken during the SAP eyes open task – eye-position continued in the straight-ahead position in the orbit. Thus, even after a top-up of 30 prism adaptation trials where errors returned to baseline

levels, these eye-position measures provided no evidence supportive of a change in ocular spatial coding. There was, however, a leftward pointing after-effect that was significantly larger than that observed during the SAP eyes closed task.

Comment: While it cannot be ruled out that this larger pointing after-effect was due to further adaptation, 50 trials have been proposed to be sufficient to establish adaptation (Bultitude et al., 2016). Indeed, after-effects including visual ones, have been recorded after as few as 30 trials (Redding et al., 2005). Further, larger pointing errors have previously been reported in OLP compared to SAP tasks in the absence of a visual shift (Hatada et al., 2006; Michel et al., 2013; Welch et al., 1974). Thus, the results of the SAP eyes open task for R-PA suggest a potential paradox - with eyes open, and in the absence of visual stimuli, participants continued to look straight ahead but pointed further leftwards than when they had their eyes closed (section 2.4.2, figs 2.12 & 2.13, tables 2.5 & 2.6).

The results of the SAP eyes open task following R-EMP conformed to the prediction of no interaction between the ocular and limb systems. There was a significant rightwards after-effect of both eye position measures, suggesting that following the additional top-up exposure eye muscle potentiation had taken place. (It is known that eye muscle potentiation effects take time to arise (Paap & Ebenholtz, 1976; Ronga et al., 2017), however, it did take longer than expected.) There was no change in straight-ahead pointing.

Comment: Combined, this suggests that this particular task precluded the opportunity for the induced misalignment between ocular and limb spatial coding to be detected. In contrast to the results of the R-PA condition for this task, and taken on its own, it suggests that in the absence of a perturbation, each effector responded independently (high confidence in its own reliability) to this task (section 2.4.2, figs 2.12 & 2.13, tables 2.5 & 2.6).

Concordant with predictions, there is a significant leftward after-effect in the R-PA condition in the open loop pointing (OLP) task. This active task is understood to reflect the combined adaptive responses of limb and ocular proprioception (i.e., linear additivity, OLP = SAP – VSA).

Comment: The results confirmed that following R-PA, OLP was significantly larger than SAP eyes closed but, given the lack of VSA after-effect, the results do not seem to reflect linear additivity. (However, the caveat of the top-up prism exposure between the SAP and OLP tasks as explanatory remains.) There was no significant

difference between the pointing after-effect of the OLP and the SAP eyes open measures. This suggests that retinal stimulation and visual re-afference are not part of the reason for the conventionally reported magnitude difference between OLP and SAP eyes closed: an interaction between the senses in the absence of visual re-afference may suffice. (However, this is not to rule out a role for retinal signals.) (section 2.4.2, fig 2.13, table 2.6)

Against predictions of a rightward after-effect, there was no error change in the OLP task following R-EMP. In fact, the results of the first four trials showed an unexpected leftward after-effect.

Comment: One possibility is that a feedback interaction did take place after all in the preceding SAP eyes open task – perhaps a tactile one, given the use of the touchscreen. This would have created an error signal and in turn resulted in a change in the reliability estimates assigned to effector positions which then became evident in the OLP task. Additionally, or alternatively, it may reflect a waning of the eye muscle potentiation effect and represent a potentiation-depression effect. It has been shown that eye muscle potentiation effects are subject to rapid decline followed by a period of depression where directional effects are reversed (Paap & Ebenholtz, 1976). However, as eye position is not reported for this task, for calibration reasons, this suggestion cannot be expanded upon. (section 2.4.2, fig 2.13, table 2.6)

The results of the finger location tasks, which followed the last exposure top-up, mirrored the predictions. For the exposed right hand, there was a rightward after-effect following R-PA and R-EMP and it was significantly larger for R-PA compared to R-EMP. For the unexposed left hand, there was a rightward after-effect following both conditions that were of the same magnitude. Combined, the finger location results reveal that the eye came to rest rightward of the imagined location of a target suggestive of an ocular mechanism underlying the effects in both conditions. (section 2.4.2, figs 2.15 & 2.16, table 2.7)

Comment: It is noteworthy that the finger location tasks took longest to complete due to the equipment set-up and the time taken to passively move the participant's arm. While this may account for the need to collapse measures following R-EMP, there was nonetheless a significant rightward deviation in eye position. This lends support to the suggestion that the tactile error feedback of the SAP eyes open task prompted a correction in the system and resulted in no change in pointing to target with eyes open (OLP) following R-EMP. This pattern of events is coherent

with the finding that even though the sensory systems are not normally fully aligned at baseline (Smeets et al., 2006), they are at the very least resistant to directional uncoupling (Schmitz & Grigorova, 2017). Inter-sensory calibration in the absence of external feedback (the goal of which is internal consistency in cue estimation) has previously been shown to take place, and to use reliability weightings (Burge et al., 2010). Thus, it is not inconceivable that the SAP eyes open task also precipitated a decline in the R-EMP eye-position shift, which resulted in the pattern of OLP after-effects. That eye-position after-effects became apparent again in the finger location tasks was due to the intervening top-up.

2.4.2 Graphs and Tables

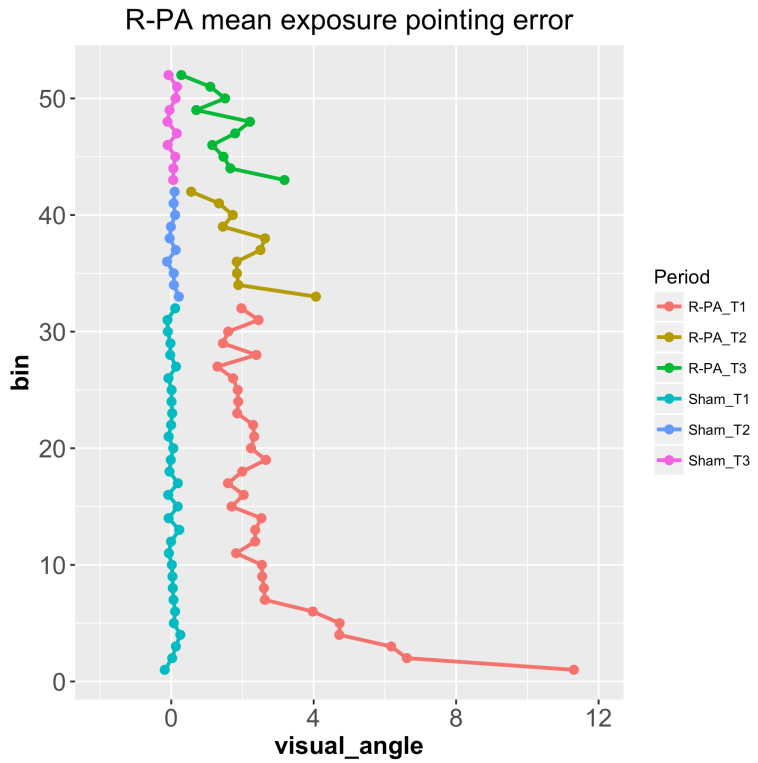


Figure 2.10: Group mean pointing error, during the sham and exposure periods of R-PA. T1 periods have 32 bins. T2 and T3 top-up periods have 10 bins. Sham T1-T3 are to the left of the image. Positive values = rightward error. (1 bin = 3 trials).

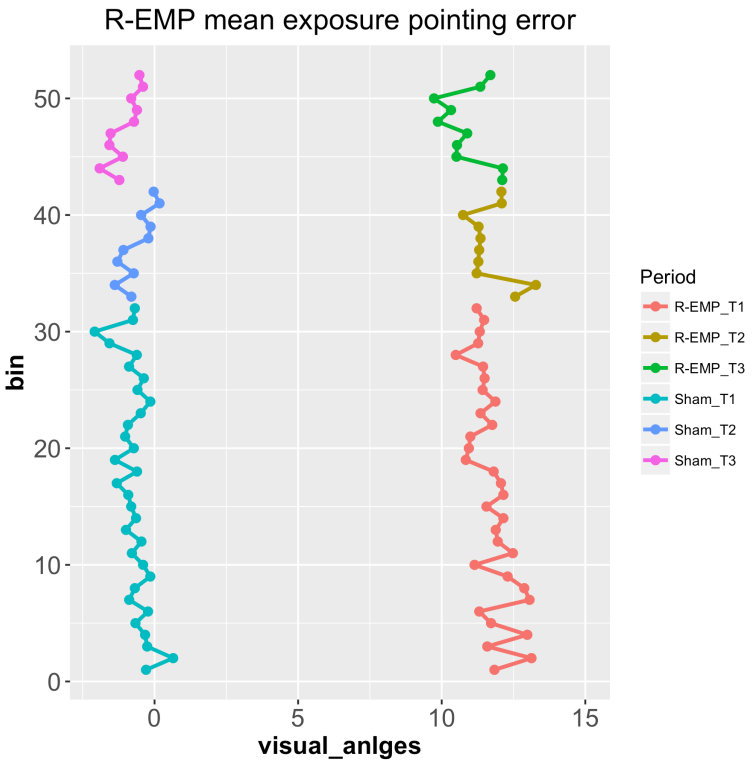


Figure 2.11: Group mean pointing error during the sham and exposure periods of R-EMP. T1 periods have 32 bins. T2 and T3 the top-up periods have 10 bins. Sham T1-T3 are to the left of the image. Positive values = rightward error. (1 bin = 3 trials).

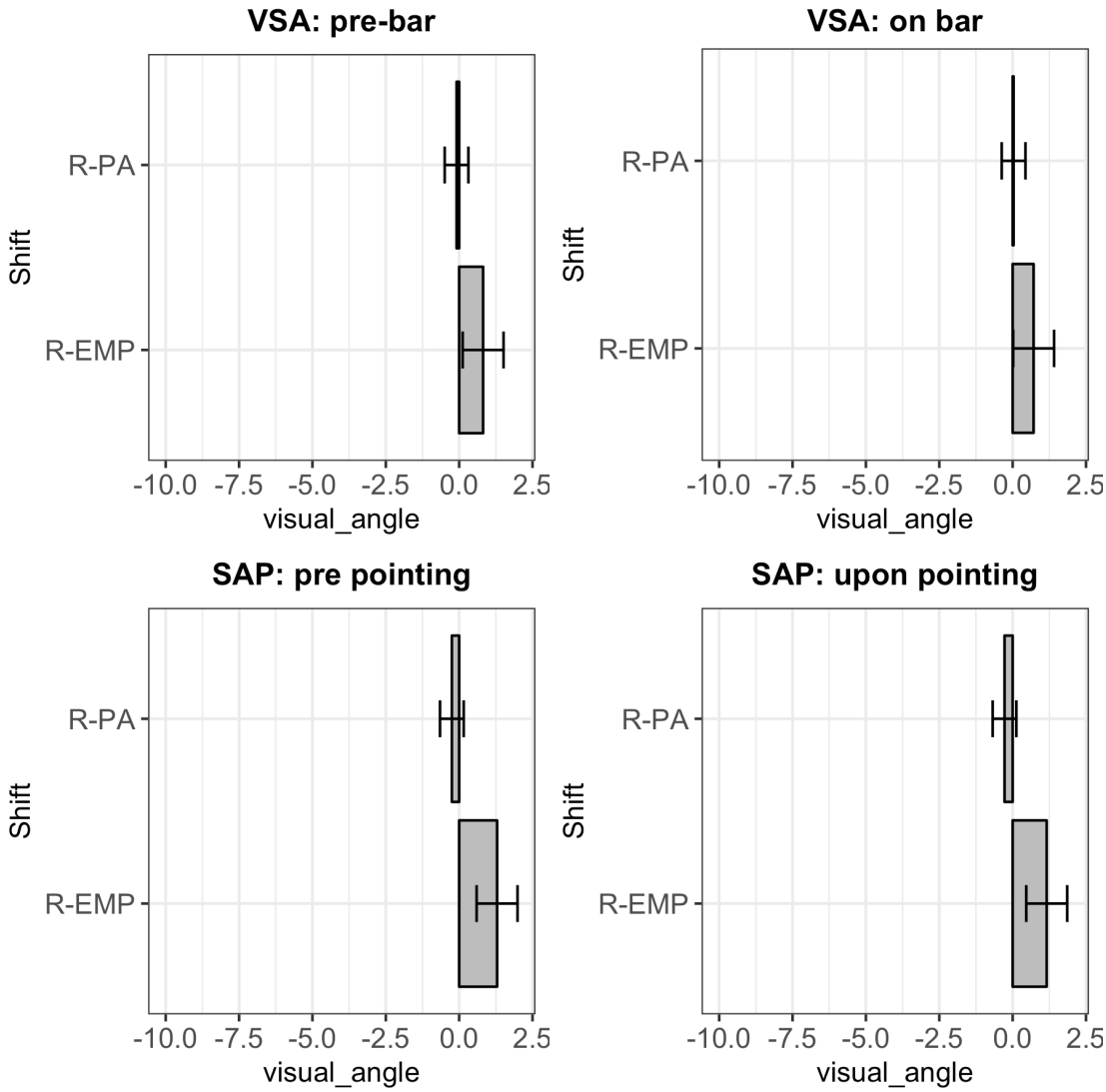


Figure 2.12: Group mean eye-position after-effects. Top row: prior to (left) and upon (right) positioning a bar to VSA with the unseen unexposed hand. Bottom row: prior to (left) and upon (left) SAP with the unseen exposed hand. Error bars are 95% confidence intervals. Negative values = leftwards after-effect.

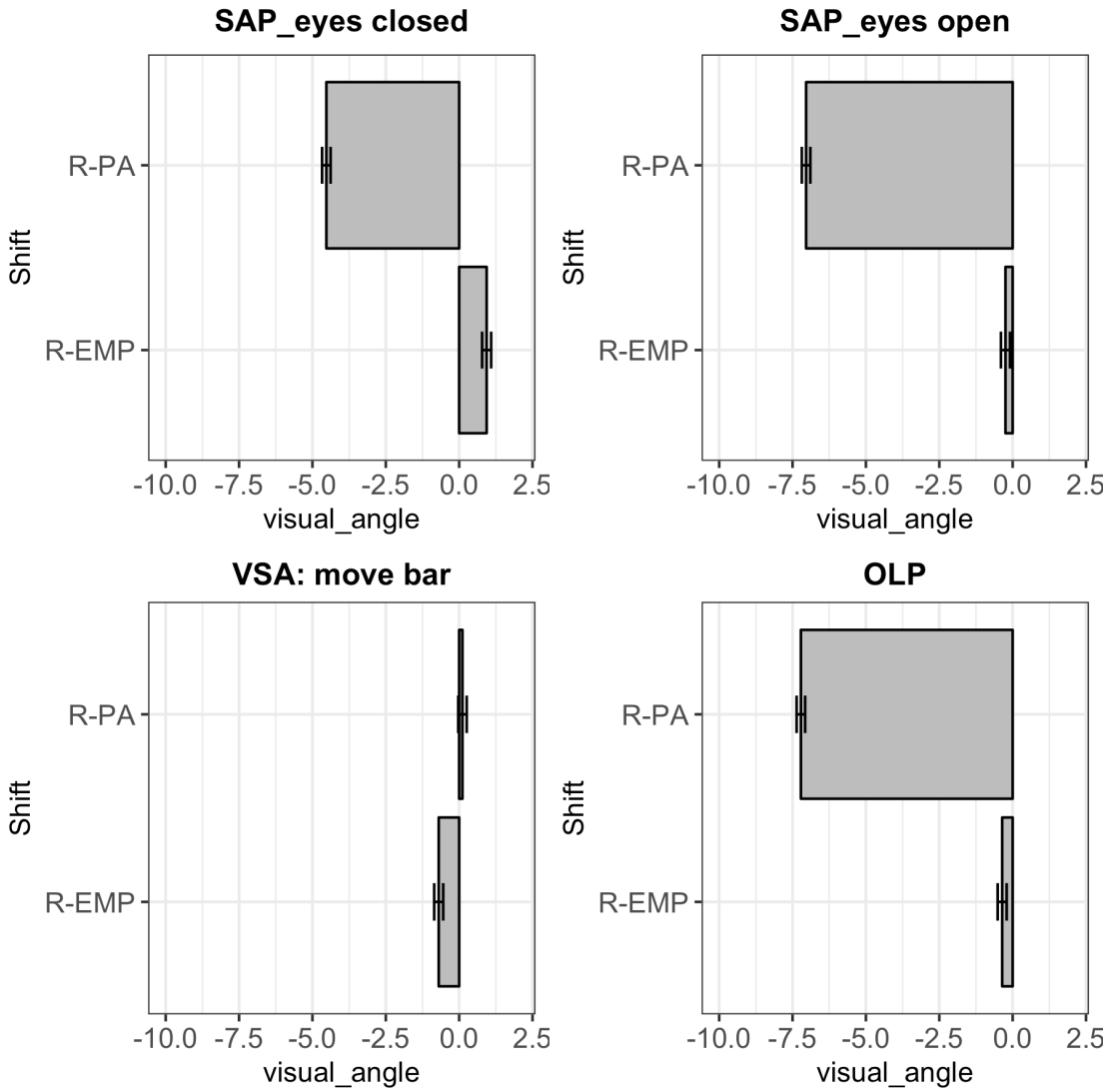


Figure 2.13: Group mean after-effects. Top row: SAP eyes closed pointing (left) and SAP eyes open pointing (right) with the unseen exposed hand. Bottom row: perceptual VSA (left), OLP pointing with unseen exposed hand (right). Error bars are 95% confidence intervals. Negative values = leftwards after-effect.

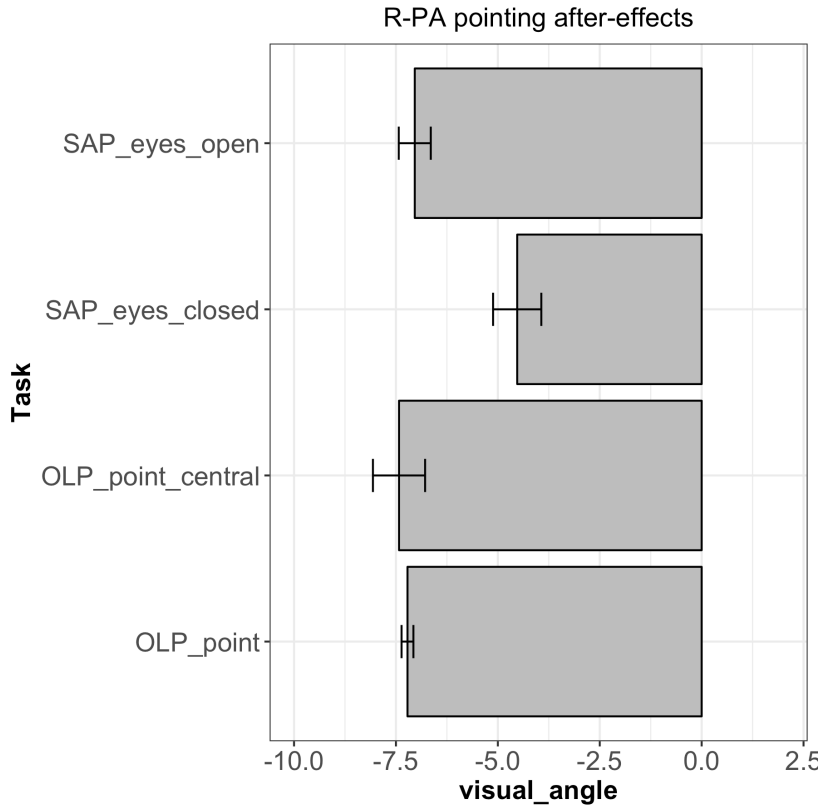


Figure 2.14: Group mean pointing after-effects following R-PA (hand unseen in all tasks). Error bars are 95% confidence intervals. Negative values = leftward after-effect. (OLP point central = the four trials that lie within the 95% confidence interval of baseline straight ahead scores, included to demonstrate no difference between them and OLP across all targets).

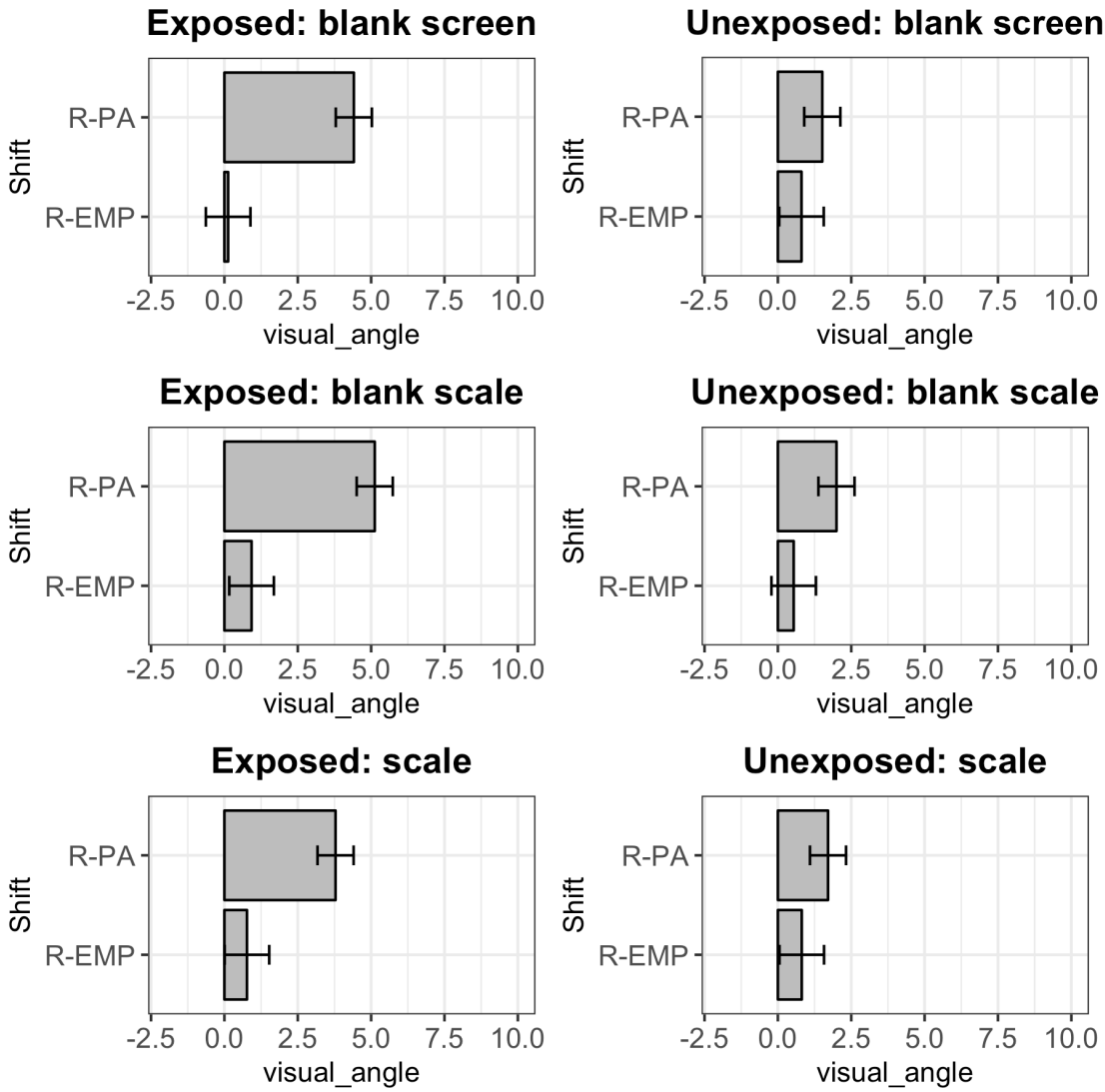


Figure 2.15: Group mean eye position after-effect of finger location tasks. Left column: exposed hand. Right column: unexposed hand. Top row: blank screen, Middle row: un-numbered scale. Bottom row: numbered scale. Error bars are 95% confidence intervals. Positive values = rightward change.

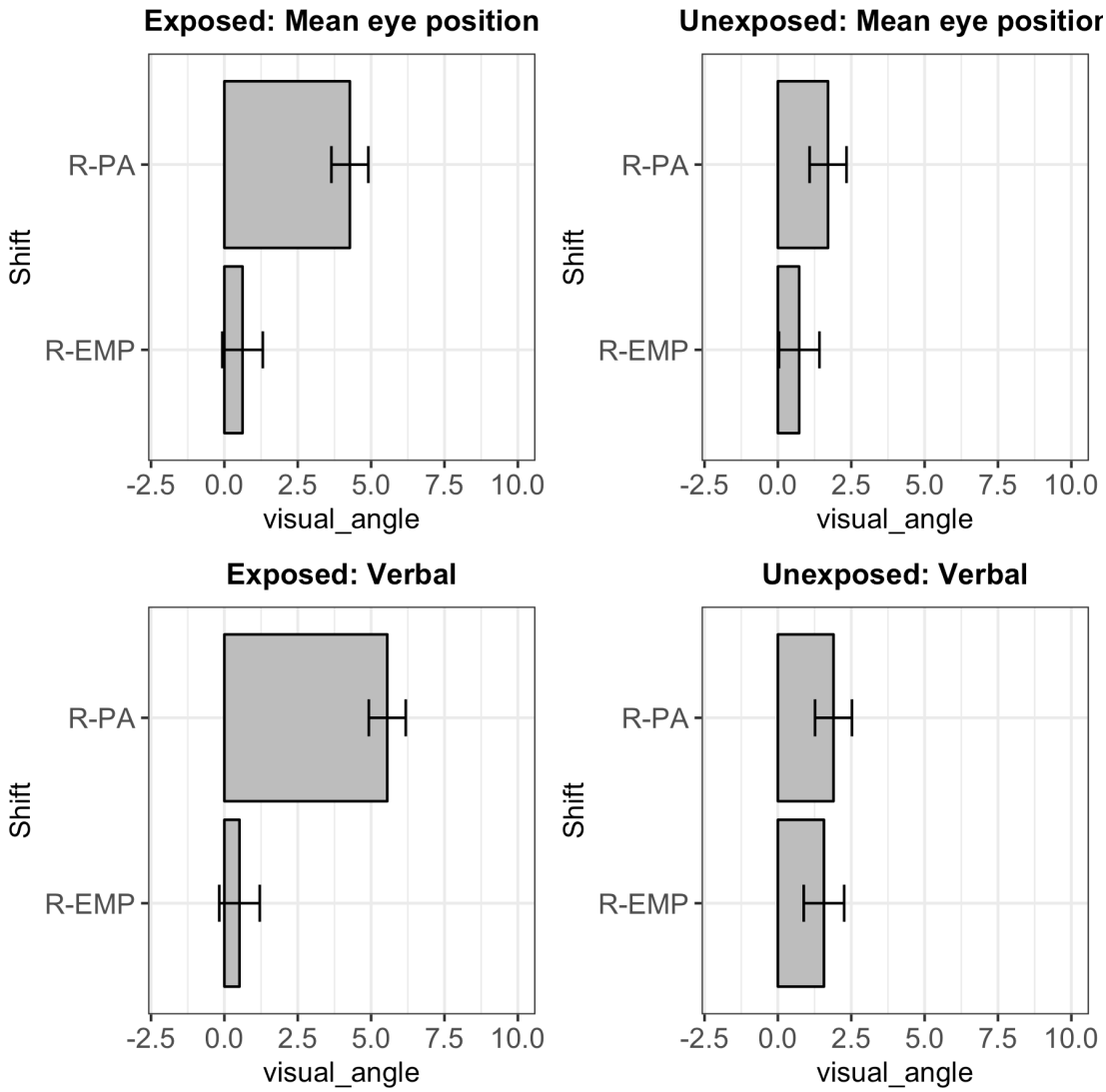


Figure 2.16: Finger location group mean after-effect. Left column: exposed hand. Right column: unexposed hand. Top row: mean eye position, Bottom row: verbal response. Error bars are 95% confidence intervals. Positive values = rightward change.

Table 2.3: Exposure pointing error, visual angles. Positive values = rightward error.

Shift	Time	Period	Bin	Mean	S.E.
R-PA	sham	T1	First	-0.18	0.13
			Last	0.11	0.08
		T2	First	0.20	0.12
			Last	0.09	0.07
		T3	First	0.03	0.16
			Last	-0.08	0.06
	post	T1	First	11.31	0.68
			Last	1.97	0.40
		T2	First	4.01	0.55
			Last	0.56	0.14
		T3	First	3.18	0.59
			Last	0.28	0.16

Table 2.4: Exposure pointing error, visual angles. Positive values = rightward error.

Shift	Time	Period	Bin	Mean	S.E.
R-EMP	sham	T1	First	-0.30	0.7
			Last	-0.69	0.8
		T2	First	-0.81	0.5
			Last	-0.03	0.6
		T3	First	-1.23	0.5
			Last	-0.53	0.7
	post	T1	First	11.84	0.8
			Last	11.22	1.0
		T2	First	12.56	0.6
			Last	12.08	0.7
		T3	First	12.11	0.8
			Last	11.69	0.7

Table 2.5: Eye position error, in visual angles, for VSA and SAP eyes open tasks. Statistics based on unfitted values. Negative values = leftward error.

Task	Measure	Time	Shift	Mean	S.E.
VSA pre bar	Eye position	sham	R-PA	0.690	0.282
		post		0.558	0.330
		sham	R-EMP	0.084	0.234
		post		0.825	0.256
Upon VSA bar	Eye position	sham	R-PA	0.710	0.086
		post		0.715	0.075
		sham	R-EMP	0.161	0.085
		post		0.877	0.110
SAP pre pointing	Eye position	sham	R-PA	0.569	0.175
		post		0.296	0.133
		sham	R-EMP	-0.334	0.146
		post		0.898	0.138
SAP upon pointing	Eye position	sham	R-PA	0.926	0.217
		post		0.701	0.146
		sham	R-EMP	-0.299	0.226
		post		0.930	0.161

Table 2.6: Error, in visual angles, for the traditional tasks. Statistics based on unfitted values. Negative values = leftward error.

