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Effects of prism adaptation and visual scanning training on perceptual and response bias in unilateral spatial neglect

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ABSTRACT

In some patients with unilateral spatial neglect, symptoms reflect impaired lateralized spatial attention and representation (perceptual bias) whereas in others the inability to respond to stimuli located in contralesional space (response bias). Here, we investigated whether prismatic adaptation (PA) and visual scanning training (VST) differentially affect perceptual and response bias and whether rehabilitation outcome depends on the type of bias underlying symptoms. Two groups of neglect patients in the subacute phase were evaluated before, immediately after, and two weeks following 10 days of PA ($n = 9$) or VST ($n = 9$). Standard neuropsychological tests (i.e., Behavioural Inattentional Test, Diller cancellation test, and Line Bisection test) were administered to assess neglect symptoms, while the Landmark task was used to disentangle perceptual and response biases. Performance on the Landmark task revealed that PA was more effective in improving the perceptual bias, while VST mainly modulated the response bias. Neuropsychological tests performance suggested that VST is better suited to modulate neglect in patients with response bias, while PA may be effective in patients with both types of bias. These findings may offer novel insights into the efficacy of PA and VST in the rehabilitation of perceptual and response biases in patients with neglect.

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Introduction

Unilateral spatial neglect is a complex and debilitating syndrome mainly occurring after a right hemispheric stroke. Neglect patients are unable to orient,

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attend to, or act upon stimuli located in the contralesional space (Bisiach & Berti, 1995; Heilman et al., 2003). An important but often neglected distinction is that between symptoms occurring at the input and/or output stages of space processing (Bisiach, Ricci, Lualdi et al., 1998; Harvey et al., 1995; Milner et al., 1993; Ricci & Chatterjee, 2004; Vossel et al., 2010). Since neglect can affect different aspects of spatial cognition (Bisiach, Ricci, Berruti et al., 1999; Gammeri, Iacono et al., 2020; Ricci et al., 2016; Rode et al., 2017) one of the first steps in rehabilitating patients should be to understand how symptoms occurring at the input and/or output stages of spatial processing can affect patients' recovery (Di Monaco et al., 2011; Kinsella & Ford, 1985; Nys et al., 2005).

Neglect may primarily reflect impaired lateralized spatial attention and representation (i.e., the input stage) or arise from the patient's inability to respond (i.e., the output stage) to stimuli presented contralesionally (Bisiach, Ricci, Lualdi et al., 1998; Ricci et al., 2000; Ricci & Chatterjee, 2004; Saevarsson et al., 2014; Vossel et al., 2010). While the input-related deficit is generally referred to as representational or attentional neglect, the output-related impairment has been named directional hypokinesia or intentional neglect (Heilman et al., 1985; Watson et al., 1978), aiming deficit (Fortis, Chen et al., 2011; Fortis, Goedert 2011; Schwartz et al., 1997), premotor neglect (Bisiach, Ricci, Lualdi et al., 1998; Vossel et al., 2010), or response bias (Bisiach, Ricci, Berruti et al., 1999; Bisiach, Ricci, Lualdi et al., 1998). Here, we used the terms *perceptual* and *response bias* for input- and output-related biases, respectively, and employed the Landmark task to quantify them (Bisiach, Ricci, Lualdi et al., 1998).

Although patients might benefit from treatment based on the affected stage of spatial processing, perceptual and response-related components are rarely considered in clinical or experimental settings (Bisiach, Ricci, Lualdi et al., 1998; Harvey et al., 1995; Milner et al., 1993). Among the various neglect rehabilitation treatments, prism adaptation (PA; Rossetti et al., 1998) and visual scanning training (VST; Diller et al., 1974) are the two most widely used bottom-up and top-down approaches, respectively (Gammeri, Iacono et al., 2020; Luaute et al., 2006). PA is a sensorimotor training that, by shifting vision laterally temporarily modifies sensorimotor mapping (Helmholtz, 1866; Redding and Wallace, 2006; Rossetti et al., 1998) and modulates high-level cognition such as spatial attention and feedback learning (e.g., Oliveri et al., 2013; Rabuffetti et al., 2013; Schintu et al., 2014, 2018). Some evidence shows that PA mainly affects visuomotor or motor-intentional "aiming" components of spatial cognition (Barrett et al., 2012; Fortis, Goedert et al., 2011; Striemer and Danckert, 2010), while other findings indicate its main influence on perceptual components (Nijboer et al., 2010; Pisella et al., 2006; Saevarsson et al., 2011). VST, on the other hand, trains voluntary orienting of spatial attention by asking patients to actively attend to contralesional stimuli (Diller et al., 1974).

Both techniques show promise in rehabilitating neglect symptoms (Luaute et al., 2006; Mizuno et al., 2011) although to date there is no consensus on

their effectiveness (Kerkhoff et al., 2013; Nys et al., 2008; Qiu et al., 2021; Serino et al., 2009). In this respect, only a few studies have specifically examined the possible role of perceptual and/or response biases in the effectiveness of PA, while no studies have directly investigated the role of such biases in relation to the effects of VST, limiting the understanding of the rehabilitative potential of these interventions. Twenty sessions of either VST or PA similarly improved neglect performance on ecological tasks (Priftis et al., 2013) and other tests of functional independence (Spaccavento et al., 2016). However, the above comparisons did not take into account putative differences in the efficacy of the two interventions in relation to the spatial component (i.e., input- versus output-related bias) mainly affected by the disorder. Barrett and colleagues, who directly investigated PA-induced effect on response and perceptual biases, found the greatest PA-induced improvement in patients with response bias on the functional Catherine Bergego Scale, with no differences on the Behavioural Inattention Test (Fortis, Chen et al., 2011; Goedert et al., 2014).

Inspired by the above findings, we investigated: (1) whether PA and VST differentially affect perceptual and response biases in patients with neglect, as assessed via the Landmark task (Bisiach, Ricci, Lualdi et al., 1998); (2) whether the efficacy of PA and VST in rehabilitating neglect depends on which stage of stimulus processing is involved (i.e., input or output), and thus on the type of bias (i.e., perceptual or response) exhibited by the patient, as quantified by the Landmark task (Bisiach, Ricci, Lualdi et al., 1998). The Bisiach's version of the Landmark task (Bisiach, Ricci, Lualdi et al., 1998) was chosen because it reliably disentangles and quantifies the perceptual and response bias responsible for neglect symptoms and thus it clarifies the nature of neglect behaviour, with perceptual bias indicating impairment at the input and response bias at the output stage (Bisiach, Ricci, Lualdi et al., 1998). Several studies have successfully used this tool (Bisiach, Ricci, Berruti et al., 1999; Bisiach, Ricci, Lai et al., 1999; Bisiach, Ricci, and Neppi-Mòdona, 1998; Capitani et al., 2000) and findings from the original paper by Bisiach and colleagues (1998) have been validated by subsequent works using advanced techniques such as voxel-based lesion-symptom mapping (Vossel et al., 2010), TMS (Brighina et al., 2002), and interleaved TMS/fMRI (Ricci et al., 2012).

Consistent with previous studies (Priftis et al., 2013; Spaccavento et al., 2016), we expected an overall improvement in neglect symptoms at the group level after both types of training. However, we expected that the efficacy of the two trainings would differ when response and perceptual biases were taken into account. Because VST trains patients to focus their attention on the neglected side (Spaccavento et al., 2016), we expected greater efficacy on response bias and neglect recovery in patients showing this type of bias. On the other hand, because PA acts on both visuomotor and perceptual aspects of spatial processing, we might have expected an effect on both types of biases, or, based on previous evidence, greater efficacy on response bias (Barrett et al., 2012; Fortis, Goedert et al., 2011;

Striemer and Danckert, 2010) or perceptual bias (Nijboer et al., 2010; Pisella et al., 2006; Saevarsson et al., 2011). Given the heterogeneity of patients with neglect and the possibility that response and perceptual biases may coexist in the same patient, we also examined individual responses since those may reveal effects that are hidden in group analyses.

