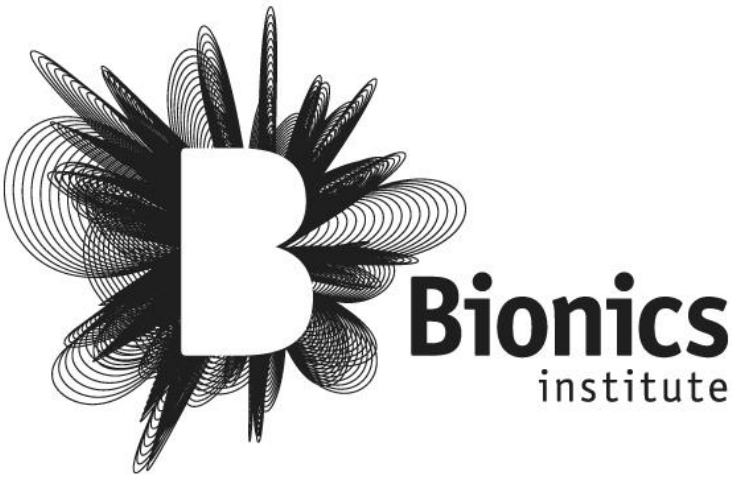




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# Effects of prismatic adaptation on spatial gradients in neglect: a comparison of visual and auditory target detection with central attentional load

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Abstract

Prismatic adaptation is increasingly recognised as an effective procedure for rehabilitating symptoms of spatial neglect – producing relatively long-lasting improvements on a variety of spatial attention tasks. The mechanisms by which the aftereffects of adaptation change neglect patients' performance on these tasks remain controversial. It is not clear, for example, whether adaptation directly influences the pathological ipsilesional attention bias that underlies neglect, or whether it simply changes exploratory motor behaviour. Also, while there is considerable evidence for prism effects on neglect symptoms in the visual, proprioceptive and tactile systems, few studies have examined the generalization of aftereffects to sensory systems that are not directly involved in the adaptation procedure itself. Here we used visual and auditory versions of a target detection task with central attentional load. Under these conditions, patients with spatial neglect demonstrated a spatial gradient in their ability to detect peripheral visual or auditory targets. The effect of prism adaptation on the patients' pathological attention gradient on these two tasks was compared. The findings have implications for understanding the level at which prism adaptation may be acting on neglect symptoms.

Keywords: hemispatial neglect, auditory perception, visual attention, attentional load

## Introduction

Spatial neglect is a common consequence of unilateral stroke, particularly when the lesion affects the right cortical hemisphere (Driver & Mattingley, 1998; Stone, Halligan, & Greenwood, 1993). This syndrome is characterised by reduced awareness for stimuli arising from the contralesional side of space, despite intact sensory functioning. The deficit is thought to reflect damage to internal representations of contralesional space (Bisiach & Luzzati, 1978; Karnath, Niemeier, & Dichgans, 1998) and a pathological ipsilesional bias in spatial attention (Kinsbourne, 1993). This lateralized impairment can affect patients' perception of stimuli in any modality, including vision, audition (see Pavani, Husain, Ladavas, & Driver, 2004) and tactile processing (e.g., Guerrini, Berlucchi, Bricolo, & Aglioti, 2003; Schindler, Clavagnier, Karnath, Derex, & Perenin, 2006; Vallar, Rusconi, Bignamini, Geminiani, & Perani, 1994). The presence of neglect is a major predictor of poor functional recovery; furthermore, it is accompanied by profound unawareness of the deficit, which is a major obstacle to rehabilitation and recovery (Vuilleumier, 2004). Over the past decade, prism adaptation has emerged as a potentially effective therapy for reducing neglect on a range of attentional tasks and behavioural measures, with improvements lasting several hours and in some studies, days or weeks (Frassinetti, Angeli, Meneghello, Avanzi, & Ladavas, 2002; Rossetti, Rode, & Pisella, 1998; Serino, Angeli, Frassinetti, & Ladavas, 2006). Although there is accumulating positive evidence for the efficacy of prism adaptation, not all manifestations of neglect improve with this treatment (Ferber, Danckert, Joanisse, Goltz, & Goodale, 2003; Morris et al., 2004; Nijboer, McIntosh, Nys, Dijkerman, & Milner, 2008; Sarri, Kalra, Greenwood, & Driver, 2006), and there is evidence that some patients may not respond to prism adaptation (Sarri et al., 2008).

Insight into the specificity of prism effects is crucial for developing this approach as a clinical tool, and also for understanding the mechanisms that underlie adaptation. Although there is now considerable evidence that prism adaptation can influence a variety of different spatial processing tasks, the generality of its effect on spatial processing is not clear because most of the tasks used to date have concerned visual (e.g., Berberovic, Pisella, Morris, & Mattingley, 2004; Bultitude, Rafal, & List, 2009; Farne, Rossetti, Toniolo, & Ladavas, 2002; Frassinetti et al., 2002; Nijboer et al., 2008; Rossetti et al., 1998; Saevarsson, Kristjansson, Hildebrandt, & Halsband, 2009; Serino et al., 2006; Striemer & Danckert, 2007), proprioceptive (Tilikete et al., 2001) or tactile modalities

(Dijkerman, Webeling, ter Wal, Groet, & van Zandvoort, 2004; Maravita et al., 2003; McIntosh, Rossetti, & Milner, 2002) – which are directly involved in the visuo-manual procedure required for adaptation. In order to determine whether prism effects are restricted to the visual and somatosensory systems or whether it reflects higher-level changes in spatial attention, we investigated whether prism adaptation can ameliorate spatial neglect symptoms in a sensory system that is not directly involved in adaptation – in this case, audition.

*Auditory processing and prism adaptation*

Auditory symptoms of neglect can manifest in a number of ways, such as auditory extinction (De Renzi, Gentilini, & Pattacini, 1984; Deouell & Soroker, 2000; Karnath, Zimmer, & Lewald, 2002; Shisler, Gore, & Baylis, 2004), contralesional deficits in sound lateralization or localization (Bisiach, Cornacchia, Sterzi, & Vallar, 1984; Pavani et al., 2004; Pavani, Ladavas, & Driver, 2002; Pavani, Meneghello, & Ladavas, 2001), and biased judgment of the temporal order of auditory stimuli (Karnath et al., 2002). Also, we have previously demonstrated that neglect can manifest as an ipsilesional attentional gradient (see below) on auditory search as well as visual search tasks (Eramudugolla & Mattingley, 2009).