Task	Measure	Time	Shift	Mean	S.E.
VSA	Set bar unseen unexposed hand	sham	R-PA	-0.343	0.077
		post		-0.230	0.062
		sham	R-EMP	0.422	0.172
		post		-0.275	0.074
SAP eyes closed	Touch point	sham	R-PA	0.075	0.318
		post		-4.45	0.334
		sham	R-EMP	-1.36	0.330
		post		-0.425	0.344
SAP eyes open	Touch point	sham	R-PA	0.254	0.182
		post		-6.78	0.169
		sham	R-EMP	-0.663	0.217
		post		-0.909	0.209
OLP	Touch point	sham	R-PA	0.051	0.059
		post		-7.17	0.082
		sham	R-EMP	-0.853	0.119
		post		-1.21	0.108

Table 2.7: Error, in visual angles, for the finger location tasks. Exposed right hand: top un-shaded rows, Unexposed left hand: bottom shaded rows. Statistics based on unfitted values. Negative values = leftward error.

Task	Measure	Time	Shift	Mean	S.E.
Finger location: blank screen	Eye position	sham	R-PA	4.07	0.366
		post		8.41	0.438
		sham	R-EMP	3.65	0.338
		post		3.75	0.396
Finger location: unnumbered scale	Eye position	pre	R-PA	3.64	0.381
		post		8.68	0.425
		pre	R-EMP	2.14	0.459
		post		2.90	0.471
Finger location: numbered scale	Eye position	sham	R-PA	3.93	0.452
		post		7.74	0.663
		sham	R-EMP	2.60	0.428
		post		3.42	0.443
Finger location: verbal	Verbal	sham	R-PA	3.16	0.379
		post		8.71	0.496
		sham	R-EMP	2.06	0.348
		post		2.57	0.367
Finger location: blank screen	Eye position	sham	R-PA	-0.589	0.337
		post		0.917	0.442
		sham	R-EMP	-1.73	0.351
		post		-0.892	0.451
Finger location: unnumbered scale	Eye position	sham	R-PA	-1.45	0.361
		post		0.785	0.463
		sham	R-EMP	-1.97	0.342
		post		-1.62	0.429
Finger location: numbered scale	Eye position	sham	R-PA	-0.471	0.569
		post		1.02	0.699
		sham	R-EMP	-1.83	0.414
		post		-1.02	0.655
Finger location: verbal	Verbal	pre	R-PA	-1.50	0.335
		post		0.395	0.424
		pre	R-EMP	-2.88	0.312
		post		-1.31	0.588

2.4.3 Results per Task and Comparison Analysis

Right sham/prism exposure.

A comparison was made of the average of the last 3 trials of each sham and prism exposure period to assess via exposure pointing errors (the direct effects) whether there was a reduction in pointing errors across exposure tasks. It must be noted however that direct effects, unlike after-effects, are not a measure of adaptation *per se*. The results of the Bonferroni corrected Tukey follow-up tests to a linear mixed effects analysis on pointing errors with time (sham R-PA, R-PA) and period (T1, T2, T3) as fixed effects are presented in Appendix B. (Due to convergence issues the interaction between time and period could not be included as a random effect.)

As expected there were no significant differences between any of the sham errors: pointing errors were stable at baseline. There was a significant difference between sham T1 and post T1 meaning that pointing errors had not returned to baseline following 96 trials of adaptation; and a significant difference between the last three pointing errors at post T1 and post T2 meaning that further error correction had taken place by the end of post T2. There was no significant difference between post T2 and post T3 suggesting error correction was similar at the end of those last two exposure periods. However, there was a trend toward a significant difference between the last three pointing errors of pre T3 and post T2 (but not between pre T3 and post T3). Error details for the first and last bin of each period are provided in table 2.3. In sum, it appears that direct effects did not reach stability until the end of T2 (fig 2.10).

Right sham/EMP exposure.

A comparison was made of the average of the last 3 trials of each sham and prism exposure period as per the approach for the R-PA data. The stability of the errors during the sham pointing, during the exposure pointing, and the stability of the difference between sham and exposure were confirmed. There were no significant differences in the errors between the sham periods, there were no significant differences in the errors between the exposure periods, and each combination of sham and exposure period errors were significantly different from each other. The details of the fifteen tests are not presented for reasons of brevity. The lack of reduction in pointing errors during R-EMP exposure is illustrated in figure 2.11. With the prism in place a mean rightward after-effect error of 12.33° (SE = 0.49°) was produced across all R-EMP exposure trials. Variability in pointing due to lack of visual feedback of

the hand is apparent from the baseline sham data in figure 2.11. Error details for the first and last bin of each period are provided in table 2.4.

The following analyses use a baseline model against which to compare a test model. The baseline model contains the dependent variable, random effects (Time (post-sham, post-shift) and Shift (R-EMP, R-PA)) and their interaction and any control predictors (e.g., annulus/stimulus position). The test model contains the predictors of interest - Time (post-sham, post-shift) and Shift (R-EMP, R-PA)) and their interaction. The dependent variable is the error from the objective target that is pertinent to the task. Where the test model is significantly different from the baseline model and the interaction between the predictors is significant follow-up tests are conducted. See section 2.3 for further details.

Task 1: visual straight ahead.

Task 1 element 1: Look straight ahead before bar appears (Eye position)

The model is not significantly different from baseline (χ^2 (3) = 2.05, p =.562): Neither R-PA nor R-EMP produced a significant eye position after-effect while looking to subjective straight-ahead. There is a weak correlation between the fitted and observed values, R^2 = .25. See Appendix C, table C1 for model details. Descriptive statistics: table 2.5, after-effect illustration: figure 2.12 top left.

Task 1 element 2: Positioning an on-screen bar to subjective visual straight-ahead

The model is not significantly different from baseline (χ^2 (3) = 2.44, p = .487), (appendix C table C2): Neither R-PA nor R-EMP produced a significant VSA after-effect on perceptual visual straight-ahead. There is a strong correlation between the fitted and observed values, R^2 = .73. Descriptive statistics: table 2.6, after-effect illustration: figure 2.13 bottom right.

Task 1 element 3: Looking at on-screen bar post positioning it straight ahead (Eye position)

The model is not significantly different from baseline (χ^2 (3) = 2.59, p = .459), (appendix C table C3): Neither R-PA nor R-EMP produced a significant eye position

after-effect when looking at perceptually defined subjective straight-ahead. There is a strong correlation between the fitted and observed values, $R^2 = .71$. Descriptive statistics: table 2.5, after-effect illustration: figure 2.12 top right.

Finally, for this task it could be considered appropriate to test the difference between eye position prior to positioning the line and the visual positioning of the line; as well as the difference between eye position upon positioning the line and the line position. These differences were calculated and the tests run, null findings were returned – no changes were evoked by either condition. The details are not presented for reasons of brevity.

Task 2: straight-ahead pointing – eyes closed.

The model is significantly different from baseline (χ^2 (3) = 28, $p<.001$), appendix D. There is a strong correlation between the fitted and observed values, $R^2 = .89$. A significant rightward after-effect in pointing to subjective straight-ahead with eyes closed was found following R-PA (M = -4.39, SE = 0.67, $t(552) = -6.55$, $p<.001$) but there was no change following R-EMP (M = 0.936, SE = 0.613, $t(552) = 1.53$, $p = .13$) as confirmed by least squared means testing. Descriptive statistics: table 2.6, after-effect illustration: figure 2.13 top left.

Task 3: straight ahead look & point.

Task 3 Element 1: Look straight-ahead prior to SAP (Eye position).

The model approached significant difference from baseline (χ^2 (3) = 7.25, $p = .064$). There is a strong correlation between the fitted and observed values, $R^2 = .78$. Model details are presented in table 2.8. Given the trend here (and in element 3 of this task, see below) the interaction was inspected. There was a significant rightward eye position after-effect when looking straight ahead prior to pointing to subjective straight-ahead with the unseen hand following R-EMP (M = 1.28, SE = 0.44, $t(533) = 2.92$, $p = .004$) but no change following R-PA (M = -0.214, SE = 0.316, $t(533) = -0.68$, $p = .500$) as confirmed by least squared means testing.. Descriptive statistics: table 2.5, after-effect illustration: figure 2.12 bottom left.

Table 2.8: Predictive model details: effect of shift-type on eye position prior to SAP. Items in grey refer to baseline model. Position is a control predictor for left/right appearance of annulus. Model df = 555.

Fixed Effects	*b*	SE *b*	95% CI	*t*-value	*p*-value
Intercept	0.273	0.233	[-0.183, 0.728]	1.17	.242
Position	0.271	0.070	[0.134, 0.408]	3.86	<.001
Shift	-0.179	0.240	[-0.647, 0.290]	-0.75	.456
Time	0.533	0.210	[0.122, 0.944]	2.54	.012
Shift:Time	1.50	0.642	[0.239, 2.72]	2.33	.020

Task 3 Element 2: SAP eyes open (hand unseen, no visible target).

The model is significantly different from baseline (χ^2 (3) = 58.4, p<.001), appendix E. There is a strong correlation between the fitted and observed values, R^2 = .91. Least squared means testing confirmed a significant leftward after-effect in pointing to subjective straight ahead with the unseen hand and with eyes open following R-PA (M = -6.94, SE = 0.344, t(548) = -20.16) but no change following R-EMP (M = -0.275, SE = 0.430, t(548) = -0.64 , p = .524). Descriptive statistics: table 2.6, after-effect illustration: figure 2.13 top right.

Task 3 Element 3: Look straight ahead while pointing straight ahead with unseen hand, no visible target (Eye position).

The model approached significant difference from baseline (χ^2 (3) = 7.64, p = .054). There is a strong correlation between the fitted and observed values, R^2 = .78. Model details are presented in table 2.9. Given the trend here (and in element 1 of this task, see above), the interaction was inspected. There was a significant rightward eye position after-effect for pointing to subjective straight-ahead with the unseen hand following R-EMP (M = 1.14, SE = 0.414, t(364) = 2.75, p = .006) but no change following R-PA (M = -0.221, SE = 0.257, t(364) = -0.86, p = .388) as confirmed by least squared means testing. Descriptive statistics: table 2.5, after-effect illustration: figure 2.12 bottom right.

Table 2.9: Predictive model details: effect of shift-type on eye position upon SAP eyes open. Items in grey refer to baseline model. Position is a control predictor for left/right appearance of annulus. Model df = 386.

Fixed Effects	*b*	SE *b*	95% CI	*t*-value	*p*-value
Intercept	0.510	0.268	[-0.026, 1.05]	1.90	.058
Position	0.317	0.091	[0.134, 0.499]	3.47	<.001
Shift	-0.238	0.252	[-0.742, 0.266]	-0.95	.345
Time	0.456	0.155	[0.147, 0.765]	2.95	.003
Shift:Time	1.36	0.621	[0.117, 2.60]	2.19	.029

Task 4: open loop pointing.

Task 4 Element 1: OLP (visual target, hand unseen).

The model significantly differed from baseline (χ^2 (3) = 67.2, p<.001), appendix F. R^2 = .89 represents a strong correlation between the fitted and observed values. A significant OLP leftward after-effect was found following R-PA (M = -7.22, SE = 0.287, t(2569) = -25.13 p <.001) but there was no change following R-EMP (M = -0.370, SE = 0.285, t(2569) = -1.29, p = .195) as confirmed by least squared means testing. Descriptive statistics: table 2.6, after-effect illustration: figure 2.13 bottom right.

A significant rightward pointing after-effect in OLP had been expected following R-EMP (and indeed it would be expected following the rightward eye position after-effect captured in the preceding task). It was therefore decided to investigate only the initial trials on the basis that the multiple eye-movements between calibration and 36 trials of the task may have weakened the effect. A simplified version of the model was run (no random intercepts or controls were necessary as only the first trial was included).

The model significantly differed from baseline (χ^2 (3) = 93.4, p<.001). R^2 = .81 represents a strong correlation between the fitted and observed values. Least squared means testing confirmed a significant leftward OLP after-effect (M = -7.85, SE = 0.611) of R-PA t(51) = -12.83 p <.001, and an unexpected *leftward* after-effect of R-EMP (M = -1.15, SE = 0.612), t(51) = -1.88, p = .034 one-tailed**.**

R-EMP continued to have a significant leftward effect on OLP for the first four trials, (M = -0.556, SE = 0.314), t(266) = -1.77, p = .039 one-tailed**.** However,

inspection following eight trials (chosen because it is the amount of trials in the SAP tasks) reveals that by this point the effect had disappeared and OLP did not differ from baseline (M = -0.398, SE = 0.307), $t(554) = -1.29$, $p = .098$ one-tailed**.**

Comparisons across R-PA pointing tasks after-effects.

Following PA OLP after-effects are conventionally reported as larger than SAP with the difference attributed to the summation of two erroneous sensory errors (eye and limb) to a visual target compared to a uni-sensory response (limb only). The current results for R-PA present a potential conundrum with regard to conventional accounts of additivity (i.e., OLP = SAP eyes closed – VSA). No VSA after-effect was found yet OLP was greater than SAP eyes closed. Furthermore, figure 2.14 appears to show no difference in after-effects between pointing without or to a visual target (SAP eyes open and OLP respectively) and that both these tasks prompted a larger after-effect than SAP eyes closed.

Due to the different number of trials per task, the means of the three tasks were submitted to a repeated-measure ANOVA with the factors Time (sham, post R-PA) and Task (SAP eyes closed, SAP eyes open, OLP). There was a main effect of Time ($F(1, 17) = 294.9$, $p<.001$, $\eta_G^2 = .63$) reflecting the leftward pointing after-effect brought about by all tasks. The Greenhouse-Geisser corrected main effect of Task, ($F(1.31, 22.19) = 3.29$, $p= .07$, $\eta_G^2 = .06$), was not significant – all tasks induced a leftward pointing after-effect. The Time by Task interaction was significant, ($F(1.5, 25.5) = 13.5$, $p<.001$, $\eta_G^2 = .06$). Multiple follow-up Bonferroni-adjusted comparisons were conducted, details in appendix G. As expected, there were no significant differences between any of the sham-errors among the tasks (not shown in appendix for brevity); and the within-task after-effects were significantly different from null.

The results also revealed that there was no difference between the post-errors of OLP and SAP eyes-open and there were differences between the post-errors of each of those tasks and that of SAP eyes closed (shaded rows in appendix G).

The significant difference between OLP and SAP eyes closed alongside the lack of a VSA after-effect confirmed that the larger after-effect in the OLP task compared to SAP with eyes closed, cannot be attributable to additivity of ocular and limb errors as conventionally described.

However, although there was no shift in eye position in the SAP eyes open task, paradoxically the pointing error in this task was larger than that found in SAP

eyes closed and equal to that found in OLP. These comparisons, alongside the larger OLP compared to SAP eyes closed, indicate that despite the lack of additivity, a change had occurred in the ocular system, perhaps specifically in how it interacts with the limb, and that it was not dependent on retinal stimulation or visual reafference.

Comparisons across R-EMP pointing tasks after-effects.

Following R-EMP there were no significant after-effects in any of the pointing tasks (SAP eyes closed, SAP eyes open, OLP). Numerically, the pointing deviated to the right somewhat following SAP eyes closed, but it was not a statistically reliable after-effect. (This was true also of the first trial, not reported). This finding demonstrates that the task did not result in any significant limb muscle potentiation. This may be explained by the way the limb was exercised. It partook in a mix of radial (forwards-backwards) and sustained lateral pointing and was raised against gravity. This combination of muscle use guarded against any focused potentiation effects.

In SAP eyes open, both in the first trial (not reported) and across all eight trials combined, there was no significant after-effect. Because of the lack of visual feedback during the exposure manipulation, the CNS received no signals that the normal alignment between eye and hand state-estimates was no longer present. Given that eye position was significantly deviated to the right but the limb pointed straight-ahead, this suggests that during the task there was no interaction between the signals – in the absence of a visual target both effectors went to their current default settings for straight-ahead.

Consistent with findings reported in the EMP literature, it had been predicted that OLP pointing would be deviated in the direction of displacement. That is, in the presence of a visual target there would be a spatial coherence between the eye and the limb, such that the limb would point to where the deviated eye was positioned. This would occur because no error had been detected and the CNS had not been alerted to downgrade the reliability of the eye-position estimate. Unfortunately, given the calibration issues (discussed in the methods section) we do not have useful information on eye position after-effects in this task. What was observed was that there was no pointing after-effect across the combined entirety of the 36 trials, but that for the first four trials there was a leftward pointing after-effect (i.e., opposite the direction of displacement). There are three potential explanations, that together or on

their own may have caused this result: a potentiation decay effect across time; a decay effect following calibrations; and a degree of inter-sensory recalibration. Inter-sensory recalibration in the absence of explicit feedback, thought to be useful for internal consistency, has been reported (Burge et al., 2010). The set-up resulted in pointing that was accompanied by tactile feedback. Pressure felt to either side of the tip of the finger could constitute an error feedback. Touch feedback following R-EMP exposure began during SAP eyes closed. That feedback returned during SAP eyes open, and along with potential eye-limb motor plan comparisons, may have precipitated an up-weighting of the reliability of the limb proprioception signal and/or a down-weighting the ocular signal – the net effect being straight-ahead pointing.

Task 5: Finger localisation (exposed/pointing hand).

Task 5 Element 1: Look to where unseen finger of the pointing hand is located on a blank screen (Eye position).

The model was significantly different from baseline (χ^2 (3) = 23.5, p<.001), appendix H, table H1. There is a strong correlation between the fitted and observed values, R^2 = .71. A significant rightward eye position after-effect for visually locating the unseen finger on a blank screen was found following R-PA (M = 4.28, SE = 0.707, t(538) = 6.05, p<.001) but there was no change following R-EMP (M = 0.208, SE = 0.710, t(538) = 0.293, p = .385 one tailed) as confirmed by least squared means testing. Descriptive statistics: table 2.7, after-effect illustration: figure 2.15 top left.

Task 5 Element 2: Look to where unseen finger of the pointing hand is located on an un-numbered scale (Eye position).

The model was significantly different from baseline (χ^2 (3) = 27.9, p<.001), appendix H, table H2. There is a strong correlation between the fitted and observed values, R^2 = .74. A significant rightward eye position after-effect for visually locating the unseen finger of the exposed hand on an un-numbered scale was found following R-PA (M = 4.70, SE = 0.679, t(479) = 6.93, p<.001) but there was no change following R-EMP (M = 0.7842, SE = 0.637, t(479) = 1.32, p = .093 one tailed) as confirmed by least squared means testing. Descriptive statistics: table 2.7, after-effect illustration: figure 2.15 middle left.

<u>Task 5 Element 3</u>: Look to where unseen finger of the pointing hand is located on a numbered stimulus (Eye position).

The model was significantly different from baseline (χ^2 (3) = 30.2, p<.001), appendix H, table H3. There is a moderate correlation between the fitted and observed values, R^2 = .53. A significant rightward eye position after-effect for visually locating the unseen finger of the exposed hand on a numbered scale was found following R-PA (M = 4.54, SE = 0.626, t(543) = 7.26, p<.001) and following R-EMP (M = 0.943, SE = 0.550), t(543) = 1.72, p = .044 one tailed**)** as confirmed by least squared means testing. Descriptive statistics: table 2.7, after-effect illustration: figure 2.15 bottom left.

Task 5 Elements 1-3

It had been predicted that there would be a rightward eye position after-effect in the R-EMP condition. Taking the directional hypothesis into account one of the above three measures of R-EMP eye position was significant and the other two were not. Given this inconsistency, it was decided to collapse the means of the three eye position measures by participant and to conduct a repeated-measure ANOVA with the factors Time and Shift. The results returned normally distributed residuals and revealed main effects of Time (F(1,17) = 40.4, p < .001, η_G^2 = .11) and Shift (F(1,17) = 25.9, p < .001, η_G^2 = .15) and a significant effect of their interaction (F(1,17) = 15.3, p = .001, η_G^2 = .06). On average, there was a significant rightward eye position after-effect for locating the finger of the unseen adapted hand following R-PA (M = 4.28°, SE = 0.334) and R-EMP (M = 0.619°, SE = 0.254), the change following R-PA was significantly larger than that following R-EMP. See figure 2.16 top left.

<u>Task 5 Element 4</u>: Verbal localisation on a numbered scale of the unseen finger of the pointing hand

The model was significantly different from baseline (χ^2 (3) = 33.3, p<.001), appendix H, table H4. There is a strong correlation between the fitted and observed values, R^2 =.76. A significant rightward after-effect for verbally locating the unseen finger of the exposed hand on a numbered scale was found following R-PA (M = 5.21, SE = 0.616) of R-PA t(552) = 8.47, p<.001, and a trend towards a significant rightward after-effect following R-EMP (M = 0.587, SE = 0.431, t(552) = 1.36, p =

.087, one-tailed) as confirmed by least squared means testing. Descriptive statistics: table 2.7, after-effect illustration: figure 2.16 bottom left.

Task 6: Finger location (non-pointing hand).

Task 6 Element 1: Look to where the unseen finger of the non-exposed hand is located on a blank screen (Eye position).

The model was not significantly different from baseline (χ^2 (3) = 6.21, p = .102). R^2 = .69 represents a strong correlation between the fitted and observed values. There was no change in eye position for locating the unseen finger of the unexposed hand on a blank screen following either condition. However, there is a main effect of Time within the model and a graphical indication (fig 2.15) that there is a rightward after-effect for both R-PA and R-EMP. This is further investigated below by testing the collapsed means of the three eye position tasks. Model details are presented in table 2.10. Descriptive statistics: table 2.7, after-effect illustration: figure 2.15 top right.

Table 2.10: Predictive model details: effect of shift-type on eye position when locating unseen finger of non-exposed hand on a blank screen. Items in grey refer to baseline model. Position is a control predictor for left/right appearance of annulus. Model df = 569.

Fixed Effects	*b*	SE *b*	95% CI	*t*-value	*p*-value
Intercept	-0.577	0.772	[-2.09, 0.933]	-0.75	.455
Position	-0.680	0.241	[-1.15, -0.209]	-2.83	.005
Shift	-1.48	0.667	[-2.79, -0.181]	-2.23	.026
Time	1.15	0.577	[0.023, 2.28]	1.99	.047
Shift:Time	-0.671	0.909	[-2.45, 1.11]	-0.74	.479

Task 6 Element 2: Look to where the unseen finger of the non-exposed hand is located on an un-numbered stimulus (Eye position in orbit).

The model was significantly different from baseline (χ^2 (3) = 8.96, p = .029), appendix I. There is a strong correlation between the fitted and observed values, R^2 = .71. A significant eye position after-effect for visually locating the occluded unexposed finger on a screen with an un-numbered scale was found following R-PA

(M = 2.00, SE = 0.641, $t(477) = 3.12$, $p = .002$) but not after R-EMP (M = -0.308, SE = 0.5636, $t(477) = 0.485$, $p = .314$ one tailed) as confirmed by least squared means testing. Descriptive statistics: table 2.7, after-effect illustration: figure 2.15 middle right.

Task 6 Element 3: Look to where the unseen finger of the non-exposed hand is located on a numbered stimulus (Eye position in orbit).

The model was significantly different from baseline (χ^2 (3) = 14.6, $p = .002$), and there was a significant effect of Time and no significant interaction between Time and Shift. A significant, and similar, rightward eye position after-effect for visually locating the unseen unexposed finger on a screen with a numbered scale was found following R-PA and R-EMP (M = -0.944° ±0.837 SE). There is a moderate correlation between the fitted and observed values, $R^2 = .48$. Model details are presented in table 2.11. Descriptive statistics: table 2.7, after-effect illustration: fig 2.15 bottom right.

Table 2.11: Predictive model details: effect of shift-type on eye position when locating unseen finger of non-exposed hand on a numbered scale. Items in grey refer to baseline model. Position is a control predictor for left/right appearance of annulus. Model df = 563.

Fixed Effects	*b*	SE *b*	95% CI	*t*-value	*p*-value
Intercept	-0.416	0.829	[-2.04, 1.21]	-0.501	.616
Position	-1.09	0.372	[-1.82, -0.361]	-2.93	.004
Shift	-1.86	0.538	[-2.91, -0.805]	-3.45	<.001
Time	1.87	0.578	[0.737, 3.00]	3.23	.001
Shift:Time	-0.944	0.837	[-2.58, 0.693]	-1.13	.259

Task 6 Elements 1-3.

Given the inconsistency in the results across the eye position measures of this finger location task, it was decided to collapse the means of the three eye position measures by participant and to conduct a repeated-measure ANOVA with the factors time and shift. The results returned normally distributed residuals and revealed main effects of Time ($F(1,17) = 5.05$, $p = .04$, $\eta_G^2 = .03$) and Shift ($F(1,17) = 5.60$, $p = .03$,

η_G^2 = .05) but no significant effect of their interaction ($F(1,17) = 1.48$, $p = .24$, η_G^2 = .004). On average, there was a significant rightward eye position after-effect when locating the finger of the non-pointing hand following R-PA (M = 1.71°, SE = 0.316) and R-EMP (M = 0.726, SE = 0.346). See figure 2.16 top right.

Task 6 Element 4: Verbal location on a numbered scale of the unseen finger of the non-exposed hand.

The model was significantly different from baseline (χ^2 (3) = 9.79, $p = .021$). There is a strong correlation between the fitted and observed values, $R^2 = .77$. Model details are presented in table 2.12. A significant, and similar, rightward after-effect for verbally locating the unseen finger of the unexposed hand on a numbered scale was found following R-PA and R-EMP (M = 1.47° ±0.516 SE). Descriptive statistics: table 2.7, after-effect illustration: figure 2.16 bottom right.

Table 2.12: Predictive model details: effect of shift-type on verbal location of unseen finger of non-exposed hand on a numbered scale. Items in grey refer to baseline model. Position is a control predictor for left/right appearance of annulus. Model df = 574.

Fixed Effects	*b*	SE *b*	95% CI	*t*-value	*p*-value
Intercept	-1.45	0.807	[-3.03, 0.126]	-1.79	.072
Position	-0.828	0.194	[-1.21, -0.449]	-4.27	<.001
Shift	-1.80	0.614	[-3.00, -0.602]	-2.94	.004
Time	1.47	0.516	[0.457, 2.48]	2.84	.005
Shift:Time	-0.859	0.633	[-2.10, 0.380]	-1.36	.176

Comparisons between significant eye position measures.

The R-PA after-effect measures that were thought to be related uniquely to ocular signal changes were compared in an ANOVA with the within subject factor of Task. These after-effect measures were: The differences between the pointing after-effects of SAP eyes closed and SAP eyes open and between the pointing after-effects of SAP eyes closed and OLP, and the after-effects of the different measures for non-exposed hand passive proprioception. A Greenhouse-Geisser corrected ANOVA revealed no significant difference between the *magnitude* of the after-effect for all the

measures $F(2.14, 36.5) = 0.910$, p=.418, $\eta_G^2 = .022$. This suggests that all the measures may represent the same change in estimates of eye position in the orbit and that when the change emerged it remained at a constant level. The mean change of these measures is M = 2.05°, SE = 0.282°.

The significant rightward eye position after-effects across the different R-EMP tasks were compared to assess whether any changes occurred over the length of the experiment. These direct measures were from the SAP eyes open and each of the finger location tasks. A Greenhouse-Geisser corrected ANOVA revealed no significant difference between the after-effects $F(3.08, 52.3) = 0.497$, p=.691, $\eta_G^2 =$ .018. This indicates that the eye position after-effect provoked by R-EMP once it appeared following the first top-up exposure remained the same magnitude until experiment end. The mean change of these measures is M = 0.821°, SE = 0.223°.

2.4.4 After-Effects Summary

The predicted and observed after-effects are presented in table 2.13.

Table 2.13: Overview of after-effect statistical testing. Tasks are grouped by shading. No after-effect is the equivalent of straight-ahead.

	Task	Position Measure	Shift	After-effect direction predicted	After-effect direction observed
1.1	VSA pre bar	Eye	R-PA REMP	right	no after-effect
1.2	VSA	Bar	R-PA REMP	right	no after-effect
1.3	Upon VSA bar	Eye	R-PA REMP	right	no after-effect
2.1	SAP eyes closed	Point	R-PA	left	left
			R-EMP	No after-effect (straight ahead)	no after-effect
3.1	SAP eyes open, pre pointing	Eye	R-PA	Left if aligned and interacting with limb/right if adapted but not interacting with limb	no after-effect
			R-EMP	Straight-ahead (no after-effect) if guided by limb/ right if eyes not interacting with limb	right
3.2	SAP eyes open, eyes open	Point	R-PA	left	left
			R-EMP	Straight-ahead (no after-effect) if guided by limb / Right if limb interacting with eyes	no after-effect
3.3	SAP eyes open, upon pointing	Eye	R-PA	Left if aligned and interacting with limb/right if adapted but not interacting with limb	no after-effect
			R-EMP	Straight-ahead (no after-effect) if guided by limb/ right if eyes not interacting with limb	right
4	OLP	Point	R-PA	left	left
			R-EMP	right	no after-effect *
5.1-5.3	Finger exposed hand	Eye	R-PA R-EMP	right (R-PA > R-EMP)	right
5.4		Verbal	R-PA REMP	right (R-PA > R-EMP)	right
6.1-6.3	Finger unexposed hand	Eye	R-PA R-EMP	right	right
6.4		Verbal	R-PA R-EMP	right	right

* a leftward after-effect for the initial four trials.

2.5 Discussion

The current investigation into the PA induced visual shift was motivated by: 1) an assumed, but not previously experimentally validated, role of ocular proprioception in PA, 2) confounding factors in past PA studies of sensorimotor after-effects. As far as is known, this is the first time that lateral-shifting PA and EMP induced effects have been compared within participants on a battery of after-effect tasks. The use of eye tracking equipment permitted proxy measurement of changes in state estimates of eye position in the orbit.

The results suggest that following prism adaptation a person may continue to be able to correctly look straight ahead, but when they point with the unseen hand or make an eye movement to a target (the person's unseen hand or external visual target), an incorrect ocular signal is employed. This is suggestive of a dissociation between actual eye position in the orbit and the ocular signal of eye position that is used for localising targets. It is tentatively speculated that this dissociation may be supported by two distinct types of ocular muscle fibres and the position signals that are associated with them, along with the flexible manner in which the sensory systems can achieve adaptation. In the following paragraphs, the results from the R-EMP and R-PA conditions that have led to this interpretation are elaborated.

