

**A single blinded randomized controlled pilot trial of prism adaptation for improving self care
in stroke patients with neglect**

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ABSTRACT

Prism Adaptation has been shown to alleviate the symptoms of unilateral spatial neglect following stroke in single case and small group studies. The purposes of this single blinded pilot randomized controlled trial were to determine the feasibility of delivering prism adaptation treatment in a clinically valid sample and to assess its impact on self care. Thirty seven right hemisphere stroke patients with unilateral spatial neglect were randomised into either prism adaptation (using 10 dioptre, 6 degree prisms) or sham treatment (using plain glasses) groups. Treatment was delivered each weekday for two weeks. Pointing accuracy, without vision of the finger, was recorded each day before treatment. Outcome was measured, by blinded assessors, four days and eight weeks after the end of treatment using the Catherine Bergego Scale (CBS) and the conventional neuropsychological tests from Behavioural Inattention Test (BIT). Thirty four patients received treatment: 16 with prisms, 18 sham. Mean compliance was 99% and 97% respectively. Over the treatment days only the prism treated group showed increased leftward bias in open loop pointing to targets on a touch screen. However, despite the group level changes in pointing behaviour no overall effect of the treatment on self care or BIT were found.

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INTRODUCTION

Unilateral neglect is a common consequence of stroke that greatly hinders rehabilitation (Paolucci, Antonucci, Grasso, & Pizzamiglio, 2001). The brain's system for orienting to the contralesional side of space is affected and this results in an impairment of the person's ability to take notice of, or make movements towards one half of their environment (Heilman, Watson, & Valenstein, 2003). Neglect behaviour can be evident in dissociable domains of space: personal, peripersonal or reaching space, and far space (Guariglia & Antonucci 1992; Halligan & Marshall, 1991). As a result the patient with neglect may have difficulty in carrying out everyday self care tasks in these domains, for example getting dressed, eating a meal or finding things in a room (Katz, Hartman-Maeir, Ring, & Soroker 1999).

In clinical practice unilateral neglect is typically treated by encouraging the patient to scan and search the environment or body on the affected side. This is often done in the context of practising personal care or other activities of daily living, but also may be practiced in search training tasks that are specifically devised to concentrate on spatial attention. Cueing and scanning training seems to help some patients to improve performance in neuropsychological tests of spatial attention (Bowen & Lincoln, 2007), but some patients continue to have difficulty in self-care. To be effective these 'top down' treatment methods depend on the patient becoming aware of their neglect. However neglect is often associated with poor insight and arousal (Azouvi, Marchal, Samuel, Morin, Renard, Louise-Dreyfus, et al 1996; Robertson, Manly, Beschin, Daini, Haeske-Dewick, Hömberg, et al. 1997] and even the most cognizant and alert patient may have difficulty in maintaining compensatory search strategies throughout the day.

Treatment methods that do not depend on such 'top-down' processes may be more effective. In recent years prism adaptation has been shown to help stroke patients attend to the affected side of space (Rossetti, Rode, Pisella, Farné, Li, Boisson, & Perenin, 1998; Farne, Rossetti, Toniolo, & Làdavas, 2002; McIntosh, Rossetti, & Milner, 2002; Pisella, Rode, Farne, Boisson, & Rossetti,

2002; Frassinetti, Angeli, Meneghello, Avanzi, & Làdavas, 2002; Maravita, McNeil, Malhtra, Greenwood, Husain, & Driver, 2003; Redding & Wallace, 2006; Serino, Angeli, Frassinetti, & Làdavas, 2006; Humphreys, Watelet, & Riddoch, 2006). By wearing base-left wedge prisms in spectacles visual space is systematically perturbed to the right. When the wearer is asked to point to a target, a conflict between proprioception and vision results and he or she will typically mispoint to the right. The participant quickly adapts to the prisms over subsequent trials and pointing becomes accurate. Adaptation to the prisms is evident when the glasses are removed and the participant is asked to point without visual feedback. The pointing movement then terminates to the left of the target. Prism adaptation has been found to have greater amplitude in patients with spatial neglect, than in normal subjects (Rossetti, et al. 1998). However more importantly after prism adaptation patients with neglect have shown long lasting higher order effects with improved performance on neuropsychological tests of spatial attention (Rossetti, et al. 1998; Farne, et al.2002; McIntosh, et al. 2002; Pisella, et al. 2002; Frassinetti, et al. 2002; Maravita, et al. 2003; Redding & Wallace, 2006; Serino, et al. 2006; Humphreys, et al., 2006). It is thought that the treatment triggers a realignment of the egocentric coordinate system that is responsible for the localisation of the body in space and of object position in relation to the body (Redding & Wallace, 2006).