The effect of prism adaptation on auditory processing has rarely been addressed in the literature. In their review of prism use in neglect, Rode et al. (2003) reported that two patients with asymmetric performance on a dichotic listening task demonstrated improvements in reporting left ear stimuli following prism adaptation. However, the use of dichotic listening tasks to assess auditory spatial attention is problematic, because the stimuli are presented monaurally to either the left or right ear. In this context, contralesional detection deficits during bilateral stimulation could be interpreted as suppression of auditory input to that side (Beaton & McCarthy, 1995; Bellman, Meuli, & Clarke, 2001; Pavani et al., 2004) which is not consistently associated with the presence of spatial neglect, and can follow a range of cerebral lesions, including callosal disconnection (Milner, Taylor, & Sperry, 1968; Sparks & Geschwind, 1968). In our study, we presented binaural auditory stimuli over headphones, where the stimuli were spatialized using head-related transfer functions (HRTF), such that participants perceived the sounds as emanating from locations in extrapersonal space. Thus, the stimuli were not restricted to one or the other ear but to either the left or right hemifield, similar to free-field sound presentation.

Because prism adaptation directly induces a lateral bias in arm and eye movements (Angeli, Grazia Benassi, & Ladavas, 2004; Ferber et al., 2003; Redding, Rossetti, & Wallace, 2005; Redding & Wallace, 2006), these motor biases alone may explain neglect improvements on spatial tasks that require manual or ocular exploration (Angeli et al., 2004; Serino et al., 2006). Thus, in order to ensure that any prism effects on audition reflect attentional changes, and are independent of changes to motor behaviour following adaptation, we employed an auditory task that did not require a manual localisation response, required central fixation of gaze, and that explicitly examined neglect patients' spatial gradient of attention (see below).

*Neglect as a spatially graded bias in attention*

Unilateral spatial neglect is not a hemifield-based deficit, but instead reflects increasingly reduced awareness for stimuli that are positioned at *relatively* more contralesional locations in space (Bartolomeo et al., 2004; Halligan & Marshall, 1991; Kinsbourne, 1993; although see Karnath et al., 1998). Thus, patients show a spatial gradient in their visual awareness, with latency and accuracy for detecting visual stimuli worsening as a function of the target's degree of laterality towards the contralesional side. This graded performance of neglect patients is exacerbated by increasing the attentional demands of a visual search task (e.g.,Eglin, Robertson, & Knight, 1989; Riddoch & Humphreys, 1987), and also when patients have to perform a secondary attentional load task at fixation while monitoring peripheral space for brief visual targets (Mattingley, Berberovic, Rorden, & Driver, 2003). Thus, in order to test patients' spatial gradient of attention in the present study, we used visual and auditory versions of a dual task in which patients had to monitor a central stream of stimuli for a target while responding to brief peripheral stimuli presented at varying locations within the left and right hemifield.

*Prism adaptation and effects on spatial attention*

It remains controversial as to whether prism adaptation directly influences the spatial bias (or gradient) in attention underlying neglect (Newport & Jackson, 2006; Pisella, Gilles, Farne, Tilikete, & Rossetti, 2006; Redding & Wallace, 2006), or whether it acts on related aspects of neglect behaviour, such as exploratory eye movements (Angeli et al., 2004; Ferber et al., 2003; Serino et al., 2006). Prism adaptation is achieved by a brief period of pointing to visual targets while wearing

prism lenses that laterally shift the visual field towards the right side by 10-15°. Initially, the prism-induced shift in the visual field causes participants (including neglect patients) to make rightward errors in pointing to the visual target. With subsequent pointing movements, participants compensate for the shift and these errors are abolished. Once the prism lenses are removed, participants demonstrate a temporary bias (or aftereffect) in visually guided pointing, and in their proprioceptive judgement of a point straight ahead. This aftereffect is in the opposite direction to the prism-induced shift.

Patients with left spatial neglect following right hemisphere stroke respond only to adaptation with right-shifting prisms that induce a leftward aftereffect in pointing movements (Rossetti et al., 1998; Tilikete et al., 2001). This leftward bias in pointing appears to generalise to patients' attentional performance, as the initial motor effect is outlasted by a reduction in patients' ipsilesional (rightward) bias on unrelated spatial tasks such as cancellation and line bisection (e.g., Farne et al., 2002; Frassinetti et al., 2002; Rossetti et al., 1998; Sarri et al., 2008; Serino et al., 2006). Although tasks such as these involve a motor component, there is evidence from a number of studies that prism adaptation can affect patients' attentional bias on a range of purely perceptual tasks (Berberovic et al., 2004; Striemer & Danckert, 2007) as well as on tasks of mental imagery and mental number line judgments (Rode, Rossetti, & Boisson, 2001; Rossetti et al., 2004). This suggests that the initial visuo-motor aftereffect induced by adaptation somehow transfers to functions of spatial attention (Pisella et al., 2006; Redding et al., 2005). Indeed, it has been postulated that prism adaptation may act on higher spatial cognitive functions by the enlargement of contralesional spatial representations (Redding & Wallace, 2006), and 'rebalancing' of the pathological ipsilesional spatial gradient of attention (Pisella et al., 2006).

Empirical evidence for the effect of prism adaptation on tasks that explicitly assess biases in spatial attention has been somewhat mixed. Morris et al. (2004) examined the effects of prism adaptation on a speeded visual search task that excluded any manual component typical of cancellation tasks. In this task, participants reported the presence or absence of a single target in an array of distractors, within a limited time period. Neglect patients demonstrated a significant spatial gradient of performance on this task. Following prism adaptation, patients demonstrated significant leftward aftereffects on their proprioceptive judgment of straight ahead, and most showed changes in their

performance on a line bisection task, but there was no change in their spatial gradient of attention on the visual search task. It was suggested that the effects of prism adaptation on neglect might not reflect changes in the spatial attention bias underlying the disorder. A similar finding was reported for speeded visual search in a recent study (Saevarsson et al., 2009). However, in a follow-up experiment involving different patients and a visual search task that was not time limited and did not include feedback about performance, significant increases in left sided target detections were found post- prism adaptation. The authors suggest that the provision of feedback may lead to 'de-adaptation'. Another possibility is that extended search time may have allowed ocular exploration to contribute more to search performance.