2.5.1 Results Recap

Here, following the initial (96) exposure trials it was seen that while eye position began to rotate in the rightward displacement direction under R-EMP, there was no change following R-PA (VSA task measures, figure 2.12 top). With further prism exposure (top-up 30 trials), the rightward displacement of eye position became significant following R-EMP but there continued to be no change following R-PA (SAP eyes open eye position measures, figure 2.12 bottom). However, at the same time, the R-PA pointing after-effects in the absence (SAP eyes open) and presence (OLP) of a visual target, were the same as each other, and were significantly larger than SAP eyes closed (figure 2.13). This suggests that, despite the lack of an observable eye position after-effect, a change had taken place in the ocular system following R-PA, and that the change only became apparent when there was an interaction between the eye and limb. Importantly, in the R-EMP condition in the SAP eyes open task, despite a deviated eye position after-effect, pointing continued to

aim at straight-ahead (just as there was no pointing after-effect under SAP eyes closed).

Finally, following the final top-up prism exposure period (30 trials), eye position deviated in the displacement direction when looking to the imagined location of both the exposed and unexposed hands (figure 2.16). This occurred for both the R-EMP and R-PA conditions. Because following R-EMP, there was no change in pointing with the exposed hand when asked to point straight-ahead, this precludes transfer of either motor learning or a changed proprioceptive signal from the exposed to the unexposed hand. In turn, this suggests that the observed eye position deviation in R-EMP is solely attributable to ocular changes. On average, for the unexposed hand there was no difference in the eye-position after-effects between R-PA and R-EMP. (For an in-depth description of results, see section 2.4.1)

2.5.2 Manipulation Comparison

What can the R-EMP results tell us about the R-PA after-effects and the 'visual shift'? Firstly, taken together, it shows that adaptation occurred and the senses were re-aligned – unlike R-EMP there were no error signals during the post R-PA tasks that appeared to prompt any de-adaptation or re-adaptation. It confirms that EMP after-effects can emerge with symmetrically placed targets. However, the differences in the R-PA and R-EMP conditions suggest that potentiation effects do not dominate the adaptation process. Finally, the pattern of OLP after-effects attributed to the consequences of the SAP eyes open task in the R-EMP condition (see section 2.4.1), supports the notion, discussed later, that simply opening the eyelid engenders the use of an eye position, specifically ocular proprioceptive, estimate.

2.5.3 Ocular Contradictions

The most striking finding is the apparent contradiction of both the absence of an ocular after-effect (eye position measure) and the presence of it (an increased error in pointing with eyes open compared to pointing with eyes closed) in the SAP eyes open task.

What might account for such findings? One suggestion is that, in the face of inter-sensory conflict, the ocular system retains access to a neutral straight-ahead setting. It has been put forward that for adaptation to occur the system has to keep access to the individual (i.e., non-integrated) estimates (Ernst & Bülthoff, 2004).

Additionally, it has been suggested that the main function of ocular proprioception is long term calibration of eye position (Wang, Zhang, Cohen, & Goldberg, 2007) – in the face of conflict, adherence to a spatial coding that is the product of a lifetime's worth of experience would fit with that function. Nonetheless, flexibility is required. Such flexibility might be achieved through maintaining the original spatial proprioceptive coding and adjusting the motor command. However, there is also reason to believe that the interpretation of the spatial coding signal provided by the extra-ocular muscle proprioceptors has changed. These alternative accounts are discussed below. Ultimately, the current evidence cannot tease apart these differing accounts. However, evidence from the literature, elaborated upon in the last part of this section, appears to favour a proprioceptive explanation.

An ocular proprioceptive response to PA.

One parsimonious possibility is that although the eye is in the primary position in the orbit the interpretation of that position has shifted. That the eye has remained in or returned to primary position may be thanks to the symmetrical nature of the exposure targets and/or a completion of adaptation. However, the objective physical position and the interpretation of that position by the brain no longer coincide.

Building on that premise, an alternative tentative proposal that arises is that the absence of a straight-ahead eye position after-effect may be explained by dissociations in the use, in computing state estimates, of two different types of ocular proprioceptors on two different types of muscle fibres in the global layer of extra-ocular muscles (EOM). The non-twitch muscle fibres, unique to the extra-ocular muscles, are fatigue resistant and their activation does not generate action potentials. They are thought to be involved in generating the fine-tuned tonic tension in eye muscles, required for fixation and ocular alignment, and their control can be traced back exclusively to premotor networks for gaze-holding, convergence, and smooth pursuit. Palisade endings, a unique putative sensory receptor found only on non-twitch EOM fibres, have been associated with ocular proprioception. Morphologically unique muscle spindles are found on *twitch* fibres of the EOM. These twitch muscle fibres are not fatigue resistant and do release action potentials. They are related to driving eye movements, such as saccades and vestibulo-ocular reflexes, and receive inputs from all oculomotor premotor networks (Bruenech & Kjellevold Haugen, 2015; Büttner-Ennever, 2007; Spencer & Porter, 2005).

The uniqueness of human extra ocular muscle receptors has created conflicting views around the usefulness of each type of receptor, and even whether they do have a sensory role (Rao & Prevosto, 2013). However, the layering and compartmentalisation of the different muscles fibres within the EOM, and the richness of their innervation, suggest the need for accurate and detailed feedback of eye position to and from the CNS (Bruenech & Kjellevold Haugen, 2015). The two sets of proprioceptive receptors are suggestive of supporting flexible behaviour. The current findings could be reconciled with a lack of/resistance to adaptation of the straight-ahead position courtesy of the fatigue resistant non-twitch muscles, but an adaptation for movement courtesy of the potentiation of the twitch muscles. (The twitch muscles would be the source of the R-EMP effects.) Although somewhat satisfying as an explanation, it is, needless to say, highly speculative and would require invasive methodology to explore it further.

An oculomotor change.

Apart from ocular proprioception, the oculomotor command can be used to calculate eye position. Corollary discharge is a copy of a movement command, for eye movements it specifies the goal end state of the movement. Because the eyes, unlike skeletal muscles, are not subject to external loads and are cushioned from gravity, the ocular corollary discharge signal can be judged as an accurate source of position information. Studies assessing the relative importance of the two extra-retinal signals, ocular proprioception and corollary discharge, have generally come down in favour of corollary discharge (e.g., Bridgeman & Graziano, 1989; Guthrie, Porter, & Sparks, 1983; Lewis, Zee, Hayman, & Tamargo, 2001).

The contradiction apparent in the current results, therefore, raises the possibility that the SAP eyes open task results following R-PA revealed a dissociation between the spatial coding of ocular proprioception and that of the motor command - specifically, no change in ocular proprioception and a change only in the oculomotor command.

This account is not mutually exclusive from the idea discussed above that the twitch muscle fibres, that drive eye movements/saccades, were the ones that "adapted". No simple correlation has been found between the possession of extra-ocular muscle spindles and the oculomotor repertoire of any species (Buttner-Ennever, Horn, Graf, & Uglioni, 2002), and indeed they are thought to be under-

developed in man (Rao & Prevosto, 2013). Thus, the position signals of twitch fibres may be exclusively bound to the oculomotor command.

Indeed, there is physiological evidence against an ocular proprioceptive role in sensorimotor integration from non-human primate studies. Investigations into projections into the posterior parietal cortex (PPC), specifically ventral lateral intraparietal area ($LIP_{v)}$ and medial intraparietal area (MIP), have found evidence only for indirect ocular proprioceptive inputs to the PPC from area 3a in the somatosensory cortex. Additionally, there are only a few disynaptic inputs to the LIP_{v}, and virtually none to the MIP, from EOM afferents to the spinal trigeminal nucleus and other trigeminal afferents from the ophthalmic branch. In contrast, tonic position signals during gaze holding, and eye velocity and position signals during eye movements ascending from the nucleus prepositus hypoglossi, an oculomotor centre for horizontal movements in the brainstem, through the thalamus project to LIP_{v} and MIP in the PPC (Prevosto, Graf, & Uglioni, 2009, 2011). This supports the assertion of the predominance of oculomotor efference copy over ocular proprioception in visual guidance (Lewis, Zee, Gaymard, & Guthrie, 1994) and a role for ocular proprioception, in view of the relative slowness of the signal, for long-term calibration of eye position (Wang et al., 2007).

However, the time lag that supports a down-weighting of ocular proprioception in everyday visually guided action, may not apply in PA which takes time to develop. Important too is the evidence, discussed in the introductory chapter, that whereas the early errors during prism exposure appear to be primarily under the control of the PPC, ultimately visual sensory realignment appears to be supported by the anterior cerebellum and the ventro-caudal dentate nucleus.

Nonetheless, multiple reference frames are produced to guide everyday action (McGuire & Sabes, 2009); thus, a disassociation between the oculomotor and ocular proprioceptive signals may be manageable.

Extra-retinal signals.

In summary, the current results downplay a role for eye muscle potentiation in PA after-effects, refute a simple account of linear additivity of after-effects, and are not unambiguously supportive of a change in ocular proprioception. Nonetheless, there is evidence that opening the eyelid is a signal to the brain to use ocular proprioceptive signals – a feature that fits with the current findings. Additionally, there is evidence in

the literature that supports a role of ocular proprioception in particular when variability or perturbation occurs. These areas are addressed in turn.

2.5.4 What's so Special About an Open Eyelid?

It was observed in the R-PA condition, that even in the absence of retinal stimulation, pointing errors were larger with eyes open than with eyes closed. It is acknowledged that some of that difference may be due to further adaptation that took place during a top-up prism exposure session. However, as discussed in the results section (2.4.1) it is unlikely to be the only source of difference.

There is evidence to suggest that simply having the eyes open can, if necessary, prompt an interaction between the senses through the availability of an ocular proprioceptive eye position estimate. Even with the guarantee of no visual information, it has been demonstrated that there is a difference in behaviour with eyes open versus eyes closed. Yelnik et al. (2015) compared healthy people walking with eyes open, eyes closed, eyes open wearing blacked-out goggled, and eyes open wearing whitened-out goggles. They found that while walking with eyes closed impaired walking performance, it deteriorated further in both goggle conditions. They concluded that voluntarily closing the eyes sends a signal to the CNS to give zero weighting to the visual system and to up-weight other sensory sources, while even in the absence of visual stimuli, simply leaving the eyes open signals to the CNS to include visual inputs in any necessary computation of state estimates. As there was no difference between the whitened-out and blackened-out goggles, they showed that the decline was independent of retinal stimulation. (Rougier (2003) made similar findings using tests of postural control.) Importantly, the eyes open in the dark/under goggles set-up may be assumed to control for the influence of oculomotor commands given that voluntary eye movements under the goggles would have served no purpose. This pattern of results suggests that the 'visual' signal being used in the walking task was an ocular proprioceptive one.

Using a scleral search coil technique, it has been reported that prolonged voluntary eyelid-closure (i.e., not a blink) provokes a stereotypical vertical ocular deviation (upwards or downwards dependent on individual) in a slow tonic fashion (Collewijn, Van der Steen, & Steinman, 1985; Takagi, Abe, Hasegawa, & Usui, 1992). The fact that closing the eye is accomplished with a stereotypical movement gives backing to the premise that it is a useable signal, and one that fits into the

redundancy mechanisms of the cerebral system. In terms of the current experiment, the lack of such an eye movement-to-position signal, even if retinal stimulation is absent, is, therefore, a message to the CNS to continue to use (extra-) ocular signals.

In sum, these different findings lend support to the interpretation that it is ocular proprioceptive changes that are driving the effects found here that are attributed to visual changes following R-PA.

2.5.5 Suppression or Up-grade of Proprioception

It is of interest to note the evidence that proprioceptive suppression reduces inter-sensory conflict during sensorimotor adaptation, thus, facilitating a novel re-alignment of sensory inputs. In particular, it appears that different afferents into the proprioceptive system may be differentially suppressed. There are a number of studies that have found that degraded (and therefore made less reliable or suppressed) limb proprioceptive information actually improves performance in cases of sensory conflict during a mirror drawing paradigm (Balslev et al., 2004; Ingram et al., 2000; Pipereit, Bock, & Vercher, 2006; Vercher, Sarés, Blouin, Bourdin, & Gauthier, 2003), and interestingly, that the suppression follows a temporal pattern, at least within the somatosensory cortex (Bernier, Burle, Vidal, Hasbroucq, & Blouin, 2009). However, in the case of perturbing ocular afferents during adaptation, the results are different. van Donkelaar, Gauthier, Blouin, & Vercher (1997), used a suction lens to perturb the proprioceptive signal, and reported that compared to an unperturbed condition there was no change in the ability to adapt to a smooth pursuit paradigm but, that the saccadic after-effect was reduced by 50%.

Balslev et al. (2012) tested a patient with a focal lesion of the right postcentral gyrus, a cortical area that processes ocular proprioception. The task involved locating visual straight-ahead in a LED array under regular viewing, and while ocular proprioception was perturbed via eye-push. The authors concluded that afferent eye proprioception is incorporated into the oculomotor command only in cases where there is a conflict between the two sources. Thus, as per the van Donkelaar et al. (1997) study ocular proprioception appears to be up-regulated, not suppressed, in instances of conflict. In both these studies the conflict was within one reference frame, whereas in the limb proprioceptive suppression examples there was between reference frames conflict. Taken together, it seems reasonable to suggest that different

aspects of the proprioceptive system may react differentially to a prism perturbation, and by extension different ocular parts of that system.

2.5.6 Extra-retinal Signals

Given the emphasis being placed here on ocular proprioception it is worth noting that for decades its role was controversial, physiologically and theoretically, by comparison to corollary discharge (Weir, 2006). In part, this is due to the difficulty in experimental isolation of ocular proprioception. Nonetheless, a slowly growing body of evidence has revealed that proprioceptive signals of the extra-ocular muscles do play a role in several different types of eye movements and in visual perception – e.g., in detecting eye position (Skavenski, 1972); in central use of eye position to judge target position with respect to the body (Gauthier, Nommay, & Vercher, 1990); in the processing of the oculomotor and visual control structures for visually guided saccades (Knox, Weir, & Murphy, 2000) and for smooth pursuit eye movements (Weir & Knox, 2001); memory-guided saccades (Allin, Velay, & Bouquerel, 1996); fixation (Lennerstrand, Tian, & Han, 1997); and behaviourally defined visual straight-ahead (Balslev & Miall, 2008).

A consensus appears to be emerging that both extra-retinal signals, corollary discharge and proprioceptive, contribute to the computation of a state-estimate of eye position in the orbit. And that they may be used (flexibly) in combination and/or that they provide the same information such that experimentally at least ocular proprioception can be seen as redundant (Lewis et al., 2001; Weir, Knox, & Dutton, 2000). Notably, there is some agreement that ocular proprioception particularly comes into its own when there is a mismatch between it and efference copy such as occurs in cases of perturbation (Balslev et al., 2012; Gauthier, Vercher, & Zee, 1994; Lewis et al., 2001).

A recent paper (Poletti, Burr, & Rucci, 2013) has shed light on the flexible and optimal manner in which both extra-retinal signals combine dependent on their reliability. It showed that ocular proprioception contributed to 20% of eye position information following one saccade, but as the number of saccades increased it became the dominant source of information. That is, because the cumulative variance in the signal quality of corollary discharge will increase with increasing saccades (particularly in the absence of retinal feedback as per the design) its reliability, and hence usefulness, will decrease. Whereas, while the ocular proprioceptive signal may

be relatively slow and imprecise, it affords a constant error across time and, therefore, its reliability increases as that of the corollary discharge decreases. The same pattern was revealed in the presence of a visual reference point, although the scale was reduced.

2.5.7 Interim Conclusion

The reports of an up-weighting of ocular proprioception input in the face of conflict and variability, and the use of the ocular proprioceptive signals in the absence of retinal stimulation and oculomotor usefulness, lend support to the interpretation that ocular proprioception adapts to PA. Nonetheless, it does not preclude the possibility that efference copy signals are affected by PA. Ultimately the current evidence is limited, and it remains possible that the results reveal either an ocular proprioceptive response to R-PA, or a dissociated motor and ocular proprioceptive response. Alternatively, and possibly most likely, it reflects some combination of both responses.

2.5.8 Comparisons to other Visual Straight-Ahead Findings

The widespread reporting of traditional VSA after-effects, including after as few exposure trials as 30 (Redding et al., 2005), and the lack of such a finding in the current study might cast doubt on the reliability of the testing conditions employed here. However, the combination of precautions and inducements are unlikely to have resulted in unreliable tests of after-effects.

Multiple precautions were taken to minimise any environmental influences on the task that could bias participant responses: the room was in darkness; the equipment was matt black and the stimuli were presented on a black background to minimise light pollution from the monitors; the experimental monitors were kept on dim, blinkers were placed either side of the participant's head; the participant entered the room with their eyes closed and closed their eyes between tasks; a chinrest and forehead was employed to stabilise the head; the participant was coached, before and throughout the experiment, on keeping still in order to facilitate the eye-tracking process – that and the equipment set-up meant the participant was, as much as possible, in the same position and in the same posture for the measures taken before and after PA; and finally, the touchscreen was positioned off-centre and its boundaries extended with an off-set frame to ensure it was not spatially informative.

Likewise, attempts were made in the task design and analysis to ensure a visual shift if present would be captured: terminal pointing was employed as it is associated with a larger VSA shift compared to concurrent pointing (Redding et al., 2005); the darkness would facilitate a down-weighting of visual reliability and induce adaptation; sham exposure was included, VSA was measured before the other after-effects in order to minimise any potential effects of de-adaptation; a non-verbal response was taken in the behavioural task to avoid head movements; the calibration was programmed with a jitter to minimise any spatial information that it might contain; the left/right starting positions of the stimuli (annulus and bar) were accurately counter-balanced to minimise any spatial bias they could provoke; those positions were also included within the analysis as a control predictor to factor out any potential influence; multiple measures were taken (with the eye position ones being at high resolution); the sham/prism exposure targets were randomly presented to reduced any non-perturbation motor adaptation effects, and finally, a specific analytical approach was employed to facilitate both the incorporation of all trial data and the control of random factors in order to ensure that any weak signal would not be lost in the analysis.

Indeed, as discussed in the introduction, a visual shift has not always been observed in PA studies in healthy people (Bornschlegl et al., 2012; Choe & Welch, 1974; Harris, 1963; Herlihey & Rushton, 2012; Michel et al., 2013; Morton & Bastian, 2004; Newport et al., 2009). Some investigators have reported no VSA and nonetheless a larger OLP compared to SAP (Michel et al., 2013), others have found OLP to be larger than SAP following a full decay of VSA (Hatada et al., 2006), and others have observed OLP to be greater than VSA and SAP combined (e.g., Welch et al., 1974). These results showing a difference between OLP and SAP yet no VSA are similar to the findings here, and are supportive of the current interpretation that conventional measures may not capture a visual shift and hence not return linear additivity. The fact that VSA after-effects have and have not been observed, suggest that both the timing of the test, and the type and number of tests employed, are important for capturing the visual shift after-effect.

2.5.9 Future Directions

Although the current findings are supportive of a change in state estimate of eye position in PA, several design weaknesses should be addressed in future studies.

These include counter-balancing sessions (if a comparison condition is included), counter-balancing after-effect tasks, and either a blanket increase in the number of exposure trials in the first session or a continuation of that block until each individual no longer displays any pointing errors. The last factor would directly address whether the larger SAP eyes open compared to SAP eyes closed after-effects found here was due to further adaptation rather than an inter-sensory interaction. While it is not discounted that part of the increase may be due to further adaptation, it is unlikely that it is the cause of the entire difference. OLP is routinely found to be larger than SAP and, as discussed, it has been found to be so in the absence of visual shift. Indeed, spatial realignment is understood to be established after approximately 50 pointing actions (Bultitude et al., 2016), nearly half of the 96 movements that were included in the current first exposure task. Nonetheless, it is a design limitation and warrants further investigation.

It would also be informative to include a finger localisation task that used the hands (rather than the eyes) as the identifier. Comparison of those results with SAP and visual finger localisation would help to isolate a motor adaptation element, and to verify whether eye position after-effects (seen here in the finger localisation R-PA results) were driven by ocular or limb changes. Counter-balancing these tasks would also be necessary to address questions regarding a transfer of adaptation to the unexposed hand.

Further experimentation with the calibration technique may be fruitful. Ultimately, attempts to cleanly extract eye position information from the OLP task and the PA exposure trials were unsuccessful. For the exposure trials, calibration without the prism in place followed by the use of a smaller dioptre shift lens may be a better approach. Elimination of touch feedback whilst facilitating concurrent eye tracking would be tricky and labour intensive.

2.6 Conclusion

The current experiment aimed to investigate the visual after-effect of PA. It was found that PA does not induce an after-effect shift in a visual straight-ahead judgment task, while it does induce after-effects in other tasks that are attributable to a change in state estimates of eye position in the orbit. These results suggest that PA prompts complex changes within ocular proprioception and highlight that the

conventional assumption of linear additivity of PA sensorimotor after-effects is a concept requiring re-examination.

Chapter 3

Prism Adaptation as a Therapy for Left Hemisphere Lesions

Abstract

Right-shifting prism adaptation (PA) has been shown to have ameliorative value for patients with unilateral left neglect following right-hemisphere lesions, and left-shifting PA has been shown to simulate neglect-like deficits in healthy individuals. One account of spatial cognitive after-effects of PA posits an alteration in hemispheric balance for these right hemisphere tasks. Here, this premise was investigated in a group of left hemisphere stroke patients and a group of matched controls. In separate sessions both groups completed an associative priming task before and after left- and right-shifting PA. It was predicted that left-shifting PA would increase the priming effect in the patient group, consistent with the account of hemispheric rebalancing of lateralised functions following PA. However, both left and right prismatic displacements resulted in increased priming. While practice effects are a possibility, the pattern of reaction time changes suggests that there was a specific influence of both directions of PA on priming effects in the patient group. In this instance PA may have worked on a symmetrical or distributed inter-hemispheric mechanism.

3.1 Introduction

The experiment in this chapter set out to investigate the premise that prism adaptation (PA) could have rehabilitative benefits for deficits induced by left hemisphere (LH) strokes via an inter-hemispheric balance restoration mechanism.

The theoretical underpinnings for this viewpoint can be traced to Kinsbourne (1970, 1980) and Sprague (1966). Kinsbourne (1973) highlighted two aspects of inter-hemispheric activities of particular interest: asymmetry of function and mutual inhibition (or hemispheric rivalry). Asymmetry of function, or hemispheric specialisation, refers to the lateralisation of functions to each of the two hemispheres. Specifically verbal-analytic and spatial-synthetic functions are most commonly dominant in the left and right hemispheres, respectively.

Kinsbourne (1993) described this lateralisation of functions as evidence of hemispheric rivalry and posited that mutual inhibition between the hemispheres was the key to lateralisation. Thus, following a unilateral lesion, rather than thinking in terms of impaired-intact hemispheres, the situation is better conceptualised in terms of over-activated and under-activated hemispheres. Stimulating the under-active or suppressing the over-active hemisphere may then have a restorative effect (Kinsbourne, 1980). In support of this view, Kinsbourne (1971) cited evidence of blocking of language output in post LH stroke aphasics through anaesthesia of the RH (the Wada test) but no disruption of residual function through anaesthesia of the LH. Disruption of the natural inhibition of the LH over RH for language, he argued, may release a compensatory capability in the intact hemisphere or, alternatively, its now disinhibited/over-activated state may suppress even further residual functions of the insulted hemisphere, the severity and size of the primary lesion being the determining factor.

Neuroimaging studies have since offered support for mutual inhibition. As hemispheric specialisations (around the age of six for both language; (e.g., Friederici, Brauer, & Lohmann, 2011) and visuospatial skills (Groen, Whitehouse, Badcock, & Bishop, 2012) develop, inter-hemispheric connectivity decreases and intra-hemispheric connectivity increases, with inter-hemispheric inhibition playing an important role in the establishment and on-going effectiveness of hemispheric specialisation (Hervé, Zago, Petit, Mazoyer, & Tzourio-Mazoyer, 2013).

Two rare neuropsychological case studies also provide evidence for hemispheric rivalry. Abrupt recovery from deficits (unilateral left neglect, and right-

sided hemiparesis) induced by a unilateral stroke has been reported following a subsequent contralateral stroke (see Vuilleumier, Hester, Assal, & Regli 1996 and Sauerbrei & Liepert 2012, respectively). Such restoration of function following a bi-hemispheric network rebalancing has also been observed in cats (Sprague, 1966).

Converging evidence also comes from non-invasive repetitive transcranial magnetic stimulation (rTMS) studies. LH under-activation and RH over-activation have been reported in aphasic patients with damage to Broca's area (Naeser et al., 2004; Rosen et al., 2000). Improvements in picture naming in LH aphasics following rTMS induced neurodisruption of the right pars triangularis was interpreted as resulting from improved modulation of the RH as well as in the remaining temporo-parietal regions in the LH (Naeser et al., 2005, 2011). Using simultaneous TMS and PET imaging, Thiel et al. (2006) further showed that when TMS-induced neurodisruption of the left IFG led to increased right inferior frontal gyrus (IFG) activation during language tasks, this could be attributed to reduced transcallosal inhibition from LH to RH.

Andoh & Paus (2011) conducted fMRI before and after the application of off-line 10 Hz rTMS over either the left or right posterior superior temporal gyrus (pSTG) in participants while they auditorily processed foreign or native words. Following rTMS they observed increased task-related activity in the contralateral non-stimulated homologue regions (independent of stimulated hemisphere). Behaviourally there was a significant decrease in RT for native compared to foreign words after rTMS of the left pSTG only. Extrapolating from a study on melody discrimination, they suggested that improved task performance was likely due to an up-weight of activity in the RH auditory cortex (rather than LH suppression) and that it would be most apparent in those subjects with stronger baseline inter-hemispheric connectivity.

Oliveri et al. (1999, 2001) and Koch et al. (2012) used neurodisruptive rTMS on the intact left hyperactive PPC in right brain-damaged patients to transiently reduce contralesional extinction and visuospatial neglect deficits. These rTMS-induced improvements in neglect have been mirrored by right-shifting PA-induced benefits. Rossetti et al.'s (1998) seminal study demonstrated improved performance following right-shifting PA by left neglect patients on classic neglect tests including line cancellation, line bisection, and copying. Since then researchers have reported improvements in various neglect symptoms including: postural stability (Tilikete et al., 2001), wheelchair navigation (Jacquin-Courtois et al., 2008), visual search

(Saevarsson et al., 2009; Vangkilde & Habekost, 2010), leftward ocular exploration (Angeli et al., 2004; Serino et al., 2006), left directed voluntary attention (Nijboer et al., 2008), tactile extinction (Maravita et al., 2003), pressure sensitivity and position sense (Dijkerman et al., 2004), visual imagery (Rode et al., 2001), neglect dyslexia (Farnè, Rossetti, Toniolo, & Làdavas, 2002), auditory extinction (Jacquin-Courtois et al., 2010), and haptic exploration (McIntosh, Rossetti, & Milner, 2002).

Thus, PA appears to affect tasks that reflect asymmetric hemispheric functional specialisation i.e., visuospatial tasks. As mentioned above, right-shifting PA can reduce visuospatial deficits in patients following RH insult, and, left-shifting PA can simulate neglect-like visuospatial deficits in healthy people (Bultitude & Woods, 2010; Loftus et al., 2009; Michel et al., 2003). More specifically, in some cases a neglect-like rightwards after-effect in the landmark task of line bisection following left-shifting PA can *only* be found in those healthy participants with a leftwards bias at baseline (Herlihey et al., 2012). And indeed, posterior parietal cortex (PPC) inter-hemispheric inhibition appears to be stronger in participants with a baseline leftward bias in the line bisection task (Koch et al., 2011).

Taniguchi, Hiyamizu, Tominaga, & Morioka (2012) correlated improvements in measures of neglect following right-shifting PA with increases in activity in the frontal and parietal cortices of the lesioned right hemisphere. In contrast, increased activity in the anterior inferior parietal lobe and angular gyrus in the hemisphere contralateral to prism shift direction has been noted in later realignment stages of PA in healthy people (Chapman et al., 2010). However, a proposal that is currently gaining ground is that PA cognitive after-effects are due to an *initial* inhibition of the PPC contralateral to the prismatic shift *followed* by a modulation of inter-hemispheric balance. This hypothesis is supported by evidence from neuropsychology (Pisella et al., 2006; Striemer & Danckert, 2010), fMRI (Crottaz-Herbette et al., 2014) and TMS (Magnani et al., 2013).

If, like the TMS and neuropsychological studies mentioned above suggest, PA does eventually rebalance inter-hemispheric activity, then improvements in tasks lateralised to the LH should also be seen following PA intervention for deficits in LH function. There are several PA studies of particular interest in this regard. The first is a single-case study showing an improvement in right neglect, due to LH ischaemia, following left-shifting PA, i.e., it is consistent (but opposite in direction) with an improvement in left neglect, due to RH insult, following right-shifting PA (Bultitude

& Rafal, 2010). The second study relates to a spatial task, but, crucially, a non-lateralised one. Global and local processing are right and left hemisphere specialisations, respectively. A local processing bias, i.e., a hyper attention to the details of a scene with a correlative lack of awareness of the overall context, can occur alongside left neglect. Bultitude, Rafal, & List (2009) used right-shifting PA to reverse this deficit in five left neglect patients. Furthermore, it has been shown in healthy adults that leftward PA reduces the normal global processing bias (Bultitude & Woods, 2010) by enhancing local processing (Reed & Dassonville, 2014). Taken together the results suggest that there is reason to investigate the effects of PA on deficits associated with LH lesion. If PA modulates hemispheric asymmetry, then any effect on LH functions will be invoked by the prismatic shift opposite to that which acts on RH functions. Specifically, in a healthy population LH dominant functions would be influenced by right-shifting PA and in a LH damaged population the same functions would be influenced by left-shifting PA.

The current study investigated the effects of left- and right- shifting PA on performance in a language task in 16 participants with left-hemisphere damage and 16 matched controls. Left-shifting PA was predicted to increase priming and right-shifting to make no difference in the patient group. In the control group it was expected that there would be no effect of either direction of prism displacement (given that cognitive behavioural after-effect testing in healthy individuals do not always yield differences; (Martín-Arévalo et al., 2016)), but it was also considered possible that right-shifting PA would increase priming.