So far evaluation of prism adaptation treatment has been based on single case design (Farne, et al.2002; McIntosh, et al. 2002; Pisella, et al. 2002; Maravita, et al. 2003; Humphreys, et al., 2006) or small group studies (Rossetti, et al. 1998; Frassinetti, et al. 2002; Serino, et al. 2006), in which most of the outcome measures have been performance on neuropsychological tests of neglect. The effect of prism adaptation on everyday self-care tasks has not been investigated. One of the recommendations of a recent Cochrane review was that trials of psychological interventions for unilateral neglect should address effects of treatment on self care (Bowen & Lincoln, 2007). In this study we assessed the feasibility and potential efficacy of prism adaptation for improving independence in daily living in a sample of stroke patients with neglect who were receiving

rehabilitation. This was an assessor blinded pilot randomised controlled trial, a phase two study, according to the MRC framework for trials of complex interventions (2000).

METHODS

Participants

All procedures were approved by the local NHS research ethics committee.

Recruitment to the trial was carried out from November 2004 to August 2006 in two hospitals in Bristol, UK. Stroke patients admitted consecutively over the period were considered for inclusion. The eligibility criteria were: a right hemisphere stroke occurring at least 20 days before entry to the study, self-care problems due to neglect identified by an Occupational Therapist, the ability to sit and point with the unaffected hand, ability to understand and follow instructions and medical fitness to participate. Our cut off time of 20 days post stroke was based on the recovery profile published by Stone, Patel, Greenwood, & Halligan (1992) showing that most recovery of neglect occurs in the first three weeks and is markedly slower after that.

The presence of neglect was confirmed by performance on the star cancellation task and/or line bisection test from the Behavioural Inattention Test (BIT) battery (Wilson, Cockburn, & Halligan 1987). Patients were included even if the stroke was not the first reported, however the presence of neglect had to be associated only with the recent event. This was confirmed by reference to medical notes.

Patients were asked to give informed consent. If there was doubt that the patient may not fully understand, or remember the information given, then a family member was asked to consider giving assent.

[Figure 1 about here]

Intervention

The treatment procedure involved repeated pointing movements to targets, using the right ‘unaffected’ hand, while wearing the prism glasses and was similar to that reported by Frassinetti et al. (2002). Ten dioptre prisms that shifted the field of view 6° to the right were held in optician’s trial frames. The frames were fitted with felt blinkers to prevent interference from peripheral vision.

The participant, positioned directly in front of a box containing a touch-screen (figure 1), was required to use the index finger to touch a bold vertical line (width 15mm), which appeared either directly in the centre or 100 mm to the left or right of centre on the screen. Target lines were presented in an unpredictable sequence with each block comprising ten central, ten right and ten left of centre targets, in three blocks of 30 trials. The pointing arm was screened from view with the starting position for each movement marked by a Velcro disc, under the screen. The participant was able to see only the terminal part of each pointing movement to allow visuomotor adaptation.

Before wearing the glasses, participants were given some pointing practice, with vision of the terminal part of the movement, to ensure they understood the task. The purpose-written software allowed the duration of target presentation to be set to suit the performance of individual participants and the onset of each trial was controlled by the Occupational Therapist who delivered the treatment. The therapist gave prompts to look left in cases when participants were clearly not registering targets.

For each trial, the software recorded the coordinates of the target and touch response in pixels and reaction time in milliseconds. To enable a later check for adaptation to the prisms, data was also collected for 30 trials, without vision of the end point accuracy (i.e. open loop pointing), before the 90 treatment trials.

Participants in the control group received the same pointing procedure but instead of prisms they wore flat plain glass in the trial frames.

The pointing procedure was delivered once a day, each working day, for two weeks alongside

the routine rehabilitation programme.

Outcomes

The primary endpoint was four days after finishing the course of treatment. Measures were also taken at a follow-up assessment eight weeks later to see if any differences between groups were long lasting.

The primary outcome measure was the CBS (Azouvi, et al. 1996; Azouvi, Olivier, Montety, Samuel, Louis-Dreyfus, & Tesio, 2003). Neglect in ten self-care behaviours are rated (table 1) to give a total score out of 30 points. The Occupational Therapists decided a decrease of four points should be regarded the minimal clinically significant change.