Neglect is also associated with deficits in re-orienting or disengaging attention away from ipsilesional stimuli (Posner, 1980). Studies that have investigated the effect of prisms on reflexive re-orienting to peripheral stimuli have produced conflicting results. Streimer and Danckert (2007) reported that right brain damaged patients with right disengage deficits on a Posner cueing task (using exogenous cueing), were faster to reorient from a right cue to a left target following a single session of prism adaptation. In contrast, a recent study that also investigated prism-effects on the exogenous cueing version of the Posner task, found improvements across two baseline testing sessions but not following prism-adaptation (Nijboer et al., 2008). Interestingly, the same patients demonstrated prism-induced improvements on the Posner task with endogenous cueing. The authors suggested that the effect of prism adaptation on neglect symptoms might occur primarily through improvements in voluntary orienting, rather than by influencing patients' automatic orienting to peripheral onsets. Certainly, the majority of positive prism-effects have been seen in non time-limited tasks, including paper-and-pencil tests, which allow voluntary exploratory behaviours to compensate for attentional biases. Also, several studies have reported that neglect patients' ipsilesional bias in ocular exploratory movements shifts to the neglected side following prism adaptation, and such ocular-motor changes correlate with improvements on clinical neglect tasks following prism adaptation (Angeli et al 2004; Serino et al 2006). Nevertheless, patients may continue to show deficits on some attentional tasks such as the judgement of chimeric faces *despite* a leftward shift in exploratory eye movements (Ferber et al 2003). Thus, it is as yet unclear whether prism adaptation acts on the underlying spatial attentional bias in neglect. A secondary motivation

of the present study was to examine the effect of prism adaptation on patients' attentional gradient for detecting brief peripheral stimuli.

## Methods

### *Participants*

A group of twelve individuals with recent right hemisphere stroke (see Figure 1), allof whom demonstrated left neglect on clinical tests, were recruited from stroke units in Brisbane (Mean age = 66 years (SD=14.85)). Although participants had varying degress of hearing loss as measured by pure-tone audiometry (frequency range: 0.25 – 8kHz), none had an asymmetric hearing loss (difference between thresholds > 20 dB) (see Table 1). Approval was obtained from The University of Queensland and hospital committees for Ethical Research involving Humans. Informed consent was obtained from all participants prior to testing. A control group of eight neurologically normal participants (Mean age = 68.6 years (SD=7.26) were recruited via the Australasian Aging Research Centre research participant database. These participants also had no asymmetric hearing loss on pure-tone audiometry (Table 1).

### *Design and Procedure*

Patients were tested on four separate occasions within the space of one to two weeks. The two initial sessions obtained baseline levels of performance on a cancellation task, a line bisection task, a computerised visual dual task and a computerised auditory dual task (see below). The final two sessions involved 5-10 minutes of prismatic adaptation followed by repeat testing on cancellation, line-bisection, visual and auditory target detection. The order in which the four tasks were presented in each session was balanced across participants. The healthy control participants were tested on the line bisection task, visual dual task and auditory dual task, but did not undergo prism adaptation or post-adaptation tests.

### *Cancellation and Line-Bisection tasks*

The cancellation task employed was The Balloons Test (Edgeworth, Robertson, & McMillan, 1998). This test consists of two parts. In Part A patients are required to cancel target symbols resembling "Q" from an array of symbols resembling "O", presented on an A3 page. The

presence of a unique feature in the targets of Part A places minimal demands on focused attention, and thus yields very efficient search in normal observers (Treisman & Gelade, 1980). In Part B, the patients are asked to cancel target Os within an array of Qs. Part B of the test requires the serial allocation of focused attention, which yields less efficient visual search and is generally more sensitive to visual neglect symptoms than Part A (Riddoch & Humphreys, 1983). Administration involved asking the participant to mark as many of the target stimuli on the page as possible using a felt-tip pen. Criteria for neglect were the presence of more than three omissions, with a larger number of omissions on the left compared to the right side of the page, and/or right to left direction of scanning.

On the line-bisection task, patients were presented with 20 horizontal lines, each on a separate A4 page. Lines were of two different lengths: 15 or 20cm. The location of each line on the page was varied across trials such that the midpoint of the line could be shifted 3-6° to the left, to the right, up or down relative to the centre of the page when viewed from 30cm away. Patients were required to mark the perceived midpoint of each line.

*Dual Tasks*

Increasing the attentional demands of a task can exacerbate neglect symptoms and augment the associated ipsilesional bias in attention (Mattingley et al., 2003; Robertson & Frasca, 1992; Vuilleumier et al., 2008). Specifically, performance of a secondary task on non-lateralized stimuli impairs patients' detection of irrelevant peripheral stimuli within left space relative to right space. Here we employed a dual task paradigm adapted from Mattingley et al. (2003), where patients had to perform a target detection task on serial stimuli at fixation/midline while also reporting the occurrence of lateralised stimuli in the periphery. The experimenter also monitored patients' maintenance of central gaze during testing.

Procedurally identical auditory and visual versions of the dual task were programmed using Psychophysics Toolbox (MATLAB) and presented on a Dell XPS laptop with a 17' liquid-crystal display. In the dual task, patients were required to monitor a central stream of eight sequentially presented stimuli (400 ms per item) for a designated target stimulus (henceforth referred to as the 'fixation task'). Catch-trials, in which the target was absent from the stream, constituted 40% of trials in the experiment. On target-present trials, the target occurred once on 40% of trials and on two occasions in 20% of trials. The two-target trials ensured that patients maintained attention and

fixation on the central stimulus stream throughout each trial. While performing the fixation task, participants also had to make a speeded mouse-button press with their ipsilesional hand in response to an occasional 200-ms stimulus presented within the left or right hemifield, peripheral to the fixation stimuli. The mouse was positioned in front of the laptop at the patient's midline.