Materials and method

Patients

Patients with a right-hemisphere stroke were consecutively recruited from the Service of Neuropsychological Rehabilitation of the Presidio Sanitario San Camillo. Patients were screened for eligibility to participate in the study and when they met the inclusion/exclusion criteria, they were assigned in an alternate manner to one or the other training. Eighteen patients participated in the study: VST group ($N = 9$, 7 females; mean age = 71.6; $SD = 2.88$) or PA ($N = 9$, 7 females; mean age = 75; $SD = 2.54$). Patients, who were also undergoing physical rehabilitation, received a clinical and neuropsychological evaluation, and the following inclusion criteria were adopted: (1) presence of a unilateral right hemisphere lesion confirmed by radiological evaluation (CT scan or MRI); (2) presence of neglect as assessed by the Diller and/or line bisection tasks (see section 2.3); (3) Mini Mental State Examination (MMSE) score > 24 ; (4) no history of other concurrent neurological or psychiatric disorders (Ricci et al., 2016). Patients gave informed consent, the study was approved by the local Institutional Review Board and was conducted following the ethical standards of the 1964 Declaration of Helsinki (World Medical Association, 2013).

Procedure

The study consisted of three sessions, one before and two after training, and lasted a total of six weeks. As depicted in Figure 1, during week one patients underwent a brief anamnestic interview along with cognitive functioning and neglect evaluation (pre-training). During week two and three patients received either PA or VST, once a day and five days per week, for a total of ten sessions. At week four neglect symptoms were re-evaluated to assess the immediate training-induced effect (post). Two weeks from the end of training neglect symptoms were again assessed (follow-up). While it was not possible for the practitioner to be blind to the type of training (PA or VST) patients could be considered partially blind since they were not aware of the possible difference between the two trainings' effectiveness.

Neglect assessment

The presence of neglect was defined on the basis of either one (or both) of the following criteria (Bisiach, Ricci, Lai et al., 1999; Ricci et al., 2019):

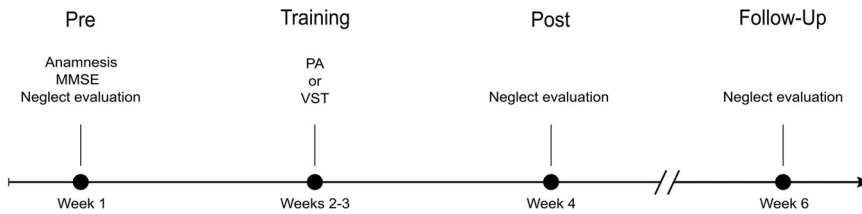


Figure 1. Study Timeline. Each group of patients underwent two weeks of prismatic adaptation (PA) or visual scanning training (VST). Neglect was evaluated the week before (pre), immediately after (post) and 2 weeks after (follow-up) the end of training.

(1) contralesional side minus ipsilesional side omissions on the Diller cancellation task being ≥ 5 ; (2) mean line bisection error towards the ipsilesional side exceeding 10 mm. Neglect was also quantified using a battery, i.e., the Behavioural Inattention Test, commonly employed in experimental and clinical settings.

Behavioural inattention test (BIT)

This standardized battery assessing neglect presence and severity (Halligan et al., 1991; Wilson et al., 1987) is composed of six *conventional* sub-tests (BIT-C) quantifying personal and representational neglect by employing paper and pencil tests, and nine *behavioural* sub-tests (BIT-B) quantifying the severity of peripersonal neglect, using tasks designed to simulate daily life activities (Wilson et al., 1987). The total BIT-C and BIT-B scores were the dependent variables. Neglect presence is indexed by a score below the cut-off (<129 out of 146 for the BIT-C and <67 out of 81 for the BIT-B).

Diller cancellation test

In this test, used to assess neglect presence (Diller & Weinberg, 1977), patients were presented with a series of letters scattered across an A3 sized (420 mm $\times$ 295 mm) sheet of paper centred on patients' sagittal midplane and asked to cross out all the letters H. The modified version employed here displayed 53 letters H on each half of the paper. The total number of omissions constituted the dependent variable. A difference between left-side omissions and right-side omissions ≥ 5 indicated the presence of neglect.

Line bisection task

This test is used to assess attention orientation bias (Chillemi et al., 2018; Diller & Weinberg, 1977; Palermo et al., 2018; Ricci et al., 2014) and spatial neglect (Schenkenberg et al., 1980; Serino et al., 2007). It consisted of ten 180 mm long and 1 mm thick black horizontal lines printed on an A4 sized (297 mm $\times$ 210 mm) sheet of paper. Each line was placed in front of the patients and centred on their sagittal midplane. Patients had to mark with a pencil the

perceived centre of each line. The distance between the mark placed by the patient and the true centre was measured to the nearest mm. Positive values indicated a rightward deviation and negative values a leftward deviation. For each patient, the average of the ten performances constituted the dependent variable. A rightward bias ≥ 10 mm indicated the presence of neglect (Bisiach, Ricci, Berruti et al., 1999).

The Landmark task: Assessment of perceptual and response bias

The Landmark task consists of four blocks of nine, 180 mm long and 1 mm thick, black pre-bisected lines (36 lines in total) centrally positioned on an A4 sheet of paper. Each line is bisected either exactly in the centre or to the right or the left of the true centre. In half of the trials, the patients were asked to point to the longer segment ("longer task"), in a binary forced-choice condition. In remaining half of the trials, they were asked to point to the shorter segment ("shorter task"). In patients suffering from left neglect, the presence of a perceptual bias leads to misjudge left segments as "shorter" and right segments as "longer." This type of behaviour produces a high number of choices of the left segment as shorter and the right segment as longer. The presence of a response bias instead leads to consistently choosing the right segments in either the "longer" and "shorter" task conditions. The converse would be the case in patients suffering from right neglect. Responses were quantified using a perceptual bias score [PB = (percentage of left segment choices during the "shorter task" plus percentage of right segment choices during the "longer task")/2] and a response bias score [RB = (percentage of the right segment choices, in "shorter task" plus right segment choices, in the "longer task")/2]. In order to give an estimate of the strength of each kind of bias in individual patients, Bisiach and co-workers (1998) obtained means and SDs of the PB and RB indexes from a control group of 20 healthy subjects. The mean value of PB score was found to be 52.60% (SD 3.77); that of RB score was found to be 49.54% (SD 1.10). The authors arbitrarily considered the expression of medium and strong PB or RB scores above (or below) normal means plus (or minus) 2 and 3 standard deviations, respectively (see Bisiach, Ricci, Lualdi et al., 1998 for details). Accordingly, higher and lower cut-offs for medium PB were set at 60.15 and 45.05%, respectively; higher and lower cut-offs for strong PB were set at 63.91 and 41.29%, respectively. Higher and lower cut-offs for medium RB were set at 51.74 and 47.34%, respectively; higher and lower cut-offs for strong RB were set at 52.84 and 46.27%, respectively. As the original (1998) and following works (Bisiach, Ricci, Berruti et al., 1999; Bisiach, Ricci, Lai et al., 1999; Bisiach, Ricci, Lualdi et al., 1998; Bisiach, Ricci, and Neppi-Mòdona, 1998), the above cut-offs were employed to classify patients' biases. PB and RB values > of the higher cut-offs represent rightward biases, typical of patients with left neglect, whereas PB or RB values < of the lower cut-offs indicate leftward biases, typical of

patients with right neglect or, in patients with right hemisphere lesion but symptom of ipsilesional neglect/bias. As in previous work, patients were classified using the above cut-offs as showing perceptual or response bias or a combination of both.

Neglect trainings

Prism adaptation (PA)

Similar to Serino et al., (2007) patients were comfortably seated in front of a table, on the top of which a box (30 cm high, 75 cm wide and 34 cm deep) open on both sides was aligned to the patients' body midline. Patients were instructed to point with their right index finger to the visual target (a pen) presented by the experimenter on the other side of the box at three locations: centre (0°), right (+21°) and left (−21°) in a pseudorandom order. For each pointing movement, the only possible visual feedback was the terminal part of the movement (i.e., right index fingertip) since the beginning of the movement was concealed by a cloth tied around the patients' neck and the pointing movement was performed inside the box. Patients were adapted to 11.4° rightward deviation.

The PA protocol included three phases:

1. *Pre-exposure phase*: on the first day of training patients, without wearing prismatic goggles, performed 60 pointing movements. Half of the pointing movements were performed with visual feedback and the other half without.
2. *Exposure phase*: while wearing the goggles, patients performed 90-pointing movements. Visual feedback was provided solely for the final part of the pointing (i.e., the patient's fingertip).
3. *Post-exposure phase*: immediately after goggles removal, patients performed 30-pointing movements without visual feedback.

Each daily session lasted approximately 45 min.