[Table 1 about here]

The protocol for the CBS was clarified so that all items could be completed in a single morning. The assessment required two staff; an observer to rate performance and an assistant to provide help to the participant in the self care tasks if needed. Whenever possible outcome assessments were carried out by the same person, however to check agreement between observers ten CBS assessments were carried out in the presence of two observers. There was zero mean difference in total scores between raters, with 95% limits of agreement: ± 2 points.

The conventional pencil and paper tests from the BIT (Wilson, et al. 1987) were used as an impairment level assessment.

Outcome assessments were carried out with assessors blind to group allocation.

Other Assessments

In addition to the assessments of neglect, the participant's were assessed for the presence and severity of motor and sensory deficits and general independence in activities of daily living. Strength of the limbs on the contralesional side was assessed using the Motricity index (Demeurisse, Demol, & Roboye, 1980). An adapted version of the Nottingham Sensory Assessment (Lincoln, Jackson & Adams, 1998) was employed to test for appreciation and localisation to light

touch. Areas of the upper limb, face and upper body on the contralesional side were touched three times using a piece of cotton wool. Visual field loss was crudely assessed using a confrontation method. Participants were asked to fixate on the examiner's nose. The examiner held a pen and moved it from directly in front of the participant in an arc around their head, first to the ipsilesional side and then to the contralesional side. The participant was asked to report when the pen disappeared from their peripheral vision on each side. The participant's Occupational Therapist completed the Barthel assessment of activities of daily living (Collin, Wade, Davies & Horne 1988).

Randomisation and allocation to group

Randomisation and allocation to groups took place after completion of an initial assessment. A minimisation method (Pocock & Simon, 1975) using a 4:1 element of chance was implemented and automated using Microsoft Excel for pseudo-random allocation to groups. This method made it probable that the groups would be balanced for age, severity of neglect behaviour (based on the CBS) and days post stroke. It also increased the likelihood that the number of participants in each group would be balanced

A secretary who was located outside of the stroke services administered the randomisation procedure. The participant's group was revealed, via telephone, to the Occupational Therapist who delivered the intervention.

Data Analysis

Pre-treatment pointing data

The horizontal position of the touch responses, in pixels, was subtracted from the target position for the open loop pointing pre-treatment trials for each day. Positive errors represented a response to the left of the true target position; negative errors to the right. Median errors in pointing for each target were calculated and averaged to give an average daily error. The mean (SD) daily error for each group was plotted as a function of treatment days. Rate of change in pointing bias represented

by slope for week one and week two were calculated and the differences in slopes between groups compared.

Neglect assessment scores

Repeated measures analysis of variance with two factors (assessment session and group) were performed for the CBS and BIT scores at both the four days and eight weeks outcome points. As the CBS is a rating scale and a few participants were close to ceiling a second analysis was carried out with the CBS scores transformed to logits (Bond & Fox, 2007; Svensson, 2001). Throughout all statistical analysis significance was set to $p < 0.05$.

RESULTS

Participants flow through the study

Figure 2 shows the plan of the study and flow of patients. A total of 641 stroke patients were admitted to the rehabilitation wards during the period of the trial. 73 patients were referred by Occupational Therapists to be considered as potential participants. Of these, 29 did not fit the criteria and seven declined to participate. Thirty-seven were recruited but one of these failed to complete the baseline assessment leaving 36 who were assigned to group. Two were lost due to illness before they had completed the intervention. The remaining 34 participants were assessed at the first outcome four days after the end of treatment and 28 were available for follow up assessments eight weeks later.

[Figure 2 about here]

Baseline demographics and clinical characteristics of each group

As a result of the minimisation method the groups were well balanced for severity of neglect, age and time since stroke (table 2). However there was a large variation in severity of neglect determined by the CBS and BIT and some participants were close to ceiling when they entered the trial. In addition although the mean number of days post stroke is closely matched between groups

the standard deviations show more variation in the control group. This was largely due to one control group participant who was close to six months post stroke on entry to the study. The groups were balanced in terms of motor and sensory impairments and general independence in activities of daily living.

[Table 2 about here]

Compliance

The treatment was successfully delivered by the Occupational Therapist to patients in hospital and in six cases at home. Most found the daily treatment acceptable and some reported enjoying it. Compliance was 99% for the experimental and 97% control group; the missed sessions (2/160 for the experimental group and 5/180 control) were due to illness.

Protocol violations and adverse events

Six assessments were carried out 'unblinded'. There were no adverse events.