*Auditory task.* Spatialized auditory stimuli were presented in virtual auditory space (VAS) over headphones (Sennheiser HD 437). VAS is generated by measuring the direction-dependent filtering properties of a listener's outer ears, head, and torso – the Head-Related Transfer Functions (HRTFs). Here, the (left- and right-ear) HRTFs for each spatial location were expressed as a function of frequency and were convolved with the stimuli. The resultant waveforms were presented through headphones, producing the percept that the stimuli were emanating from the location in extrapersonal space for which a given pair of HRTFs were measured (Carlile, 1996). VAS stimuli can be localised with comparable accuracy to external stimuli (Hartung, Sterbing, Keller, & Takahashi, 1999; Martin, McAnally, & Senova, 2001). A set of standard HRTFs from a representative participant was used in these studies because of the difficulty of measuring HRTFs for individual patients. The central stimulus stream in the auditory task was a series of steady complex tones, presented at the listener's midline in VAS, and pseudorandomly selected from a 'library' of 12 complex tones with fundamental frequencies ($F_0$) ranging from 390-740Hz. No two successive tones had the same $F_0$. Each tone was played for 400 ms and the frequency difference between sequential tones was between 25-40Hz. The listener was instructed to monitor this stream of tones for a target tone. The target tone was a frequency modulated (FM) complex tone (henceforth referred to as the FM tone); the $F_0$ range was modulated sinusoidally over the range 164-273 Hz, at a depth of 10 Hz and frequency 5Hz. Thus, the target FM tone for the auditory central task was unique relative to the distractor steady tones in the stream. The FM tone was never the first item in the series of eight 'fixation' stimuli, and on trials in which two FM tones were presented, there was always a gap of 1.6 s (or 4 stimuli) between the first and second occurrence of the target. The auditory peripheral stimuli were 200 ms white noise bursts (3-ms amplitude ramps) presented at one of four locations in VAS: left extreme (270°), left proximal (220°), right proximal (140°) or right extreme (90°) (Figure 2A). These noise stimuli never coincided with FM targets in the 'fixation' stimulus stream. The noise stimuli occurred randomly on 75% of trials, and with equal frequency in the left and right hemifields. Upon detecting the noise target, patients made a speeded

button press with the ipsilesional hand (via a mouse). At the conclusion of each trial, the patient verbally reported the number of FM tone targets detected in the fixation stream (0,1 or 2).

*Visual task*. The central stimulus stream in the visual task was a series of eight red alphabetic characters (1° high) randomly selected from the following letters (A,B,C,D,E,F,G,H,I,J,K,L,M,N,O,P). Each letter was presented for 400ms (at a frequency of 2.5Hz) (Figure 2B). The participant was instructed to monitor this stream of letters for a target letter, which was a green "X". Thus, the target letter for the visual central task was unique relative to the distractor letters in the stream. The target letter was never the first item in the series of eight 'fixation' stimuli, and on trials in which two green X's were presented, there was always a gap of 1.6 s (or 4 stimuli) between the first and second occurrence of the target. The visual peripheral stimuli were presented within one of four square placeholders (1.5° x 1.5°) located at a radius of 12° from fixation and a horizontal distance of either 12° (extreme) or 6° (proximal) to the left and right (see Figure 2A). All four placeholders appeared at the onset of each trial and were continuously present until the end of a trial. On 75% of trials a single red square (1°x1°) (the target) was presented for 200ms within one of the placeholders. The peripheral target red square never coincided with the green X target of the 'fixation' letter stream. Upon detecting the peripheral target, patients made a speeded button press with the ipsilesional hand (via a mouse). At the conclusion of each trial, the patient verbally reported the number of green Xs detected in the fixation stream (0, 1 or 2).

Prior to the Visual Dual Task, patients completed a computerised test of their visual fields. This involved maintaining fixation on a cross at the centre of the screen while monitoring either the left or right visual field (indicated by the experimenter) for a brief visual target (black 1°x1° square). The visual target was initially presented at 20.6° from fixation and this distance was incrementally reduced until the patient reliably reported detection of the target. Left and right lateral and inferior quadrants were assessed in this way. Only one patient (Patient 9) in the sample demonstrated a visual field deficit on this test (left inferior quadrantanopia) and the distance from fixation of placeholders in the Visual Dual Task was adjusted to be within this patient's intact visual field (6° from fixation). All other patients were tested with the placeholder eccentricity set at the standard 12°.

Although patients did not demonstrate significant asymmetries (i.e. > 20dB difference) in their pure-tone thresholds for the left and right ear, there was considerable variability in the overall hearing level across individuals. Thus, prior to the Auditory Dual Task, patients were presented each tone stimulus in isolation, and the computer sound output was adjusted to a level that ensured adequate detection of these tones.

*Prism adaptation protocol*

The adaptation protocol employed here was similar to that used in numerous previous studies (Rossetti et al., 1998). The effectiveness of adaptation was assessed by measuring aftereffects on patients' subjective straight ahead (SSA) – the standard method of quantifying adaptation aftereffects (Sarri et al., 2008). During each session of prism adaptation, patients first engaged in an open loop pointing task to measure their pre-adaptation SSA, then engaged in a pointing task while wearing the prism lenses (adaptation), which was immediately followed by a repetition of the open loop pointing task for measuring the post-adaptation SSA.

*Open-loop pointing task.* In the open-loop pointing tasks, patients sat at a table with their eyes closed and the index finger of their ipsilesional hand resting on their chest at midline. The experimenter sat at the opposite end of the table and an A1 sheet of cardboard was placed on the surface of the table. Centimetre gradations were attached to the experimenter's side of the cardboard, which was not visible to the patients, and the central point of the gradations was visually aligned with the patients' midline. On each trial, the patients were asked to point to a location on the surface of cardboard that was straight ahead of them, with their eyes closed. On each trial, the experimenter recorded the deviation of the patients' index finger from the central point before the patients returned their finger to their chest. Ten measures of SSA were obtained for each of the pre-adaptation and post-adaptation pointing tasks.

*Adaptation*. Patients wore spectacle-mounted wedge-based prisms that shifted the visual field to the right by 10° (Optique Peter, Lyon, France). Two brightly coloured vertical strips (3cm x 0.5cm) were placed on the surface of the cardboard at arms length (50cm) and 11.3° to the left and right of the patient's sagittal plane. These served as the targets for visually guided pointing movements. A

textured pad (1cm x 1cm) was positioned on the table, directly in front of the patient's chest. This served as the starting point for all pointing movements. A cardboard panel (31cm x 46cm) was positioned under the patients' chin to occlude their vision of the starting point of their index finger and the initial part of the reaching movement. Only the endpoint of the movement and the targets were visible. On each trial, patients made a rapid pointing movement to the target that was verbally indicated by the experimenter (left/right). The patients were instructed not to correct their movements online, but to aim for accuracy with each successive movement. Fifty pointing movements were made, with the side of the target varied randomly over trials.