Although the pointing error reduction during prism exposure was not formally measured, the practitioner was instructed to verify that patients adapted to PA, i.e., that each patient showed error reduction during prism exposure and made no errors in pointing by the end of training (i.e., before the prism goggles were removed). The practitioner was instructed to discontinue the training if the patient did not show any adaptation in the first two training sessions. All nine patients adapted well to the prismatic optical displacement induced during exposure. In addition, tall patients showed the expected leftward pointing error after exposure to prism, indicating that PA was successful.

Visual scanning training (VST)

The VST protocol was designed for this study based on Diller and colleagues (1974) methodology. Patients were presented with letters arranged in rows

on an A3 sheet of paper and they were asked to cancel a target letter among distractors. To facilitate spatial exploration patients were provided with visual cues (numbers and coloured lines) acting as an attentional anchor. The protocol consisted of six levels of progressively increasing difficulty. Each level was characterized by a different amount and type of anchors: (1) numbers and a thick red line presented on both sides of the sheet; (2) numbers and a thick red line only on the left side; (3) thick red line on the left side; (4) thin red line on the left side; (5) no anchorage was provided but the patient was allowed to draw one on the left side; (6) no anchors were provided and patients could not create it. For each of these six levels, three additional sub-levels differing in the number of targets and distractors included: (a) 20 targets and 40 distractors; sub-level; (b) 30 targets and 60 distractors; (c) 40 targets and 80 distractors. The target letter changed in each of the three sub-levels and, for each sub-level there was a backup target letter in case a sub-level had to be repeated. Each sub-level was administered four times using the same target letter. Suggestions and feedback were provided only in the first three sub-levels, while in the fourth one the patient had to perform the task autonomously. A minimum of 80% accuracy at the fourth sub-level was required to pass to the next level.

Statistical analysis

We used non-parametric tests since the data were not normally distributed as assessed by the Shapiro-Wilk test ($p < 0.05$) and because of the small sample size. Within-group analyses were conducted on the scores of standard neuropsychological tests (i.e., BIT-C, BIT-B, LBT, and Diller cancellation task) using the Friedman test having time (pre, post, follow-up) as a within-subject factor, using Kendall's W to determine the effect size (w). Post-hoc comparisons were performed using the Wilcoxon test. Between-group analyses were performed on age, education, and length of illness, as well as on standard neuropsychological tests at baseline using the U Mann-Whitney test. For both tests, effect size (r) was calculated by dividing the Z statistic by square root of N , where N represents the number of observations in Wilcoxon test and the sample size in U Mann-Whitney test. All statistical analyses were performed using SPSS (IBM, Version 26.0) with alpha set at .05 (two-tailed). Given the groups' sample size, effects of VST and PA on PB and RB were assessed using "N-1" Chi-squared test (Campbell, 2007; Richardson, 2011) to compare proportions of patients showing improvement of pathological biases (i.e., from pathological to non-pathological score), from baseline to subsequent post-training evaluations, according to the Landmark task cut-offs (Bisiach, Ricci, Lualdi et al., 1998). To corroborate the categorization of individual patients' scores on the Landmark task and relative changes at the different time points (i.e., pre, post and follow-up), we used a modified t-test (the Crawford's test, Crawford & Garthwaite, 2002; Ricci et al., 2019) to compare the individual scores of each patient versus a normative sample of healthy

subjects (i.e., mean, standard deviation and sample size from Bisiach, Ricci, Lualdi et al., 1998); see also paragraph 2.4 for control group values). Effect size was calculated using single-case's score, controls' group mean and standard deviation, as indicated by Crawford and colleagues (2010).

Results

Patients

Patients' clinical and demographic data are reported in Table 1. PA and VST groups did not differ in age ($U = 33$, $Z = -0.664$, $p = 0.507$, $r = -0.156$), education ($U = 34$, $Z = -0.594$, $p = 0.605$, $r = -0.140$), and length of illness ($U = 20$, $Z = -1.816$, $p = 0.069$, $r = -0.428$) according to the Mann-Whitney test. Importantly, neglect scores before training did not differ among groups (BIT-C: $U = 35$, $Z = -0.486$, $p = 0.627$, $r = -0.114$; BIT-B: $U = 34$, $Z = -0.574$, $p = 0.566$, $r = 0.135$; Line Bisection: $U = 27$, $Z = -1.192$, $p = 0.233$, $r = -0.280$; Diller: $U = 31$, $Z = -0.839$, $p = .402$, $r = 0.197$) ruling out the possibility that baseline differences drove significant effects and interactions.

Neglect neuropsychological assessment

Consistent with previous studies (Priftis et al., 2013; Spaccavento et al., 2016), the two groups of patients undergoing PA and VST did not differ on

Table 1. Demographic and clinical data of neglect patients exposed to prism adaptation or visual scanning training.

Patient	Sex	Age	Education (years)	Lesion (CT/MRI scan)	Etiology	Length of illness (days)
Visual scanning training group						
S1	Female	83	18	Temporo-Occipital/Thalamus/Insula/Internal Capsule/BG/Postcentral G.	Ischemic	25
S2	Female	66	13	Insula/Internal Capsule/BG/Postcentral G./precentral G.	Neoplastic	109
S3	Female	75	8	Insula/Internal Capsule/Thalamus/BG	Hemorrhagic	20
S4	Male	76	5	Frontal/Insula/Internal Capsule /BG	Ischemic	37
S5	Female	72	5	Fronto-Temporo-Parietal	Ischemic	21
S6	Female	65	5	Fronto-Parietal	Ischemic	77
S7	Female	72	8	Fronto-Temporo-Parietal	Ischemic	38
S8	Male	55	13	NA	Ischemic	27
S9	Female	81	5	Fronto-Parietal	Ischemic	55
Prism adaptation group						
S10	Female	80	5	Fronto-Temporo-Parietal	Ischemic	31
S11	Female	75	13	Temporo-Parietal	Hemorrhagic	11
S12	Male	65	13	F P O	Ischemic	20
S13	Female	67	13	Fronto-Temporo-Parietal	Hemorrhagic	53
S14	Female	85	8	Parietal	Ischemic	16
S15	Female	70	11	Internal Capsule/Thalamus/BG	Ischemic	23
S16	Female	85	5	Fronto-Temporo-Parietal /MCA	Ischemic	23
S17	Male	79	8	Occipital	Ischemic	23
S18	Female	69	12	Thalamus/Internal Capsule	Hemorrhagic	27

S, subject; MCA, medium cerebral artery; G, gyrus; and BG, basal ganglia.

neuropsychological tests according to the U Mann-Whitney test (*all* $p < 0.05$). However, for both trainings, within-group analyses, showed differences across conditions (pre, post and follow-up).

Behavioural inattention test (BIT)

Friedman test on the BIT-C score revealed a significant main effect of time for both VST (χ^2 (2, $N = 9$) = 14.114; $p = 0.001$, $w = 0.784$) and PA [χ^2 (2, $N = 9$) = 6.229; $p = 0.044$, $w = 0.346$] group. Wilcoxon *post-hoc* analyses revealed that both groups improved their performance at post (VST: $Z = -2.666$, $p = 0.008$, $r = -0.51$; PA: $Z = -2.547$, $p = 0.011$, $r = -0.49$) and follow-up (VST: $Z = -2.666$, $p = 0.008$, $r = -0.51$; PA: $Z = -2.310$, $p = 0.021$, $r = -0.44$) as compared to pre (Figure 2(a)). However, performance at follow-up was not different from post for both VST ($Z = -0.420$, $p = 0.674$, $r = -0.09$) and PA $Z = -0.140$, $p = 0.889$, $r = -0.03$) group. Similarly, Friedman test at BIT-B showed a significant main effect of time for both VST [χ^2 (2, $N = 9$) = 11.529; $p = 0.003$, $w = 0.641$] and PA [χ^2 (2, $N = 9$) = 14.114; $p = 0.001$, $w = 0.784$] group. In the VST group, *post-hoc* comparisons showed significant improvement from pre to post ($Z = -2.547$, $p = 0.011$, $r = -0.60$) and from pre to follow-up ($Z = -2.666$, $p = 0.008$,