Priming in a lexical decision task (LDT) manifests through faster decision-making regarding the lexical status of a stimulus (word / nonword) when it is preceded by a related (e.g., *bread-butter*) rather than an unrelated prime (e.g., *dog-alien*; (Meyer & Schvaneveldt, 1971)). Semantic priming is specific to words related by meaning only, whereas, association priming often includes but is not limited to semantic priming, e.g., arm and leg are associated through meaning (body parts) and through common phrases (“it cost an arm and a leg”). Using a LDT design, Henik, Dronkers, Knight, & Osimani (1993) found that semantic priming –as measured by changes in reaction time– is reduced in LH damaged patients regardless of lesion site. This experiment investigated effects of leftward and rightward PA on associative priming in a group of aphasic patients with left hemisphere lesions and matched neurologically healthy controls. Given the generalisation value of Henik et al.'s

(1993) findings with regard to lesion site, inclusion criteria were limited only to non-progressive left-hemisphere lesions, and the prediction was faster RT to related compared to unrelated targets (i.e., increased priming) following left-shifting PA but not following right-shifting PA.

3.2 Methods

The effectiveness of the sensorimotor adaptation of PA was assessed using an open loop pointing (OLP) task before and after sham adaptation (SA), before and immediately following PA, and at the end of experimental session. All participants were tested on a LDT after SA and after PA in each session. The main dependent variable (DV) was reaction time, and within-subject factors included Time (post SA, post PA); prime Type (related/unrelated to target); SOA (stimulus onset asynchrony: short/ long); and Shift (prism displacement: left/right).

3.2.1 Participants

Nineteen aphasic patients with left-hemisphere only lesions were recruited from Bangor University's clinical research panel. Three participants were dropped from the study: One due to inability to complete the practice session, another due to inability to concentrate sufficiently, a third due to having experienced a stroke between the two testing sessions. See Table 3.1 for demographic and clinical details and Figure 3.1for lesion scans. Lesion information is taken from research MRI scans, except for patients GM and JL where it is from clinical CT scans.

Patient-participants were interviewed by a consultant neurologist to assess aphasia at the time of the experiment (Table 3.1). The interview included word and expression repetitions, comprehension checking, and analysis of speech output for anomia and agrammatism.

Sixteen neurologically intact healthy controls were recruited via the university community panel to match the patients by age, gender, handedness, and self-reported mono- (English) or bilingualism (Welsh/English). All controls had normal or corrected-to-normal vision and self-reported normal (non-dyslexic) reading competency. Mean control participant age was 55.6 years (range: 28-69), gender mix was 50/50 male/female.

Informed consent was sought in line with university ethics committee approved guidelines, NHS guidelines, and the 1964 Declaration of Helsinki. The consultant neurologist deemed all patient participants as having capacity to give

informed consent. All participants were compensated for their time and received a verbal debrief.

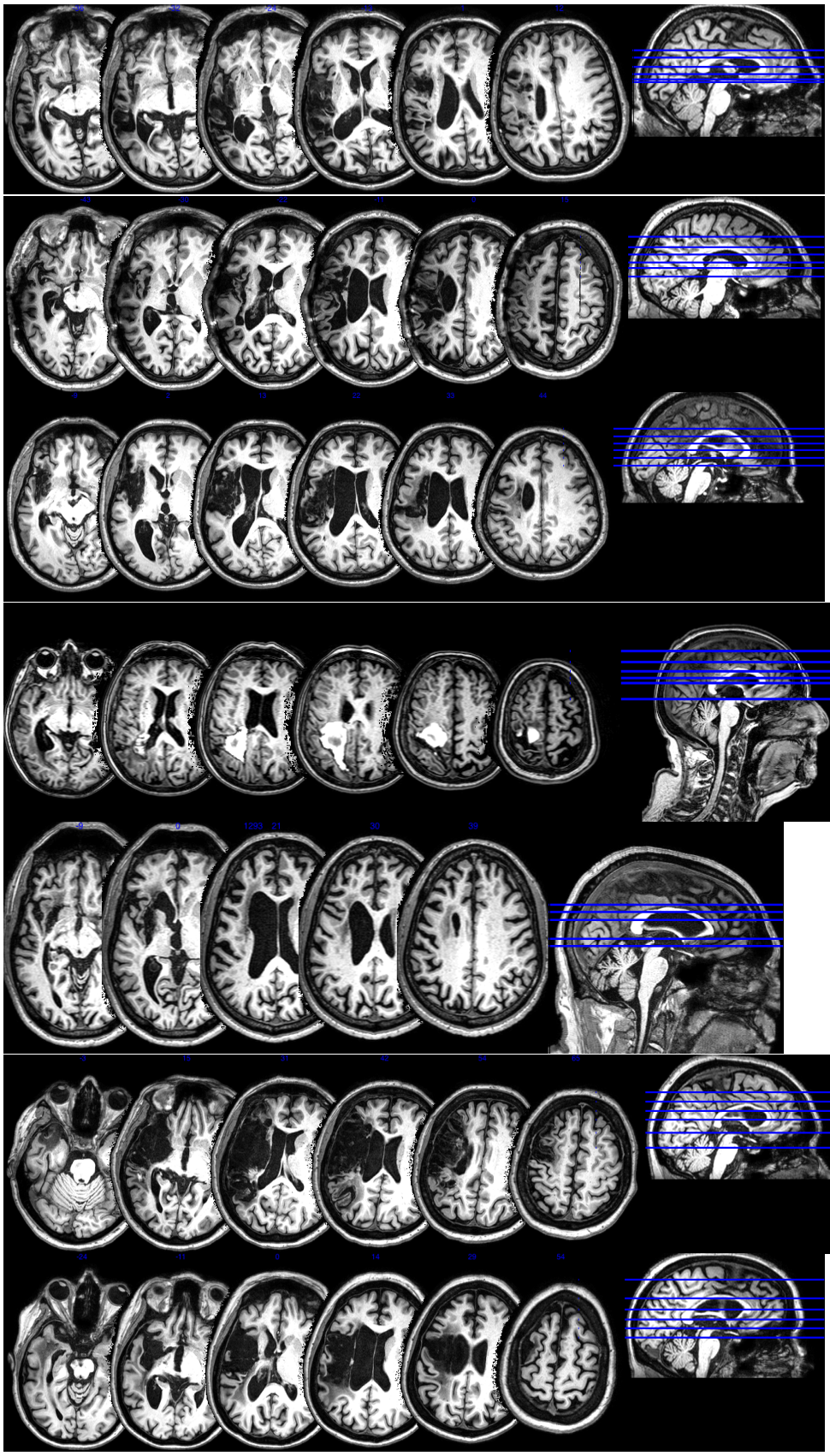
Table 3.1: *Patient-Participant Clinical Details and Demographic Information*

Patient	**Sex, Age (yrs), Handed, Lesion type, Time post onset (yrs)**	**Lesion location (left hemisphere)**	**Clinical neurological deficits (language only)**
DB	M, 69, R, MCA Stroke, 1.9	Inferior frontal gyrus and frontal operculum, including parts of Broca's area, the insula, the mid and posterior parts of the superior temporal gyri, including Wernicke's area, Heschl's gyrus (primary auditory cortex), parietal operculum, and parts of the inferior parietal lobule (supramarginal and angular gyri). Intraparietal cortex is spared.	Anomic, but able to correctly articulate single words. Very poor naming, comprehension and repetition.
DE	M, 27, R, AVM haemorrhage, 4.5	Extensive damage to deep left frontal and parietal white matter extending to lateral ventricle that will have damaged the arcuate fasciculus. Also destruction of the basal ganglia including putamen, globus pallidus and body of the caudate but sparing ventral striatum and head of the caudate. Much of the left posterior insula is destroyed sparing the most ventral and anterior gyri (including sparing of the limen). The extreme capsule, claustrum and external capsule are destroyed. The thalamus is also damaged including dorsal pulvinar, mediodorsal thalamic nuclei. There is damage in the most caudal part of inferior frontal gyrus including the caudal and rostral part of Broca's area (pars opercularis) as well as ventral premotor cortex and the most ventral parts of the pre and post central gyri. Anterior parts of the middle and superior temporal gyri are damaged, but most caudal part of the STG (area22) including Wernicke's area is spared, as is Heschl's gyrus. The parietal operculum and supramargical gyrus is damaged, but the angular gyrus and the IPS are intact. The posterior segments of the inferior and middle frontal gyri are damaged including caudal area 46, but sparing the frontal eye field.	Residual aphasia. Able to name objects without effort and with clear articulation. Poor repetition. Reading unimpaired.
DS	M, 56, R, Stroke, 1.3	Small lesion left thalamus inc. dorso-medial nucleus. Extensive cortical and subcortical infarction: Inferior frontal gyrus and ventro-	Broca's aphasia (non-fluent), intact comprehension.

		lateral orbitofrontal cortex; Anterior part of the superior temporal gyrus but sparing posterior Heschl's gyrus and Wernicke's area. Frontal and parietal operculum and ventral and rostral part of the supramarginal gyrus. Most of the lesion is in deep subcortical and periventricular white matter and includes the insula, caudate nucleus and putamen, (ventral striatum spared). The white matter lesion undercuts Broca's area, but the cortex of Broca's area is intact.	
DSf	F, 80, L, Intracerebral haematoma, 5	Lateral occipital cortex, Heschl's gyrus, temporo-parietal junction including the posterior part of the superior temporal gyrus (Wernicke's area (22)) and supramarginal gyrus, angular gyrus, lateral and medial intraparietal cortex and superior parietal lobule, extending rostrally into the post and pre-central gyri involving motor and dorsal premotor cortex, paracentral lobule (supplementary motor area) and caudal part of the superior frontal gyrus. Sparing frontal eye field.	Broca's aphasia (non-fluent): impaired naming & repetition, intact comprehension.
FG	M, 58, L, Intracerebral haemorrhage, 9	Extensive damage to the putamen, globus pallidus, claustrum, and sub-cortical frontal white matter. Damage to caudate and medial insular cortex, but mostly spared.	Word finding difficulties, impaired repetition, limited agrammatism.
GM	M, 68, R, MCA Stroke, 0.2	Parietal cortex angular gyrus, posterior inferior parietal lobe. Small lesion in left subcortical frontal white matter.	Anomia, paraphasia, poor speech. Comprehension intact.
JL	M, 56, R, Stroke post angiogram, 2.5	Lesion involves lateral occipital gyrus, middle temporal gyrus, posterior part (area 22) superior temporal gyrus and TPJ (Wernicke's area), angular gyrus and ventral/caudal supramarginal gyrus. IPS spared.	Word finding difficulties.
LL	F, 60, R, MCA stroke, 2	Anterior temporal pole and lateral amygdala. Inferior, middle and superior temporal gyri including Heschl's gyrus, Wernicke's area and the temporo-parietal junction.Middle and inferior frontal gyri including lateral ventral orbito-frontal cortex. Parietal lobe inc supramarginal and angular gyri extending to the lateral border of the intra-parietal sulcus in its ventro-posteior segment. Lateral parts of the pre and posterior central gyri (lateral to the hand area knob) are damaged as well as the frontal and parietal operculum, Broca's area and most of the insula. Damage to the	Residual non-fluent aphasia. Unable to repeat words. Comprehension intact.

		middle frontal gyrus extends into the frontal eye field. The lesion extends deep into the internal capsule and damages most of the basal ganglia.	
LM	F, 49, R, MCA stroke, 4.8	Left MCA stroke involving posterior segments of left inferior and middle frontal gyri (including frontal eye field and dorsolateral prefrontal cortex), pars opercularis of Broca's area and ventral parts of precentral and postcentral gyri. Destruction of most of the amygdala and gloisis in middle segments of middle and superior temporal gyri, sparing Heschl's gyrus and lateral part of Wernicke's area in STG (area 22), but involving the planum temporale. Complete destruction of insula and extends deep into internal capsule and basal ganglia (with sparing of only part of the head of the caudate). Involvement of the inferior parietal lobule is limited to the supramarginal gyrus with sparing of angular gyrus, IPS and superior parietal lobule.	Residual non-fluent aphasia. Unable to repeat even single syllables. Comprehension intact.
MB	F, 81, R, MCA stroke, 6	The lesion involves parts of the left inferior and middle frontal gyri (areas 44 and 46), including part of Broca's area, the frontal operculum, anterior insula and subjacent extreme capsule. The lesion appears to spare the most inferior part (limen) of the anterior insula and the external capsule.	Anomia, mild repetition impairment, mild articulation impairment. Intact comprehension.
MJ	M, 59, R, Stroke, 1.75	Insula quite focal, some surrounding white matter.	Expressive dysphasia, word finding difficulties.
MJf	F, 55, R, Stroke, 10.5	Inferior lobe in Broca's region and frontal eye field. On T2 weighted images there is increased signal in the left temporal region and also in both occipital lobes.	Mild word finding difficulties
NP	M, 59, R, MCA Stroke, 4	Posterior segment of the superior temporal gyrus (area 22) and upper banks of the middle temporal gyrus as well as Heschl's gyrus. Posterior insula. Temporo-parietal junction including including supramarginal and angular gyri and up to the lateral bank of the horizontal segment of the interparietal cortex. Extends deep into the parietal white matter to the trigone of the lateral ventrical, undercutting the bottom of the post-central sulcus	Aphasia: impaired naming and repetition, phonemic paraphasias.

PJ	M, 57, R, MCA Stroke, 10	Posterior segment, superior temporal gyrus (area 22) and crown of Heschl's gyrus. temporo-parietal junction including supramarginal and angular gyri and lateral occipital gyrus.	Aphasia: impaired naming and repetition, intact comprehension
RH	M,66, R, Stroke, 0.9	Anterior temporal pole, insula, striato-capsula	Expressive dysphasia, impaired naming, agrammatism
WC	F, 51, R, Stroke, 1.9	Left parietal including intraparietal sulcus, maybe A5.	Word finding difficulties.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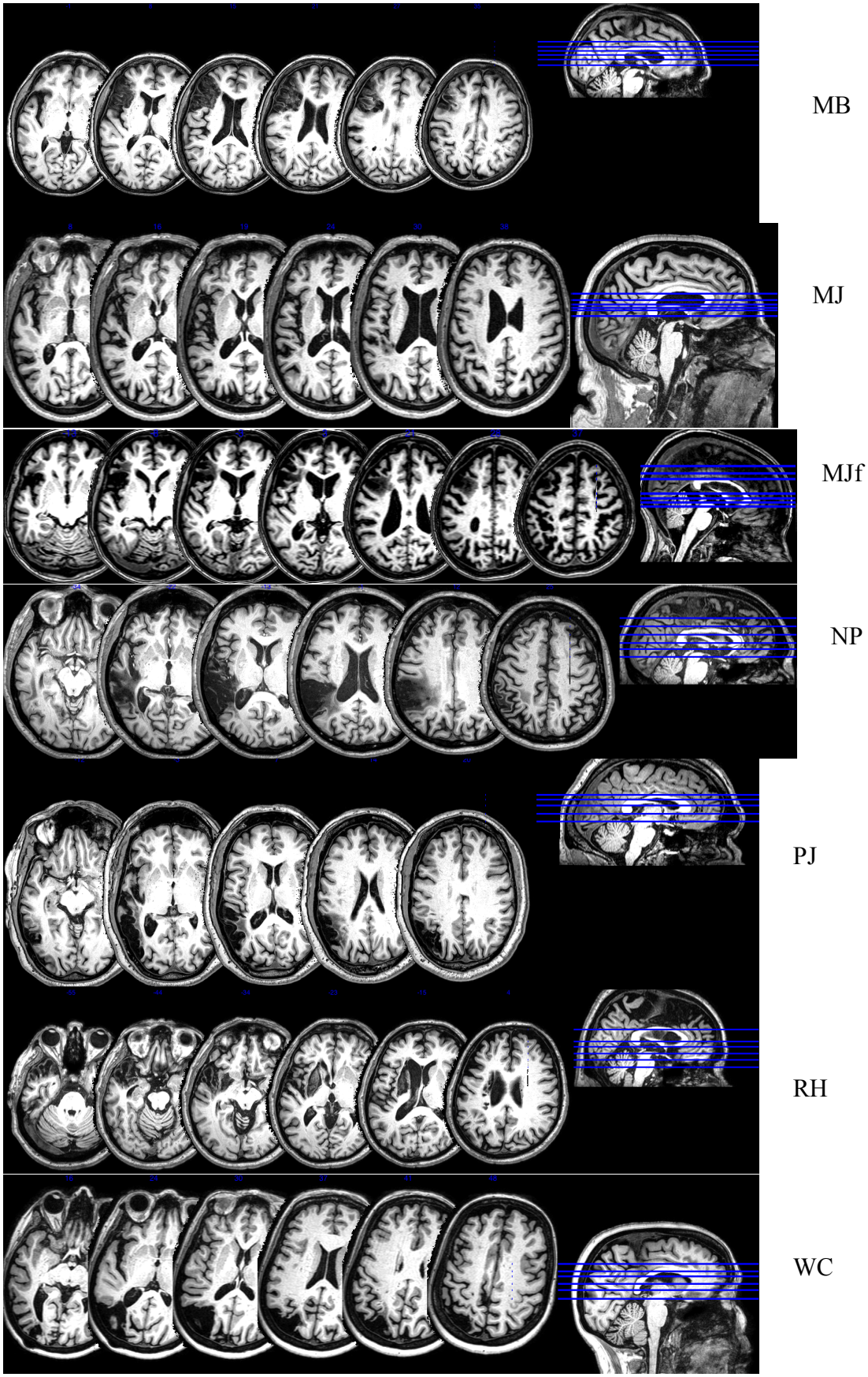


Figure 3.1: T1-weighted MRI axial slices showing lesion damage of patients (excluding GM and JL). Left side of brain is presented on left of image.

3.2.2 Apparatus

Prism goggles were Risley bi-prisms goggles fitted into welding frames that allow only the displaced field of vision to be seen. The prism adaptation box was built using wood and cardboard based on the design proposed by Berberovic & Mattingley (2003) and measured 72 cm wide x 35 cm high x 70 cm deep. This box was used for adaptation and after-effects measurement. The box is open at opposite ends, with the participant and experimenter sitting at either end. When the lid of the box is removed, circles on the base of the box can serve as targets for pointing with visual feedback during adaptation. The surface of the lid has target markings, with the lid in place participants can point into the box below the targets, without seeing their hand. There are markings on the underside of the lid spaced in increments of 0.5° to allow measurement of OLP accuracy by the experimenter. Targets placed at the 0° midpoint (objective straight-ahead) and at 10° angles to its left (-) and right (+) are marked on the box base and on the upper-side of the lid for the adaptation and OLP tasks, respectively (see Figure 3.2).

Figure 3.2a. Open loop pointing: Markings under the lid (in-situ) facilitate pointing accuracy measurement by the experimenter.

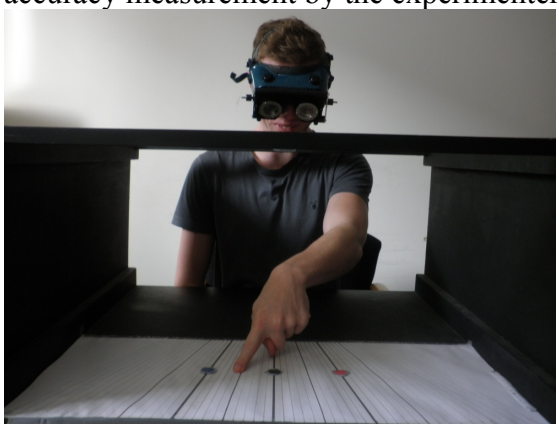


Figure 3.2b. Prism adaptation: With lid removed, and using the frame as a chin rest, participants peer into box and point to targets on its base while wearing goggles.

Stimuli were presented centre screen on a CRT monitor placed 57 cm from the participant's eyes. The experimental task was programmed and presented using E-prime® version 1.0 software (Psychology Software Tools, Inc.). Answers were recorded using a keyboard. A chin-rest was used during the LDT to ensure participants' head position was maintained with the stimuli at eye level and to reduce movements/minimise de-adaptation.

3.2.3 Stimuli

Stimuli for the LDTs consisted of two sets, one for baseline (post sham adaptation, SA) and one for post-PA use, each containing 32 related prime-target word pairs (e.g., *bread-butter)*, 32 unrelated prime-target word pairs (e.g., *car-book*), and 64 prime-nonword pairs (e.g., *horse-surne*). Equal probability of relatedness is common in priming studies (Hutchison, 2003; McRae & Boisvert, 1998). Practice stimuli consisted of 8/8/16 pairs, respectively.

Stimuli were selected from the University of South Florida free association norms (Nelson, McEvoy, & Schreiber, 2004). These norms facilitate the choice of related pairs, where the priming effect occurs through associations, in a context free scenario, that are built through world experience (they may include semantic relationships but not exclusively). Stimulus sets were matched for word length and association primacy (McRae & Boisvert, 1998). Average word length was 5.3 letters per prime and 4.4 per related target, 4.6 per unrelated target, 4.9 per non-word target. Related targets had an average forward association strength of 0.8 (the percentage of respondents choosing the target as a first response to prime). Non-words were designed to be orthographically and phonologically plausible ((McRae & Boisvert, 1998); see Appendix J).

Primes were presented in upper case and targets in lower case to simplify task instructions for the patients; and to minimise perceptual priming thus favouring lexical-associative priming (Ferrand & New, 2003). Stimuli were presented in black on an opaque white background in Courier New font. Upper case words had a height of 0.6° and width ranged from 2° to 5°. Lower case words ranged from 0.45° to 0.6° in height and 1.7° to 4.8° in width.

The facilitating effect of related primes in lexical decisions increases with longer 'get ready to answer time' or stimulus-onset-asynchrony (SOA). SOA relates to length of time from onset of prime presentation until target presentation. Short

SOA (S-SOA, < 250 ms) is thought to test automaticity, i.e., processing without awareness, attention or intention, and long SOA (L-SOA) to facilitate conscious strategic processing, e.g. expectancy generation, retrospective checking, and inhibition, resulting in slower decisions for unrelated words (Neely, 1977). There is some, unresolved, speculation that each hemisphere may be differentially involved in processing each SOA (Abernethy & Coney, 1993; Kandhadai & Federmeier, 2010; Koivisto, 1997). Hence, it is of interest in the current context to include both levels.

3.2.4 Procedure

Controls.

Each participant completed a series of nine steps in a pre-determined order; see Figure 3.3. To minimise de-adaptation participants were wheeled, on their computer chair, between adaptation box and computer, and kept their eyes closed between tasks.

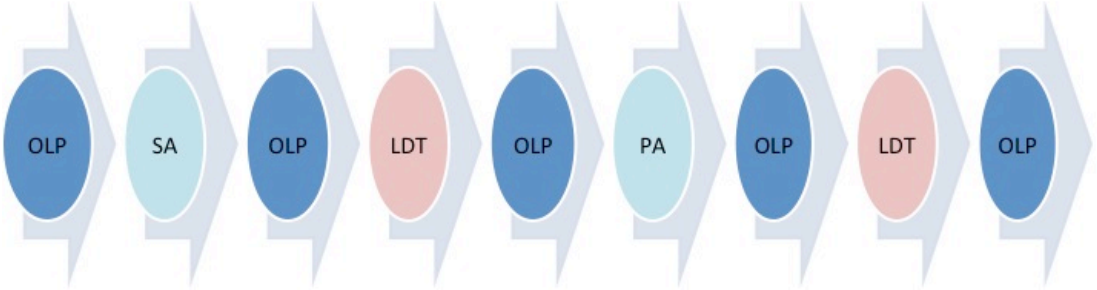


*Figure 3.3. E*xperiment procedure from left to right. OLP = open loop pointing, SA = sham adaptation, LDT = lexical decision task, PA = prism adaptation

Open loop pointing (Fig 3.2a). Participants rested their chin on the box edge, box-lid in place, and using their unseen straightened left arm pointed under each target line as directed, returning their hand to their sternum between movements. Each of the three target lines served as a target four times in pseudorandom order (12 trials in total).

Adaptation (Fig 3.2b). The lid was removed from the box. Their chin resting on the box edge, participants completed left arm pointing movements to the targets in a set order (left-middle-right-middle), starting from a self-determined point on their sternum. In time with a metronome, 150 ballistic movements were completed within 150 s. Since the cognitive effect of adaptation is not specific to which hand is used for the adaptation task (Pisella et al., 2005), participants used their left hands as this

would be more straightforward for the patients, who might have difficulty using their right arm due to their left hemisphere lesion. Participants closed their eyes when finished and kept their eyes closed between the remaining tasks to minimise de-adaptation from then on. For SA, participants wore goggles set to 0 dioptres (0°) and for PA set to 26 dioptres (15°) left or right shifting. SA allows each participant to act as their own control and also controls for any incidental effects of physical exercise on the language task.

Lexical decision task. Participants read on screen a series of trials of pairs of letter strings. They responded to the second letter string by indicating, as quickly and as accurately as possible, whether or not it was an English word. They responded by pressing one of two buttons on a keypad using the middle and index fingers of their non-dominant left hand. Key assignment was counterbalanced between participants.

Each trial proceeded as follows: presentation of a fixation cross for 500 ms; a prime word for 150 ms; a blank screen lasting 100 ms for the S-SOA condition and 600 ms for the L-SOA condition; the target letter-string. Targets remained on screen until the participant responded. Inter-trial interval was 500 ms (Figure 3.4).

A block included 256 trials, 128 each at S-SOA and L-SOA. Each word pairing was repeated at each SOA within each block. On half the trials the target was a non-word, in the remainder the target was split equally between related and unrelated words. Order of stimuli (word type x SOA) presentation was pseudo-randomised. Order of stimulus set usage was counter-balanced across conditions (Ferrand & New, 2003). In total each participant was presented with 512 word pairs over two blocks (post SA, post PA) during each session.

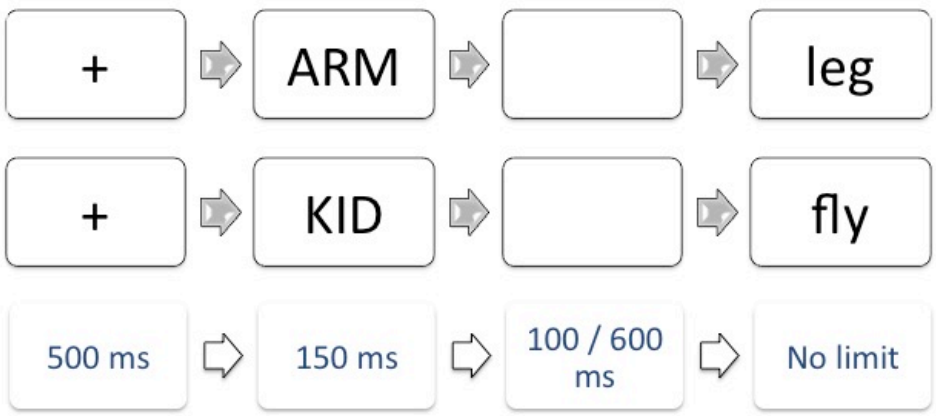


Figure 3.4. Trial timings (bottom row) featuring a related (top) and an unrelated word (middle) pair.

Participants began the experiment with practice stimuli to confirm their understanding of the task.

Patients.

The patients completed the same experimental procedure as the controls, with some exceptions: Due to physical constraints, i.e., inability to accommodate a wheelchair bound participant, the box was not used. In its place for the OLP task an instrument similar to the box lid in respect of angle measurement, but semi-circular in shape (600 mm radius), was held under the participant's chin by a collaborator, markings on its underside were used to measure OLP errors. To accommodate for physical fatigue needs and language impairment the adaptation task was amended. The patient-participant sat facing the experimenter at arm's length and alternatively pointed to the experimenter's left and right index finger (held up in the air in turn). Participants completed 50 such movements with encouragement to do so as quickly as possible, the metronome was not used. For the computer task the chin rest was abandoned when not tolerated by the participant.

During the practice LDT patient understanding was confirmed and adjustments made as necessary. For PJ and NP reminder stickers were placed on response keys ('W' for 'word', 'N' for 'non-word'). PJ responded to the computer task using his right hand due to pain in his left hand. For DSf the inter-trial interval was extended to 1500 ms. DSf gave verbal responses with 'yes' for word and 'no' for non-word, the experimenter took the first answer given and pressed the appropriate response key. DB used his left and right hand to respond at keyboard (as opposed to index and middle finger of left hand) because of manual perseveration when using only the left hand.

3.2.5 Analysis

In a mixed design, per session participants completed sham adaptation followed by a LDT, then prism adaptation followed by a second LDT. Direction of prism adaptation (leftward/rightward) was allocated in a counter-balanced manner, and sessions were held one month apart.

RT data for related and unrelated target words were analysed; accurate responses over 200 ms were included in the analysis. Median RT was used in order to minimise the influence of outliers and the generally wider spread of responses in the patient data. A mixed ANOVA including the patients and controls had been planned

but Levene's test, calculated on the priming effect over both shifts, indicated unequal variance between the groups ($F = 5.11$, $p = .031$). Thus, repeated-measures ANOVA were conducted separately for the patient and control groups with RT as the dependent variable, and Shift (left PA, right PA), Time (post SA, post PA), SOA (short, long) and Prime-Type (related to target, unrelated to target) as independent variables. All illustrative graphs are presented according to the axis scales of the patient group. In addition to the statistical analysis, a difference score between the post-SA and post-PA RTs was calculated to assist interpretation and presentation of results.

To confirm that adaptation had taken place, repeated-measures ANOVA with within-subject factors of Phase (baseline, post, late) and the dependent variable of OLP error were conducted per shift direction. Given that the patient group completed fewer adaptation trials both groups were analysed separately. As the sham adaptation was conducted without any visual displacement (and produced no change in pointing, verified by *t*-test per shift per group), the OLP error scores from pre and post SA and pre PA were averaged to obtain the most representative baseline scores per participant.

The sensorimotor after-effects of PA are conventionally understood to be symmetrical. To verify this, within the parameters of testing primarily cognitive after-effects, the magnitudes of OLP after-effects per session were compared. To enable this comparison, Post and Late OLP after-effects were calculated (Post OLP after effect = post-baseline pointing error; Late OLP after-effect = late-baseline pointing error). The OLP after-effect for the left-shifting session was multiplied by -1 in order to have the same sign as the right-shifting session. To ascertain similarity of after-effect magnitude, the Post and Late OLP after-effects were subjected to a repeated-measure ANOVA. Within-subject factors were Shift (Left-shift PA, Right-shift PA) and Phase (Post, Late), and the DV was OLP after-effect.