## Results

### *1.Left inattention and stability of symptoms over sessions*

Performance on each of the four tasks (line bisection, cancellation, visual and auditory dual tasks) during the baseline sessions was assessed. The patient group demonstrated significant asymmetries in performance on all four tasks, and these deficits were stable across the first and second baseline administrations.

*Cancellation Task*. On both versions of the Balloons test (A and B), patients showed reduced cancellation of targets located within the left hemifield relative to targets located within the right hemifield (Figure 3A). Importantly, this asymmetry was preserved across the first and second administrations at baseline. The presence of stable left neglect symptoms on each task was confirmed by repeated measures ANOVA on the number of targets detected. In Task A, there was a significant main effect of target location ($F(1,11) = 8.56$, $p<0.025$, $\eta_p^2=0.44$), but no main effect of session ($F(1,11)< 1.0$), and no interaction between target location and session ($F(1,11)< 1.0$). A similar pattern was evident for cancellation Task B, where there was a significant effect of target location ($F(1,11) = 11.821$, $p<0.01$, $\eta_p^2=0.52$), but no effect of session ($F(1,11)< 1.0$), nor an interaction between session and target location ($F(1,11)< 1.0$).

*Line Bisection*. Patients' responses on the line bisection task were expressed as a percentage of the line length, and this was compared against the performance of healthy age-matched control

participants on the same task. Patients demonstrated a strong rightward bias in their responses in both baseline sessions (Session 1: Mean= +7.08%; SEM=2.52; Session 2: Mean=+4.87%; SEM=2.50), in contrast to the small leftward bias apparent in controls' performance (Mean= -2.42%; SEM=0.75). There was also a significant difference between patients' and control participants' performance on both baseline sessions: Session 1 ($t(17)=3.61$, $p<0.01$), and at Session 2 ($t(17)=2.79$, $p<0.025$). Importantly there was no significant change in patients' performance across the two baseline sessions ($t(11)=1.37$, $p>0.10$).

*Visual Dual Task.* Spatial neglect on the visual dual task could be reflected in the number of peripheral targets detected and/or in the response latency of correct detections. In order to account for performance on both these measures, accuracy and response times at each target location were combined into a single measure reflecting "target detection efficiency" (Accuracy/ RT). This is the inverse of the "inverse efficiency coefficient" typically used to control for potential speed/accuracy trade-offs (Townsend & Ashby, 1983). Patients' target detection efficiency on the visual dual task was compared against that of the healthy participants and over the course of the two baseline sessions. As evident in Figure 3B, controls demonstrated a high level of target detection efficiency and this was similar across all locations of the target. In contrast, patients demonstrated generally worse performance than the controls and a prominent spatial gradient in their target detection, with performance that deteriorated as the target was positioned further to the left. A mixed ANOVA revealed a main effect of target location ($F(3,54) = 10.69$, $p<0.001$, $\eta_p^2=0.37$) and of participant group ($F(1,18) = 21.99$, $p<0.001$, $\eta_p^2=0.55$), but not for session ($F(1,18) = 2.82$, $p>0.10$). There was also an interaction between location and group ($F(3,54) = 14.48$, $p<0.001$, $\eta_p^2=0.45$). None of the other interactions reached significance (all $p>0.10$). Simple effects on the interaction revealed no effect of target location in the control group ($F(3,21) = 1.07$, $p>0.10$), and a significant effect of target location in the neglect patients ($F(3,33) = 20.23$, $p<0.001$, $\eta_p^2=0.65$). Comparisons indicated that patients' target detection improved from left extreme to left proximal locations ($t(11)=3.61$, $p<0.01$), and from left proximal to right proximal locations ($t(11)=4.22$, $p<0.01$), but there was no difference between right proximal and right extreme targets ($t(11)=1.75$, $p>0.10$). Patients' performance was also worse than that of controls at all except the right proximal target location ($p<0.01$). Thus, patients demonstrated a pathological rightward spatial gradient in their detection of targets on the visual dual task, and this did not vary across the two baseline administrations.

*Auditory Dual Task.* Target detection accuracy and response latency on the auditory task were also transformed into a single measure of target detection efficiency. Patient performance was again compared across the two baseline sessions and against the performance of healthy participants. Figure 3B shows that controls demonstrated a high level of target detection efficiency that did not vary with target location, whereas patients demonstrated a subtle but reliable spatial gradient in their target detection with deteriorating performance with leftward target locations. Analysis revealed a main effect of target location ($F(3,54) = 3.50$, $p<0.05$, $\eta_p^2=0.16$) and of participant group ($F(1,18) = 6.43$, $p<0.05$, $\eta_p^2=0.26$), but not of session ($F(1,18)<1.0$). There was also an interaction between location and group ($F(3,54) = 2.64$, $p=0.05$, $\eta_p^2=0.13$). None of the other interactions reached significance (all $p>0.10$). Simple effects on the interaction revealed no effect of target location in the control group ($F(3,21) <1.0$), and a significant effect of target location in the neglect patients ($F(3,33) = 6.10$, $p<0.01$, $\eta_p^2=0.36$). Comparisons indicated that patients' target detection improved from left proximal to right proximal locations ($t(11)=2.68$, $p<0.025$), but not between left extreme and left proximal locations ($t(11)=1.20$, $p>0.10$) or right proximal and right extreme locations ($t(11)=1.35$, $p>0.10$). Patients' performance was also worse than that for controls at all except the right proximal and right extreme target locations ($p<0.01$). Thus, patients demonstrated a rightward spatial gradient in their detection of auditory targets, and this did not vary across the two baseline administrations.

*2. Correlation between attention gradients on the visual and auditory dual tasks*

In order to examine whether there was an association between visual and auditory deficits on the dual tasks, the Spearman rank correlation coefficient was calculated for each patient's performance on the auditory dual task and visual dual task as a function of target location. These coefficients were used as an index of the patients' spatial gradient of target detection. Analysis of the association between auditory and visual spatial gradients for the patient group revealed a significant positive correlation (Spearman $\rho = 0.58$, $p<0.05$).

