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Research report

Repetitive long-term prism adaptation permanently improves the detection of contralesional visual stimuli in a patient with chronic neglect

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ARTICLE INFO

Article history:
Received 25 May 2009
Reviewed 4 August 2009
Revised 1 October 2009
Accepted 28 June 2010
Action editor Sergio Della Sala
Published online 11 July 2010

Keywords:
Neglect
Visual fields
Perimetry
Prism adaptation
Rehabilitation

ABSTRACT

The aim of the current study was to investigate long-term effects in spatial awareness after daily exposure to prism adaptation during three months in a patient with hemispatial neglect. Results showed improvement in the detection of stimuli in the contralesional visual field, as measured with perimetry, in the contralesional visual field up to 24 months after ending prism adaptation. These perimetrical results suggest that compensatory eye movements are an unlikely candidate for an underlying mechanism.

1. Introduction

Unilateral spatial neglect occurs frequently following a brain lesion in especially the right hemisphere (25–30% of all stroke patients, Appleros et al., 2002), resulting in a failure to report or respond to stimulation in contralesional hemispace. These symptoms are not due to primary sensory or motor deficits (Heilman and Valenstein, 1979). For a high proportion of patients, the disorder is chronic (Samuelsson et al., 1997); only 43% of neglect patients will spontaneously improve in the acute phase and only 9% will recover completely (Farne et al., 2004). Functional outcome of stroke patients suffering from neglect is worse than that of stroke patients without neglect (Nys et al., 2005); recovery patterns are slower and more attenuated (Katz et al., 1999). As a result, many studies aim at alleviating the symptoms of neglect with different treatments such as visual scanning training, limb activation, mental imagery training, sensory stimulation, and prism adaptation (Luaute et al., 2006).

Prism adaptation was first described by Rossetti et al (1998) and has been widely used since; exposure to prisms produces

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doi:10.1016/j.cortex.2010.07.003

a lateral shift of the visual field so that targets appear displaced. Adaptation to such an optical shift critically requires a set of successive visuo-motor pointing movements. Rossetti et al (1998) demonstrated a significant reduction in spatial neglect following a brief period of prism adaptation with rightward prisms. Effects of prism adaptation have been reported across clinical measures of neglect, but also in more daily situations, such as wheelchair navigation (Rossetti et al., 1999) and postural control (Tilikete et al., 2001). The beneficial effects of prism adaptation have been reported to last 2 h (Rossetti et al., 1998) up to one week (Dijkerman et al., 2004; Pisella et al., 2002) after a single adaptation session, and even up to 6 weeks following repetitive prism adaptation (Shiraishi et al., 2008; McIntosh et al., 2002). Additionally, long-term prism training has been reported to show long-lasting beneficial effects, from weeks (Frassinetti et al., 2002; Serino et al., 2006; Serino et al., 2009; Serino et al., 2007) up to a year (Humphreys et al., 2006) after ending adaptation.

Despite ample evidence that prism adaptation can successfully ameliorate the signs of neglect, the underlying mechanisms by which low order visuo-motor adaptation may produce a recovery in high-level visuo-spatial representations are largely unknown. It has been suggested that prism adaptation produces a resetting of ocular scanning behaviour, which facilitates the exploration of the neglect visual field (Angeli et al., 2004; Serino et al., 2006).

The current study will focus on the effects of an intensive programme of exposure (i.e., daily exposure during three months) and whether permanent changes in spatial awareness can be objectified using perimetry. Perimetry is a commonly used, well-controlled method to carefully map (primary visual and/or attentional) deficits in the visual field. Targets with differential light intensities need to be detected on a defined background, *while keeping the gaze fixed* on a central fixation point. The fixed gaze allows for careful mapping of visuo-spatial defects within the visual fields. An improvement in detecting targets in the neglected field in the absence of eye movements would reveal that the beneficial effects of prism adaptation are not the result of compensatory strategies, such as scanning behaviour, but of primary improvement/enlargement of visuo-spatial awareness. Using perimetry to measure improvements of signs of neglect after prism adaptation will therefore provide insight in the underlying mechanisms of recovery.