Generalised eta squared (η_G^2) is used to report effect size in the repeated-measure ANOVAs. The common guideline is that .02, .13 and .26 represent small, medium, and large effect sizes respectively. Generalised eta squared (as opposed to eta squared, η^2, and partial eta squared, η_p^2) can be used across studies regardless of whether the factor of interest in the design is within or between subjects. Thus its value is in affording comparability across studies and the development of an effect size range applicable to the area of interest (Bakeman, 2005).

3.3 Results

3.3.1 Adaptation After-effects

It was expected that left- and right- shifting PA would produce rightward and leftward OLP after-effects, respectively, that would be apparent at both post and late measurements time-points, and that there would be no difference between PA shift directions in the magnitude of OLP errors produced. For both groups and both prismatic shifts the results matched these predictions. Details of all tests to follow, for descriptive statistics see tables 3.2 (controls) and 3.3 (patients), for graphical overview see figure 3.5.

Control group.

Left shift PA.

There was a significant main effect of Phase, $F(1.99, 29.82) = 84.3$, $p < .001$, Greenhouse-Geisser corrected, $\eta_G^2 = .450$). The rightward errors produced at Post were significantly different (by M = 5.53, 95% CI [4.59, 6.48], $p < .001$,) to those produced at baseline. The errors apparent at Late were also significantly different compared to those at baseline (by M = 2.31, 95% CI [1.40, 3.23]), $p < .001$). Thus, despite the large decline between post and late in this left-shifting PA session participants remained adapted until the end.

Right shift PA.

There was a main effect of Phase $F(1.99, 29.88) = 70.4$, $p < .001$, Greenhouse-Geisser corrected, $\eta_G^2 = .397$). The leftward errors produced at Post were significantly different (by M = -4.42, 95% CI [-5.26, -3.59], $p < .001$) to those produced at baseline. The errors apparent at Late were also significantly different compared to those at baseline (by M = -3.17, 95% CI [-4.00, -2.34], $p < .001$).

Table 3.2: OLP error scores per phase per shift direction for the control group.

Shift	Phase	Mean	SE
Left shift	baseline	0.170	0.389
Left shift	post	5.70	0.773
Left shift	late	2.48	0.714
Right shift	baseline	0.427	0.445
Right shift	post	-4.00	0.650
Right shift	late	-2.75	0.658

Adaptation magnitude.

There was a main effect of Phase ($F(1, 15) = 79.8$, $p < .001$, $\eta_G^2 = .328$) with a larger after-effect immediately following adaptation (M = -4.98 , SE = 0.307) than at the end of the experiment (M = -2.75, SE = 0.295). There was a significant interaction between Shift and Phase, $F(1, 15) = 15.5$, $p = .009$, $\eta_G^2 = .087$, this was driven by a larger decline between post and late in the after-effect in the left-shifting session compared to the right-shifting session.

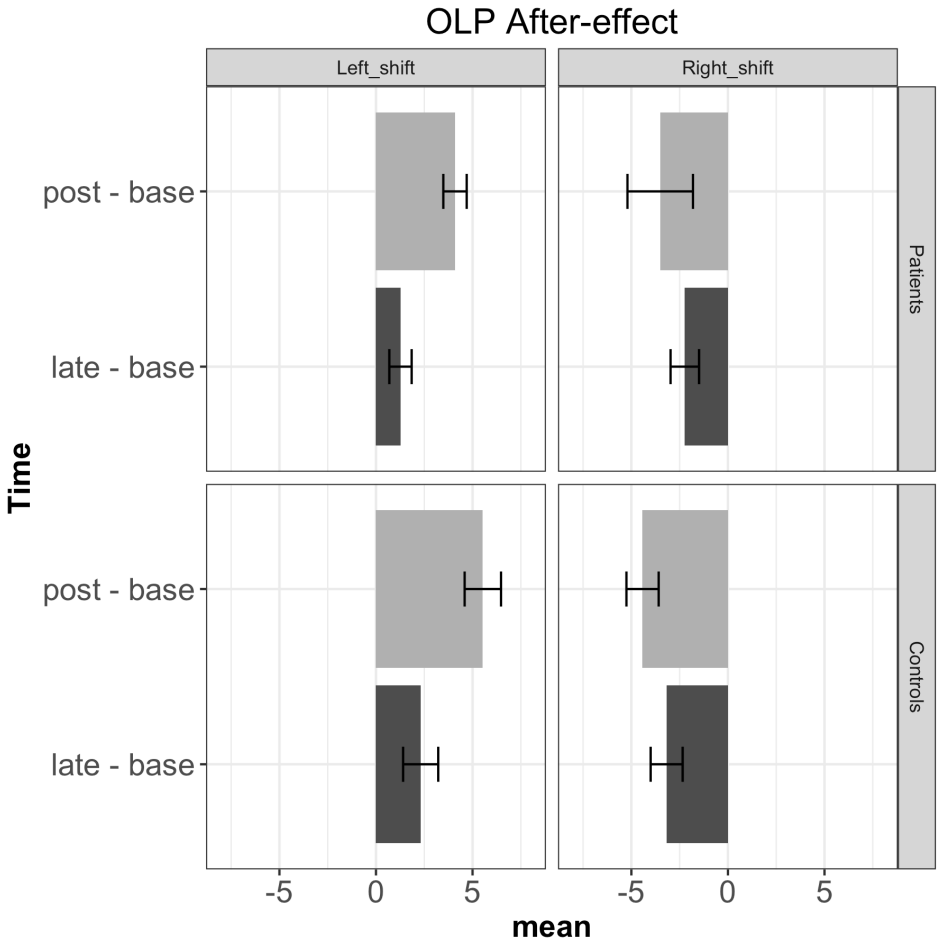


Figure 3.5: Open loop pointing (OLP) after-effect immediately following PA (post-base) and at the end of the experiment (late-base) for each shift direction and group.

Patient group.

Details of all tests to follow, for descriptive statistics see table 3.3, for graphical overview see figure 3.5.

Left shift PA.

There was a significant main effect of Phase, $F(1.33, 19.90) = 73.44$, $p < .001$, Greenhouse-Geisser corrected, $\eta_G^2 = .375$). Rightward errors produced at Post were

significantly different (by M = 4.09, 95% CI [3.49, 4.70], $p < .001$) to those produced at baseline. The errors apparent at Late were also significantly different compared to those at baseline (by M = 1.27, 95% CI [0.689, 1.85], $p < .001$).

Right shift PA.

There was a significant main effect of Phase, $F(1.30, 19.47) = 14.07$, $p < .001$, Greenhouse-Geisser corrected, $\eta_G^2 = .216$). Leftward errors produced at Post were significantly different (by M = -3.51, 95% CI [-5.20, -1.81], $p < .001$) to those produced at baseline. The errors apparent at Late were also significantly different compared to those at baseline (by M = -2.23, 95% CI [-2.97, -1.50], $p < .001$).

Table 3.3: OLP error scores per phase per shift direction for the patient group.

Shift	Phase	Mean	SE
Left shift	baseline	1.20	0.537
Left shift	post	5.29	0.628
Left shift	late	2.47	0.540
Right shift	baseline	1.23	0.439
Right shift	post	-2.28	0.978
Right shift	late	-1.00	0.613

Adaptation magnitude.

There was a main effect of Phase ($F(1, 15) = 27.08$, $p < .001$, $\eta_G^2 = .236$) with a larger after-effect immediately following adaptation (M = -3.80 , SE = 0.419) than at the end of the experiment (M = -1.75 , SE = 0.233). There were no other main effects or interactions.

3.3.2 LDT Reaction Time Results

Control group.

A repeated-measure ANOVA with within-subject factors of Shift (Left-shift, Right-shift), Time (post-SA, post-PA), Type (Related target, Unrelated target), SOA (short, long) and the dependent variable median RT revealed main effects of Time ($F(1,15)= 20.46$, $p < .001$, $\eta_G^2 = .023$), Type ($F(1,15)= 88.67$, $p < .001$, $\eta_G^2 = .224$), and SOA ($F(1,15)= 74.36$, $p < .001$, $\eta_G^2 = .580$). RT was significantly faster following prism (M = 547, SE = 8.2) compared to following sham (M = 570, SE = 7.1) adaptation, for related (M = 519, SE = 7.7) compared to unrelated (M = 598, SE = 5.9) targets, and for long (M = 540, SE = 8.2) compared to short (M = 577, SE = 6.8) priming intervals, respectively. The large effect sizes for Type and SOA are

consistent with the large literature on the robustness of the priming effect for associated words and for long relative to short priming intervals. The relevant descriptive statistics can be found in tables 3.4.

Table 3.4a: Control group reaction time data in ms for the right-shifting PA session

Time	Type	SOA	Mean	SE
Post-SA	Related	short	553	16.3
Post-SA	Unrelated	short	613	15.9
Post-SA	Related	long	513	20.6
Post-SA	Unrelated	long	602	16.5
Post-PA	Related	short	542	24.7
Post-PA	Unrelated	short	611	15.9
Post-PA	Related	long	481	22.4
Post-PA	Unrelated	long	584	19.1

Table 3.4b: Control group reaction time data in ms for the left-shifting PA session

Time	Type	SOA	Mean	SE
Post-SA	Related	short	555	15.9
Post-SA	Unrelated	short	619	15.5
Post-SA	Related	long	512	22.5
Post-SA	Unrelated	long	592	17.1
Post-PA	Related	short	526	17.8
Post-PA	Unrelated	short	595	17.8
Post-PA	Related	long	469	25.5
Post-PA	Unrelated	long	568	16.6

There was a significant interaction between Type and SOA ($F(1,15)= 5.63$, $p = .003$, $\eta_G^2 = .009$). Related targets were responded to more quickly compared to unrelated targets and this relatedness effect held true at both long and short priming intervals, which in turn were responded to comparatively faster and slower (related_short: M = 544, SE = 9.4; related_long: M = 494, SE = 11.4; unrelated_short: M = 610, SE = 8.0; unrelated_long: M = 587, SE = 8.6).

There was a significant interaction of Time and Type ($F(1,15)= 5.76$, $p = .03$, $\eta_G^2 = .002$), indicating that RT to target type differed following adaptation. RT to related targets significantly decreased (M = -28.8, 95% CI [-42.2, -15.4]) following PA, and so did RT to unrelated targets (M = -16.6, 95% CI [-24.9, -8.2]). Comparison of the confidence intervals indicates that the interaction effect is driven by a significantly greater decrease in RT to related compared to unrelated targets. See figure 3.6. Nonetheless, the priming effect did not change, figure 3.7.

There was a significant interaction of Time and SOA ($F(1,15)= 4.94$, $p = .004$, $\eta_G^2 = .002$). RT following short intervals significantly decreased (M = -16.32, 95% CI [-25.6, -6.99]) following PA, so too did RT following long intervals (M = -29.05, 95% CI [-42.4, -15.7]). Comparison of the confidence intervals indicates that the interaction effect was driven by a significantly greater decrease in RT to long compared to short intervals.

No other main effects or interactions were significant.

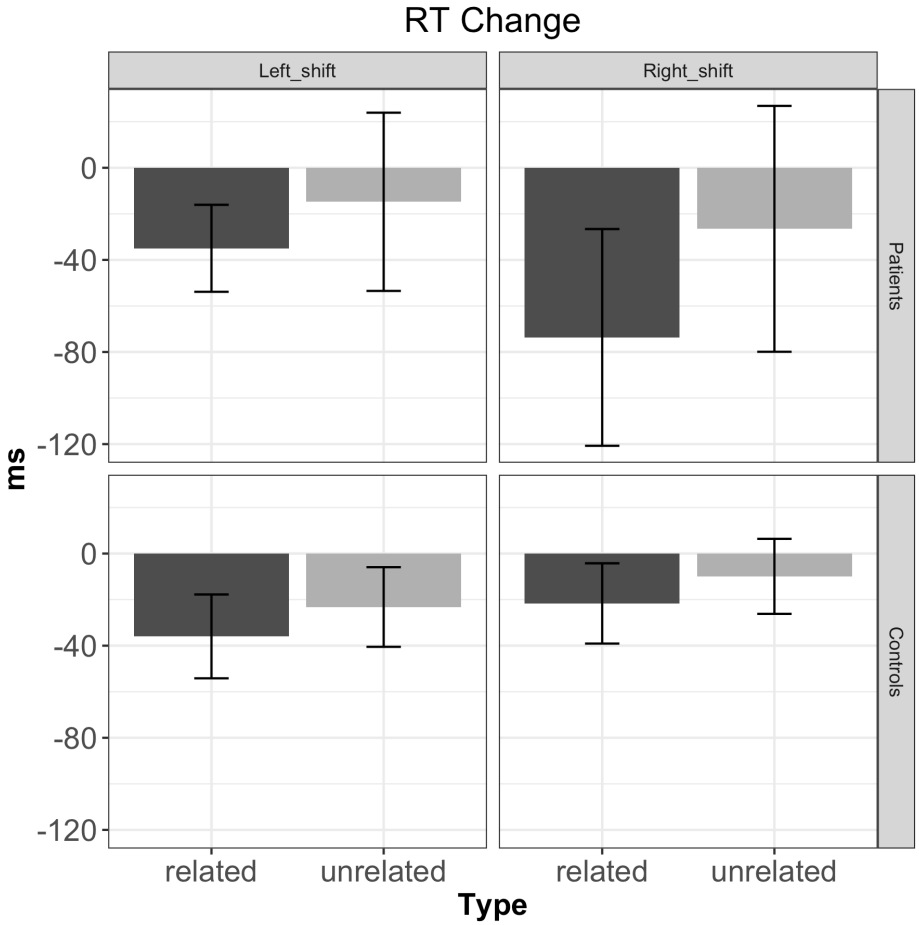


Figure 3.6: RT change in ms per target word type for each prism direction per group. (Error bars represent 95% confidence intervals).

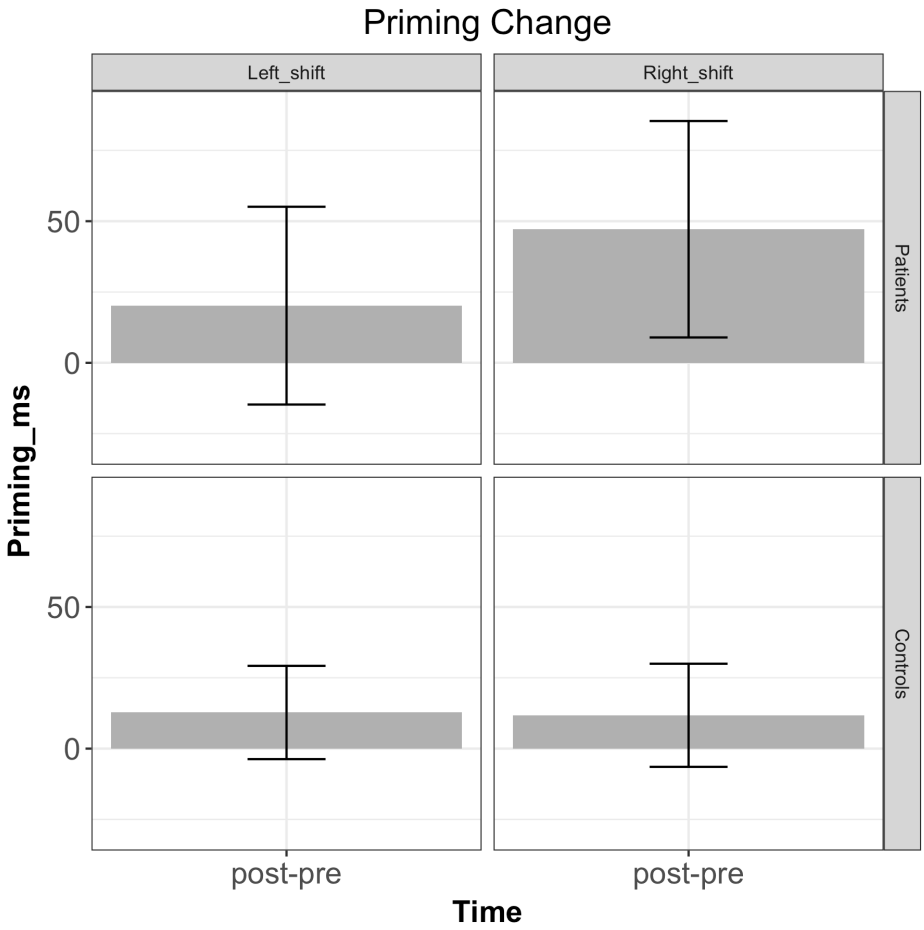


Figure 3.7: Mean change in priming effect in ms for each prism direction per group (Error bars represent 95% confidence intervals).

Patient group.

A repeated-measure ANOVA with within-subject factors of Shift (Left-shift, Right-shift), Time (post-SA, post-PA), Type (Related target, Unrelated target), SOA (short, long) and the dependent variable median RT revealed main effects of Time ($F(1,15)= 7.27$, $p = .016$, $\eta_G^2 = .007$), Type ($F(1,15)= 32.21$, $p < .001$, $\eta_G^2 = .027$), and SOA ($F(1,15)= 4.56$, $p = .049$, $\eta_G^2 = .004$). These results revealed that RT was significantly faster: following prism (M = 795, SE = 40.5) compared to following sham (M = 833, SE = 19.31) adaptation, for related (M = 777, SE = 20.11) compared to unrelated (M = 851, SE = 19.28) targets, and for long (M = 800, SE = 21.15) compared to short (M = 828, SE = 18.63) priming intervals, respectively.

Table 3.5a: Patient group reaction time data in ms for the right-shifting PA session

Time	Type	SOA	Mean	SE
Post-SA	Related	short	846	57.4
Post-SA	Unrelated	short	875	49.9
Post-SA	Related	long	805	67.3
Post-SA	Unrelated	long	870	58.2
Post-PA	Related	short	762	52.4
Post-PA	Unrelated	short	854	58.5
Post-PA	Related	long	742	67.7
Post-PA	Unrelated	long	837	65.6

Table 3.5b: Patient group reaction time data in ms for the left-shifting PA session

Time	Type	SOA	Mean	SE
Post-SA	Related	short	794	48.4
Post-SA	Unrelated	short	874	51.2
Post-SA	Related	long	771	58.8
Post-SA	Unrelated	long	826	49.0
Post-PA	Related	short	760	46.9
Post-PA	Unrelated	short	859	57.5
Post-PA	Related	long	735	60.1
Post-PA	Unrelated	long	811	54.6

A significant interaction between Time and Type ($F(1,15)= 8.78$, $p = .009$, $\eta_G^2 = .001$), indicated that RT to target type differed following adaptation. RT to related targets decreased significantly (M = -54.3, 95% CI [= -82.3, -26.3]) following PA, whereas RT to unrelated targets did not (the confidence interval of that change crossed zero (M = -20.6, 95% CI [-56.2, 14.9]) (figure 3.6). There were no other main effects or interactions. Specifically, there was no significant difference in the manner in which both prism shifts increased priming effects in the patient group (Time x Type x Shift, ($F(1,15)= 1.10$, $p = .311$, $\eta_G^2 < .001$). Thus, the results reveal that adaptation to both prism directions increased the priming effects (figure 3.7).

3.3.3 Patient Individual Differences

The average baseline priming effect for the patient group fell below the lower 95% confidence interval of the control group's average baseline. Further details in table 3.6.

Table 3.6: Priming effects (ms) per patient based on median scores were collapsed across SOA before and after PA. The average baseline is the average of the baseline scores in the two sessions. Bold italics = below lower 95% confidence interval [57.5, 88.6] of control group average baseline, Underlined = above the upper 95% confidence interval of controls. * = pre-stroke bilingual, gm and lm remain bilingual, ^ = experimenter entered responses.

		Right Shift			**Left Shift**		
Subject	**Average Baseline**	**Priming - pre**	**Priming - post**	**Change in Priming**	**Priming - pre**	**Priming - post**	**Change in Priming**
db	***26.8***	3.75	13.5	9.75	49.8	24.8	-25.0
de*	146	164.5	207	42.3	127	137	9.50
ds	***46.0***	43.3	31.8	-11.5	48.8	50.8	2.00
dsf^	***-97.3***	-165	31	196	-29.3	60.0	89.3
fg	96.9	149	112	-36.8	45.0	146	101
gm*	69.1	61.5	26.8	-34.8	76.8	27.3	-49.5
jl	***3.63***	-97.3	55.5	153	105	120	15.0
ll	59.6	57.5	89	31.5	61.8	33.8	-28.0
lm*	155	162	192	29.8	147	79.3	-67.8
mb	100	120	68.8	-50.8	80.8	276	196
mj	114	89.0	191	102	139	160	21.3
mjf	***-2.13***	-26.0	94.3	120	21.8	20.0	-1.75
np	***49.5***	22.8	107	84.0	76.3	78.0	1.75
pj	***48.5***	62.8	160	97.5	34.3	23.3	-11.0
rh	***25.9***	15.3	19.8	4.50	36.5	109	72.3
wc	74.5	85.0	103	17.5	64.0	62.8	-1.25
Average	***57.2***	**46.7**	**93.8**	**47.2**	**67.8**	**87.9**	**20.2**

3.3.4 LDT Accuracy Results

Control group.

An average accuracy of 98.1% precluded meaningful analysis of the data for PA induced change in accuracy. Details of accuracy by condition are provided in tables 3.7a&b for left and right shifting PA respectively.

Table 3.7a: Control group mean percentage accuracy for the right-shifting PA session

Time	Type	SOA	Mean	SE
Post-SA	Related	short	98.6	0.492
Post-SA	Unrelated	short	95.9	1.48
Post-SA	Related	long	99.8	0.195
Post-SA	Unrelated	long	96.7	0.830
Post-PA	Related	short	98.8	0.630
Post-PA	Unrelated	short	98.4	0.494
Post-PA	Related	long	99.0	0.470
Post-PA	Unrelated	long	97.3	0.691

Table 3.7b: Control group mean percentage accuracy in the left-shifting PA session

Time	Type	SOA	Mean	SE
Post-SA	Related	short	99.4	0.315
Post-SA	Unrelated	short	97.9	0.793
Post-SA	Related	long	98.8	0.391
Post-SA	Unrelated	long	95.1	1.03
Post-PA	Related	short	99.0	0.470
Post-PA	Unrelated	short	98.0	0.562
Post-PA	Related	long	98.8	0.484
Post-PA	Unrelated	long	97.3	1.36

Patient group.

An average accuracy of 96.1% precluded meaningful analysis of the data for PA induced change in accuracy. Details of accuracy by condition are provided in tables 3.8a&b.

Table 3.8a: Patient group mean percentage accuracy in the right-shifting PA session.

Time	Type	SOA	Mean	SE
Post-SA	Related	short	98.8	0.484
Post-SA	Unrelated	short	92.6	2.07
Post-SA	Related	long	97.7	0.781
Post-SA	Unrelated	long	92.4	1.89
Post-PA	Related	short	98.2	0.568
Post-PA	Unrelated	short	94.1	0.941
Post-PA	Related	long	98.2	0.568
Post-PA	Unrelated	long	94.7	1.61

Table 3.8b: Patient group mean percentage accuracy in the left-shifting PA session.

Time	Type	SOA	Mean	SE
Post-SA	Related	short	99.0	0.470
Post-SA	Unrelated	short	95.3	1.43
Post-SA	Related	long	98.4	0.403
Post-SA	Unrelated	long	93.0	2.53
Post-PA	Related	short	98.6	0.697
Post-PA	Unrelated	short	94.9	1.17
Post-PA	Related	long	98.0	0.748
Post-PA	Unrelated	long	93.9	1.35

3.4 Discussion

Analysis of OLP after-effects reveals that patient and control groups adapted to both leftward and rightward prism displacement and the adaptation remained significant until the end of each experimental session. The RT results indicate that both patients and controls displayed baseline priming effects. However, a detailed inspection reveals that average baseline priming for the patients fell below the lower 95% confidence interval for the controls, indicating it was reduced. RT decreased following both directions of PA for both groups, suggestive of practice effects. However, the faster RTs following PA were limited to related words in the patient group, implying that PA did influence priming effects.

3.4.1 Target Type

A comparison of effect sizes in the ANOVAs across the groups reveals interesting differences. The controls had a large effect size ($\eta_G^2 = .224$) of target type with RT for related targets significantly faster than unrelated targets. This was expected from the literature (Meyer & Schvaneveldt, 1971). However, the effect size is small in the patient group ($\eta_G^2 = .027$), particularly when considered in the context of the priming literature in which effect sizes are generally larger (and this difference is exaggerated for baseline data only with $\eta_G^2{}_{\text{controls}} = .252$ and $\eta_G^2{}_{\text{patients}} = .002$). It suggests that, unlike in the control group, priming is not normal in the patient group. Coherent with this interpretation is the finding that the average baseline priming effect for the patient group was just below the lower 95% confidence intervals of the control group (see table 3.6). (At the same time, it is of note that some patients are above the upper 95% confidence interval of the control group, suggestive of a dysregulation of another kind. While not discounting the importance of individual differences, the discussion focuses on the group average.)

The finding of reduced priming in left hemisphere lesioned patients is not universal: there are findings that are both consistent with (Hagoort, Brown, & Swaab, 1996; Henik et al., 1993; Milberg, Blumstein, & Dworetzky, 1987) and contradict (Blumstein, Milberg, & Shrier, 1982; Hagoort, 1993; Milberg et al., 1987; Milberg & Blumstein, 1981) the possibility of a deficit. It is worth noting that effect sizes were not reported in those studies and thus the current contrast between *p* significance and effect size may go towards explaining the mixed findings.

3.4.2 Priming Time

In relation to the time interval between the presentation of the prime and the target, the effect size comparison is striking. The control group showed a large effect size of SOA ($\eta_G^2 = .580$) in the ANOVA as expected (McRae & Boisvert, 1998). However, for the patient group the effect size of SOA was very small ($\eta_G^2 = .004$) as in other aphasia studies (Henik et al., 1993); this difference is smaller but present when the baseline data are considered alone, with $\eta_{G\ controls}^2 = .055$ and $\eta_{G\ patients}^2 = .005$.

Taken together, the contrasting effects of target type and priming time results suggest that associative priming for the patient group was not within normal performance range.

3.4.3 A Practice Effect or a PA Effect?

The absence of a sham exposure – sham exposure session makes it difficult to definitively determine whether the increased priming effect over the sessions is due to practice, or a PA effect on priming that is independent of shift direction. However, an important difference between the two groups is the change in RTs across target word types. In the control group, RT to both target types sped up, with a bigger decrease for related compared to unrelated pairs (although it did not translate into a significant increase in priming effect size). However, in the patient group, the increase in priming was driven exclusively by a decrease in RT for related pairings, there was no change in RT to unrelated word pairs. This suggests that both directions of PA had a specific effect for the patient group – increased access to related words. This interpretation must be tempered by the practically non-existent interaction effect size of Time x Type ($\eta_G^2 = .001$), even though the effect size of the RT change in related targets only ($d_{unb} = -0.234$) was non-trivial if still small.

3.4.4 An Effect of Both PA Shift Directions

The interpretation of a PA induced priming increase in the patient group is perhaps complicated by the fact that it was elicited by both PA shifts. Indeed it would appear not to fit within a hemispheric re-balancing mechanism. However, studies of recovery from aphasia have shown that a network of bi-hemisphere areas can be recruited, with their usefulness determined by the phase of recovery and the extent of

the lesion (Saur et al., 2006; Turkeltaub, Messing, Norise, & Hamilton, 2011; Winhuisen et al., 2007).

This pattern was also reflected in a review of motor deficit rehabilitation. Lesion size or structural reserve (the post-stroke integrity of the lesioned hemisphere) was shown to be an important determinant for choosing how best to treat a patient with non-invasive brain stimulation techniques. This is captured in the 'Bimodal Balance-Recovery' model. Where lesion size is large, recruitment of more distant or even contralesional areas appears important for recovery, and in these cases further up-regulation or facilitation of the contralesional hemisphere may be beneficial. However, where structural integrity of the lesioned side remains high, e.g. where the lesion is relatively small or involves only a part of the region subserving the function under consideration, inter-hemispheric imbalance may be more of a hindrance to recovery and down-regulation or inhibition of contralesional hemisphere may be beneficial (Di Pino et al., 2014). Taken together, it cannot be ruled out that either shift could be helpful for different patients or that both shifts could help within the same patient but for different reasons.

Additionally, there is growing evidence that semantic processing is widely distributed in the healthy brain with bilateral anterior and ventral temporal areas playing a key role (Acosta-Cabronero et al., 2011; Lambon Ralph, Ehsan, Baker, & Rogers, 2012; McClelland & Rogers, 2003). It has been posited that the bilateral anterior temporal lobes are integration points for semantic information from different modalities and that the apparent left dominance as witnessed in anomia is due to the left anterior lobe being more strongly connected to the left lateralised speech production regions (Lambon Ralph, McClelland, Patterson, Galton, & Hodges, 2001). Therefore a resultant redundancy across both lobes can be compensatory following stroke according to the level and extent of damage caused (Lambon Ralph et al., 2012) with the integrity of the functional connectivity between the left and right anterior temporal lobes being key (Warren, Crinion, Lambon Ralph, & Wise, 2009). This suggests that language, or at least semantic processing, is not as lateralised as had been previously assumed. This lends further support to the idea that depending on the site of over/under activation within an individual one or other PA shift could be ameliorative. If that were to be the case what might be the inter-hemispheric mechanism that can be acted on by PA? The next section attempts to shed light on this question.

A physiological mechanism for hemispheric balance.