Efficacy of treatment on self-care and spatial inattention

The median and interquartile ranges of neglect behaviour scores at each time point are shown in figure 3 and mean (SD) changes scores within groups and differences between groups are listed in table 3. Both groups significantly improved their performances on both the CBS and the BIT (two factor repeated measures analysis of variance: assessment session CBS $F(1,32) = 49.6, p < 0.001$; BIT $F(1,32) = 17.0, p < 0.001$) but there was no difference between groups. Mean (SD) change scores for the CBS were similar for both groups: experimental group $-3.5 (3.1)$, control group $-3.3 (2.5)$. Mean (SD) change scores for BIT assessments, were $14.8 (18.7)$ and $9.7 (15.9)$ respectively. The results of the analysis of variance using logits instead of raw CBS score were similar with no significant difference between groups. In addition the results at the follow up assessment ($n=28$) showed no difference between groups in CBS or BIT test performances.

[Figure 3 about here]

[Table 3 about here]

Prism adaptation

Open loop pointing errors before treatment each day revealed a small but robust carry over effect of the prism adaptation (figure 4). The experimental group showed leftward pointing bias of ~30 pixels over the period of the intervention. With pointing being at arm's length this is estimated to be equivalent to 1°. The greatest change in bias appeared after two days of treatment with more gradual change occurring after that. This group difference only partially reduced over the weekend, when there was no treatment delivered, showing that the effect was not short term. The control group maintained a small and consistent rightward pointing bias throughout (mean error -8 pixels). Rate of change in pointing bias was significantly different between groups in week one, (slope: control group 1.2 pixels/day, experimental group 8.3 pixels/day; $t = -2.5$, $p=0.02$, 95% CI -17.3 to -1.8), but not in the second week (slope: control group 1.5 pixels/day, experimental group 6.7 pixels/day; $t = -1.8$, $p=0.09$, 95% CI -11.0 to 0.8).

[Figure 4 about here]

DISCUSSION

The study demonstrates that the prism adaptation treatment is deliverable in a stroke rehabilitation service. The daily treatment sessions were found acceptable by the patients. Unlike previous studies, the current study was a substantial randomised controlled investigation of an ecologically valid sample of patients who were participating in rehabilitation after a recent stroke. We have compared well-matched groups who received ten prism adaptation or sham treatments in addition to the usual therapy for neglect, measured the efficacy of the intervention on neglect specific daily living behaviours and looked for clinically important lasting effects. Although the series of prism adaptation treatments delivered over two weeks clearly had a cumulative influence on pointing bias there was no effect on everyday neglect behaviour or performance on the conventional pencil and paper tests from the BIT at either four days or eight weeks after the end of

treatment.

Previous small group studies have shown statistically significant long lasting effects of prism adaptation on left sided spatial neglect measured by the BIT (Frassinetti, et al 2002; Serino, et al. 2006). However these studies have used different control interventions and less rigorous trial methodology: Rather than a sham prism adaptation control intervention these studies delivered unspecified cognitive and motor treatments. The control group for the study of Frassinetti et al (2002) were recruited from a different hospital from the experimental group. In addition only those patients who showed improvement in the first two days were followed up.

Aside from difference in the control intervention there are other possible explanations for the lack of any differences between groups in self care behaviour or impairment level test performance in this study. First outcome was measured four days after the end of treatment and so it may be that any effects were short in duration and may have worn off by the time of the assessment. The pointing bias data showed a partial lapse in adaptation over the weekends when treatment was not delivered. A time series study of a single patient with chronic neglect treated with prism adaptation has demonstrated some incomplete decay of spatial attention performance with time after treatment (Humphreys, et al. 2006) suggesting that 'top up' sessions are needed to maintain benefit.

Alternatively it could be that the prisms used in this study did not shift the field of view sufficiently to lead to change in neglect behaviours. In this study ten dioptre prisms that shifted the field of view 6° to the right were used. Previous studies have used 10° and 15° prisms (Redding & Wallace 2006). Although the majority of these studies reported improvements on neuropsychological tests of spatial attention due to the intervention there has been one study of ten patients in which no benefit was found (Rousseaux, Bernati, Saj, & Kozlowski, 2006). There have not been any studies reporting on the effects of different strengths of prisms in patients with neglect, but recovery of attention well over the actual angle of the prisms has been observed following treatment suggesting that the prism adaptation provides a trigger to attention rather than just a