*3. Effectiveness of prism adaptation - aftereffects on judgements of SSA*

All patients demonstrated a significant change in their mean estimate of pre-adaptation SSA following *at least one* of the two adaptation sessions. In all except one patient (Patient 9), the SSA

shifted towards the left (Figure 3C). Patient 9, who also demonstrated a left superior quadrantanopia with macular sparing, showed a reliable and strong leftward bias in her pre-adaptation SSA judgement (Mean= -4.29°) that became significantly less biased following adaptation (Mean= +0.91°). A similar trend was evident on her second session of adaptation (Pre-adaptation: -8.81°; Post-adaptation: -7.50°). This bias in SSA towards the scotoma has previously been reported in patients with visual field deficits (with or without neglect) (Ferber & Karnath, 1999; Kerkhoff, 1993). It is interesting to note that Patient 9's leftward SSA significantly reduced following the first administration of prism adaptation ($t(9)=9.58$, $p<0.001$). Nevertheless, because of the potential effects of visual deficits on Patient 9's SSA judgement, her data were excluded from group analysis of the aftereffects. Paired t-tests revealed that the patient group demonstrated a significant leftward shift in SSA following the first session of prism adaptation ($t(10)=2.40$, $p<0.05$) and also following the second session of prism adaptation ($t(10)=3.72$, $p<0.01$).

*4. Prism effects on spatial inattention*

Because spatial inattention symptoms on all four tasks were found to be stable across the baseline sessions, mean baseline performance for each was compared against performance in the post-adaptation sessions.

*Cancellation Task.* Performance on task A did not change between baseline and post-adaptation sessions. Analysis indicated a main effect of target location ($F(1,11) = 9.14$, $p<0.025$, $\eta_p^2=0.45$), but no main effect $F(2,22)=1.23$, $p>0.10$, or interaction with session $F(2,22)=2.44$, $p>0.10$). On task B, detection of left sided targets increased following prism adaptation, but performance for right sided targets was unchanged (Figure 4A). There was a main effect of session ($F(2,22) = 4.04$, $p<0.05$, $\eta_p^2=0.27$), a main effect of target location ($F(1,11) = 8.52$, $p<0.05$, $\eta_p^2=0.44$) and an interaction between session and target location ($F(2,22) = 3.32$, $p=0.05$, $\eta_p^2=0.23$). This interaction revealed an effect of session for the detection of left side targets ($F(2,22) = 4.96$, $p<0.05$, $\eta_p^2=0.31$), where detection was significantly higher between baseline and the second post-adaptation session ($t(11)=3.00$, $p<0.01$), but not between baseline and the first post-adaptation test ($t(11)=1.75$, $p>0.10$) or between the first and second post-adaptation sessions ($t(11)=1.48$, $p>0.10$). Furthermore, the impairment in left target detection relative to right target detection was apparent at baseline

(t(11)=3.45, $p$<0.017), and after the first post-test (t(11)=2.43, $p$<0.05), but was no longer evident following the second post-test (t(11)<1.0).

*Line Bisection.* The rightward bias in line bisection showed a decreasing trend following the adaptation sessions (Figure 4C), but this was not statistically reliable (F(2,22) = 2.03, $p$>0.10, $\eta_p^2$=0.16).

*Visual Dual Task.* Performance on the visual dual task showed a general increase in detection efficiency following the adaptation sessions (Figure 4B), however the spatial gradient remained unchanged (Figure 3b). This was confirmed statistically, where there was a significant main effect of session (F(2,22) = 6.04, $p$<0.01, $\eta_p^2$=0.36) and an effect of target location (F(3,33) = 15.85, $p$<0.01, $\eta_p^2$=0.59), but no interaction between session and location (F(6,66) < 1.0). Target detection efficiency improved between baseline and the first post-test (t(11)=2.85, $p$<0.017), and between baseline and the second post-test (t(11)=2.64, $p$<0.025) but not between the two post-adaptation tests (t(11)<1.0). Detection efficiency was worse for targets at left extreme than left proximal locations (t(11)=3.92, $p$<0.017) and worse for left proximal than right proximal locations (t(11)=3.71, $p$<0.017) but not different between right proximal and extreme locations (t(11)=1.80, $p$>0.10).

*Auditory Dual Task.* Performance on the auditory dual task did not change following prism adaptation (Figure 4B lower panel). There was a main effect of target location (F(2,22) = 8.85, $p$<0.001, $\eta_p^2$=0.45) but no main effect of session (F(3,33) = 1.98, $p$>0.10) and no interaction between session and target location (F(6,66)<1.0). Patients' target detection was worse for left proximal than right proximal locations (t(11)=2.46, $p$<0.05), but not between left extreme and left proximal locations (t(11)<1.0, $p$>0.10) or right proximal and right extreme locations (t(11)=1.82, $p$>0.05).

*5. Individual analyses*

Although we did not observe a change in the spatial gradient of visual attention following adaptation, it is important to note that individual patients demonstrated marked changes and even reversals in their spatial gradient on the visual dual task.

*Patient 2.* This patient demonstrated a strong rightward spatial gradient on the visual dual task that reduced following prism-adaptation (Figure 5A). Analysis revealed a significant interaction between target location and session ($F(6,62) = 2.29$, $p<0.05$, $\eta_p^2=0.18$), where there was a rightward spatial gradient at baseline ($F(3,35) = 9.48$, $p<0.001$, $\eta_p^2=0.45$), but no gradient at either the first ($F(3,16) = 2.13$, $p>0.10$) or second post-adaptation sessions ($F(3,15)<1.0$). He also demonstrated a significant leftward shift in his SSA following the first adaptation session (Mean shift= -2.92°, $p<0.05$) (Figure 5A).

*Patient 5.* As is evident from Figure 5B, Patient 5 showed little evidence of a spatial gradient on the visual task at baseline, but after prism adaptation showed a strong *leftward* gradient. This was more marked after the first than second post-tests. A repeated measures ANOVA on her target detection efficiency scores revealed a significant interaction between target location and session ($F(6,108) = 9.40$, $p<0.001$, $\eta_p^2=0.34$), where there was no spatial gradient at baseline ($F(3,56) = 1.61$, $p>0.10$), but there was a marked leftward gradient following the first post-test ($F(3,26) = 41.06$, $p<0.001$, $\eta_p^2=0.83$), but not the second ($F(3,26) = 2.07$, $p>0.10$). This patient also demonstrated a very strong proprioceptive aftereffect following her first adaptation session (Mean shift = -16.05°, $p<0.001$) (Figure 5B).