A second advantage of perimetry is that it is relatively resistant to practise or learning effects. Behavioural measures are more susceptible to practise or learning effects after multiple experimental sessions. This makes perimetry a better and more precise measure to characterise the location and amount of alleviation of *attentional* deficits after prism adaptation than the commonly used neuropsychological tests. Behavioural measures will be included as control measures to substantiate commonly found beneficial effects of prism adaptation on widely used behavioural tests.

2. Method

2.1. Case report

LZ is a 66-year old right-handed female, who suffered an acute subarachnoid haemorrhage (SAH) in September 2000, 70 months before the start of the present testing. The ruptured aneurysm was successfully clipped, but one day after surgery, she developed severe vasospasms, resulting in a large ischemic infarction of the right hemisphere, involving the parietal and temporal lobes, with extensions into the frontal region (see Fig. 1). The infarct of the right hemisphere also affects the white matter of the temporo-parietal junction. Although a hemianopia may be due to damage of the optical radiations, the calcarine cortex is visible on the scan and is not involved in the lesion, making additional hemianopia less likely.[1] Early neuropsychological testing revealed perceptual impairments (visual perception and construction) and severe left-sided visual neglect, but no memory or language deficits. Five years after the SAH, she suffered a subdural haematoma (SDH) over the left hemisphere, resulting in language problems. Evacuation of the SDH via a burr hole left LZ with no additional impairments (i.e., the language problems disappeared). By the time she was examined in our laboratory for the first time (July 2006), she showed above average language and memory functioning and moderate left-sided visual neglect (see Table 1).

2.2. Design

Effects of repetitive long-term prism adaptation were measured at 5 different moments in time: at the start of prism adaptation (T0), at 3 months immediately following the prism adaptation cycle (T1), and 3 (T2), 6 (T3), and 24 months after ending prism adaptation (T4) (6, 9 and 27 months after starting prism adaptation, respectively). Perimetry was performed at all sessions and behavioural measures were obtained at T0, T1, T2, and T4.[2] At each of these moments in time, behavioural measures were assessed five days in a row (1 and 2 days prior to T0/T1/T2/T4, at T0/T1/T2/T4, and 1 and 2 days after T0/T1/T2/T4), in order to control for attentional fluctuations.

2.3. Prism adaptation

The prism adaptation procedure was similar to that employed by Rossetti et al (1998), with the exception that it was repeated on a daily basis for 3 months. Prism adaptation was performed with a pair of goggles fitted with wide-field point-to-point prismatic lenses, inducing a rightward optical shift of 10°. Exposure consisted of 100 fast pointing movements per day for 3 months, made to visual targets presented 10° to the left or right of the body midline at a distance of approximately 65 cm, with 50 responses made to each in a random order. A board was held under the patient's chin to prevent viewing of the hand at its starting position, but allowing an unobstructed view of the targets and terminal errors. LZ was told to be as fast and accurate as possible. Following every prism exposure,

[1] A recent study provided additional evidence for a lack of hemianopia in LZ (Van der Stigchel and Nijboer, 2010). In an oculomotor distractor paradigm, LZ was able to accurately execute an eye movement to a contralesional target in the absence of distractors. On the contrary, hemianopic patients were not able to make accurate saccades to stimuli presented within a scotoma.

[2] No behavioural data could be obtained for the perimetrical session T3.