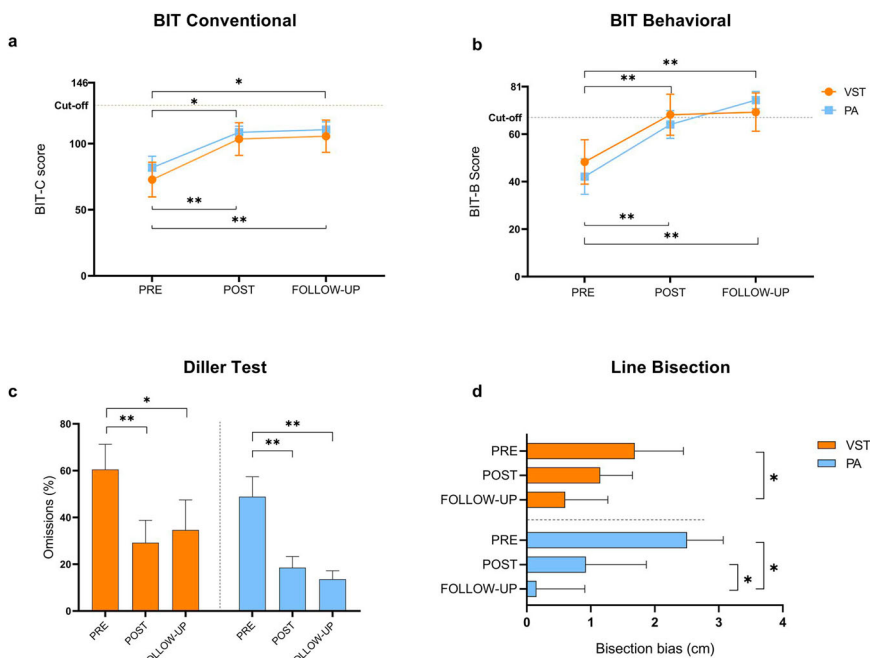


Figure 2. Patients' performance on the different neuropsychological assessments at the different times. (a) BIT conventional score (b) BIT Behavioural score; (c) Sum of left and right omissions at the Diller task; (d) Line bisection task performance positive values indicate a rightward bias. The different assessments were performed before training (pre), at the end of the training (post), and two weeks from the end of training (follow-up). * $p < 0.05$, ** $p < 0.01$. Data are presented as mean and standard error of the mean (SEM). VST, visual scanning training and PA, prismatic adaptation.

$r = -0.62$). In the PA group, post-hoc analyses showed improvement from pre to post ($Z = -2.521$; $p = 0.012$; $r = -0.59$), from pre to follow-up ($Z = -2.666$, $p = 0.008$, $r = -0.62$). However, performance at follow-up was not different from post for both VST ($Z = -0.339$, $p = 0.735$, $r = -0.07$) and PA ($Z = -1.955$, $p = 0.51$, $r = -0.46$) group.

Diller cancellation task

As shown by the Friedman test, the number of omissions decreased over time for both the VST [$\chi^2 (2, N = 9) = 10.667$; $p < 0.005$, $w = 0.593$] and PA [$\chi^2 (2, N = 9) = 14.889$; $p < 0.001$, $w = 0.827$] group. Wilcoxon *post-hoc* analyses showed improvement, for both groups, at post (VST: $Z = -2.668$, $p = 0.008$, $r = -0.62$; PA: $Z = -2.666$, $p = 0.008$, $r = -0.62$) and follow-up (VST: $Z = -2.192$, $p = 0.028$, $r = 0.51$; PA: $Z = -2.666$, $p = 0.008$, $r = -0.62$) as compared to pre (Figure 2(c)). Comparisons between post and follow-up were not statistically significant (VST: $Z = -0.356$, $p = 0.722$, $r = -0.08$; PA: $Z = -1.007$, $p = 0.314$, $r = -0.23$).

Line bisection task

Both groups showed a pathological rightward bias (>10 mm) at baseline and both trainings modulated patients' performance. The VST group showed a main effect of time [$\chi^2 (2, N = 9) = 8.000$; $p < 0.018$, $w = 0.444$] in the Friedman test, and *post-hoc* analyses revealed that the rightward bias decreased from pre to follow-up ($Z = -2.073$, $p = 0.038$, $r = -0.48$). Comparisons between pre and post ($Z = -1.362$, $p = 0.173$, $r = -0.26$) and between post and follow-up ($Z = -1.599$, $p = 0.110$, $r = -0.37$) were not statistically significant. Also, the PA group manifested a main effect of time [$\chi^2 (2, N = 9) = 6.222$; $p = 0.045$, $w = 0.346$]. Post-hoc analyses showed a decrease of the rightward bias from pre to follow up ($Z = -2.310$, $p = 0.021$, $r = -0.54$) and from post to follow-up ($Z = -2.310$, $p = 0.021$, $r = -0.54$; Figure 2(d)), indicating that the rightward bias continued to decrease after the end of the training. However, comparisons between pre and post failed to reach statistical significance ($Z = -1.718$, $p = 0.086$, $r = -0.40$).

The Landmark task: Perceptual and response bias

The effects of PA and VST on patients' perceptual and response biases were measured using PB and RB scores obtained on the Landmark task. To categorize the patients' biases, as in previous studies (Bisiach, Ricci, Berruti et al., 1999; Bisiach, Ricci, Lai et al., 1999; Bisiach, Ricci, and Neppi-Mòdona, 1998, see section 2.4), we used the following cut-offs: for PB, medium bias <45.05 or >60.15 and strong bias <41.29 or >63.91 ; for RB, medium bias <47.34 or >51.74 and strong bias <46.27 or >52.84 .

Figure 3 reports patients' scores and changes in severity in the different evaluation phases (pre-training, post and follow-up). Given the heterogeneity

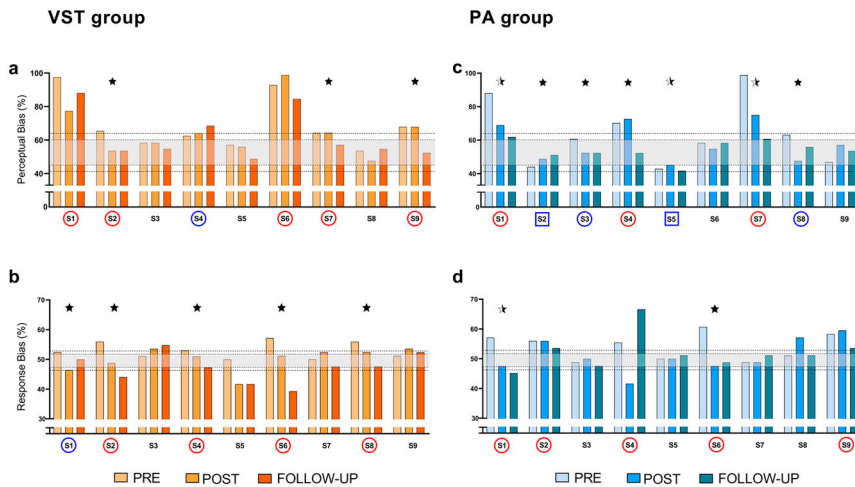


Figure 3. Performance of individual patients at each time point for each treatment group according to their bias. (a, b) VST group; (c, d) PA group; (a, c) perceptual bias; (b, d) response bias. The shaded area shows the range of the non-pathological score; the areas above or below indicate a bias to the right or to the left, respectively. More specifically, the areas between the two outermost dashed horizontal lines and the shaded area represent the two ranges of medium bias, while the areas above or below the two outermost dashed horizontal lines represent the range of strong bias (3). Black stars refer to patients who achieved a non-pathological score at post and/or follow-up. Half-coloured stars indicate patients who improved from strong to medium bias. The circle/square around the patient's number/label indicates patients with pathological rightward (circle) or leftward (square) bias at the baseline; the colour red indexes a strong bias and the colour blue a medium bias. VST, visual scanning training; PA, prismatic adaptation; and S, subject.

of patients with neglect and the small sample size, we mainly focused the analysis on scores improvement, without scrutinizing differences in the severity of the patients' scores.

Perceptual bias

Looking at the PB baseline scores of individual patients, 6 out of 9 (67%) in the VST group and 5 out of 9 (56%) patients in the PA group showed a rightward medium (S = subject, VST: S4; PA: S12, S17) or strong (VST: S1, S2, S6, S7, S9; PA: S10, S13, S16) perceptual bias, according to Bisiach and colleagues' categorization (Bisiach, Ricci, and Neppi-Mòdona, 1998). Two patients of the PA group (17%) exhibited a medium leftward perceptual bias (S11, S14). Comparison of the two proportions did not show any significant difference (χ^2 (1, $N = 18$) = 0.258, $p = 0.618$) between the proportion of patients showing perceptual bias at the baseline in the two groups of patients, i.e., PA (7/9) vs VST (6/9).