## Discussion

We investigated whether the effects of prism adaptation on spatial neglect are evident as a change in patients' spatial gradient of attention, and whether this generalises to attention biases in the auditory modality. We found that patients demonstrated significant aftereffects of prism adaptation as measured by leftward shifts in their SSA, and that this effect generalised to patients' neglect symptoms on a cancellation task, in the context of unchanged baseline performance over the previous two weeks. Following prism treatment, patients demonstrated an overall improvement in target detection efficiency on the visual dual task although the pathological spatial gradient of attention was unchanged. There was, however, evidence of an effect on the spatial gradient of attention in individual patients. In the auditory dual task, no improvement was apparent in either overall performance or the spatial gradient of attention, which was maintained across all sessions.

### *Spatial gradient of attention for visual and auditory stimuli*

Patients in the present study demonstrated a graded performance in their detection of peripheral events on both the visual and auditory versions of the dual task. This is consistent with previous studies that have found impaired awareness of contralesional auditory stimuli in neglect patients, in the absence of asymmetric hearing loss (see Pavani et al., 2004). In the present sample, deficits in the two modalities were significantly correlated. Prior studies have reported associations between auditory and visual attention deficits (see Pavani et al, 2004). The overall severity of the attention bias differed across the two modalities, however, in that the observed gradient was steeper for the visual dual task than the auditory dual task. This could reflect differences in the level of difficulty of the target detection tasks and/or differences in the severity of visual and auditory spatial attention biases in the neglect syndrome. Nevertheless, it is important to note that at a group level, performance on the auditory dual task was impaired in our patient sample. At baseline, patients demonstrated a significant spatial bias in their detection of auditory targets relative to the controls, and patients' performance for contralesional stimuli was worse than their performance for ipsilesional stimuli.

*Effect of prism adaptation on cancellation and line-bisection tasks*

All patients in our sample demonstrated significant negative aftereffects of prism adaptation as indexed by their estimates of SSA (Sarri et al., 2008). Thus, following adaptation to right-shifting prism lenses, patients' proprioceptive judgment of a point straight ahead was shifted significantly to the left. We also found that prior to adaptation, patients showed poorer detection of contralesional than ipsilesional items on a cancellation task. After adaptation, however, patients improved in their detection of contralesional items, and the observed spatial asymmetry in performance was abolished. This is consistent with several previous reports (e.g., Rossetti et al, 1998; Frassinetti et al, 2002; Serino et al, 2009; Nys et al, 2008; Rode et al., 2006) and indicates that the aftereffects of adaptation generalised to neglect behaviour in our patient sample. Neglect symptoms on the line bisection task, however, did not change significantly following prism adaptation, although a trend suggested reduced rightward bias after adaptation.

*Effects of prism adaptation on the spatial gradient of attention*

Although changes in patients' SSA and in their pen-and-paper task performance indicate that our prism adaptation procedure was effective, the majority of patients in the present sample did not display a change in their spatial gradient of attention, for either visual or auditory stimuli, following prism adaptation. In the visual task, there was an overall improvement in target detection efficiency, but the ipsilesional bias in attention was maintained across sessions. This suggests that the prism adaptation procedure influenced the exploratory behaviour of patients, but in the majority of cases did not change the attentional bias evident on the visual dual task. Of note are two patients for whom a significant change in the attentional bias *was* evident. One of these patients showed a significant amelioration of his ipsilesional attentional bias following prism adaptation. A possible mechanism by which this amelioration is achieved is suggested by the pattern of performance of the second patient (Patient 5). This patient had a circumscribed lesion involving the anterior inferior parietal lobe (supramarginal gyrus) and little bias at baseline, but following adaptation demonstrated a strong proprioceptive aftereffect and a marked reversal of her attentional bias on the visual dual task. This trend was apparent following both sessions of adaptation. Although these are individual cases, the findings, suggest that in some patients, prism adaptation may 'rebalance' the attentional weighting of visual input such that ipsilesional items may become less salient and contralesional items more salient – thereby reducing or reversing the manifestation of left neglect

(e.g., Pisella et al., 2006). Indeed, a patient described by Rode, Rossetti and Boisson (1999) displayed a complete reversal of his ipsilesional bias on a mental imagery task following prism adaptation, such that he began neglecting ipsilesional locations and reporting only contralesional locations. Similarly, in another case report, a patient with severe neglect and ipsilesional perseveration on cancellation tasks demonstrated not only reduced neglect following prism adaptation, but a contralesional shift in her perseverative responses (Nys, Seurinck, & Dijkerman, 2008). Thus, for most patients, prisms may influence exploratory behaviour and thereby reduce neglect on some measures, without significantly altering the spatial bias in attention that affects patients' reflexive orienting to peripheral stimuli. However, individual cases can show marked changes in their spatial bias in reflexive orienting. This may depend on a variety of factors such as lesion location, degree of bias at baseline, or the strength of adaptation aftereffects. Such individual factors may help explain the mixed evidence in the literature regarding prism effects on measures of exogenous attention (Nijboer et al, 2007; Streimer & Danckert, 2007) and other attention tasks requiring minimal exploratory movements (e.g., Berberovic et al, 2004; Morris et al, 2004; Saevarsson et al, 2009).

*Effect of prism adaptation on auditory attention bias*

We found no evidence for an effect of prism adaptation on the auditory spatial attention bias in neglect patients. Following adaptation, there was no change in patients' target detection efficiency and no change in the spatial gradient of performance. There were also no individual cases that suggested a response to prism adaptation. Although the spatial bias on the auditory dual task was less pronounced than that observed for the visual task, the lack of a prism effect is unlikely to reflect a ceiling effect, because a significant spatial gradient was apparent even after the prism sessions. Thus the present findings do not suggest that visuo-motor adaptation to prisms influences spatial biases in auditory awareness. This result differs from previous case reports of a prism-induced increase in detecting stimuli presented to the contralesional ear on a dichotic extinction task (Rode et al., 2003). Unlike dichotic listening conditions, the auditory stimuli in our task were presented binaurally with sound sources simulated within a virtual auditory space. Thus patients' deficits on the task can be attributed to spatial or attentional disturbances, particularly in the context of similar biases on an analogous visual task.