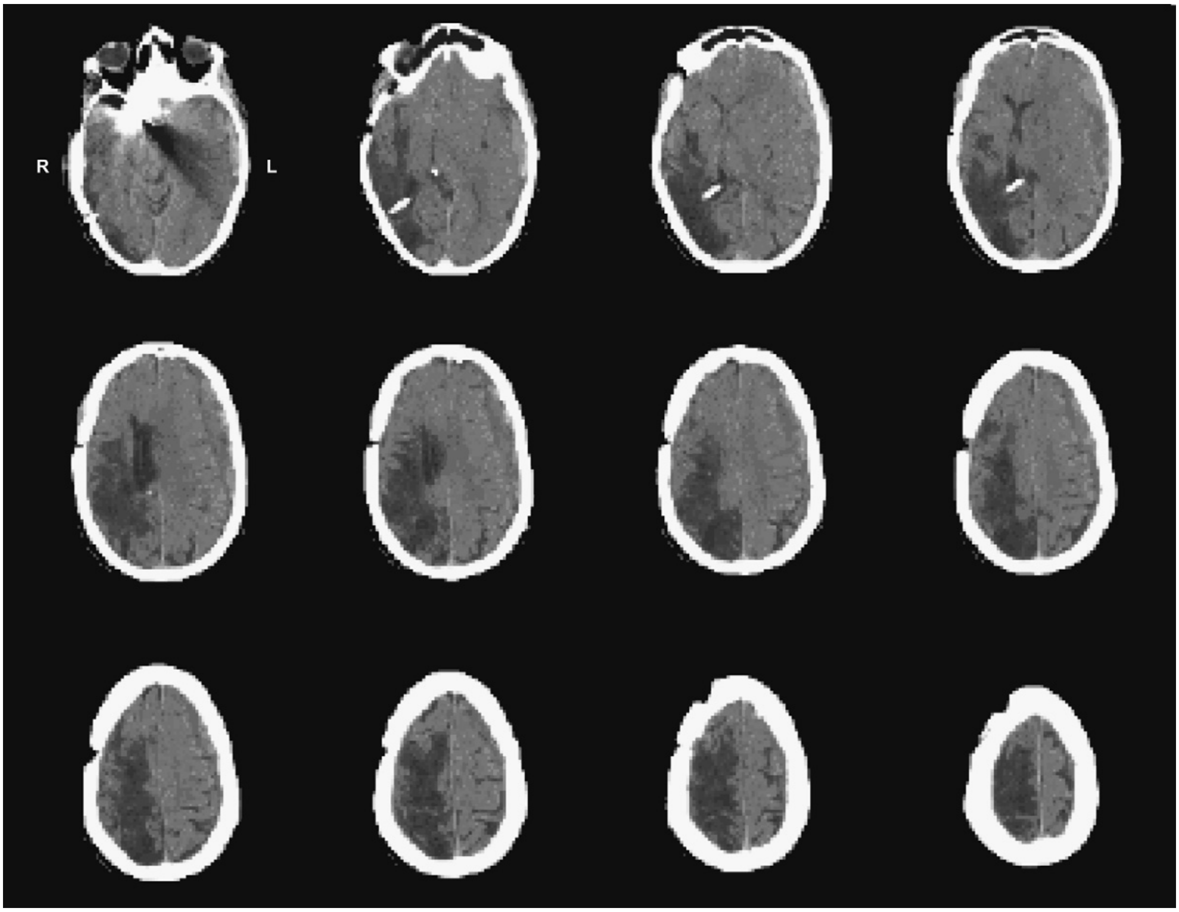

Fig. 1 – CT scan (2005) showing clip artefacts in the right frontal region, a ventricular peritoneal drain from the right lateral ventricle, a large cortical infarct in the right hemisphere, and a SDH in the left hemisphere.

the prismatic after-effect was tested; LZ was asked to point to one of the two targets with her eyes closed to prevent online adjustment of the pointing movement towards the target due to visual feedback. For a successful prism adaptation procedure, a leftward shift of 3 cm of the landing position was required (as measured by a ruler). If the shift was less than 3 cm, the prism adaptation procedure was continued.

2.4. *Behavioural measures*

The Behavioural Inattention Test (BIT: Wilson et al., 1987) is a standardised, objective instrument frequently used for measuring visual neglect. Two conventional subtests were chosen as behavioural measures in the current study: Line Bisection and Star Cancellation.

In the Line Bisection test, LZ was presented with a page containing 3 horizontal lines (8 inch each) spread in a staircase fashion across the page. LZ was asked to indicate the centre of each line. For each line, deviations from the actual centre were measured in mm.