After VST, 3 (S2, S7, S9) out of 6 (50%) patients achieved a normal PB score at post and follow-up (S2), or only at follow-up (S7, S9), while the other three patients (S1, S4, S6) did not improve after the training (Figure 3(a)).

After PA, patients (100%) with a baseline rightward (5/7) and leftward (2/7) perceptual bias showed some improvement. More specifically, 3 out of 5 patients with rightward bias achieved a normal score at post and follow-up (S12, S17) or only at follow-up (S13), while the other two (S10, S16) went from strong to medium rightward bias at follow-up. Interestingly, after rightwards deviating PA, the two patients with leftward bias reached a normal score at post (S14) or both at post and follow-up (S11; [Figure 3\(c\)](#)).

The Crawford *t*-test comparisons confirmed the presence of perceptual bias in correspondence of the same scores classified as pathological by Bisiach's cut-offs. Notably, only the scores that were classified as pathological based on the Landmark cut-offs resulted to be statistically different from the mean value of the control group, while the scores categorized as non-pathological were not statistically different from the mean value of the control group (see Appendix 2).

A significant difference [χ^2 (1, $N = 18$) = 4.200, $p = 0.040$] between the proportion of patients showing improvement was finally observed after PA (7/7) as compared to VST (3/6).

In summary, the above data suggest relatively greater beneficial effects of PA compared to VST on patients' *perceptual biases*. In addition, the finding that PA improved perceptual bias independently of its initial orientation suggests that this technique can restore spatial representation rather than purely shifting the direction of the perceptual bias.

Response bias

When looking at the baseline scores of individual patients, 5 out of 9 (56%) patients who received PA and 5 out of 9 (56%) patients who received VST showed a medium (VST: S1) or strong (VST: S2, S4, S6, S8; PA: S10, S11, S13, S15, S18) rightward *response bias*. Thus, at baseline, the two groups showed the same proportions of patients with pathological RB score, i.e., PA (5/9) vs VST (5/9).

After VST, 5 out of 5 patients (100%) decreased their bias either at post or at follow-up. It is worth noting that while two patients (S1, S8) achieved a normal score at follow-up, the other three (S2, S4, S5) normalized it at post but progressed into a leftward bias at follow-up ([Figure 3\(b\)](#)). Surprisingly, three patients who showed a normal score (3/4) at baseline manifested pathological leftward (S5) or rightward (S3 and S9) bias after training.

After PA, 2 out of 5 (40%) patients who initially showed a rightward response bias, improved their bias at post. However, among them only one (S15) patient maintained a normal score at follow-up, while the other one progressed into a leftward bias (S10; [Figure 3\(d\)](#)).

When comparing the score of the two groups with a normative sample, Crawford *t*-test confirmed the presence of response bias in correspondence of the same scores classified as pathological by Bisiach's cut-offs. Also, in

this case, pathological scores resulted to be statistically different from the scores of the control sample, while the non-pathological scores were not (see Appendix 2).

Comparison of the two proportions showed a significant difference [$\chi^2(1, N = 18) = 3.857, p = 0.049$] between the proportion of patients showing some improvement after VST (5/5) vs PA (2/5).

In summary, these data suggest a relatively greater modulatory effect of VST on patients' *response bias* compared to PA. They also suggest that VST, and to some extent also PA, may mainly affect the direction of patients' response bias without improving spatial representation processing. It is worth highlighting that in some instances VST produced a pathological response bias in patients not manifesting it at baseline.

Neuropsychological outcomes in patients with pure perceptual or response bias

In line with previous studies (Bisiach, Ricci, Berruti et al., 1999; Bisiach, Ricci, Lai et al., 1999; Bisiach, Ricci, and Neppi-Mòdona, 1998), the majority of patients (10/18, 56%) showed a combination of both types of bias. We, therefore, scrutinized at a qualitative level the efficacy of PA and VST on neuropsychological outcomes in patients *categorized at baseline as having solely perceptual or response bias* (see Appendix 1 for individual data and Figure 4).

Figure 4 shows the performance of the individual patients on the neuropsychological tasks for the two trainings at different time points. After VST, the two patients with strong *perceptual bias* (S7, S9), showed relatively modest improvement on all tests (all scores <20%) with only a spike in improvement at follow-up for S7 on the cancellation task (Figure 4(c)). In contrast, the patient with a strong *response bias* (S8) improved remarkably in the Diller (Figure 4(c)) and BIT-C (Figure 4(a)), along with a marked improvement in the BIT-B (Figure 4(b)). In summary, although patients with pure perceptual or response biases were rare, these data seem to suggest greater effects of VST in the patient with a pure response bias.

After PA, the three patients with *rightward perceptual bias* (medium: S12, S17; strong: S16) showed remarkable improvements on the Diller cancellation task (Figure 4(c)), greater than those manifested by the two patients with (strong) *rightward response bias* (S15, S18). The opposite pattern was observed on the BIT-B sub-test (Figure 4(b)), where the two patients with response bias showed overall greater improvement than patients with perceptual bias. Mixed results were instead found on the BIT-C (Figure 4(a)). In summary, when looking at individuals with pure perceptual or response biases, the trend that seems to emerge suggests greater improvement on the cancellation task for patients with perceptual bias and on the BIT-B sub-test for patients with response bias.

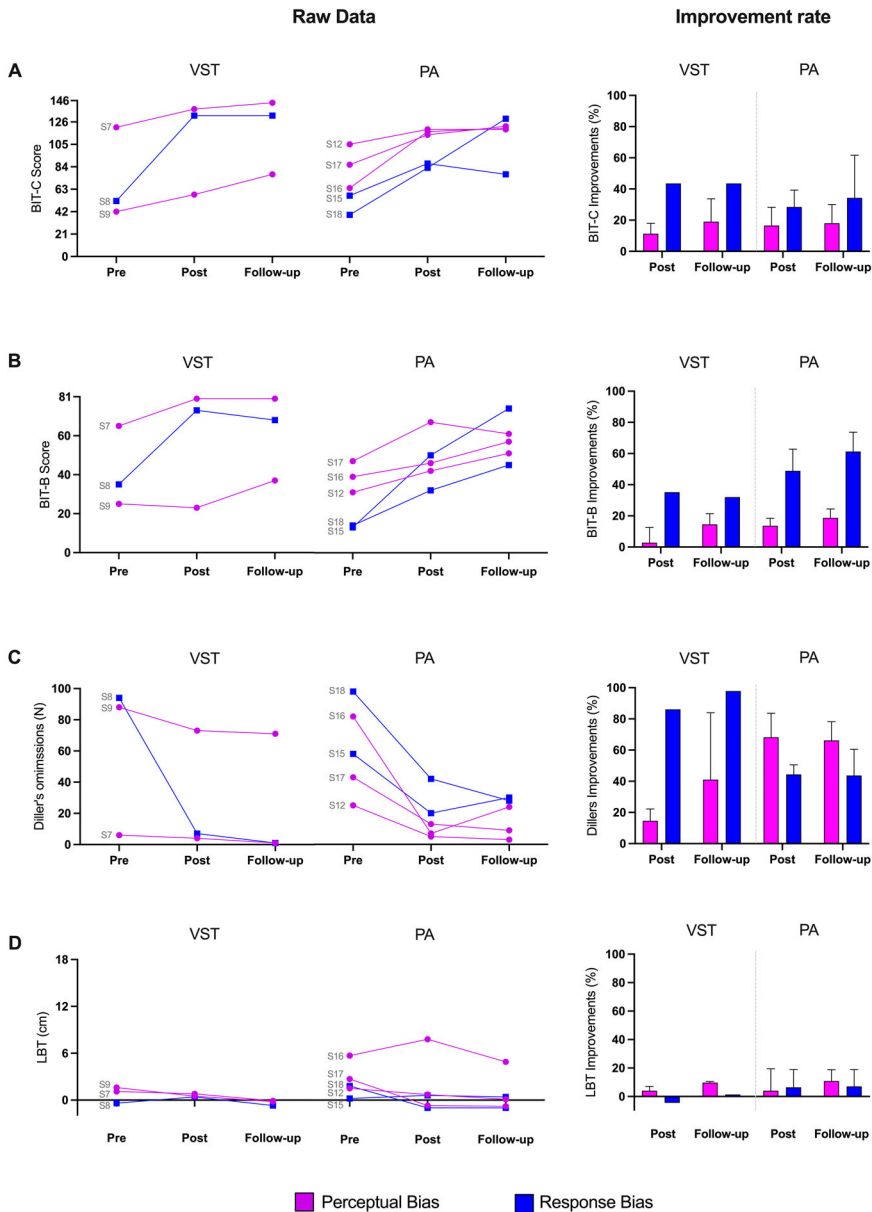


Figure 4. Performance of individual patients showing a pure perceptual or a pure response bias at baseline. The graphs show the performance on the neuropsychological tasks (a: BIT-C, b: BIT-B, c: Diller cancellation task, d: Line Bisection task) of patients who showed a pure perceptual (purple colour) or pure response (blue colour) bias at baseline, as determined by the Landmark task. In the graphs on the left, raw data for all time points of the evaluation (pre, post, and follow-up) are shown. In the graphs on the right, mean values of patients with pure perceptual or response bias are shown as percent increase (or decrease) from the baseline after training (VST: Perceptual Bias $N = 2$, Response Bias $N = 1$; PA: Perceptual Bias $N = 3$, Response Bias $N = 2$). For all raw data, see Appendix 1.