Koch et al. (2011) used a tri-focal TMS paradigm and DTI analysis to examine hemispheric lateralisation of visuospatial function. They reported an asymmetrical inhibitory inter-hemispheric relationship between the posterior parietal cortices (PPC) that was mediated by direct transcallosal projections running through the posterior corpus callosum. Specifically, the PPC stimulation site was the posterior part of the IPS within the inferior parietal lobule. This site is known to enhance activity of the M1 when stimulated, implying activation of a cortico-cortical pathway. A first sub-threshold conditioning pulse was applied to the contralateral PPC site, a second sub-threshold conditioning pulse on the ipsilateral PPC followed by a third test pulse on the ipsilateral M1 from which a physiological recording was made. An asymmetry became apparent in that the right PPC exhibited strong inhibitory activity over its left homologue (resulting in a smaller physiological response) but not so for the left over the right PPC. This finding provided a neurophysiological mechanism for the results of Fierro et al. (2000) who, using rTMS on the right PPC, simulated neglect-like rightward visuospatial biases while similar leftward biases were not elicited with left PPC simulation. Notably, both sets of findings support Kinsbourne's model of inter-hemispheric rivalry, and contribute to explaining why, for spatial attentional control, the RH can override a more inhibited LH (Koch et al., 2011).

Evidence is increasing in support of PA acting on this physiological asymmetry. Imaging studies have shown PA to act on the PPC bilaterally (Crottaz-Herbette et al., 2014; Martín-Arévalo, Schintu, Farnè, Pisella, & Reilly, 2017; Saj et al., 2013). For example, Martín-Arévalo et al. (2017) tested whether left and/or right shifting PA effects inter-hemispheric inhibition (IHI) in healthy individuals. They measured IHI between the motor cortices (M1) using the ipsilateral silent period (iSP) method, which is understood to represent inhibitory action within transcallosal fibres. Changes in the onset and duration of the iSP were taken, before and after PA, in the left-to-right and right-to-left direction. They found a change in IHI from the left to the right motor cortex only, and only following left PA. This change at the motor level was interpreted as due to left PA inhibiting the right PPC, creating a reduced right-to-left parietal IHI, in turn leading to a disinhibited left PPC and hyper-excitability between the left PPC and left M1 that finally was expressed in greater transcallosal IHI of the left M1 over the right M1.

These findings can explain why left PA simulates neglect in healthy individuals. They may also explain, at least partially, why right PA is ameliorative to those with left neglect. In the absence of any knock-on effects occurring in the right hemisphere because of the IHI asymmetry, the right PA inhibits the left PPC thereby reducing its intra-hemispheric hyper-excitability and restoring (at least some) inter-hemispheric balance (Martín-Arévalo et al., 2017). Others have also proposed that PA spatial cognitive after-effects are due to an initial inhibition of the PPC contralateral to the prismatic shift that is followed by a modulation of inter-hemispheric balance (Luauté et al., 2006; Striemer & Danckert, 2010).

Thus, for right hemisphere specialised spatial cognition at least, it appears that PA mechanisms do capitalise on a neurophysiological asymmetry in the direction of IHI between the PPC. Such an asymmetry is not thought to exist in the connection between the anterior and ventral temporal lobes, the putative bilateral integrative hubs for semantic knowledge (Acosta-Cabronero et al., 2011; Lambon Ralph et al., 2012; McClelland & Rogers, 2003). These lobes are connected via the anterior commissure and studies of patients with herpes encephalitis do not suggest a directional asymmetry (Esiri, 1982). If direction of travel were to be symmetrical, this would support the potential ameliorative roles of either direction of prismatic displacement.

In terms of frontal lobe involvement in language, the contention that up-regulation of the right hemisphere following a focal disruption of the left hemisphere is a result of reduced IHI has been challenged as simplistic. Hartwigsen et al. (2013) found that focal TMS disruption of the left posterior IFG resulted in a speeding up of RT for reading pseudowords aloud. Importantly, their fMRI effective connectivity analysis revealed that the left posterior IFG had been rendered more sensitive to a facilitory influence of its homologue due to increased connectivity from the right to the left. Additionally, increased activation was noted bilaterally in the middle temporal gyrus, right STG, and right middle frontal gyrus. This study highlights two aspects of interest. Firstly, that language processing could be supported by a bilateral network. Secondly, the notion of a purely asymmetrical inhibition of the right posterior IFG by the left is questionable.

However, Andoh & Paus (2011) showed asymmetrical activity changes following 10 Hz offline rTMS of the left and right pSTG during auditory recognition of foreign and native words. Following left stimulation, increases in task-related fMRI activation were observed in the right MTG and STG, and the left cerebellum, and

decreases in the left MTG and STG. In contrast, following right stimulation, increases in task-related activation were noted in the left STG, left cingulate gyrus, the right cerebellum, and the superior and middle frontal gyri bilaterally; and decreases in the left posterior cingulate and left precentral gyrus.

In summary, it is likely that semantic representation in the temporal lobes is bilateral, with inherent redundancy in the bilateral anterior and ventral areas, and there may not be asymmetrical inter-hemispheric inhibition between the posterior inferior frontal gyri. Indeed, suppressing activity in left posterior IFG reduces left temporal activity, both not *vice versa*; whereas excitatory stimulation of the left and right pSTG produces asymmetrical patterns of increases and decreases of activity across temporal, cerebellar and frontal regions. In other words, the picture is not simple, nor does it offer up a single putative physiological mechanism of post-insult compensation. However, there is no reason militating against the plausibility of both PA directions having an effect on associative priming.

Neuroanatomy of PA cognitive after-effects.

It is not firmly established that PA has knock-on effects on the anterior and ventral temporal lobes. Published studies of the cognitive after-effects of PA are almost exclusively related to spatial cognition and have implicated the SPL (Striemer et al., 2008), the PPC (Magnani et al., 2013), the dorsal PPC (attentional network) (Martín-Arévalo et al., 2016), and the ventral attentional network (specifically left angular gyrus activity increases and right supramarginal gyrus decreases, (Crottaz-Herbette et al., 2014)). Interestingly, Chen, Goedert, Priyanka, Foundas, & Barrett, (2014) found a significantly greater beneficial effect of PA on left neglect in patients with frontal lobe lesions. This improvement was linked to the integrity of the medial temporal and subcortical regions, followed with a less conservative cut-off threshold (5%) by the medial temporal gyrus, the superior temporal area, the anterior transverse temporal area, and the inferior longitudinal fasciculus. These findings suggest that PA may act on the temporal lobes for the improvement of neglect. There are also other indications that PA acts on temporal areas and on transcallosal pathways outside of the PPC.

Although it was not a study of cognitive after-effects, upon elimination of pointing errors, Luauté et al. (2009) noted activity bilaterally in the superior temporal sulcus (STS) extending into the superior temporal gyrus. The authors further suggested that such STS activity is underpinned by sustained activity in the

cerebellum. As noted in the general introduction, the involvement of the cerebellum and its interaction with the IPS, and STS, is key to true adaptation (sensory realignment). Cerebellar outputs from the dentate nucleus to the STS and to frontal lobe areas 9 and 46 have been documented (Dum & Strick, 2003; Salmi et al., 2010). The cerebellum has been implicated in sensory realignment, it links to the STS and frontal lobe, and both cerebellar hemispheres are though to play a role in the control of language processing (for reviews see: De Smet, Paquier, Verhoeven, & Mariën, 2013; Murdoch, 2010).

The once strict dichotomy of visual processing into dorsal and ventral streams is now better understood as a collaborative flexibly interactive arrangement (Vossel, Geng, & Fink, 2014). This may serve, in part, to reconcile the findings separately implicating the dorsal network involving the angular gyrus and STS (part of the temporo-parietal junction (TPJ) in the ventral network) in PA. Notably, deficits in global-local processing due to RH TPJ lesion can be reversed following right PA (Bultitude et al., 2009). However, this cannot necessarily be taken as evidence that the TPJ is subject, at least solely, to the same IHI process as identified by Koch et al. (2011). A connectivity-based analysis of the region (identified as the cortex from the ventral bank of the intraparietal sulcus to the dorsal bank of the horizontal and main branches of the STS) in the RH has revealed three sub-divisions. A dorsal cluster in the middle part of the IPL connected with the lateral anterior prefrontal cortex; a ventral anterior TPJ region interacted with ventral prefrontal cortex and anterior insula; and finally a posterior TPJ cluster linked with posterior cingulate, temporal pole, the anterior medial prefrontal cortex, and the cerebellum bilaterally (Mars et al., 2012). This posterior TPJ region with links to the temporal pole and cerebellum would be a candidate for the bi-directional effects of PA in the current study.

Lastly, Calzolari, Gallace, Moseley, & Vallar (2016) reported an unusual effect of rightward, but not leftward, shifting PA on thermoregulatory control in healthy individuals. The authors linked the sensorimotor after-effects and their effects on bodily spatial reference frames with basic physiologic parameters such as body temperature. Temperature was measured with digital thermometers attached to the hand from 20 minutes before to 23 minutes after adaptation to left-, right-, and zero-shifting prisms. The rightwards-shifting PA resulted in no change in temperature during or after exposure followed by a drop twenty minutes later, whereas the other two conditions resulted in an increase during exposure followed by a gradual return to

baseline. Notably, this pattern of results does fit with a hemispheric balance account of PA. Thermoregulation is RH specialised in the anterior insular and orbitofrontal cortices with a directionally lateralised (left-to-right) flow of information across the callosal pathway between the insular cortices (Craig, 2002). This indicates that PA may act on inter-hemispheric channels outside of the PPC and is supportive of the possibility of PA acting, most likely indirectly, through the anterior commissure.

Alternative Perspectives

It must be acknowledged that the variability in the patient data is a complicating factor. However, it may be unreasonable to expect patient data to tell a simple story. The data variability resulted in an inability to directly compare it against the control data in one ANOVA. Additionally, a graphical inspection of the patient RT results, and particularly the priming effects, suggests that only right-shifting PA effected a change in priming. Although this is not a statistically reliable result, the inherent noisiness of small sample patient data (here and in general) suggests that it should be taken seriously as an alternative interpretation.

Where the cognitive effect in question is lateralised to the left cortical hemisphere, an exclusive effect of right-shifting PA goes against a simple hemispheric balancing account of cognitive after-effects. Rather, what it may point to is an influence of the cerebellum – home of the 'true adaptation/spatial realignment'. In this scenario, right-shifting PA activated the right cerebellum, in turn the right cerebellar hemisphere acted on the left cortical hemisphere. Blood flow increases in the right cerebellum (dentate nucleus and lobule V) and activation decreases in left medial temporal cortex have been noted following right-shifting PA in left unilateral neglect patients (Luauté et al., 2006). Both, or either, of these actions may plausibly increase priming. There is a growing literature on cerebellar influence on language, particularly in temporally and sequentially associated language (e.g. "bread and butter") (for reviews see: De Smet, Paquier, Verhoeven, & Mariën, 2013; Murdoch, 2010). The potential of the cerebellum to influence language processing is explored further in chapter four.

A note of caution.

It is possible that the PA induced increased priming effect may not be ameliorative. The baseline decreased priming effect of the patients may represent a compensatory process that facilitates processing of words under difficult (i.e., neural damage) circumstances. This idea conforms with the views put forth by the centre

surround hypothesis of Carr & Dagenbach (1990) and in a patient study by Bushell (1996), whereby sequential/associated words are suppressed in order to facilitate retrieval of the current word. Interestingly, and consistent with this idea, the RH lesion patients in the Henik et al. (1993) study displayed priming effects larger than controls, suggesting an opposite direction of dysregulation within the system – i.e., moving on too quickly before fully establishing the current meaning. Indeed, some of the patients in the current study also had larger priming effects than controls suggesting an inadequate compensation. This leads to an interpretation in which the present results do not reflect a potential therapeutic value of PA for LH lesion patients.

Given that a practice effect cannot be fully ruled out nor, on the other hand, is it definitive that both shift directions are both equally effective, the discussion of an underpinning mechanism must be speculative. However, taken together, the current results and the neuroanatomical literature suggest that it is reasonable to leave open the possibility that both directions of PA may impact associative priming in LH aphasics. Further testing incorporating better control conditions and in-depth lesion analysis will help clarify this matter.

3.5 Conclusion

In summary, in this study a group of sixteen LH patients were found to have associative priming effects that were not within normal performance measures. Following both left- and right- shifting PA their RT to related words speeded up while there was no change to their RT to unrelated words indicating an increase in priming. The findings did not lend themselves to a simple account of hemispheric rebalancing of a lateralised function. Given that both prismatic directions produced the effect, PA appeared to work on a bi-directional or distributed inter-hemispheric mechanism. The bilateral anterior and ventral temporal areas and their inter-connection via the anterior commissure are candidate sites for such a process. Links between the STS and the cerebellum, and previous ameliorative action of PA on the TPJ (of which the STS is a part), lend support to this suggestion.

Chapter 4

An Opponent Process Cerebellar Asymmetry for Regulating Word Association Priming

Abstract

A consensus has emerged that the cerebellum makes important contributions to a spectrum of linguistic processes, but that the psychobiology of these contributions remain enigmatic (Mariën et al., 2014). One aspect of this enigma arises from the fact that, although the language dominant left cerebral hemisphere is connected to the right cerebellum, distinctive contributions of the left cerebellar hemisphere have been documented (Murdoch & Whelan, 2007), but remain poorly understood. Here we report that neurodisruption of the left and right cerebellar hemispheres have opposing effects on word association priming (WAP) in a lexical decision task. Reaction time was measured during deciding whether a target letter string constituted a word (e.g. bread) or, with equal probability, a pronouncable non-word (e.g. dreab). A prime word was presented for 150 ms before the target and could either, and with equal probability, be related (e.g. BUTTER) or unrelated (TRACTOR). WAP was computed as the reduction in lexical decision RT on trials with related primes. Left cerebellar hemisphere continuous theta-burst transcranial magnetic stimulation (TMS) decreased, and right hemisphere stimulation increased, WAP. The results suggest that the cerebellum contributes to predictive language processing through an opponent process mechanism co-ordinated by both cerebellar hemispheres.

4.1 Introduction

At the end of his career, Robert Stone Dow, an authority on the cerebellum, drew focus to the non-motor functions of the cerebellum (Dow & Moruzzi, 1958). Leiner, Leiner, & Dow (1993) highlighted, in particular, the likely contributions of the cerebellum to language. They cited: 1) the enormous enlargement of the lateral cerebellum in humans; 2) the expansion of cerebellar connections to prefrontal cortex (including Broca's area) via projections both to pontine nuclei and via the rubro-olivary pathway; 3) the emergence of a neodentate (parvocellular) component of the deep cerebellar nuclei in primates, whose projections are dominantly to frontal lobe and in particular; and 4) the enormous size of these projections in humans. Subsequent anatomical and clinical observations provided strong support for a role of the cerebellum in both cognitive and affective domains (Schmahmann & Sherman, 1998) with the heuristic hypothesis that cerebellar damage in humans results in a 'dysmetria of thought' (Schmahmann, 1998) – the idea that there is a disturbance in the coordination of thought analogous to that seen with movements.

Indeed the wide range of mild linguistic deficits documented following cerebellar damage (e.g., impairments in lexical access, phonological and semantic verbal fluency, syntax processing, reading, writing, and speech) has led to the idea of cerebellar aphasia gaining ground and an agreement that the problems relate to control of language processes rather than an impairment in language components (Fabbro et al., 2004; Fabbro, Moretti, & Bava, 2000; Mariën, Engelborghs, Pickut, & De Deyn, 2000). In a MEG study, that facilitated analysis of the time courses of activation of brain areas during reading, Kujala et al. (2007) identified the cerebellum (along with the left inferior occipitotemporal cortex) as the main forward driving nodes of the reading network. Important to the current study is the fact that both left and right cerebellar damage has been implicated in language deficits (for reviews see: De Smet, Paquier, Verhoeven, & Mariën, 2013; Murdoch, 2010). However, the psychobiology of cerebellar contributions to language remains enigmatic (Mariën et al., 2014).

Recent interest has focused on the potential role of the cerebellum in providing a prediction mechanism that facilitates not only language production but also language comprehension (Argyropoulos, 2016; Moberget & Ivry, 2016). Lesage et al., (2012) employed a 'Visual World' paradigm (Altmann & Kamide, 1999), wherein they recorded eye movements of people listening to sentences, while viewing

four pictures, one target and three distracters, at the corners of an imaginary square. The target was a picture of an object named at the end of the sentence. The sentences were either predictive or non-predictive. For example, in a predictive sentence, 'the man will sail the boat', the pictures could be a boat/bird/car/house, and a non-predictive sentence might be 'the man will watch the boat', with the same set of pictures. When a sentence was predictive, participants made anticipatory eye movements toward the target (boat). The reduced latency of the first saccade toward the target picture when sentences are predictive vs. non-predictive, provides a measure of predictive language priming. Participants were tested before and after offline 1hz repetitive transcranial magnetic stimulation (TMS) of the right cerebellar hemisphere for 10 minutes. TMS reduced the effect of prediction on saccade latencies to target pictures.

Using a different off-line repetitive TMS procedure (continuous theta-burst), Argyropoulos (2011) examined the effects of medial right cerebellar hemisphere disruption in a word association priming paradigm in which prime words were phrasally/temporally (e.g., pigeon-HOLE) or categorically (e.g., penny-COIN) related to the target. Disruption of the right cerebellum resulted in an increase in phrasal associative word priming but had no effect on semantic priming. That is, the observed change was in the condition in which there was a temporal relationship between the words. In an extension of that study, disruption of the lateral right cerebellar hemisphere resulted in enhancement of semantic noun- to-verb priming based on association (e.g. 'soap–cleaning'), but had no effect of priming based on categorical similarity (e.g. 'robbery–stealing') (Argyropoulos & Muggleton, 2013).

Reflecting those findings, some authors have called upon the work of Ivry & Richardson (2002) to propose cerebellar-induced linguistic deficits are due to a timing disorder (e.g., Ackermann, Gräber, Hertrich, & Daum, 1999). Building on studies of ataxic dysarthria (a disruption of speech articulation and prosody), Ackermann (2008) has specified a role for the cerebellum in the 'temporal organization' of speech, an argument that has been expanded upon by Kotz & Schwartze (2010). While some authors do support a role for the cerebellum in temporal and spatial sequencing of activities (Molinari et al., 2008), others give more weight to its function as a comparator of temporally accurate predictions or internal models (Ito, 2008) with the actual sensory feedback of action (reafference). It has recently been pointed out that all predictions contain a 'what' and a 'when' element (to some degree). Moberget &

Ivry (2016) argue that for now the evidence for a predictive role of the cerebellum in language is predominated by the 'when' element. Whereas, Argyropoulos (2016) argues that in fact the evidence for any cerebellar role in language to date remains inconclusive.

Both the Lesage et al., (2012) and the Argyropoulos (2011) experiments employed TMS disruption of the right cerebellum. The former resulted in a reduced benefit of prediction in the visual world experiment whereas, paradoxically, in the latter the priming effects of prediction were increased. Working from the observation that both used different intervals between the presentation of the prime and target words, the hypothesis suggested by the current research could reconcile this apparent contradiction. Here we report that TMS disruption of the right and left cerebellar hemispheres with sub-threshold cTBS have opposite effects on associative word priming in which there is a forward (i.e., predictive) relationship between prime and target words in a lexical decision task. We relate our findings to evidence from several domains, including language priming, neuropsychology of aphasia and contemporary hypotheses of cerebellar function, and suggest that any cerebellar role in predictive language processing is mediated by a coordinated opponent processes mechanism involving both hemispheres.

4.2 Methods

In a mixed group design, automatic word association priming effects (WAP) were measured in a lexical decision task (LDT) before and after 40 seconds of continuous theta-burst TMS. One group of participants was stimulated over the left medial cerebellum and another group over the right medial cerebellum. All participants were also stimulated at a vertex control site, with half stimulated first over the cerebellum or vertex in sessions one week apart. The order of site of stimulation (cerebellum/vertex) was counterbalanced across participants.

4.2.1 Participants

Forty-one self-reported neurologically healthy participants, 21 women (mean age 23.4 years, SD = 5.5) were recruited from the University community. All were right-handed (Oldfield, 1971) with normal or corrected-to-normal vision, non-dyslexic, and mono-lingual English speaking. Bangor University Ethics Committee approved the research, which was conducted in concordance with the Declaration of

Helsinki, and a health screen/medical history questionnaire was employed to ensure individuals with a medical history (of epilepsy, brain disease, migraine or use of psychotropic medication) that would contraindicate brain stimulation were excluded. One group of participants received right (n=21) and the other left (n=20) cerebellar stimulation, participants were randomly assigned to a group. Each group was stimulated over a vertex control site in a separate session. Site order (cerebellum/vertex) was counterbalanced with sessions one week apart. Decision on sample size was based on a related study (Lesage et al., 2012).

4.2.2 Brain Stimulation

Continuous theta-burst stimulation (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005) was administered using a Magstim Super-rapid stimulator with a 70mm figure-of-eight coil. Stimulator output was individually set to 80% of each individual's resting motor cortex threshold (mean 59.2% of maximum stimulator output (SD = 9.8)); stimulation intensity was chosen based on a study that showed disruption of classic eye blink conditioning using these stimulation parameters (Hoffland et al., 2012). The location of cerebellar stimulation (1cm below and 3 cm lateral to the inion) corresponded to that used in a related (see discussion) study (Lesage et al., 2012). The coil paddle pointed posteriorly for vertex and superiorly for cerebellar stimulation.

4.2.3 Lexical Decision Task

A stimulus that activates the meaning of a word (e.g. salt) facilitates subsequent processing of other words with which it is often associated (e.g. pepper) (Meyer & Schvaneveldt, 1971). This word association priming (WAP) can be measured experimentally as a reduction in latency to recognize a target letter string as a word in a lexical decision task**.** WAP is contingent on how likely one word will bring another to mind based, for example (and as designed in this study), on the likelihood that the two words will occur in temporal contiguity. In a typical lexical decision task, the dependent variable is the time to make a decision whether a target letter string is a word (e.g. bread) or, with equal probability, a pronounceable non-word (e.g. dreab). The target string is preceded by a prime word that is either associated with the target word (e.g. butter) or, with equal probability, not associated

(e.g. tractor). The associated prime condition results in shorter response times (RT) to make the lexical decision.

4.2.4 Procedure

Experimental stimuli were pairs of letter strings sequentially presented at the centre of a CRT monitor at eye level 57 cm in front of the participant. Presentation of stimuli and recording of responses was controlled using E-Prime software on a Window's based personal computer. Participants were asked to read on screen a series of pairs of letter strings and to respond only to the second letter string by indicating, as quickly and as accurately as possible, whether or not it was an English word.

Participants started with a long practice block of 64 trials to check understanding and to minimise practice effects across experimental sessions. Participants recorded their answers by pressing one of two keypad buttons using the middle and index fingers of their left/right hand, button allocation was counter-balanced across participants.

Each experimental block consisted of two lists of 80 trials each. The presence of two lists allowed for a short break (c30 s) during the block. Each trial began with the presentation of a fixation + for 500 ms followed by the prime word in upper-case for 150 ms, followed by a blank screen lasting 100 ms (± 50ms) and then the target letter-string in lower-case. Targets remained on screen until the participant responded. The inter-trial interval was 1500 ms, and the order of stimuli presentation was pseudo-randomised. Use of the stimuli blocks before or after stimulation was counter-balanced across participants. This controlled for any differences in the stimuli beyond forward association strength (see Stimuli section). In total each participant was presented 320 word pairs over two blocks (pre and post TMS) during an experimental session.

Participants completed the practice block, two pre-stimulation blocks, received rTMS, waited 5-6 minutes, and then completed two post-stimulation blocks. Participants receiving left cerebellar stimulation were instructed to use their right hand for the task across both sessions (vertex and cerebellar stimulation), and vice versa.

4.2.5 Stimuli

Stimuli for the LDT consisted of 4 lists, two for pre-TMS use and two for post-TMS use, each containing 20 related prime-target word pairs, 20 unrelated prime-target word pairs, and 40 prime-nonword pairs; this resulted in an equal probability mix ratio. Stimuli examples are *SALT-pepper* (related), *GIRL-stamp* (unrelated), *NIGHT-henost* (non-word) (see Appendix K for lists). A practice stimuli set consisted of 16/16/32 pairs respectively.

The Semantic Priming Project database (Hutchison et al., 2013) was mined for pairs based on the following prime characteristics: forward associative strength (FAS) 0.4 and above, word length 3-10, RT and automatic priming effect size. The FAS criteria was key, the aim for the associated pairs was to produce pairs that were related over time, i.e., temporally predictive. This search resulted in 395 prime-target pairs. The pairs were searched for any repetitions across prime or target, the pair containing the repetition with the lowest FAS and/or priming effect at short SOA was eliminated, resulting in 349 pairs. A further 20 pairs were removed due to potential cultural differences between U.S. and U.K. English. The remaining pairs from this master list were ordered based on size of priming effect, and the list split in two: One with positive priming (232 pairs) and one with negative priming (97 pairs). From this master list 4 stimuli lists were prepared, with each list ultimately containing 20 related, 20 unrelated and 40 non-word pairs.

The order of the positive priming master list was randomised and 4 groups of 20 pairs were sequentially chosen and assigned to the different stimuli lists as ‘related pairs’. Then another 4 groups of 20 pairs were sequentially chosen from the remainder of the positive priming master list and assigned to the stimuli lists as ‘unrelated pairs’. All these 8 lists were then compared and adjusted, through swapping pairs, so that on visual inspection they were comparable across FAS, word length, word frequency, lexical decision task RT, automatic priming effect size, and mix of relationship types.

The remaining pairs from the original master list (all having a positive FAS but not all achieving a positive priming effect) were then randomised in order. Sequential tranches of 40 pairs were allocated to each of the 4 stimuli lists as ‘non-word pairs’. These sub-lists were then visually compared and adjusted as before so that all the stimuli lists matched as much as possible.

Next, the pairs assigned as 'unrelated' were rotated to make up unrelated pairs, and they were checked for unexpected forward or backward priming and adjusted accordingly. Finally, the non-words were created by changing the position of one or two letters in the target to create a pronounceable non-word (avoiding the creation of a pseudo-homophone) that was also orthographically and phonologically plausible, these non-words were then rotated so that they were paired with a new prime (McRae & Boisvert, 1998).

4.3 Results

After excluding errors (<4%) and trials with RTs < 200ms or > 1500 ms RT, data were submitted to a mixed repeated measure ANOVA with Group (left or right cerebellar stimulation) as a between subject factor and within subject factors including: Prime Relatedness (associated or unrelated) x Time (pre, post cTBS) x Site (cerebellar or vertex control). RT was the dependent variable; changes in it passed tests of normality (*D*), skew, and kurtosis, allowing parametric analysis. Follow-up analyses were conducted with Duncan's test to minimise false negatives that may be more prevalent due to the conservative experimental method that is TMS (i.e., it is at best a *virtual* lesion).

Table 4.1 reports mean RTs and Figure 1 shows the mean WAP in each condition. RT was shorter when primes were associated than when primes were unrelated (WAP), (F[1, 39] = 229.2, p<.001).

Cerebellar stimulation caused a change in WAP when the cerebellum was stimulated compared to vertex stimulation, and this change differed depending on the hemisphere stimulated as revealed by a significant four way interaction of Group (right cerebellar vs. left cerebellar) x Site (cerebellar vs. vertex control) x Time (pre vs. post cTBS) x Prime-Relatedness (associated vs. unrelated) (F[1, 39] = 12.7, p <.001). The Site (cerebellum vs. vertex) x Time (pre vs. post cTBS) x Prime-Relatedness (associated vs. unrelated) interaction was reliable in both right (FI[1,20] = 6.2 p = .022) and left (FI[1,19] = 6.7, p = .018) cerebellar stimulation groups**.** WAP increased after right (p = *.049*) and decreased after left (p = *.046)* cerebellar stimulation. There was no effect of stimulation of the vertex control site in either group.

Table 4.1: Mean RT (ms with SE in parentheses) in each condition for the group that received right cerebellar stimulation (top) and left cerebellar stimulation (bottom).

	Before cTBS		After cTBS	
Site	Associated Prime	Unrelated Prime	Associated Prime	Unrelated Prime
Vertex	504 (12)	549 (13)	500 (13)	537 (14)
Right	506 (13)	542 (14)	508 (16)	556 (15)
Vertex	515 (17)	542 (19)	516 (19)	549 (21)
Left	509 (19)	547 (19)	513 (20)	538 (20)

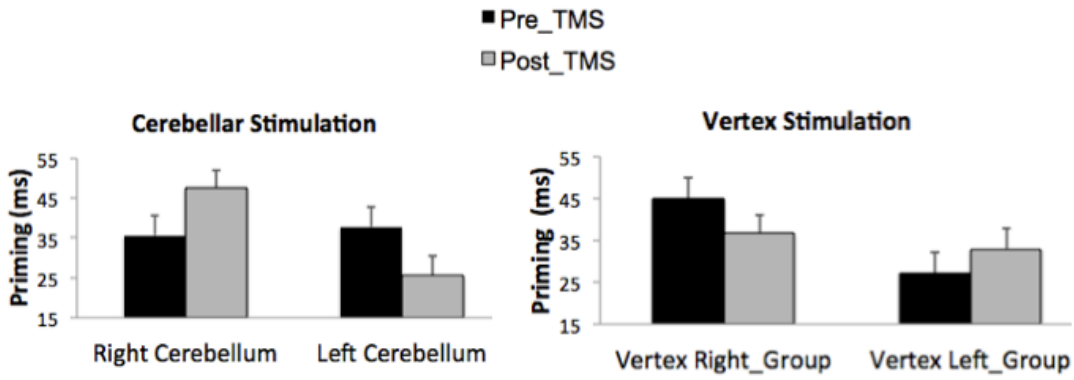
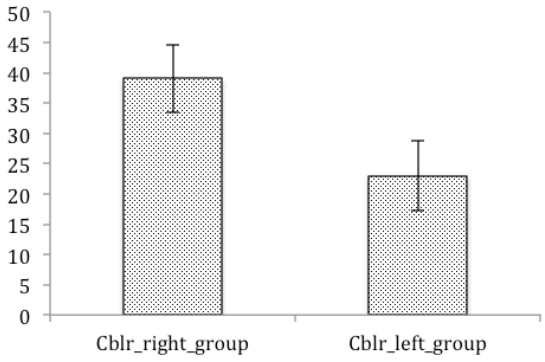


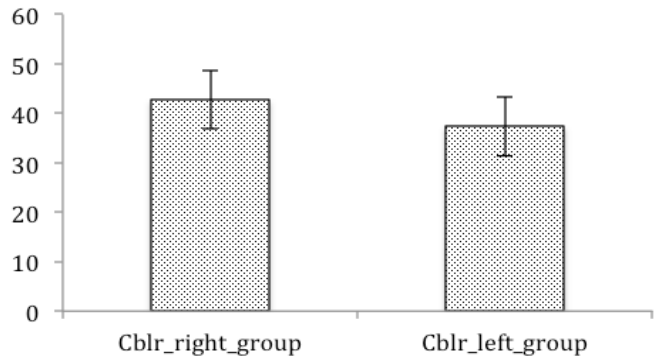
Figure 4.1: Mean WAP effect sizes in ms (RT for unrelated minus related prime conditions) before and after 40 seconds of sub-threshold continuous theta-burst rTMS in participants who had either right or left medial cerebellar stimulation, and at the vertex control site for each group.