In the Star Cancellation test, LZ was presented with a page containing 52 large stars, 13 randomly placed letters, 10 short words, and 56 small stars. LZ was asked to cross out only the small stars. Total number of omissions, number of perseverations, and total duration (sec) were recorded.

2.5. *Perimetry*

The visual fields of LZ were investigated using the Octopus 101 instrument's kinetic automated grid perimeter (SKP; Haag-Streit Inc., Bern, Switzerland). Perimetry for this study was performed 5 times [at the start of prism adaptation (T0), at 3 months immediately following the prism adaptation cycle (T1), and 3 (T2), 6 (T3) and 24 (T4) months after ending prism adaptation (6, 9 and 27 months after starting prism adaptation, respectively)]. The grid of the perimeter consisted of 59 locations within the central 30° visual field, with a background luminance of 10 cd/m^2 (31.5 asb). Stimulus characteristics were: 26′ in diameter, 100 ms in duration and a maximum luminance of 320 cd/m^2. Eye fixation was automatically controlled for with an infrared sensitive camera; if fixation was lost, no stimulus was presented. The visual fields of the left and right eyes were investigated sequentially; examinations always started with perimetry of the right eye. Mean examination times for the left and right eyes were 6.57 min (SD: .43) and 5.97 min (SD: .47), respectively. Per location, 29 stimuli were presented per examination. In total, 17.110 stimuli were presented (59 locations × 29 stimuli × 2 visual fields × 5 sessions). On catch trials, LZ responded 2/80 on positive trials (i.e., trials in which the stimulus was presented on the punctum caecum, hence never perceived with a proper

Table 1 – Performance of LZ on standard neuropsychological tests (70 months post-stroke).

Cognitive domain	Neuropsychological task	Performance	Percentile/ decile
Language	Boston naming test	162	34th Percentile[a]
Memory	Rey auditory verbal immediate recall	8/9/10/9/13	10th Decile
	Delayed recall	11/15	7th Decile
	Recognition	28/30	10th Decile
Attention[b] (BIT)	Line bisection	3/9	
	Star cancellation	47/54	
	Letter cancellation	35/40	
	Line cancellation	30/36	
	Representation drawing	2/3	
	Figure and shape copying	1/4	

a Based on Dutch norms as described by van Loon-Vervoorn and Stumpel (1994).
b Standard neuropsychological tests for neglect; BIT: Behavioural Inattention Test.

measurement) and 8/80 on negative trials (i.e., trials in which no stimulus was presented, and hence no response should be given), indicating that the measurements were reliable.

2.6. Data analysis

For the behavioural measures, a repeated-measures ANOVA was performed on the different measures. For the Line Bisection Task, the deviation from actual midpoint for the three individual lines was analyzed with line (top, middle and bottom) and session (T0, T1, T2, T4) as within subject variables. For the Star Cancellation Task, the number of misses, number of perseverations, and total duration were analyzed as separate measures with session (T0, T1, T2, T4) as within subject variable. Where significant effects and/or interactions were obtained, subsequent simple main effects analyses and trend analyses were performed.

For the perimetrical results, the raw data per eye were automatically compared to expected performance of age-matched standard observers, as calculated by the automated grid perimeter software. Data of both eyes were collapsed per visual field, as the main focus of the study was on visual field performance. The number of detected stimuli per location, split on visual field, was compared between the 5 perimetry sessions with an ANOVA with visual field (left, right) and session (T0, T1, T2, T3, T4) as within subject variables. Post-hoc tests were performed to indicate which sessions differed from one another.

3. Results and discussion

3.1. Behavioural measures: short term training effects

Behavioural measures in neuropsychological tests for neglect, such as the ones used in this study, can be susceptible to effects of training. One-way ANOVAs showed that for one of the measures used here (the top line in the Line Bisection Task) the time of measurement (i.e., 1 and 2 days prior to, at, or 1 and 2 days after perimetry) influenced performance significantly [Top Line: $F(4) = 4.850$, $p = .010$]. To compensate for this effect, in the following behavioural analyses we used a repeated-measure ANOVA, with time of measurement as repeated measure.