straight recalibration of attended space (Frassinetti, et al. 2002). The day to day effects of prism adaptation in this study were assessed by the error in visual open-loop pointing, however others have used subjective straight ahead pointing and so it is difficult to compare the degree of adaptation across all studies. Frassinetti et al (2002) using open loop pointing found the after effects decayed from 2.7° immediately after exposure to prisms to 1.3° twelve hours later, while improvements in neglect test scores were maintained. Much larger aftereffects have been found for straight ahead pointing than visual open loop pointing to a target in neglect patients (Sarri, Greenwood, Kalra, Papps, Husain, & Driver, 2007). However in a study of unimpaired participants following prism adaptation, straight-ahead pointing measures of after-effect did not correlate with induced visual or haptic spatial effects of prism adaptation (Girardi, McIntosh, Michel, Vallar, & Rossetti, 2004). The lack of a clear relationship between after-effect and improvement in spatial attention is an important problem to resolve.

Another procedural factor that is yet to be determined is the optimal amount of the pointing movement that is seen for prism adaptation. The method used in this study allowed only terminal error to be seen. Thus participants had to use knowledge of pointing accuracy, a feed-forward mechanism, to adapt their subsequent pointing. Others have allowed more of the movement to be viewed so that the adaptation occurs through the use of on-line feedback. This latter method is thought to produce realignment that is processed through the head/hand proprioceptive system while the former feed-forward recalibration is thought to be secured largely or entirely in the visual eye-head sensory-motor system (Redding, Rossetti, & Wallace, 2005) and therefore the aftereffects may reflect visual system realignment. Both methods have been reported to yield lasting improvements in neglect behavior (Pisella, et al. 2002; Frassinetti, et al. 2002; Serino, et al. 2006; Humphreys, et al. 2006).

Further, systematic investigations are needed to determine both the optimum prism strength, frequency of treatment sessions and adaptation method. The previous case reports in the literature

have indicated that prism adaptation can improve spatial attention in some patients. Trying to fit one treatment to everybody may be unrealistic. Recent studies are beginning to differentiate patients who are likely to benefit on the basis of lesion site (Sarri, et al 2007; Serino, Bonifazi, Pierfederici, & Làdavas, 2007). In addition, to understand the likely benefits of treatment, further study of the mechanism of any effects of prism adaptation is needed. Some studies have indicated that prism adaptation may change eye movement behaviour but may not lead to higher level processing of sensory information such as is needed for the interpretation of facial expressions (Humphreys, et al 2006; Ferber, Danckert, Joanisse, Goltz, & Goodale 2003). Also recently a study of two cases found prism adaptation improved for voluntary orienting only and not automatic orienting (Nijboer, McIntosh, Nys, Dijkerman, & Milner, 2008). If this proves to be a generalised effect then prism adaptation may not be superior to top down treatments that aim to promote compensatory behaviour in neglect patients. Future investigations of both the effects and mechanisms of treatment on different subgroups of neglect patients is needed before deciding whether or not prism adaptation is a valuable intervention for use in clinical practice.

Since this is the first time the CBS has been used as primary outcome measure in a clinical trial, it is worth noting some lessons learned. The protocol used in this study proved to be feasible. It was sensitive to change over the period of study. The sample we tested, although representative of the patients treated in clinical practice, were very heterogeneous; there was a large variation within groups in severity of neglect. Clinical effects need to be large to justify time intensive treatments. The standard deviation of CBS scores in our sample was four points. It is estimated that a total sample of 32 patients would be needed to observe a large (1SD) effect of treatment with 80% power and alpha level set at 0.05. With a mean change score of 3.5 points on the CBS within the groups a minimum baseline severity score of seven would be needed to demonstrate the agreed clinically important difference of four points. Five of the 34 participants in this study had CBS baseline scores of seven or less thus reducing the power of this exploratory study to detect a difference between

groups. In future trials using the CBS eligibility criteria should include a minimum baseline score to avoid such ceiling effects and to allow sufficient margin to detect differences in recovery between interventions. This exploratory trial has been important for determining the size of treatment effects important for establishing real clinical benefit.

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FIGURE LEGENDS

Figure 1

Set up for the intervention

Figure 2

Flow of participants through the study

Figure 3

Box plots showing median (black dot) inter-quartile range (box) and range (whiskers).

Figure 4

Open loop pointing error before treatment each day. Mean pointing error in pixels on the touchscreen. Positive errors represent a response to the left of the true target position; negative errors to the right.