Discussion

We examined whether the efficacy of the two most used neglect rehabilitation training, PA and VST, differentially affect perceptual and response biases in patients with neglect and whether patients' rehabilitation outcome depends on the type of bias underlying symptoms.

Patients' performance on the Landmark task (Bisiach, Ricci, Lualdi et al., 1998) suggested that PA was *relatively* more effective on the perceptual bias, whereas VST mainly modulated the response bias. The proportions of individuals manifesting improvement of pathological biases from baseline to post-training evaluations showed that the perceptual bias improved in a greater number of patients after PA than VST and, vice versa, the response bias improved in a greater number of patients after VST than PA. Interestingly, individual data also suggest that in patients with response bias VST, and in one patient also PA, mainly affected the direction of the spatial bias without restoring spatial representation, as evidenced by the fact that an opposite leftward bias emerged after training. In addition, PA improved perceptual bias also in the two patients with initial leftward bias, suggesting that this technique can restore spatial representation rather than purely shifting the direction of the perceptual bias. Previous studies using the Landmark task (for instance Bisiach, Ricci, Lai et al., 1999, Bisiach, Ricci, and Neppi-Mòdona, 1998) and other techniques (Goedert et al., 2014) have consistently observed the emergence of a leftward bias in few neglect patients with right hemispheric lesion (i.e., ipsilesional neglect/bias). Although the mechanisms underlying ipsilesional bias (ipsilesional neglect) in neglect patients with right-hemisphere lesion are not yet clear (Barrett et al., 2003; Drago et al., 2007; Kim et al., 1999), contralesional shift in the orientation of the attentional bias can especially be observed during the subacute phase of the disease when spontaneous recovery or rehabilitative interventions may trigger compensation strategies enhancing contralesionally directed attention. We speculate that these findings are consistent with theories claiming that neglect could be explained by a pathological orientation bias associated with a deficit in magnitude estimation (Chatterjee et al., 2000; Mennemeier et al., 2005). In this framework, VST and, in a few patients, PA could mainly affect the direction of the orientation component without improving magnitude estimation processing. On the other hand, PA may mainly work on the space representation (i.e., size estimation) component.

Consistent with previous studies (Bisiach, Ricci, Berruti et al., 1999; Bisiach, Ricci, Lai et al., 1999; Bisiach, Ricci, and Neppi-Mòdona, 1998), the majority of patients (56%) showed a combination of perceptual and response bias. To investigate whether the type of bias affects patients' rehabilitation outcome on standard neuropsychological tests, we examined, at a qualitative level, the individual performance of patients with pure perceptual or response bias. Although clear conclusions cannot be drawn from patients with only one

type of bias because of the low number, the trend of individual data suggests that PA had the greatest benefit for patients with perceptual bias on cancellation performance and for patients with response bias on the more ecological, functional BIT-B subtest. In addition, VST appeared to be more effective in the patient with response bias.

Our findings seem to contrast with those of Goedert et al. (2014), who showed greater PA-induced improvement in patients with response bias than in patients with perceptual bias. This discrepancy becomes apparent when differences in the protocols used are taken into account. Goedert and colleagues (2014) found PA-induced improvement in patients with response bias on the Catherine Bergego Scale (CBS), but they found no differences in the BIT total score (2014). We observed the largest PA-induced improvement in patients with response bias on the BIT-B, which quantifies ecological functioning similarly to the CBS. In addition, the tool we used to classify input- and output-related biases differs from the one used by Goedert and collaborators (2014); there is evidence that different assessment instruments may lead to inconsistent classification of perceptual and response biases (Harvey, 2004). We acknowledge that this version of the Landmark task (Bisiach, Ricci, Lualdi et al., 1998) may not be the optimal tool for distinguishing perceptual from response bias. However, it is a relatively easy, straightforward, and handy test to assess the two biases, especially in clinical setting. A shorter version of the Landmark task that provides a less time-consuming procedure with normative data based on a large group of subjects has been proposed (Capitani et al., 2000). We suggest that future studies consider the different classification procedures to clarify which among them may best meet clinical and experimental needs.

To our knowledge, there have been no studies investigating the influence of VST on perceptual and response-related neglect. However, consistent with our data suggesting that VST tends to modulate response-related behaviour, it is possible that the systematic component of this training recruits anterior brain regions which would be compatible with the finding that VST increases activity in prefrontal and temporal regions involved in goal-directed behaviour (Ekman et al., 2018).

Although the evidence regarding the effectiveness of PA is mixed (Gammeri, Iacono et al., 2020) and the long duration of VST questions its feasibility (Kerkhoff & Schenk, 2012), as in other studies (Priftis et al., 2013; Spaccavento et al., 2016) groups' performance on neuropsychological tests improved after both PA and VST with no differences between groups. Within-subject analyses showed that only PA further enhanced patients' improvement from the end of training to follow-up as measured by the line bisection task. This result is consistent with previous findings (Rossetti et al., 1998; Schintu et al., 2017) suggesting that PA induces adaptive plastic changes that are not limited to the post-training period but are amplified over time, potentially leading to

further improvements, especially in ecological activities (Antonucci et al., 1995; Frassinetti et al., 2002; Jacquin-Courtois et al., 2008; Rabuffetti et al., 2013). However, it is important to consider that the absence of a control group prevented us from completely controlling the blinding of patients, evaluating training efficacy and, since most patients were enrolled in the study during the subacute stage (< 3 months from brain damage), the interaction between spontaneous recovery and intervention's effect cannot be disentangled.

Three other limitations can be highlighted. Despite previous works have recruited a similar number of patients (Priftis et al., 2013; Spaccavento et al., 2016) and a comparison across studies is therefore possible, we are aware that others and our study may be underpowered. Furthermore, the blinding of patients and practitioners was not fully controlled. Adequate blinding is indeed one of major concern in most rehabilitation studies, especially for the application of PA. However, the most modern VR techniques make it possible to partially overcome this limitation, as shown in some recent studies (Bourgeois et al., 2021; Gammeri, Turri et al., 2020). Lastly, the lack of brain scans prevented the computation of correlations between brain lesions' location and neuropsychological outcome, along with symptoms' severity which might have helped to clarify the source of our sample heterogeneity (Gammeri, Iacono et al., 2020). For future studies, we anyway recommend analyzing the behaviour of individual cases, which may reveal individual differences that are not apparent in groups of patients with symptoms of different nature. Furthermore, virtual reality versions of VST (Ekman et al., 2018) and PA (Gammeri, Turri et al., 2020) could provide a valid alternative to better tailor treatment to individual clinical conditions and to better control patient blinding (Bourgeois et al., 2021).

In conclusion, our results show that PA more effectively improves patients' perceptual bias, whereas VST mainly modulates patients' response bias, as measured by the Landmark task. They also suggest that VST is better able to modulate neglect on canonical neuropsychological tasks in patients affected by response bias, while PA may be effective in patients with both types of bias, with the rehabilitation outcomes also dependent on the test used to assess neglect. These findings provide new insights into the efficacy of PA and VST in rehabilitating perceptual and response biases in patients with neglect.

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Disclosure statement

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Appendix

Appendix 1

Neglect patients Landmark pre-training scores and neglect evaluation pre-, post- and follow up scores.