3.2. Behavioural measures: line bisection task

A significant main effect of line was found [$F(2,8) = 480.166$, $p < .001$], indicating that the deviation from the actual midpoint differed between the three lines. This is also apparent from Fig. 2. No significant main effect of session was found [$F(3,12) = 1.963$, $p = .173$], instead a significant interaction between line and session was obtained [$F(6,24) = 5.626$, $p = .001$]. Simple main effects analysis revealed a significant deviation effect for the bottom line only [$F(3,12) = 7.757$, $p = .004$] and a subsequent trend analysis revealed a significant linear fit to session [$F(1,4) = 7.971$, $p = .048$], which implies that the size of the deviation decreased as a function of session. No simple main effects were obtained for the top and middle lines [$F(2,8) = .127$, $p = .882$ and $F(2,8) = 1.551$, $p = .270$ respectively]. This lack of an effect for the top and middle lines might result from the fact that LZ's deviations at T0 were already not very pronounced (see Fig. 2), and not much improvement could be obtained in later sessions. With most neglect patients, the smallest deviations are observed with the top line and the largest deviations with the bottom line. This might reflect over-attention to the most right-side presented

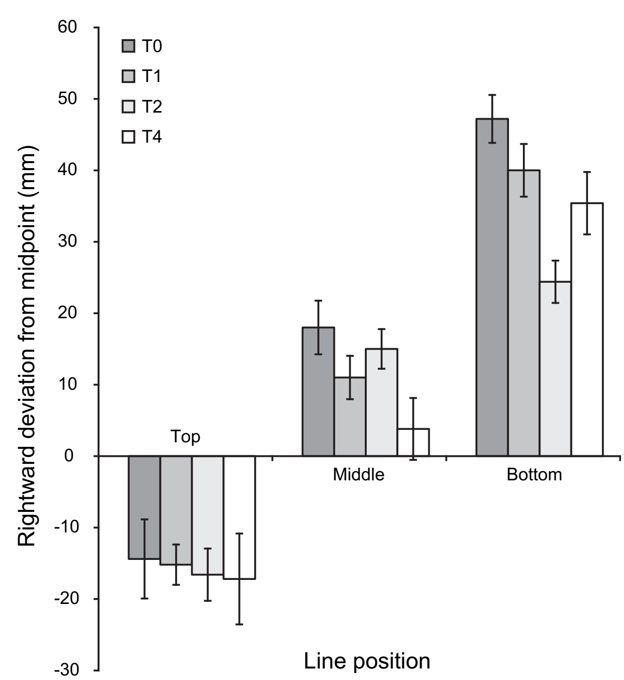

Fig. 2 – Deviation (positive score = rightward deviation, negative score = leftward deviation) from actual midpoint (mm) for the different times of testing (T0, T1, T2, T4); 5 measurements per time of testing), split for the three lines in the Line Bisection test.

line (i.e., top line) or disengagement of attention from the formerly marked midpoint; it is often observed in neglect patients that the rightward shift is greater on the bottom line, which is located more to the left.

3.3. *Behavioural measures: star cancelation task*

Since number of misses, number of perseverations and duration are separate measures (with different units) of a single task, each of these measures was analyzed separately, followed by a trend analysis if applicable.

For the Misses, an effect of session was found [$F(3,12) = 6.378$, $p = .008$], indicating that differences in number of misses were observed over sessions, with most misses in T0 and least misses in T2 (see Fig. 3). A trend analysis revealed a significant linear fit to session [$F(1,4) = 16.160$, $p = .016$].

A main effect of session was also found for the Perseverations [$F(3,12) = 11.858$, $p = .001$], indicating that the number of perseverations differed across sessions. The trend analysis revealed a significant linear fit to session [$F(1,4) = 16.220$, $p = .016$], i.e., the number of perseverations decreased with increasing session.

For the duration of the Star Cancelation Task, the effect of session was significant as well [$F(3,12) = 8.147$, $p = .003$], as was a quadratic fit in the trend analysis [$F(1,4) = 121.049$, $p < .001$] again indicating a decrease in task duration with increasing session number that came to a halt in the last session.