Although cTBS over the vertex control site had no effect on WAP in either group of participants, as can be seen in Figure 4.1, WAP appeared to be larger in the vertex stimulation session in the Right Group. We followed up a significant interaction effect of Group x Prime-Relatedness ($F(1, 39) = 4.64$, $p < .037$, $r = .326$) therefore by examining the vertex data to investigate session order i.e., vertex stimulation session a week before or a week after cerebellar stimulation. Figure 4.2 shows the mean WAP effect (average of pre- and post-vertex cTBS) for participants who had vertex stimulation the week prior to cerebellar stimulation (Figure 4.2, right), and vice versa for those who had received vertex stimulation a week post cerebellar stimulation (Figure 4.2, left). The figure reveals that the trend for a main effect of group that motivated the investigation was itself created by a trend for larger WAP ($p = .07$) in the vertex session that was entirely driven by those who had received right

cerebellar stimulation the week prior to vertex stimulation. There was no difference in WAP between the two groups for those who received vertex stimulation the week prior to cerebellar stimulation (*F[1,18]*= 0.42); whereas in participants who had vertex stimulation in Week 2 (one week post cerebellar stimulation), the difference in WAP between the two groups approached statistical reliability [*F[1,19]=4.0,* p = *.06]*. This suggests that the effects of cerebellar stimulation on Week 1 may have persisted into the second (vertex stimulation) session a week later.



Cerebellar Stimulation First Participants: Mean WAP during vertex stimulation session



Vertex Stimulation First Participants: Mean WAP during vertex stimulation session

Figure 4.2: WAP effects (in ms) during vertex stimulation session in each group (right and left cerebellar stimulation) in participants who had cerebellar stimulation in the first session (left) and those who had vertex stimulation in the first session (right).

Indeed, as shown in Figure 4.3, for participants who received cerebellar stimulation on Week 1, the WAP effect after cTBS did not change between Week 1 and Week 2 (vertex session) for either group. These results suggest that there was persistence of the increased WAP after cTBS in the participants who had had right cerebellar stimulation on Week 1, and persistence of the decrease in WAP after cTBS in the participants who had had left cerebellar stimulation.

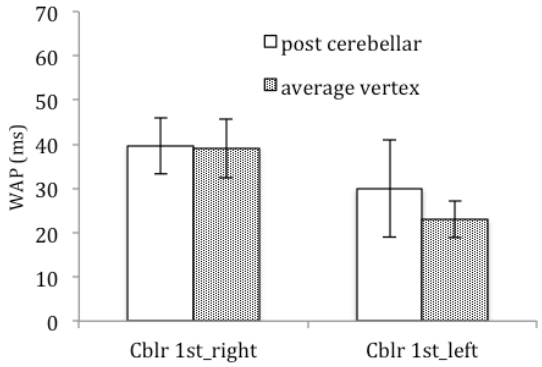


Figure 4.3: The larger WAP post-TMS in the right cerebellar stimulation group, persisted in the vertex stimulation session one week later in those participants who received cerebellar stimulation first. The WAP effect size after TMS in Week 1 is shown in light bars, and was larger in the group that received right cerebellar stimulation. The difference in WAP between right and left cerebellar stimulation persisted in the vertex control site stimulation session one week later (dark bars).

The finding that the main effect of Group (right vs left cerebellar stimulation) on the magnitude of WAP seemed to be evident in the vertex control session along with the finding that vertex stimulation *per se* had no effect on WAP was unexpected. This difference between groups in the vertex session was only evident in those participants who had undergone cerebellar stimulation first, a week before the vertex stimulation session. Indeed, in this group there was no change in the WAP in the vertex session compared to the post-cTBS block a week earlier. Although not designed or powered to examine the duration of the effect of cerebellar cTBS, the data suggest that effects may persist for as long as a week.

It seems unlikely that the 'neurodisruptive' effect of theta-burst TMS would persist that long. The duration of the effect of motor cortex stimulation on motor cortex excitability is typically in the order of an hour or two (Huang et al., 2005). It would certainly be intriguing if theta-burst TMS of the cerebellum induced a durable plasticity that essentially resets baseline priming effects, perhaps analogous to persistent perceptual adaptation after-effects (McCollough, 1965). We should note that cerebellar theta-burst stimulation did not produce any apparent change in speech or its comprehension, in our participants, and none reported any residual effects in our experiment – or other similar experiments reported in the literature. The apparent persistence effect is in need of replication, and testing at longer intervals to determine how long durable plasticity persists if indeed it does. Pragmatically, in future studies,

it would be prudent to test stimulation site between subjects with each participant only exposed to cTBS in a single session.

4.4 Discussion

Here we found that word association priming increased following right cerebellar stimulation and decreased following left cerebellar stimulation. Specifically, we found that disruption of the right medial cerebellum with cTBS results in an increase in magnitude of WAP when there is short interval between presentation of prime and target words. Thus confirming the findings of Argyropoulos (2011). The novel result of this experiment is that left cerebellar hemisphere disruption leads to a decrease in WAP. To our knowledge, this is the first demonstration of such an opponent-process cerebellar asymmetry in any domain. Building on a postulated role of the cerebellum in neural prediction, our findings offer preliminary evidence for a hypothesis specifying the contribution of the cerebellum in dynamic language processing. We will review evidence that WAP is subject to early inhibition (i.e., that potential upcoming related words are ready but not made available to cortical networks engaged in sequential language production and comprehension), and will propose that the two cerebellar hemispheres conjointly schedule the availability of these predictive signals, with the right cerebellum mediating early inhibition of words temporally associated to the prime.

4.4.1 Contemporary Concepts of Cerebellar Computation and its Contributions to Language

Internal models and prediction.

The physiological properties of cerebellar circuits enable it to acquire internal models (inverse models and/or forward models (Ito, 2008)) generated by motor commands. The forward model incorporates a corollary discharge of the motor command and predicts the expected re-afference or sensory feedback. For example, it specifies how the tongue will be placed in the mouth (re-afference) after uttering a particular word (motor command) (Bell, Grant, & Serrier, 1992). This predictive capacity of internal models gives the cerebellum a critical role in learning, originally demonstrated for classical conditioning (McCormick & Thompson, 1984). The conventional perspective emphasizes the role of cerebellar forward models in controlling movement. However, Courchesne & Allen, (1997) proposed that forward

models are generic in that they can prepare multiple systems and networks for upcoming operations, including sensory, motor, autonomic, memory-related, attention-related, affective, or linguistic operations. This is achieved by cerebellar learning, i.e., by forward models acquiring the 'predictive relationships among temporally ordered multidimensional sequences" (Courchesne & Allen, 1997)(p. 2).

Sequence timing.

The circuitry of the cerebellum suggested to Braitenberg (1967) that the cerebellum functions as a biological clock in the millisecond range. This has been supported by cerebellar lesion studies showing impaired timing in motor and perceptual tasks (Ivry & Keele, 1989) and, a dissociation in the variability of an action implementation from that of a central time keeper (Ivry, Keele, & Diener, 1988).

Ivry has highlighted cerebellar dependency on tasks that impose precise temporal constraints (Baumann et al., 2015). In eye blink conditioning, for example, it is insufficient to learn that a conditioned stimulus is reliably followed by an aversive stimulus. An effective response requires a precise computation of when the aversive stimulus will arrive. Similarly, the cerebellum is necessary for accurate visual motion discrimination (Ivry & Diener, 1991). By now, a number of studies have shown that the cerebellum supports timing in perceptual tasks. (e.g., Grube, Cooper, Chinnery, & Griffiths, 2010; Grube, Lee, Griffiths, Barker, & Woodruff, 2010; O'Reilly, Mesulam, & Nobre, 2008; Roth, Synofzik, & Lindner, 2013; Wu, Nestrasil, Ashe, Tuite, & Bushara, 2010).

Keele (1968) introduced the concept of the 'motor program' as an abstract representation of an intended movement, containing not only the goal of the action, but also the possible processes necessary to implement it. The concept implies the program of a motor sequence prepares not only the order of the sequence but also their timing such that while one element of the sequence is being activated, the next is inhibited until its predecessor is completed. One of our earlier experiments showed that the cerebellum plays a role in the *scheduling* of pre-programmed, fluent motor sequences (Inhoff, Diener, Rafal, & Ivry, 1989). We employed a paradigm developed by Sternberg, Monsell, Knoll, & Wright, (1978) in a simple RT paradigm in which a 'go' signal instructed participants to rapidly execute well practiced sequences of varying sequence length (e.g., saying "Monday; Monday-Tuesday; Monday-Tuesday-

Wednesday", etc.). It was shown that the RT to initiate the first response in the sequence increased as a function of sequence length. This sequence length effect demonstrated that the entire sequence was pre-programmed prior to initiating its execution. In our experiment, cerebellar lesions and healthy controls were tested. After training, simple RT was measured to initiate the first (and subsequent) finger movement(s) pressing: index finger; index-ring; or index-ring-middle. In healthy participants, RT to initiate the first movement increased as a function of the length of the sequence. The sequence length effect was reduced in patients with moderate and was absent in patients with severe motor disability.

According to Rosenbaum's scheduling hypothesis (Rosenbaum, 1985), a sequence of to-be-executed responses can be ordered along a time dimension. Once the delay between successive responses has been specified, the order of these responses is also determined. A motor program consists of a schedule of successive motor events, and motor programming is the process of determining which motor commands are to be employed and with which clock pulse they are to be associated. Executing a motor program is the process of allowing responses to be triggered when their associated clock pulses occur. Within this perspective, the magnitude of the sequence length effect reflects real time demands for the set-up of response schedules for individual elements. The lack of sequence length effects in cerebellar patients demonstrates an inability to schedule a sequence of successive motor events before movement onset. This scheduling hypothesis can also account for findings in the word priming literature.

4.4.2 Sequence Timing and the Dynamics of Language Production and Perception: Facilitation and Inhibition in Word Priming

Lexical access in speech production proceeds at a rate of about two to three words per second and is encoded phonologically at a rate of about 15 speech sounds per second (Levelt, 2001). The listener similarly faces a challenge in decoding the dynamic input rapidly and efficiently (Gagnepain, Henson, & Davis, 2012). Necessarily, then, language requires dynamic predictive processes to meet these challenges. Word priming affords one potential mechanism to meet these challenges.

However, while the priming of related words (as demonstrated by WAP) has the potential to facilitate dynamic efficiency that permits fluent production and perception, effective priming must precisely time the availability of predictive signals.

If a primed word is activated too soon, it can compete with its prime, delaying access to the prime or causing naming errors. Thus, the availability of primed words for sequential language processes must be modulated by brain mechanisms that facilitate *and inhibit* it with a temporal precision needed for both accuracy and fluency (Kotz & Schwartze, 2010).

Negative WAP.

And indeed, negative word priming effects have been demonstrated in lexical decision tasks. Carr & Dagenbach (1990) showed that when participants were required to deeply process a prime word, the perception of which was rendered difficult by masking, negative semantic priming was observed. They inferred that word retrieval (at least under circumstances where semantic codes are weakly activated) involves a 'center-surround neural mechanism to 'enhance activation of sought for codes and to inhibit nearby codes stored in a semantic network'. Subsequent research has validated their supposition that negative priming results from a center-surround mechanism (Deacon, Shelley-Tremblay, Ritter, & Dynowska, 2013; Frings, Bermeitinger, & Wentura, 2008).

Word priming – and negative priming – in patients with left cerebral cortex lesions.

WAP in a lexical decision task is reduced in patients with cortical lesions in the left, but not the right, hemisphere (Henik, Dronkers, Knight, & Osimani, 1993). This was true in groups of patients with both frontal and posterior lesions. The reduced priming was not attributable to a failure of lexical access, since identity priming (e.g. bread-BREAD) was preserved. One interpretation of these results is that left hemisphere lesions reduce the spreading activation of words related to the priming word. However, many left hemisphere lesioned patients with word finding difficulties make naming errors that are associatively related to the word they are trying to retrieve (semantic paraphasia; e.g. substituting spoon for fork). Thus there is a paradox. The phenomenon of semantic paraphasia implies that patients with word finding difficulties do activate associated words that compete with the word they are attempting to retrieve. Yet left hemisphere lesions tend to reduce WAP in a lexical decision task. One possibility is that word association priming is not abolished by left hemisphere lesions, but rather that it is *dysregulated;* that is, there is insufficient

inhibition of related words before completion of retrieval of the word currently being processed.

Consistent with this explanation, Bushell (1996) demonstrated negative WAP in patients with left hemisphere lesions (selected for having Broca's aphasia.) One consistent finding in WAP research is that the size of the priming effect increases as the proportion of related (vs. unrelated) primes increases (e.g., Brown, Hagoort, & Chwilla, 2000; Neely, Keefe, & Ross, 1989). Bushell replicated this effect in control participants, however, strikingly in patients, WAP *decreased* as the proportion of prime-target relatedness increased; and in blocks where there was a high probability that the target word would be related to the prime, patients demonstrated *negative* WAP; i.e. RT was longer on trials where the prime and target words were related. By contrast, identity priming in patients increased as a proportion of trials where the prime word was followed by the same word as target, just like controls.

Bushell (1996) interpreted her findings in aphasic patients as being consistent with the center-surround account of Carr & Dagenbach (1990). She argued that because aphasic patients have difficulty processing words, they must inhibit activation of related words until processing of the prime word has been completed (similar to masked primes in the Carr & Dagenbach, (1990) study). When the expectation that the target word will be related to the prime is higher, related words are more strongly activated – and thus require more inhibition, resulting in negative priming.

Facilitation and inhibition of word association priming: the role of the cerebellum.

If right cerebellar disruption impairs linguistic prediction, as demonstrated in the visual world paradigm (Lesage et al., 2012), how are we to understand the increase in WAP in a lexical decision task reported in the present study and by Argyropoulos, (2011)? The hypothesis advanced here construes the increase in WAP after right cerebellar stimulation not as an improvement in linguistic prediction, but rather as a *dysregulation* of priming; that is, there is insufficient inhibition of related words before completion of retrieval of the prime word. The intervals between prime and target were relatively short in both our experiment and that of Argyropoulos (2011), during an interval that we might assume processing of the prime word was still on-going. These intervals are comparable to the time interval at which Schriefers, Meyer, & Levelt (1990) reported interference by semantically related words in a

picture-naming task.

As discussed earlier, while negative priming (i.e. longer RTs for related compared to unrelated primes) has only been reported under conditions where access to the prime word is rendered difficult (Bushell, 1996; Carr & Dagenbach, 1990), we propose that, even under standard lexical decision task conditions, some degree of inhibition is applied to related word meanings for a brief period, until processing of the prime word has been completed. In priming experiments, the priming effect typically increases with an increasing interval between prime and target (de Groot, Thomassen, & Hudson, 1986). The conventional explanation for this time course invokes the mechanism of automatic spreading activation early after presentation of the prime – with controlled processes (often thought of as conscious prediction) emerging later (Neely, 1977). We are proposing that an additional reason that priming effect increases with increasing delay after presentation of the prime is that there is some degree of inhibition of activation of related word meaning early in the course of priming, while the prime word is still being processed.

We further propose that the cerebellum is critical in timing the availability of predictive signals, with the right cerebellum inhibiting their availability while the prime word is being processed, whereas the left cerebellum facilitates the availability of predictive signals. We interpret the increase in WAP after right cerebellar neurodisruption as a *dysregulation* of timing resulting in premature release of inhibition of the availability of related word meanings.

In the context of the scheduling account outlined earlier, during lexical access priming of related words can aid fluent and efficient sentence processing; but dynamic sequencing requires precise timing of the availability of the predictions afforded by priming to scheduling operations. While each word is being processed, related words begin to be activated, but their availability to cortical networks engaged in production (and possibly comprehension) must be inhibited until the appropriate 'clock pulse'. The current results are consistent with the hypothesis that the cerebellum provides this scheduling function. *Specifically, we hypothesize that both facilitation and inhibition of WAP is regulated by the cerebellum; and that the right and left cerebellar hemispheres function as an opponent process in which the left cerebellum inhibits and the right facilitates, WAP.*

This hypothesis makes specific predictions to be tested in future research:

1. That prime words are less efficiently processed when the right cerebellar

hemisphere is stimulated. Our study did not incorporate any measures of how efficiently the priming words had been processed. Future research could include testing of memory for prime words after completion of the post-stimulation LDT to test the prediction that recall of prime words will be better after left cerebellar stimulation than right cerebellar stimulation.

2) The pattern of increased WAP with right cerebellar disruption (and decreased WAP with left cerebellar stimulation) will occur only when there is a brief delay between prime and target (while the prime is still being processed). For longer delays (e.g. stimulus onset asynchronies (SOAs) between prime and target words > 600 ms), this pattern will not be present; and, indeed, based on the effects of right cerebellar TMS in the Visual World Paradigm, would actually be expected to be the reverse: a decrease in WAP after left and an increase WAP after right cerebellar theta-burst stimulation.

3) If our hypothesis is correct and the function of inhibition of word associates aids in accessing the prime word, then a reduction of this inhibition resulting from disruption of the right cerebellum would be expected to interfere with accessing the prime word. This could be tested by measuring the effects of cerebellar TMS on identity priming, i.e., the prime word is 'BREAD' and the target word is also 'bread'. If right cerebellar disruption disinhibits activation of related words before the prime word is fully processed, we would expect that right cerebellar TMS will reduce the RT benefits of identity priming (again compared to an unrelated prime condition); whereas, left cerebellar disruption is predicted to increase identity priming.

Chapter 5
General Discussion

This thesis examined the sensorimotor and cognitive after-effects of prism adaptation and the possible mechanisms underlying them. This chapter provides a brief summary of the key results of each empirical study, a consideration of the broader implications of those findings, and possible avenues for future research.

5.1 Visual Straight-Ahead and Ocular Proprioception

Key highlights of the eye-tracking investigation (Chapter 2) included the revelations that following right-shifting prism adaptation (R-PA) there was:

1. No change in eye position when looking straight ahead
2. No change in the perceived location of visual stimuli; i.e. stimuli that were located straight ahead were perceived as being located straight ahead
3. A larger leftward shift when pointing straight ahead with eyes open compared to pointing straight ahead with eyes closed (hand unseen in both cases).
4. A rightward shift in eye position when looking at the unseen unexposed hand.

That is, it was observed that following PA people continued to be able to correctly look straight ahead but when with eyes open they pointed with the unseen hand an incorrect ocular signal was employed. One parsimonious explanation for this apparent discrepancy is that the eye has returned to the primary position in orbit but that the interpretation of that proprioceptive signal has changed. Building on that, the phenomenon is tentatively attributed to the response of two different extra-ocular muscle fibre types and their proprioceptive signals:

1. The non-twitch muscle fibres. These are fatigue resistant, do not release action potentials but, rather, they make graded responses, and are associated with fixation and ocular alignment. Their unique putative proprioceptive receptors are the palisade endings.
2. The twitch muscle fibres. These are not fatigue resistant; they do release action potentials causing a muscle twitch that generates a saccade.Their putative proprioceptive receptors are a type of muscle spindle unique to the extra-ocular muscles. (Bruenech & Kjellevold Haugen, 2015; Büttner-Ennever, 2007; Spencer & Porter, 2005)

Following R-PA, it is speculated that the non-twitch retained, or regained, a straight-ahead position in orbit, whereas the twitch muscles revealed an adaptation to the sensory perturbation that became apparent with movement related actions. Given the paucity of understanding of ocular proprioceptive physiology in general, the proposal

is necessarily speculative. Unfortunately, too, it will be difficult to investigate the suggestion further both invasively and non-invasively.

While a literature review led to the tentative interpretation that the visual shift is driven by ocular proprioception, it is also acknowledged that the results may reflect a dissociation between the oculomotor command and ocular proprioception. In that scenario only the oculomotor command has changed. A number of improvements to the current experiment were proposed in chapter two.

More generally, the results of the eye-tracking experiment have exposed potentially significant gaps in the understanding of the sensorimotor after-effects of PA. The findings here add to a number of studies that reported no change in visual shift, as measured by verbal report of when a viewed target was straight ahead of body midline, following PA (Bornschlegl et al., 2012; Choe & Welch, 1974; Harris, 1963; Herlihey & Rushton, 2012; Michel et al., 2013; Morton & Bastian, 2004; Newport et al., 2009). It thus seems increasingly likely that, either the concept of the linear additivity of PA sensorimotor after-effects is too simplistic (Facchin et al., 2017; Hatada et al., 2006), and/or the elements that contribute to it are under-specified.

Currently, possibly for practical reasons, visual shift measures are seldom included in PA studies. This reflects a general move from investigating PA sensorimotor aspects to examining its cognitive after-effects. However, a complete appreciation of the former can only serve the latter – and hence was the starting point for this thesis. A comprehensive understanding of PA-induced sensorimotor after-effects would benefit from the systematic inclusion of visual shift measures, ideally including an eye-tracking measurement. It would also be worthwhile to consider variations on the implementation of the test. Conventionally, the task involves stopping a moving object by verbal report. However, measures that use a static stimulus (e.g., Facchin et al., 2017; Herlihey & Rushton, 2012) or other static or no-stimulus measures may minimise confounds of eye movements and may, in the future, be fruitfully compared to more conventional visual shift tasks.

The results of chapter 2 suggest that the temporal evolution of the visual shift, and/or eye position shift, remains to be fully elucidated. Improvements to the calibration approach in an eye-tracking set-up, and/or more frequent after-effect tasks, are thus desirable. It has been observed that the visual shift disappears within two hours but that shifts in passive straight-ahead pointing can last up to seven days

(Hatada et al., 2006). Would this finding hold when different measures of visual after-effects were used? And if so, why? Indeed, how do the findings of a relatively fast return to baseline of visual straight ahead (when it is found) (Hatada et al., 2006) coincide with reports of the relatively slow emergence of an asymmetrical spatial after-effect on the visual landmark task (Schintu et al., 2014)? Taken together, it appears that further investigation of the temporal unfolding of the visual after-effect is warranted.

Given that various aspects of the visual shift would benefit from re-testing, if not reconsideration of its veracity, it seems appropriate to propose that a comparison of the two lateral directions of prismatic displacement is required. The literature review for the current study revealed two over-looked side-observations. Firstly, Paap & Ebenholtz (1976) reported that the visual after-effects of rightward EMP reached asymptote at a held deviation of 22°, whereas for leftward EMP the visual after-effects continued to scale up with deviations up to 42°. Secondly, van Beers, Sittig, & Gon (1999) examined how the CNS makes use of the direction-dependent precision of visual and proprioceptive localisation (lateral and radial, respectively), and found that while their model was confirmed by no-prism and by left-shifting PA, it was not by the right-shifting PA. These two findings provide a hint that the sensorimotor after-effects of PA may not, after-all, be symmetrical. If this were the case, it would necessitate re-interpretation of the cognitive after-effects of PA, and crucially, the mechanisms through which it may hold rehabilitative value following brain injury, as well as research value for developmental and psychiatric disorders.

Finally, and most importantly, the debate over which after-effect correlates with improved neglect outcome measures following PA therapy remains unresolved (Sarri et al., 2008; Serino et al., 2006, 2007). Newport et al. (2009), following observation of no PA visual shift after-effect but an EMP induced one, had proposed that ocular rotation was not correlated with improvements from neglect. However, that examination did not include open loop pointing or passive proprioceptive measures as per the current study. Here, it is shown that eye position and visual shift after-effects may be more complicated than previously acknowledged. Improved appreciation of the role of the visual shift (whether it occurs, when it occurs, for whom it occurs, how best to test for it, what it represents etc.) may facilitate the early identification of those who will benefit from PA's rehabilitative potential.

5.2 Left Hemisphere Lesions and Association Priming

Chapter three explored the possibility of PA-induced increases in association priming. The results of (Henik et al., 1993) were replicated with the finding, at group level, that priming in a lexical decision task (LDT) is reduced following left hemisphere (LH) insult. Serendipitously, the current observations may reconcile conflicting reports of the impact of LH lesions on priming. Specifically, it was the use of effect sizes that helped reveal the reduced priming effect in the patient group. Effect sizes have not been systematically reported in patient LDT studies to date.

However, perhaps the most exciting possibility offered up by this investigation is the potential rehabilitative value of PA following LH lesion. Both lateral directions of PA appear to increase association priming in patients, with an indication that right-shifting PA (R-PA) may be more efficacious than left-shifting PA (L-PA). Increased associative priming implies increased access to potential upcoming words or meanings and thus a facilitation of fluency in language production and comprehension. Although other effects unrelated to PA, such as practice, cannot be ruled out, the pattern of faster access to related words and no change in speed of access to unrelated words nonetheless gives reason to believe that adaptation to both left or right-ward shifting prisms can increase priming effects in left brain lesioned patients. To the best of my knowledge, this represents the first potential demonstration of PA cognitive after-effects on a non-spatial LH dominant task.

Although the findings require replication, it follows another study that recently reported an effect of R-PA on autonomic thermo-regulation in healthy adults (Calzolari et al., 2016). Despite active research into prism adaptation, there is only one further study that reports an effect of R-PA in healthy people. Berberovic & Mattingley (2003) reported that both left and right-ward shifting PA produced a rightwards shift in visual midpoint judgements in extrapersonal space. These two findings stand in contrast to all other reported non-sensorimotor after-effects of PA in healthy participants that exclusively follow L-PA (Redding et al., 2005). However, an observation made by Bultitude (2009) in the study of R-PA effects on patients with right hemisphere (RH) temporo-parietal junction (TPJ) lesions may be insightful. The author reported a reversal of a stroke-evoked hyper-attention to detail following R-PA as measured in a global-local Navon task. One patient that showed improvement on this global-local task, in contrast, only showed an improvement in one of three tests of spatial neglect. This lead the author to suggest that changes in non-lateralised spatial

functions following PA may occur in parallel to, rather than as a consequence of, changes to lateralised spatial abilities. Combined, the various findings suggest that the mechanisms through which PA elicits its after-effects may be broader than previously appreciated, and by extension the reach of its potential applications.

Recruitment of LH patients into groups of either anterior or posterior lesions would serve as a basis for lesion analysis with the aim of understanding who benefits from PA and why that might be. The suggestion made here is that the cerebellum, the origin of true PA after-effects, modulates activity in the TPJ (specifically the superior temporal sulcus). This TPJ activity in turn modulates activity in the ventral and anterior temporal areas and their bi-hemispheric inter-connections through the anterior commissure. It is thus predicted that those with anterior LH lesions would demonstrate an increased effect of PA compared to those with posterior LH lesions.

Another valuable avenue of research would be testing LH TPJ patients who have a global interference deficit. If they were to benefit from PA, it would not only support the contention of a separate parallel mechanism for non-lateralised spatial function improvements, but crucially it would discount the asymmetrical inter-PPC physiological pathway (Koch et al., 2011) implicated in lateralised spatial functions as the only mechanism for hemispheric re-balancing post PA.

Several methodological approaches would assist in clarifying the underlying mechanisms of PA. Event-related potentials (ERPs), for instance, have only recently been employed within the PA field. They uncovered a rightward attentional orienting bias and a deficit in attentional disengagement from right hemispace following L-PA in healthy people that was not observable at a behavioural level (Martín-Arévalo et al., 2016). ERPs can reveal subtle alterations in neural function that may be undetectable in behavioural measures and they may thus be very insightful, especially if a wider variety of functions are to be assessed. Another method, where applicable, and as mentioned above, is lesion analysis, a method that few studies have employed thus far.

Finally, the challenges of fMRI studies of PA notwithstanding (Bultitude et al., 2016), effective connectivity analyses of PA after-effects (sensorimotor, cognitive, and, autonomic) have the potential to constitute a major advancement. In particular, it is suggested that they take advantage of recent progress in the connectivity mapping of three sub-regions with the TPJ (Mars et al., 2012). Only one of the sub-regions, a posterior cluster, is connected to the cerebellum. Given that the

cerebellum drives spatial realignment, this posterior TPJ cluster could be the cortical origin of the cognitive, and perhaps sensorimotor, after-effects of PA. Indeed, in the current findings the task is assumed to have made use of (residual) temporal functions, while the work of others has implicated temporal regions in the effectiveness of PA as a therapy (Chen et al., 2014; Luauté et al., 2009). Pinpointing the cortical origin(s) of PA cognitive after-effects will facilitate understanding of what cortical networks can be altered by PA. In particular, if this posterior TPJ cluster, with its links to the cerebellum, were shown to be the cortical origin of PA induced cognitive after-effects it would add weight to the account that those after-effects are cerebellar driven.

A note of caution should be sounded, however. The reduced association priming observed in our study is not strictly speaking a deficit; it does not infer anomia. Additionally, language, although it is LH dominant, may not be as strongly lateralised as spatial functions. It is possible, therefore, that the findings of the current study reflect a form of network re-balancing similar to that witnessed with RH patients – i.e., further facilitation of RH recruitment. Indeed, there is a hint within the study that it is exclusively R-PA that is driving the results – the same direction of PA that has ameliorative benefits for some RH lesion patients. Also, as discussed in Chapter three, it is possible that increasing priming effects may not be ameliorative – it could be that it decreases the depth to which the meaning of the current (prime) word is processed. That is, the level to which priming resettles post insult may reflect the best achievable balance between current and upcoming word processing. Taken together, this leads to an interpretation in which the present results reflect, neither a potential therapeutic value of PA for LH lesion patients, nor a potential broadening of the mechanisms through which it works. The avenues of research outlined above will be necessary to help solve this alternate interpretations conundrum.