PZ	Landmark-M		Line Bisection			Diller (# / 106)			BIT-C (# / 146)			BIT-B (# / 81)		
	PRE		PRE	POST	FU	PRE	POST	FU	PRE	POST	FU	PRE	POST	FU
	PB	RB												
Visual scanning training group														
S1	97.6**	52.4*	3.6	1.0	−0.1	101	78 (+12.8%)	100 (+0.5%)	13	41 (+51.9%)	31 (+40.9%)	4	23 (+70.4%)	19 (+65.2%)
S2	65.5**	56.0**	0.0	−0.2	−0.1	49	1 (+96.0%)	8 (+71.9%)	127	135 (+3.1%)	128 (+0.4%)	57	68 (+8.8%)	69 (+9.5%)
S3	58.3	51.1	0.8	0.6	0.4	56	38 (+19.1%)	82 (+18.8%)	70	97 (+16.2%)	91 (+13.0%)	63	68 (+3.8%)	69 (+4.5%)
S4	62.5*	53.0**	2.8	2.5	0.8	93	41 (+38.8%)	46 (+33.8%)	51	76 (+19.7%)	88 (+26.6%)	17	44 (+44.3%)	43 (+43.3%)
S5	57.1	50.0	0.4	0.1	0.0	34	7 (+65.9%)	0 (+100%)	66	129 (+32.3%)	133 (+33.7%)	60	66 (+4.8%)	68 (+6.2%)
S6	92.9**	57.1**	6.5	5.1	5.0	40	22 (+29.0%)	12 (+53.8%)	113	125 (+5.0%)	126 (+5.4%)	26	53 (+34.2%)	53 (+34.2%)
S7	64.3**	50.0	1.1	0.8	−0.6	6	4 (+20.0%)	1 (+71.4%)	121	138 (+6.6%)	144 (+8.7%)	65	79 (+9.7%)	79 (+9.7%)
S8	53.6	56.0**	−0.4	0.4	−0.7	94	7 (+86.1%)	1 (+97.9%)	52	132 (+43.5%)	132 (+43.5%)	35	73 (+35.2%)	68 (+32.0%)
S9	67.9**	51.2	1.6	0.5	−0.2	88	73 (+9.3%)	71 (+10.7%)	42	58 (+16.0%)	77 (+29.4%)	25	23 (−4.2%)	37 (+19.4%)
Prism adaptation group														
S10	88.1**	57.1**	4.4	0.4	−1.6	44	43 (+1.1%)	10 (+63.0%)	90	109 (+9.5%)	121 (+14.7%)	23	37 (+23.3%)	58 (+43.2%)
S11	44.0°	56.0**	3.0	−2.1	−3.0	22	6 (+57.1%)	0 (+100%)	121	116 (−2.1%)	118 (−1.3%)	53	73 (+15.9%)	66 (+10.9%)

S12	60.7*	48.8	1.5	0.7	0.1	25	5 (+66.7%)	3 (+78.6%)	105	119 (+6.3%)	119 (+6.3%)	31	42 (+15.1%)	51 (+24.4%)
S13	70.3**	55.5**	1.6	1.9	2.0	25	24 (+2.0%)	17 (+19.0%)	74	119 (+23.3%)	91 (+10.3%)	22	55 (+42.9%)	62 (+47.6%)
S14	42.9°	50.0	1.6	08	0.4	56	12 (+64.7%)	5 (+83.6%)	100	113 (+6.1%)	98 (−1.0%)	65	65 (+0.0%)	68 (+2.3%)
S15	58.3	60.7**	0.2	0.6	0.4	58	20 (+48.7%)	30 (+31.8%)	57	87 (+20.8%)	77 (+14.9%)	14	32 (+39.1%)	45 (+52.5%)
S16	98.8**	48.8	5.7	7.8	4.9	82	7 (+84.3%)	24 (+54.7%)	64	117 (+29.3%)	120 (+30.4%)	39	46 (+8.2%)	57 (+18.8%)
S17	63.1*	51.1	2.7	−0.7	−0.8	43	13 (+53.6%)	9 (+65.4%)	86	114 (+14.0%)	122 (+17.3%)	47	67 (+17.5%)	61 (+13.0%)
S18	46.9	58.3**	1.8	−1.0	−1.0	98	42 (+40.0%)	28 (+55.6%)	39	83 (+36.1%)	129 (+53.6%)	13	50 (+58.7%)	74 (+70.1%)

Landmark-M: PB = Perceptual Bias; RB = Response Bias; FU = Follow up; */** medium/strong bias in the direction expected with left neglect; °/°° medium/strong bias in the direction expected with right neglect. *S* = Subject. *Line Bisection*: positive values indicate rightward deviation; negative values indicate leftward deviation. *Diller*: scores indicate the sum of right and left omissions; percentages in POST and FU indicate the relative difference in the number of omissions with respect to baseline (PRE) for each subject. *BIT-C/B*: percentages in POST and FU indicate the relative difference in score with respect to baseline (PRE) for each subject.

Appendix 2

Crawford t-test comparing each patient' score to the normative sample from Bisiach et al. (1998).

	Perceptual bias			Response bias		
	Pre	Post	Follow-up	Pre	Post	Follow-up
VST group						
S1	$t = 11.649, (p < 0.001)^{***}$ $z_{cc} = 11.936 (8.145-15.719)$	$t = 6.407 (p < 0.001)^{***}$ $z_{cc} = 6.565 (4.445-8.675)$	$t = 9.187 (p < 0.001)^{***}$ $z_{cc} = 9.414 (6.410-12.408)$	$t = 2.537 (p = 0.020)^* z_{cc} = 2.600 (1.662-3.522)$	$t = -2.785 (p = 0.012)^* z_{cc} = -2.855 (-3.848 \text{ to } -1.846)$	$t = 0.399 (p = 0.694) z_{cc} = 0.409 (0.053-0.861)$
S2	$t = 3.326 (p = 0.004)^{**} z_{cc} = 3.408 (2.241-4.562)$	$t = 0.259 (p = 0.799) z_{cc} = 0.265 (-0.184-0.708)$	$t = 0.246 (p = 0.808) z_{cc} = 0.252 (-0.197-0.694)$	$t = 5.687 (p < 0.001)^{***} z_{cc} = 5.827 (3.934-7.710)$	$t = -0.657 (p = 0.519) z_{cc} = -0.673 (-1.153 \text{ to } -0.179)$	$t = -4.871 (p < 0.001)^{***} z_{cc} = -4.992 (-6.618 \text{ to } -3.352)$
S3	$t = 1.475 (p = 0.156) z_{cc} = 1.512 (0.855-2.151)$	$t = 1.488 (p = 0.153) z_{cc} = 1.525 (0.865-2.167)$	$t = 0.554 (p = 0.586) z_{cc} = 0.568 (0.088-1.035)$	$t = 1.384 (p = 0.182) z_{cc} = 1.418 (0.783-2.035)$	$t = 3.558 (p = 0.002)^{**} z_{cc} = 3.645 (2.409-4.869)$	$t = 4.631 (p < 0.001)^{***} z_{cc} = 4.745 (3.1881-6.299)$

(Continued)

Continued.