3.4. *Perimetrical measures*

A main effect of session was found [$F(4,224) = 6.294$, $p < .001$], indicating that differences in detecting stimuli were found over sessions. Also, a main effect of visual field was obtained [$F(1,56) = 94.979$, $p < .001$], indicating that detection of stimuli in the left visual field was significantly worse compared to detection of stimuli in the right visual field. Crucially, a significant interaction between session and visual field was found [$F(4,224) = 7.816$, $p < .001$].

In Fig. 4, left and right visual fields are shown for the 5 sessions, split for the left and right eyes. Absolute defects (i.e., stimuli were never reported) were found in the left visual field of both eyes before prism adaptation.[3] After 3 months of prism adaptation, a large improvement in detecting stimuli was found in the left visual field [T1 *vs* T0: $t(58) = 5.264$, $p < .001$], which did not diminish 3 months [T2 *vs* T1: $t(59) = -1.08$, $p = .284$; T2 *vs* T0: $t(58) = 3.66$, $p = .001$], or even six months after discontinuing prism adaptation [T3 *vs* T1: $t(58) = 1.469$, $p = .147$; T3 *vs* T0: $t(58) = 7.56$, $p = .001$]. Interestingly, after 27 months after the start of prism adaptation, LZ's performance was still improved when compared to start of the study [T4 *vs* T0: $t(58) = 3.76$, $p < .001$] and still of comparable magnitude as T1 [T4 *vs* T1: $t(58) = 1.19$, $p = .238$].

None of the comparisons for the right visual field were significant (all comparisons, $p > .371$).

[3] In the first session, perimetry was performed twice, before and after the first prism adaptation. No differences were found between these two measurements, so no short term improvements in detecting targets in the left visual field were demonstrated.

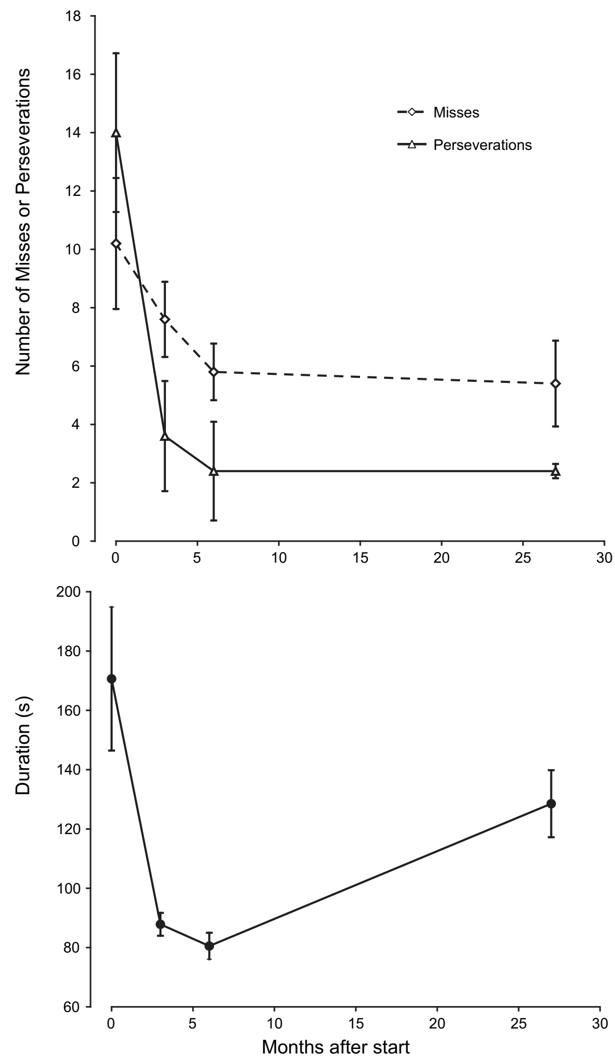

Fig. 3 – Number of misses, number of perseverations, and duration (seconds) for the different times of testing (T0, T1, T2, T4); 5 measurements per time of testing.