5.3 The Cerebellum and Associative Semantic Priming

The study, in Chapter four, tested timing and regulation within the language system. Theta-burst transcranial magnetic stimulation (TBS) of the right cerebellum increased associative semantic priming in healthy controls, whereas TBS of the left cerebellum decreased the priming effect in a LDT paradigm with a short stimulus onset asynchrony. This was interpreted as a first demonstration of an opponent processing mechanism co-ordinated by both cerebellar hemispheres. Specifically, the

cerebellum supports the wider cerebral language network by precisely timing the release and inhibition of sequentially associated words. This facilitation-inhibition dynamic allows a word to be fully processed before future alternate words become available and then, once processed, inhibits that word to allow progress onto the next one. Facilitation and inhibition are supported by the right and left cerebellar hemispheres, respectively. As such, significant increases and decreases in priming should both be considered as signs of system dysregulation. A follow-up research plan based on the current results is provided in chapter four.

Although chapters three (patient study) and four (TBS study) have associated priming as common tasks, it is not language *per se* but the cerebellum that forms the more pertinent link between these studies. The cerebellum underpins the spatial realignment of PA (Martin et al., 1996; Pisella et al., 2005) and increasing evidence, in chapter four and elsewhere (Argyropoulos, 2011; Lesage et al., 2012) supports its underpinning of associative priming. Without spatial realignment, i.e., adaptation, there are no after-effects, whether sensorimotor or cognitive. By extension, the processes affected by PA should be influenced by cerebellar disruption. The results partially support that premise: Both directions of PA, and disruptive TBS of both cerebellar hemispheres, impact priming. However, because the effects of PA on priming were specific to the patient group, and because TBS was applied to healthy participants, additional comparisons are not yet warranted.

Ultimately, the aim with this approach of cerebellar TBS and PA comparisons is to help tease apart a cerebellar account from a cerebral hemispheric re-balancing account of PA cognitive after-effects. This is the first attempt to do so. This line of thinking reflects a likely parallel involvement of cerebellar areas, cortico-cortico, and cerebello-cortico loops in PA. As noted in the introductory chapter, a lack of after-effects has been found in neglect patients in the absence of cerebellar damage (Frassinetti et al., 2002). It has also been shown that the ability to correct pointing errors during prism exposure may be the best predictor of PA therapy success for neglect (Serino et al., 2007). In fact, such benefits have been found not to correlate with after-effects in terms of magnitude (Sarri et al., 2008; Serino et al., 2006) or duration (Frassinetti et al., 2002). This is not to say that the cerebellar and cerebral hemisphere re-balancing accounts of cognitive after-effects should necessarily be considered mutually exclusive, but there continues to be grounds to investigate them separately and compare them in their own right.

In terms of advancing this comparison from a language task perspective, a combined PA and ERP study on priming may be particularly informative. As mentioned before, this combination has revealed PA effects in healthy people that are too subtle to otherwise be picked up (Martín-Arévalo et al., 2016). If PA effects on priming, as revealed by ERP, mirrored the TBS results then it would provide *some* support for the premise that the cognitive after-effects of PA are cerebellum-driven. The curtailing of the support is due to the results of a transcranial magnetic stimulation (TMS) study on auditory processing of native and foreign words (Andoh & Paus, 2011). TMS of both the left and right posterior superior temporal gyrus (pSTG) resulted in task-related activation increases in contralateral non-stimulated homologue regions (independent of stimulated hemisphere). Behavioural improvements (decrease in RT for native relative to foreign words) were only seen following suppression of the left pSTG, which was interpreted as resulting from enhanced RH activity. Thus, while it would not rule out a cortical involvement, if the PA-ERP combination mirrored the cerebellar TBS results pattern it would nonetheless be supportive of a cerebellar role in PA cognitive after-effects. Further, should that experiment be informative a follow-up study of TMS of each pSTG could be useful. While it is thought that the pSTG is connected to the cerebellum, if inhibitory TMS did not produce the same pattern of effects (opposite per hemisphere and temporally bound) as the other studies (i.e., the proposed PA-ERP study and the current cerebellar TBS study) it would strongly suggest that PA cognitive after-effects are cerebellar driven.

Studies on the effects of cerebellar TBS on measures of neglect (e.g. line bisection, cancellation, landmark test) in healthy people, and if possible in a patient population, could be fruitful. Investigations into the effect of TMS on the unaffected posterior parietal lobe have revealed a lessening of neglect symptoms in patients (Koch et al., 2012; Oliveri et al., 2001) and a simulation of them in healthy people through right hemisphere stimulation (Fierro et al., 2000). With the aim of teasing apart a cortical from a cerebellar account of PA cognitive after-effect, it would be informative, therefore, to understand the results of non-invasive cerebellar disruption on the same measures in both populations.

5.4 Summary and Conclusions

Following over a century's worth of research into prism adaptation, this procedure continues to provide intriguing insights into brain-behaviour interactions and the myriad neural connections underlying them. The experiments described in this thesis explored the low-level sensorimotor response to prism adaptation in a healthy population; the higher-level cognitive response in a neurological population; and a first step towards understanding the cerebellar contribution to those cognitive after-effects.

Previous reports that the visual shift does not contribute to the rehabilitative value of PA for neglect were not confirmed by an experiment that took advantage of eye-tracking methodology and a wide battery of sensorimotor after-effect tasks. Rather, the results obtained here suggest an unusual, and previously undocumented, dissociated response to PA by the ocular proprioceptive system. At the same time, it was made explicit that the nature and mechanisms of the visual shift remains under-specified and thus it is possible that the concept of linear additivity is somewhat simplistic. A return of focus to these fundamental aspects of prism adaptation is required in order to support the goal of refining its application for rehabilitation.

This need notwithstanding, results from the patient study demonstrated, for the first time, that left hemisphere dominant functions might be affected by prism adaptation. A potential breakthrough has been made, by linking this unique result with findings from two other studies, with the proposal that the mechanisms through which PA elicits its after-effects might be broader than previously appreciated and might not be purely asymmetrical.

Finally, a new proposal of an opponent process mechanism co-ordinated by both cerebellar hemispheres for the regulation of language processing was made based on evidence from a TBS study. This study constitutes an exciting early contribution toward investigating the cerebellar influence on prism adaptation induced cognitive after-effects.

The current body of work has exposed the complicated nature of after-effects caused by prism adaptation evoked spatial realignment. It also offers glimpses of prism adaptation's future potential to further our empirical understanding of cerebellar-cortical interactions underpinning human cognition.

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Appendix A

Data Processing Details for Chapter Two (eye-tracking)

Table A1: Details of data captured and data removed across conditions combined.

	Task	Position Measure	Total responses	Not Captured (no.)	Removed as per session notes (no.)	Removed as model outlier (no.)
1.1	VSA pre bar	Eye	1728	75 (4%)	--	--
1.2	VSA	Bar		--	26	1
1.3	Upon VSA bar	Eye		14	--	1
2.1	SAP eyes closed	Point	576	--	3	--
3.1	SAP eyes open, pre pointing	Eye	576	16	3	2
3.2	SAP eyes open, eyes open	Point		--	4	2
3.3	SAP eyes open, upon pointing	Eye		182 (32%)	--	4
4	OLP	Point	2595	--	--	1
5.1-5.3	Finger exposed hand	Eye_1	576	12	1	3
		Eye_2		72 (13%)	1	2
		Eye_3		2	1	8
5.4		Verbal		--	1	3
6.1-6.3	Finger unexposed hand	Eye_1	576	8	--	--
		Eye_2		80 (14%)	--	1
		Eye_3		2	--	11
6.4		Verbal		16	--	2

Appendix B

Right sham/prism exposure

Table B1. Details of the Bonferroni-adjusted multiple comparisons for the last 3 trials of each period of exposure pre and post R-PA. Highlighted rows are of particular interest.

Comparison	z-value	*p*-value
Sham T1 – post T1	-7.83	<.001
Post T2 – post T1	-5.69	<.001
Sham T2 – post T1	-5.12	<.001
Post T3 – post T1	-7.20	<.001
Sham T3 – post T1	-5.89	<.001
Post T2 – sham T1	2.43	.225
Post T3 – sham T1	0.940	.999
Sham T2 - post T2	-1.96	.754
Post T3 - post T2	-1.49	.999
Sham T3 – post T2	-2.82	.072
Post T3 – sham T2	0.749	.999
Sham T3 – post T3	-1.51	.999

Appendix C

Visual Straight Ahead

Table C1: Predictive model details: effect of shift-type on eye position when looking straight ahead. Items in grey refer to baseline model. Position is a control predictor for left/right appearance of annulus. Model df = 1653.

Fixed Effects	*b*	SE *b*	95% CI	*t*-value	*p-value*
Intercept	0.567	0.164	[0.238, 0.895]	3.45	<.001
Position	5.15	0.241	[4.66, 5.63]	21.3	<.001
Shift	-0.176	0.262	[-0.699, 0.347]	-0.67	.502
Time	0.334	0.264	[-0.195, 0.862]	1.26	.207
Shift:Time	0.824	0.894	[-0.964, 2.61]	0.92	.358

Table C2: Predictive model details: effect of shift-type on moving a bar to VSA. Items in grey refer to baseline model. Position is a control predictor for left/right appearance of stimulus. Model df = 1701.

Fixed Effects	*b*	SE *b*	95% CI	*t*-value	*p-value*
Intercept	-0.154	0.175	[-0.497, 0.189]	-0.88	.380
Position	0.010	0.037	[-0.062, 0.083]	0.28	.782
Shift	0.220	0.190	[-0.152, 0.593]	1.16	.246
Time	-0.218	0.217	[-0.644 0.208]	-1.00	.317
Shift:Time	-0.542	0.710	[-1.93, 0.847]	-0.76	.445

Table C3: Predictive model details: effect of shift-type on eye-position when looking at a stimulus set to VSA. Items in grey refer to baseline model. Position is a control predictor for left/right appearance of stimulus. Model df = 1713.

Fixed Effects	*b*	SE *b*	95% CI	*t*-value	*p*-value
Intercept	0.605	0.239	[0.136, 1.07]	2.53	.012
Position	-0.043	0.047	[-0.136, 0.049]	-0.92	.359
Shift	-0.243	0.222	[-0.678, 0.193]	-1.09	.276
Time	0.339	0.218	[-0.087, 0.766]	1.56	.119
Shift:Time	0.610	0.803	[-0.962, 2.18]	0.76	.447

Appendix D

Straight-Ahead Pointing – eyes closed

Table D1: Predictive model details: effect of shift-type on SAP (eyes closed). Items in grey refer to baseline model. Model df = 573.

Fixed Effects	*B*	SE *b*	95% CI	*t*-value	*p-value*
Intercept	-1.55	0.731	[-2.98, -0.119]	-2.12	.035
Shift	1.32	0.713	[-0.075, 2.72]	1.85	.065
Time	-1.71	0.311	[-2.32, -1.10]	-5.50	<.001
Shift:Time	5.33	1.13	[3.12, 7.54]	4.72	<.001

Appendix E

Straight Ahead Look & Point

Table E1: Predictive model details: effect of shift-type on SAP eyes open. Items in grey refer to baseline model. Position is a control predictor for left/right appearance of annulus. Model df = 570.

Fixed Effects	*b*	SE *b*	95% CI	*t*-value	*p*-value
Intercept	-2.06	0.313	[-2.67, -1.45]	-6.58	<.001
Position	-0.481	0.095	[-0.668, -0.296]	-5.06	<.001
Shift	2.58	0.586	[1.44, 3.73]	4.41	<.001
Time	-3.59	0.241	[-4.07, -3.12]	-14.9	<.001
Shift:Time	6.66	0.617	[5.46, 7.87]	10.8	<.001

Appendix F

Open Loop Pointing

Table F1: Predictive model details: effect of shift-type on OLP. Items in grey refer to baseline model. Position is a control predictor for left/right appearance of stimuli. Model df = 2591.

Fixed Effects	*b*	SE *b*	95% CI	*t*-value	*p-value*
Intercept	-2.30	0.338	[-2.97, -1.62]	-6.79	<.001
Position	0.402	0.037	[0.327, 0.477]	10.8	<.001
Shift	2.52	0.631	[1.26, 3.79]	3.99	<.001
Time	-3.79	0.218	[-4.23, -3.36]	-17.4	<.001
Shift:Time	6.85	0.371	[6.10, 7.59]	18.5	<.001

Appendix G

Comparisons across R-PA pointing tasks after-effects

Table G1. Bonferroni-adjusted multiple comparisons, highlighted rows are of particular interest. SAP_op = SAP eyes open, SAP_cd = SAP eyes closed.

Comparison	z-value	*p*-value
Post SAP_cd - sham SAP_cd	-7.14	<.001
Post OLP – sham SAP_cd	-11.59	<.001
Post SAP_op – sham SAP_cd	-10.82	<.001
Sham OLP - post SAP_cd	7.01	<.001
Post OLP – post SAP_cd	-4.46	<.001
Sham SAP_op – post SAP_cd	7.42	<.001
Post SAP_op – post SAP_cd	-3.68	.003
Post OLP – sham OLP	-11.47	<.001
Post SAP_op – sham OLP	-10.69	<.001
Sham SAP_op – post OLP	11.88	<.001
Post SAP_op – post OLP	0.77	.999
Post SAP_op – sham SAP_op	-11.10	<.001

Appendix H

Finger Localisation (exposed/pointing hand)

Table H1: Predictive model details: effect of shift-type on eye position when looking at a blank screen above the location of the unseen finger of the exposed hand. Items in grey refer to baseline model. Position is a control predictor for left/right appearance of annulus. Model df = 560.

Fixed Effects	*b*	SE *b*	95% CI	*t*-value	*p*-value
Intercept	4.99	0.705	[3.59, 6.41]	7.10	<.001
Position	-1.25	0.232	[-1.71, -0.786]	-5.39	<.001
Shift	-2.51	0.535	[-3.58, -1.44]	-4.69	<.001
Time	2.24	0.486	[1.26, 3.21]	4.62	<.001
Shift:Time	-4.07	1.04	[-6.15, -1.99]	-3.91	<.001

Table H2: Predictive model details: effect of shift-type on eye position when locating the unseen finger of the pointing hand on an un-numbered scale. Items in grey refer to baseline model. Position is a control predictor for left/right appearance of annulus. Model df = 501.

Fixed Effects	*b*	SE *b*	95% CI	*t*-value	*p*-value
Intercept	4.46	0.785	[2.92, 5.99]	5.68	<.001
Position	-0.898	0.260	[-1.41, -0.391]	-3.46	<.001
Shift	-3.23	0.658	[-4.51, -1.94]	-4.90	<.001
Time	2.78	0.467	[1.86, 3.69]	5.94	<.001
Shift:Time	-3.86	0.938	[-5.70, -2.03]	-4.12	<.001

Table H3: Predictive model details: effect of shift-type on eye position when locating the unseen finger of the pointing hand on a scale. Items in grey refer to baseline model. Position is a control predictor for left/right appearance of annulus. Model df = 565.

Fixed Effects	*b*	SE *b*	95% CI	*t*-value	*p*-value
Intercept	4.62	0.719	[3.22, 6.03]	6.43	<.001
Position	-1.70	0.335	[-2.36, -1.05]	-5.08	<.001
Shift	-2.82	0.526	[-3.85, -1.79]	-5.37	<.001
Time	2.73	0.377	[1.99, 3.47]	7.24	<.001
Shift:Time	-3.60	0.883	[-5.32, -1.87]	-4.07	<.001

Table H4: Predictive model details: effect of shift-type on verbal location of unseen finger of pointing hand. Items in grey refer to baseline model. Position is a control predictor for left/right appearance of annulus. Model df = 573.

Fixed Effects	*b*	SE *b*	95% CI	*t*-value	*p-value*
Intercept	4.05	0.772	[2.54, 5.56]	5.26	<.001
Position	-0.881	0.221	[-1.31, -0.448]	-3.99	<.001
Shift	-3.41	0.546	[-4.47, -2.34]	-6.26	<.001
Time	2.89	0.356	[2.20, 3.59]	8.14	<.001
Shift:Time	-4.62	0.794	[-6.18, -3.07]	-5.82	<.001

Appendix I

Finger Location (non-pointing hand)

Table I1: Predictive model details: effect of shift-type on eye position when locating unseen finger of non-pointing hand on an un-numbered scale. Items in grey refer to baseline model. Position is a control predictor for left/right appearance of annulus. Model df = 499.

Fixed Effects	*b*	SE *b*	95% CI	*t*-value	*p*-value
Intercept	-1.16	0.741	[-2.64, 0.321]	-1.57	.118
Position	-0.892	0.239	[-1.37, -0.415]	-3.74	<.001
Shift	-1.68	0.713	[-3.10, -0.253]	-2.35	.019
Time	1.16	0.522	[0.112, 2.20]	2.21	.027
Shift:Time	-1.69	0.745	[-3.18, -0.203]	-2.27	.023

Appendix J

Stimulus Lists for Chapter 3: PA as a Therapy for Left Hemisphere Lesions

Table J1: Stimuli List One

Related		Unrelated	
CUE	TARGET	CUE	TARGET
BEFORE	after	BAR	aim
BOUQUET	flowers	BURN	twig
BUMBLE	bee	CAKE	topic
COBWEB	spider	COOL	plaza
DENIM	jeans	EASY	act
EAST	west	ENDLESS	impulse
FRAME	picture	FAIL	fort
GIGGLE	laugh	FELT	game
GOOD	bad	GAG	buy
HAMMER	nail	KID	fly
HIM	her	OCEAN	thief
HUSBAND	wife	RENT	sand
JOG	run	ROCKS	small
MARGARINE	butter	SALES	white
MOO	cow	SEAM	dull
NAP	sleep	SLUM	duty
NORTH	south	SOAP	riot
OFF	on	SOUP	year
PEPPER	salt	TASK	plate
QUESTION	answer	TITLE	tools
RIP	tear	VENT	tile
SADDLE	horse	WANT	sheet
SHOVE	push	WEAK	watt
SLIPPERY	wet	SOFT	spin
THERE	here	SIGN	scene
TROUT	fish	JUNGLE	smoke
UNHAPPY	sad	VOYAGE	erupt
WASHER	dryer	LONELY	siren
WICK	candle	BUMP	worse
YOLK	egg	FEED	fray
YES	no	SCARED	cough
NEW	old	CLOG	tavern

Word-Nonword		Word-Nonword	
CUE	TARGET	CUE	TARGET
ALERT	negat	MORE	sopt
APRIL	parat	MOUTH	marad
AWAKE	thors	MULE	erif
BEING	rasel	NEWS	ahir
BONUS	ligut	NORM	nior
BOTTLE	henost	NUTS	rowk
CANAL	sesho	OATH	narb

CENTS	yallo	ODDS	kalt
CHINA	soach	PIANO	gresh
CLERK	keasn	PIECE	lamas
CLIMB	ekans	POEM	ticy
COPPER	ruqase	POKER	teraw
MOOSE	koems	PREFER	sukar
COURT	retas	PSALM	veren
CRISIS	tacave	RADIO	clisk
EIGHT	repap	SHADE	tirps
ENGINE	keruty	SHIFT	tigev
EXTRA	teads	SKIRT	rewat
FLUTE	neque	SLAVE	thous
FRUIT	rayti	SLIME	morob
GLOVE	kolco	SMEAR	sumic
GREEN	socut	SNACK	pecae
HOTEL	prash	SOUND	trosh
JAPAN	letit	SPEAK	edlab
JUDGE	peles	STARE	lafir
LILY	naip	SWEEP	nejas
LIPS	tols	SYSTEM	lopos
LOBBY	seruc	TEETH	osine
LOOP	atem	SMELL	velco
MAPLE	rodeb	NOSY	vife
MIGHT	letam	BORROW	seedir
MISS	kawe	PICK	grud

Table J2: Stimuli List Two

Related		Unrelated	
CUE	TARGET	CUE	TARGET
BEGINNING	end	ADORN	sneak
BRIDE	groom	BAT	amp
CHEDDAR	cheese	BEG	bag
DAY	night	BUZZ	tyre
DIFFICULTY	hard	CASE	venus
FOUND	lost	CHOOSE	walk
FRONT	back	COZY	cube
GIRL	boy	EMERALD	imitate
HALT	stop	ENGLISH	incline
HE	she	FACT	foil
HOUND	dog	FESTIVAL	marrow
IN	out	FRY	bog
JIGSAW	puzzle	GAMBLE	since
LEFT	right	QUICK	proof
MEOW	cat	REPLY	ruler
MUM	dad	RICE	thorn
QUEEN	king	RULE	dump
OAK	tree	SENSE	slick
OPEN	close	SNOB	ease

PERSPIRE	sweat	TAKE	glue
QUENCH	thirst	TAXI	zest
REFLECTION	mirror	TOBACCO	event
SCISSORS	cut	VENOM	shelf
SIRLOIN	steak	BECAUSE	ripped
TALL	short	BIT	ban
THREAD	needle	EVER	hand
UNCLE	aunt	FILE	gate
UP	down	SHOP	scale
WEEP	cry	UNICORN	cripple
ITCH	scratch	HAM	fan
EXHASUTED	tired	RIBS	warm
BLAZE	fire	CATTLE	toast

Word-Nonword		Word-Nonword	
CUE	TARGET	CUE	TARGET
ACTOR	leviv	MILE	elar
ALGAE	risht	MOOD	elub
ATTIC	lerpy	MOUSE	colig
BAKER	nerow	MOVIE	reyaz
BERRY	henit	MUSIC	pumjy
BROWN	verel	NIECE	shero
CARDS	mokes	OASIS	norgs
CHART	serat	PHOTO	ceday
CHUNK	gihat	ORGAN	nipot
CLICK	porof	PHASE	nalit
CLOVE	kaber	PINT	viwe
COUCH	cales	POINT	malic
COUPLE	gronts	POWER	dolob
CREST	ginat	PRICE	derit
CRUMB	nedim	PUNCH	refak
DIVER	rheet	RIGID	sumty
DWARF	norga	SCHOOL	celun
EMPTY	ablet	SHARP	misel
ESSAY	teesa	SKATE	cerof
FANGS	nereg	SKUNK	honud
FROWN	kunra	SLICE	norft
GLARE	vedar	SMART	ramay
GRAPH	revog	SORRY	dreab
HELLO	nufna	SPADE	rheat
HOUSE	terem	SPICE	halug
JOKER	romia	STIFF	dribe
JUICE	picot	SYRUP	baucs
LINES	terfa	TEACH	selta
LIST	rouf	PANTS	sayse
LOCK	liwd	DRESS	yenom
LORD	koob	DINNER	ruttle
MELT	cenk	ROBOT	surba

Appendix K

Stimulus Lists for Chapter 4 (cerebellar TBS)

Table K1: Stimuli List One

Related		Unrelated	
Cue	Target	Cue	Target
GROOM	bride	ASPIRIN	minus
SALT	pepper	HUSBAND	mirror
ARROW	bow	LAUGH	armour
ATLAS	map	ASSISTANT	kidnap
FORWARD	backward	PLUS	plant
FLESH	skin	KNOWN	near
SCUBA	dive	KNIGHT	headache
CAVERN	cave	INTERRUPT	bag
DEBATE	argue	FAR	ankle
VOLCANO	erupt	CAUTIOUS	unknown
BREED	dog	DEMON	minute
WHEN	where	HOUR	stream
ARTERY	vein	BROOK	office
TARDY	late	REFLECTION	rude
CREDIT	card	SACK	careful
GLANCE	look	ABDUCT	helper
TENT	camp	POST	cry
KLEENEX	tissue	SEED	smoke
LOOSE	tight	SPRAIN	devil
PRINCESS	prince	CIGAR	wife

Word-Nonword		Word-Nonword	
Cue	Target	Cue	Target
SUNRISE	sancakep	RIP	nakes
OBSERVE	mim	NICOTINE	epom
SCARE	fiwe	SPOILED	atil
SYRUP	cupy	COBRA	nircease
WALLET	locwn	PEANUT	cipture
INQUIRE	wol	CAMERA	cittarege
CUB	kas	BENEATH	torten
SHORTCAKE	lund	FLIPPER	tubert
SAUCER	crastch	DECREASE	sarits
FAST	brawsterry	HIM	tounmain
DAD	sheset	WAG	lodphin
TRUTHFUL	yad	SONNET	sehor
HIGH	sensut	STEPS	fieth
NIGHT	henost	MAXIMUM	mells
HUSBAND	weset	HILL	duner
CIRCUS	reab	CROOK	ckip
HONEY	trifgh	PLEAD	reat
ITCH	wols	CHOOSE	nimmium
ACRE	yemon	TROT	geb

LINEN	tawch	STENCH	har

Table K2: Stimuli list two (always immediately followed list one)

Related		Unrelated	
Cue	Target	Cue	Target
MONASTERY	monk	UNITED	parent
MANY	few	TRICYCLE	black
HIVE	bee	OLD	wet
BORROW	lend	SERVER	bicycle
TARZAN	jane	AFTER	flowers
HALT	stop	OUT	new
DESIRE	want	BOUQUET	states
HERE	there	RACKET	opening
ASTRONAUT	space	TRANSPLANT	elephant
REMAIN	stay	NIECE	before
MUTE	deaf	CLOSING	nephew
BREEZE	wind	GUARDIAN	leaves
CRESCENT	moon	WHITE	change
WINNER	loser	ALTER	waiter
MORSE	code	POSTAGE	heart
ROAR	lion	GIRL	stamp
DISLIKE	hate	MOIST	in
TOAD	frog	RAKE	tennis
JOURNEY	trip	TUSK	candle
EAST	west	WICK	boy

Word-Nonword		Word-Nonword	
Cue	Target	Cue	Target
ACTOR	bic	DIM	wol
NOW	erad	BOULEVARD	sillt
OFFENSE	zipza	BOYFRIEND	gronts
HEAVEN	lasfe	LINK	treset
BASHFUL	shub	ZEST	tehet
CIRCLE	lehil	LOBE	anc
SANDPAPER	qusare	UMBRELLA	firlgriend
NOISY	elarn	REGION	kcud
TAXI	galliator	GUMS	gilth
CASHEW	nem	GHOUL	gunher
CROCODILE	suh	HOOT	thogs
PLAYTHING	gourh	MOTIONLESS	poas
PEPPERONI	oyt	FAMINE	hinale
SHRUB	unt	CAP	torfune
WOMEN	exa	EXHALE	tuh
HATCHET	ractess	QUACK	xim
WORSE	olud	POWERFUL	aera
BOOK	tebter	BLEND	arin
UNTRUE	taler	OPENER	hacin
TEACH	fedense	FAME	aur

Table K3: Stimuli list three

Related		Unrelated	
Cue	Target	Cue	Target
REPAIR	fix	ALLERGY	shove
LIME	lemon	LISTEN	sneeze
TORCH	fire	PUSH	loving
HELIUM	balloon	SISTER	shoe
THUNDER	lightning	MORE	grandma
FEET	toes	KNOCK	mile
CLOAK	dagger	ADORABLE	throw
APPEARANCE	looks	LEAST	swamp
INDOORS	outdoors	PEDAL	brother
DIAL	phone	GRANDPA	less
OUNCE	pound	SOCK	most
VACATE	leave	ENDING	hear
ILLNESS	sick	CORPSE	door
THICK	thin	CARING	beginning
CONCLUSION	ending	CANYON	bike
WEED	grass	KILOMETER	dead
ABOVE	below	MARSH	cute
WIN	lose	BUBBLE	better
CORRIDOR	hall	WORSE	gum
DOORBELL	ring	TOSS	grand

Word-Nonword		Word-Nonword	
Cue	Target	Cue	Target
DAUGHTER	lesler	REPRIMAND	otol
RUG	rab	MEDICAL	grith
BUYER	tur	HUMILIATE	keta
LENS	pexlode	DAWN	nisuphment
SALOON	lakch	TRIBE	dirb
GANDER	sifh	KID	tocdor
GOING	nus	NECESSARY	sembarras
BLACKBOARD	noge	WINGS	horts
TREBLE	leam	BRUNETTE	rupple
MONOTONOUS	sooge	TUESDAY	rahsk
HUE	lasgess	LEFT	deni
EFFORT	ridty	ARMY	ent
FUEL	parcet	VIOLET	vany
IMPLODE	lasad	JAWS	neswedday
FEMALE	doonles	SHINGLE	dinian
OODLES	sabs	REMOVE	rofo
COD	ags	BLOUSE	rebak
RAYS	locour	NINE	dilch
DRESSING	gorbin	PLIERS	kuds
CLEAN	nus	SHATTER	deblon

Table K4: Stimuli list four (always immediately followed list three)

Related		Unrelated	
Cue	Target	Cue	Target
COMPASS	direction	BEST	pencil
CENTRE	middle	KING	dance
MAJOR	minor	TELLER	last
ENTRANCE	exit	NEEDLE	luggage
SLAY	kill	QUIZ	manners
BECAUSE	why	STAPLER	bank
DIGIT	number	REEF	worst
BULLETIN	board	ATTIRE	found
EMBRACE	hug	BALLET	shot
GOODBYE	hello	ADD	queen
AIRPORT	plane	FIRST	clothes
COMPONENTS	parts	TENSION	south
TOUCH	feel	SELF	maths
MIST	fog	PEN	me
INDIRECT	direct	BAGGAGE	stress
JOG	run	NORTH	subtract
LIPS	kiss	SLING	test
FORK	spoon	ETIQUETTE	coral
WIDTH	length	LOST	staple
TORTOISE	turtle	CALCULATOR	thread

Word-Nonword		Word-Nonword	
Cue	Target	Cue	Target
AUNT	rouys	KINETIC	thrist
AHEAD	carck	COCOON	aronge
SPREE	cunle	PRECISE	uhw
CABIN	hebind	CIGAR	focfee
CONVENT	sus	PEBBLE	cexat
TWINKLE	wut	BEAST	egerny
EVEN	amb	QUENCH	etl
COBWEB	sart	HALF	holew
GANGSTER	hopsping	WHOM	liwd
MINE	rebad	SKETCH	manial
DRAPES	horts	FATHER	mokes
DONKEY	rowld	TANGERINE	pairlane
MUSTACHE	dod	SEA	sumcle
SIX	unn	CAFFEINE	nocea
CREVICE	torsage	FLYING	orck
NAP	vesen	ALLOW	tomher
PAIR	pisder	FLEX	tubterfly
TALL	gol	PARIS	narfce
WAREHOUSE	ructains	TAME	anunally
GLOBE	lesep	YEARLY	rawd