	Perceptual bias			Response bias		
	Pre	Post	Follow-up	Pre	Post	Follow-up
S4	$t = 2.563$ ($p = 0.019$)* $z_{cc} = 2.626$ (1.681–3.555)	$t = 2.951$ ($p = 0.008$)** $z_{cc} = 3.024$ (1.967–4.066)	$t = 4.166$ ($p = 0.001$)** $z_{cc} = 4.218$ (2.811–5.611)	$t = 3.070$ ($p = 0.006$)** $z_{cc} = 3.145$ (2.054–4.223)	$t = 1.295$ ($p = 0.211$) $z_{cc} = 1.327$ (0.712–1.924)	$t = -2.032$ ($p = 0.056$) $z_{cc} = -2.082$ (–2.863 to –1.284)
S5	$t = 1.175$ ($p = 0.254$) $z_{cc} = 1.204$ (0.615–1.775)	$t = 0.867$ ($p = 0.397$) $z_{cc} = 0.889$ (0.360–1.401)	$t = -0.981$ ($p = 0.339$) $z_{cc} = -1.005$ (–1.538 to –0.455)	$t = 0.408$ ($p = 0.688$) $z_{cc} = 0.418$ (–0.045–0.871)	$t = -6.991$ ($p < 0.001$)** $z_{cc} = -7.164$ (–9.459 to –4.859)	$t = -6.982$ ($p < 0.001$)** $z_{cc} = -7.155$ (–9.447 to –4.853)
S6	$t = 10.419$ ($p < 0.001$)** $z_{cc} = 10.676$ (7.279–14.065)	$t = 11.962$ ($p < 0.001$)** $z_{cc} = 12.257$ (8.365–16.141)	$t = 8.265$ ($p < 0.001$)** $z_{cc} = 8.469$ (5.760–11.170)	$t = 6.743$ ($p < 0.001$)** $z_{cc} = 6.909$ (4.683–9.126)	$t = 1.464$ ($p = 0.160$) $z_{cc} = 1.500$ (0.846–2.136)	$t = -9.102$ ($p < 0.001$)** $z_{cc} = -9.327$ (–12.295 to –6.351)
S7	$t = 3.029$ ($p = 0.007$)* $z_{cc} = 3.103$ (2.024–4.168)	$t = 3.029$ ($p = 0.007$)* $z_{cc} = 3.103$ (2.024–4.168)	$t = 1.175$ ($p = 0.254$) $z_{cc} = 1.204$ (0.615–1.775)	$t = 0.408$ ($p = 0.688$) $z_{cc} = 0.418$ (–0.045–0.871)	$t = 2.520$ ($p = 0.021$)* $z_{cc} = 2.582$ (1.649–3.499)	$t = -1.703$ ($p = 0.105$) $z_{cc} = -1.745$ (–2.440 to –1.033)
S8	$t = 0.251$ ($p = 0.804$) $z_{cc} = 0.257$ (–0.192–0.700)	$t = -1.289$ ($p = 0.213$) $z_{cc} = -1.321$ (–1.917 to –0.707)	$t = 0.559$ ($p = 0.583$) $z_{cc} = 0.573$ (0.092–1.041)	$t = 5.687$ ($p < 0.001$)** $z_{cc} = 5.827$ (3.934–7.710)	$t = 2.520$ ($p = 0.021$)* $z_{cc} = 2.582$ (1.649–3.499)	$t = -1.703$ ($p = 0.105$) $z_{cc} = -1.745$ (–2.440 to –1.033)
S9	$t = 3.950$ ($p = 0.001$)* $z_{cc} = 4.048$ (2.692–5.391)	$t = 3.948$ ($p = 0.001$)* $z_{cc} = 4.045$ (2.690–5.387)	$t = -0.057$ ($p = 0.955$) $z_{cc} = -0.058$ (–0.496–0.381)	$t = 1.455$ ($p = 0.162$) $z_{cc} = 1.491$ (0.839–2.125)	$t = 3.575$ ($p = 0.002$)* $z_{cc} = 3.664$ (2.422–4.892)	$t = 2.520$ ($p = 0.021$)* $z_{cc} = 2.582$ (1.649–3.499)
PA group						
S10	$t = 9.187$ ($p < 0.001$)** $z_{cc} = 9.414$ (6.410–12.408)	$t = 4.245$ ($p < 0.001$)* $z_{cc} = 4.350$ (2.904–5.784)	$t = 2.394$ ($p = 0.027$)* $z_{cc} = 2.454$ (1.556–3.335)	$t = 6.743$ ($p < 0.001$)** $z_{cc} = 6.909$ (4.683–9.126)	$t = -1.765$ ($p = 0.094$) $z_{cc} = -1.809$ (–2.520 to –1.080)	$t = -3.850$ ($p = 0.001$)* $z_{cc} = -3.945$ (–5.258 to –2.620)
S11	$t = -2.226$ ($p = 0.038$)* $z_{cc} = -2.281$ (–3.115 to –1.430)	$t = -0.984$ ($p = 0.338$) $z_{cc} = -1.008$ (–1.541 to –0.458)	$t = -0.362$ ($p = 0.721$) $z_{cc} = -0.371$ (–0.820–0.087)	$t = 5.731$ ($p < 0.001$)** $z_{cc} = 5.873$ (3.965–7.770)	$t = 5.687$ ($p < 0.001$)** $z_{cc} = 5.827$ (3.934–7.710)	$t = 3.602$ ($p = 0.002$)* $z_{cc} = 3.691$ (2.441–4.928)
S12	$t = 2.099$ ($p = 0.049$)* $z_{cc} = 2.151$ (1.335–2.950)	$t = -0.057$ ($p = 0.955$) $z_{cc} = -0.058$ (–0.496–0.381)	$t = -0.057$ ($p = 0.955$) $z_{cc} = -0.058$ (–0.496–0.381)	$t = -0.648$ ($p = 0.525$) $z_{cc} = -0.664$ (–1.142 to –0.171)	$t = 0.408$ ($p = 0.688$) $z_{cc} = 0.418$ (–0.045–0.871)	$t = -1.703$ ($p = 0.105$) $z_{cc} = -1.745$ (–2.440 to –1.033)
S13	$t = 4.569$ ($p < 0.001$)* $z_{cc} = 4.682$ (3.136–6.215)	$t = 5.180$ ($p < 0.001$)* $z_{cc} = 5.308$ (3.573–7.032)	$t = -0.072$ ($p = 0.943$) $z_{cc} = -0.074$ (–0.512–0.366)	$t = 5.243$ ($p < 0.001$)* $z_{cc} = 5.373$ (3.618–7.117)	$t = -7.035$ ($p < 0.001$)** $z_{cc} = -7.209$ (–9.518 to –4.890)	$t = 15.153$ ($p < 0.001$)* $z_{cc} = 15.527$ (10.610–20.436)
S14	$t = -2.521$ ($p = 0.021$)* $z_{cc} = -2.584$ (–3.501 to –1.650)	$t = -1.905$ ($p = 0.072$) $z_{cc} = -1.952$ (–2.699 to –1.187)	$t = -2.829$ ($p = 0.011$)* $z_{cc} = -2.899$ (–3.906 to –1.878)	$t = 0.408$ ($p = 0.688$) $z_{cc} = 0.418$ (–0.045–0.871)	$t = 0.408$ ($p = 0.688$) $z_{cc} = 0.418$ (–0.045–0.871)	$t = 1.464$ ($p = 0.160$) $z_{cc} = 1.500$ (0.846–2.136)
S15	$t = 1.486$ ($p = 0.154$) $z_{cc} = 1.523$ (0.863–2.164)	$t = 0.559$ ($p = 0.583$) $z_{cc} = 0.573$ (0.092–1.041)	$t = 1.483$ ($p = 0.154$) $z_{cc} = 1.520$ (0.861–2.160)	$t = 9.910$ ($p < 0.001$)** $z_{cc} = 10.155$ (6.920–13.380)	$t = -1.703$ ($p = 0.105$) $z_{cc} = -1.745$ (–2.440 to –1.033)	$t = -0.648$ ($p = 0.262$) $z_{cc} = -0.664$ (–1.142 to –0.171)
S16	$t = 11.962$ ($p < 0.001$)** $z_{cc} = 12.257$ (8.365–16.141)	$t = 5.798$ ($p < 0.001$)* $z_{cc} = 5.942$ (4.013–7.860)	$t = 2.099$ ($p = 0.049$)* $z_{cc} = 2.151$ (1.335–2.950)	$t = -0.648$ ($p = 0.262$) $z_{cc} = -0.664$ (–1.142 to –0.171)	$t = -0.648$ ($p = 0.262$) $z_{cc} = -0.664$ (–1.142 to –0.171)	$t = 1.455$ ($p = 0.162$) $z_{cc} = 1.491$ (0.839–2.125)
S17	$t = 2.718$ ($p = 0.014$)* $z_{cc} = 2.785$ (1.796–3.759)	$t = -1.289$ ($p = 0.213$) $z_{cc} = -1.321$ (–1.917 to –0.707)	$t = 0.867$ ($p = 0.397$) $z_{cc} = 0.889$ (0.360–1.401)	$t = 1.402$ ($p = 0.177$) $z_{cc} = 1.436$ (0.797–2.058)	$t = 9.910$ ($p < 0.001$)** $z_{cc} = 6.909$ (4.683–9.126)	$t = 1.464$ ($p = 0.160$) $z_{cc} = 1.500$ (0.846–2.136)
S18	$t = -2.244$ ($p = 0.037$)* $z_{cc} = -1.504$ (–2.141 to –0.849)	$t = 1.175$ ($p = 0.254$) $z_{cc} = 1.204$ (0.615–1.775)	$t = 0.251$ ($p = 0.804$) $z_{cc} = 0.889$ (0.360–1.401)	$t = 7.798$ ($p < 0.001$)* $z_{cc} = 7.991$ (5.430–10.543)	$t = 8.854$ ($p < 0.001$)* $z_{cc} = 9.073$ (6.175–11.961)	$t = 3.575$ ($p = 0.002$)* $z_{cc} = 3.664$ (2.422–4.892)