4. General discussion and conclusion

The first aim of this study was to investigate whether longer programs of prism adaptation exposure could lead to permanent changes in spatial awareness in chronic neglect. The results showed that prism adaptation alleviated symptoms of neglect, which were objectified as an improvement on both the Star Cancellation and the Line Bisection, up to 24 months after ending repetitive prism adaptation. Importantly, this behavioural improvement was mirrored by significant improvement in detecting targets of differential light intensities within the left visual field, assessed using perimetry.

Even though our behavioural measures of neglect indicated alleviation of neglect signs, the influence of repetitive exposure (with few trials and not much variation between trials) to these tests is relatively unclear; apparent alleviation of symptoms could easily be the effect of repeated exposure to these tests, aka a learning effect. The more stable performance at the later

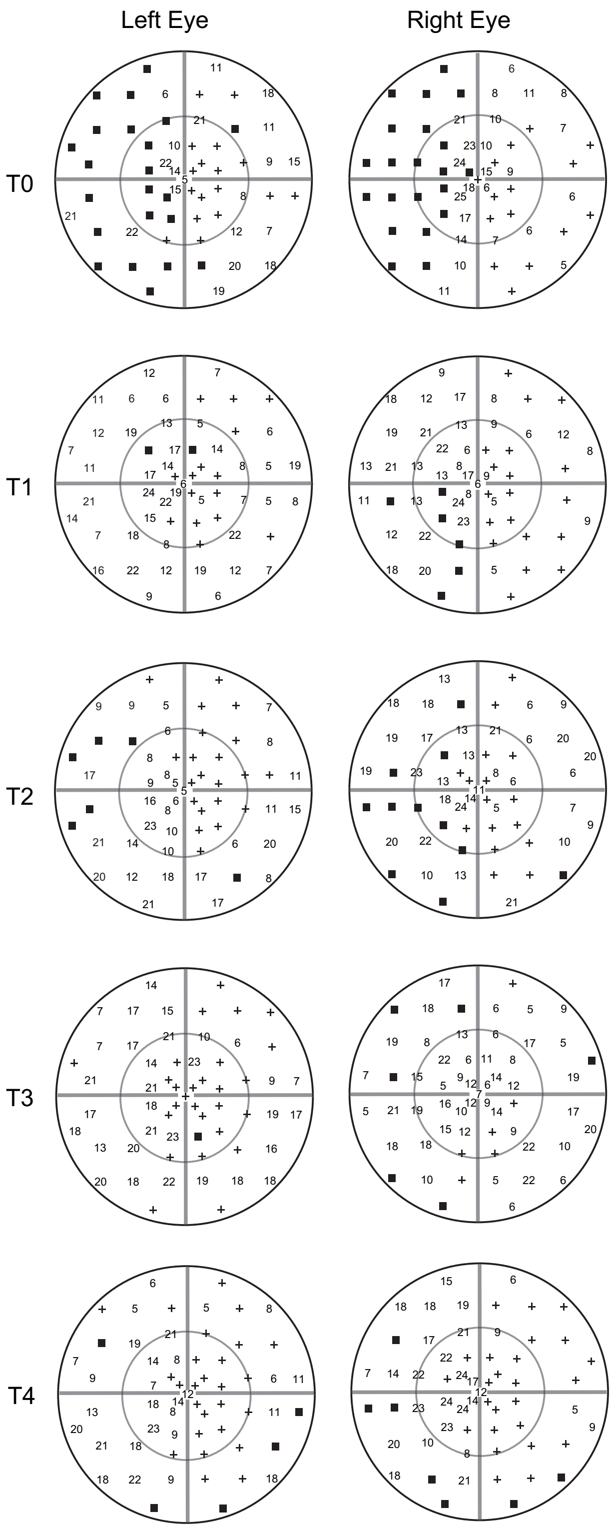

Fig. 4 – Differences between patient test results and age-matched controls (calculated by the perimetry software) are shown, at 5 perimetrical tests (T0, T1, T2, T3, T4). The + symbols indicate normal sensitivity with a tolerance of 4 dB. The values indicate a relative defect (i.e., part of the stimuli reported), and the black squares indicate an absolute defect (i.e., stimuli that were never reported).