The auditory dual task employed here assessed exogenous orienting to sound stimuli in space. Other aspects of auditory spatial processing, however, may respond to prismatic adaptation. For example, sound localisation, even in the absence of pointing responses, can be impaired in spatial neglect (see Pavani et al, 2004). Although no studies have explored the effect of prism adaptation on localisation deficits in neglect, data from neurologically normal participants indicate that sound localisation can be dynamically influenced by exposure to prisms, as well as eccentric eye-gaze in the absence of prisms. The direction of the reported effects, however, implies that auditory localisation may respond only to the superficial effects of prism lenses on gaze and visual input, rather than to its adaptive aftereffects (Cui, Bachus, Knoth, O'Neill, & Paige, 2008). Cui et al.'s study reported that when healthy participants wear either right- or left- shifting prisms for a continuous period of four hours, their localisation of free-field noise stimuli (with the prisms removed) is shifted significantly *in the direction* of prismatic displacement. The authors argued that the shift in sound localisation, in this case, probably reflected prism-induced changes in eye deviation (Razavi, O'Neill, & Paige, 2007) and/or the spatial offset between auditory stimuli and visual stimuli while wearing the prisms, which in itself can induce a shift in auditory localisation (Recanzone, 1998). In our study, prism exposure occurred in the presence of ambient noise – which on occasion may have correlated with visually perceived events. If a similar effect on auditory space perception to that reported by Cui et al (2008) was induced by prism exposure in the patients in our study, then this is unlikely to ameliorate neglect symptoms – and may explain why we did not observe a reduction in patients' auditory spatial gradient.

Another possibility is that a more intense prism adaptation protocol may be necessary to induce stronger effects that generalize more fully to sensory modalities not directly influenced by the adaptation procedure. The present study examined only the immediate effects following adaptation, where the procedure was administered twice on separate occasions. Although the optimal 'dose' of prism adaptation required for a therapeutic effect remains unknown, several studies have employed a schedule of daily sessions for a period of 1-2 weeks and observed long-lasting effects on a variety of tasks (Frassinetti et al., 2002; Serino et al, 2009; although see Nys et al, 2008). Cumulative effects of adaptation may increase the chance of aftereffects generalizing to different cognitive domains.

*Conclusions*

In summary, we found that in a sample of 12 neglect patients who underwent prism adaptation, the majority of patients did not show any changes in their attentional bias despite demonstrating significant visuomotor aftereffects of adaptation and reduced neglect behaviour on traditional pen and paper tasks. Individual patients, however, did show changes in their visual spatial gradient of attention. No such effects were apparent on an analogous measure of patients' auditory spatial gradient. Thus, the present findings do not show generalization of prism effects on visual neglect to similar deficits in the auditory modality. The findings highlight the need for further research focussed on the role of individual factors such as lesion site and symptom severity on responsiveness to prism adaptation – as well as optimal adaptation protocols for producing therapeutic effects.

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Table 1

Clinical details of participants in patient and control group

| Participant | Sex | Age | Hemianopia | Time post-stroke (months) | Mean Hearing Thresholds* (dB) | |
|---|---|---|---|---|---|---|
| | | | | | Left | Right |
| Patient 1 | F | 58 | No | 2 | 37 | 29 |
| Patient 2 | M | 78 | No | 1 | 53 | 50 |
| Patient 3 | F | 85 | No | 2 | 41 | 46 |
| Patient 4 | F | 48 | No | 4 | 36 | 17 |
| Patient 5 | F | 74 | No | 5 | 49 | 46 |
| Patient 6 | F | 82 | No | 3 | 55 | 73 |
| Patient 7 | M | 74 | No | 4 | 54 | 56 |
| Patient 8 | M | 79 | No | 1 | 48 | 42 |
| Patient 9 | F | 60 | Quadrant. | 15 | 17 | 22 |
| Patient 10 | M | 63 | No | 3 | 35 | 34 |
| Patient 11 | F | 40 | No | 4 | 23 | 28 |
| Patient 12 | F | 80 | No | 2 | 55 | 46 |
| | | | | | | |
| Control 1 | M | 84 | - | - | 43 | 32 |
| Control 2 | F | 59 | - | - | 11 | 16 |
| Control 3 | M | 71 | - | - | 30 | 32 |
| Control 4 | F | 72 | - | - | 39 | 35 |
| Control 5 | M | 66 | - | - | 40 | 45 |
| Control 6 | M | 71 | - | - | 32 | 27 |
| Control 7 | F | 63 | - | - | 31 | 48 |
| Control 8 | M | 63 | - | - | 26 | 25 |

* Mean threshold for each ear over the frequency range 0.5-8Hz. Difference between mean left and right ear thresholds <20dB for inclusion.

Figure Captions

Figure 1. Lesion maps for nine of the 12 patients, manually mapped using MRIcro. Scans were unavailable for Patients 2, 3 and 8.

Figure 2. A) Upper panel shows the screen display for the visual task. Patients maintained fixation on the central white cross. Peripheral targets could appear in one of the four placeholders. Each placeholder was 12° (radius) from the fixation cross (Horizontal distance: extreme=12°, proximal=6°). Lower panel is a schematic indicating the virtual location of peripheral targets in the auditory task. B) Time course of displays for a single trial of the visual dual task (left) and auditory dual task (right). Patient monitored the central stream for the appearance of 0, 1 or 2 central targets (Visual: green X; Auditory: FM tone). At the same time, they made a speeded button press response to a peripheral target (Visual: red box; Auditory: white noise burst symbolised here as red loudspeaker).

Figure 3. A) Baseline performance of patients on the cancellation task, for left and right targets over the two baseline sessions. Grey bars represent Task A, black bars Task B. B) Upper panel shows the mean target detection efficiency for controls (dotted line) and patients (blocked line) as a function of target location for the Visual task, and Lower panel for the Auditory task. C) Mean estimate of subjective straight ahead before and after adaptation for each of the two prism adaptation sessions. Relative to pre-adaptation SSA estimates, the post-adaptation estimates are shifted to the left of true centre (0). Error bars represent 1 standard error of the mean.

Figure 4. A) Performance on the cancellation task (Task B only) as a function of session (baseline, post-adaptation 1 and post-adaptation 2). Grey bars represent target detection on the left, black bars target detection on the right. B) Upper panel shows mean target detection efficiency as a function of target location for each of the three sessions in the Visual dual task, and Lower panel shows the same for the Auditory dual task. C) Mean line bisection bias across the three sessions. A positive bias indicates a rightward bias (expressed as a percentage of line length). Error bars represent 1 standard error of the mean.

Figure 5. A and B) Individual data for Patients 2 and 5, respectively: Left panel for each shows target detection efficiency as a function of target location and testing session. Right panel shows mean estimate of SSA before and after adaptation for the two adaptation sessions. Middle panel in B shows Patient 5's rendered structural MRI brain scan, and axial slice, with arrows indicating a discrete lesion involving right supramarginal gyrus; no scan was available for Patient 2.