times of testing (i.e., smaller standard errors at T1 and T2)[4] might also indicate that repetition of these behavioural measures can lead to a better, at least more stable performance. It might be that the additional decrease in number of omissions, number of perseverations, and total duration reflect a combination of influence of prism adaptation and familiarity with the tests. In contrast, perimetry allows accurate objectification of the size and the location of the defects within the left visual field, without the possible confounding learning effects. Additionally, compensatory effects, such as (strategic) eye movements, are controlled for by perimetry, making this a more precise and more sensitive measure than the commonly used neuropsychological tests for neglect.

The improvement in detecting stimuli in the left visual field was observed up to 24 months after repetitive prism adaptation, which is in line with an earlier study showing beneficial effects up to a year (Humphreys et al., 2006). Prism adaptation has been widely used as a rehabilitation technique, ever since it was first described by Rossetti et al (1998). The results of the current study partly exceed these results, as this study shows significant changes in detecting stimuli within the left visual field that lasted at least up to 24 months after ending prism adaptation.

One influential hypothesis is that prism adaptation produces a resetting of ocular scanning behaviour which facilitates the exploration of the neglect visual field (Angeli et al., 2004; Serino et al., 2006). Based on the current results found with perimetry, it can be concluded that the resetting of ocular scanning behaviour can not be the sole explanation of the beneficial effects op PA. In perimetry, targets need to be detected on a defined background, while keeping the gaze fixed. As significant improvement in detecting targets was found in LZ, ocular scanning behaviour does not appear to be crucial for the alleviating of signs of neglect. It appears that at least part of the beneficial effect of prism adaptation is more low-level than strategic resetting of ocular scanning behaviour.

One might argue that the current improvements are not necessarily the result of prism adaptation, but of unrelated recovery processes. This kind of recovery, however, is most likely to occur in the first three to six months post-stroke (Skilbeck et al., 1983) and LZ participated in this study 70 months post-stroke. Additionally, hetero-anamnestic information from LZ's husband indicates that she had shown signs of neglect since her SAH. These behavioural signs of neglect have lessened since she started with this intensive programme of daily prism adaptation. We therefore argue that the intensive program of prism adaptation is the most probable cause of neglect recovery.

In addition, it might be argued that the effects of prism adaptation on perimetry are due to improvement of a possibly associated visual field deficit rather than to an improvement of spatial attention. There are a number of reasons, however, why we consider this possibility unlikely. First of all, previous studies that have used prism glasses to ameliorate the symptoms of hemianopia have shown that, although prism glasses can be used to reduce the apparent visual field loss by

[4] Error bars at T4 are larger, indicating more variation between the adjacent days within the fourth session. This might suggest that after 21 months the practise or learning effects faded.

shifting stimuli from the blind field into the patient's unaffected field (e.g., Peli, 2000), this reduction *disappears* when the glasses are removed. As such, prism glasses lead to a field relocation rather than field expansion in hemianopia (Lane et al., 2008). A similar result has been obtained with compensatory visual field training in hemianopia. Such training may lead to an improvement in the detection of, and the reaction to, visual stimuli in the hemianopic field, but only when exploratory eye movements are allowed, that is: the improvement disappears during central fixation, a condition that applies during, and is a prerequisite for, accurate perimetry (Nelles et al., 2001). Finally, earlier studies have revealed the presence of additional hemianopia in patients with neglect to *negatively* influence the efficacy of prism adaptation (Angeli et al., 2004). For these reasons we argue that it is unlikely that the observed improvements after PA are due to an improvement of an associated visual field deficit, and conclude that perimetry is indeed a valid test for assessing the improvement of neglect after prism adaptation.

In sum, the current findings suggest that intensified rehabilitation may boost recovery, even in chronic patients up to 70 months following stroke. As prism adaptation takes little time (about 10 min) and can be taught easily to non-clinicians such as relatives, implementation of such programs should be feasible.

Disclosure

The authors report no conflicts of interest.

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