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Presence of Motor-Intentional Aiming Deficit Predicts Functional Improvement of Spatial Neglect with Prism Adaptation

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Abstract

Spatial neglect is a debilitating disorder for which there is no agreed upon course of rehabilitation. The lack of consensus on treatment may result from systematic differences in the syndromes' characteristics, with spatial cognitive deficits potentially affecting perceptual-attentional *Where* or motor-intentional *Aiming* spatial processing. Heterogeneity of response to treatment might be explained by different treatment impact on these dissociated deficits: prism adaptation, for example, might reduce Aiming deficits without affecting Where spatial deficits. Here, we tested the hypothesis that classifying patients by their profile of Where-vs-Aiming spatial deficit would predict response to prism adaptation, and specifically that patients with Aiming bias would have better recovery than those with isolated Where bias. We classified the spatial errors of 24 sub-acute right-stroke survivors with left spatial neglect as: 1) isolated Where bias, 2) isolated Aiming bias or 3) both. Participants then completed two weeks of prism adaptation treatment. They also completed the Behavioral Inattention Test (BIT) and Catherine Bergego Scale (CBS) tests of neglect recovery weekly for six weeks. As hypothesized, participants with only Aiming deficits improved on the CBS, whereas, those with only Where deficits did not improve. Participants with both deficits demonstrated intermediate improvement. These results support behavioral classification of spatial neglect patients as a potential valuable tool for assigning targeted, effective early rehabilitation.

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Keywords

spatial neglect; prism adaptation; spatial cognition; lesion mapping; motor-intentional; stroke rehabilitation

Introduction

Spatial neglect is a debilitating cognitive disorder in which impaired contralesional response, reporting, or action causes functional disability. Stroke survivors with neglect experience longer hospitalizations and poorer rehabilitation outcomes., While treatment may reduce neglect severity,, there is not yet consensus on the best clinical standards for rehabilitation to restore daily life function.

Translational block affects treatment trial validity

Studies of neglect treatment might yield conflicting findings regarding its efficacy because treatments may differently affect distinct brain-based spatial processing systems. Because neglect may result from deficits in one or more brain-behavior systems supporting different stages of spatial-cognitive information processing,, considering its taxonomy should be an early step in designing treatment trials. Both group assignment and outcome measures must be designed to be sensitive to differences in neglect subtypes. We are unaware of any spatial neglect treatment trials designed to take deficit profiles into account: this may have reduced the ability of prior neglect studies to detect treatment effects.

Classification of spatial neglect deficits is based on analyzing abnormal spatial behaviors and can be laboratory-based, but is also relevant to examination at the bedside., Impairment of input-related stages of information processing may lead to deficits in the spatial distribution of attention and perception, affecting stimulus encoding: These are Where spatial deficits. They include difficulty with contralesional perceptual awareness, difficulty focusing or disengaging spatial attention, and a reduced capacity to allocate perceptual resources across the entire spatial field.– Impairment at output-related stages disturbs spatial action planning and execution.,,, These are motor-intentional, or Aiming, deficits, which can potentially affect the limbs, body, and eyes. They include impairment of movement of the contralesional body (limb akinesia); impairment in the gain, duration, or force of movements in contralesional space referenced to body center (hemispatial hypokinesia); and impairment of contralesionally-directed movements performed in either contralesional or ipsilesional space (directional hypokinesia).

Does Prism Adaptation Treatment (PAT) target Aiming neglect symptoms?

Prism adaptation is a promising spatial neglect treatment reported to exert long-lasting benefits that generalize beyond the laboratory to self-care, navigation, and other functional tasks.– Nevertheless, not all efficacy studies reported that neglect improved with prism treatment., Even in responsive patients, PAT may not ameliorate all neglect symptoms: this may be related to a specific effect of PAT on Aiming, but not Where, bias.,, Using a computerized line bisection task that separately quantifies Where and Aiming spatial biases, we demonstrated that five participants with left neglect experienced an improvement in

Aiming bias after two sessions of PAT, with no reliable change in Where bias. This specific effect of prism adaptation on Aiming bias was also observed in a large group of neurologically healthy individuals.

Objective

The current study addressed a major block in translation of prism adaptation to the clinical setting. We asked whether classifying patients by their spatial deficit profile (Where versus Aiming) predicted improvement following PAT. Neglect patients completed a computerized line bisection task for assessing their Where and Aiming spatial biases prior to two weeks of PAT, allowing for classification based on their baseline deficit. The Behavioral Inattention Test (BIT) and the Catherine Bergego Scale (CBS), were administered weekly thereafter for a total of six follow-up assessments. Because prism adaptation may specifically target Aiming bias in neglect, we hypothesized that participants with Aiming deficits would show greater improvement than those with isolated Where deficits.

Method

The study was approved by the institutional review boards of the Kessler Foundation and Seton Hall University.

Participants

A consecutive sample of 24 right-brain-damaged stroke survivors was recruited from inpatient rehabilitation hospitals. The participants (17 men; 7 women; aged 30 to 90, all premorbidly right-handed) were screened for neglect and hemianopia 6–47 days post stroke (see *Neglect Assessment* below). Patients demonstrating rightward error on the computerized line bisection task and presenting with spatial neglect (BIT≤129 or CBS>1) were included. Patients more than 60 days post-stroke, with left hemisphere lesions, a prior history of neurological or psychiatric conditions, or uncorrected ocular disorders were excluded. Patients with leftward line bisection error were also excluded, as these errors suggest ipsilesional neglect, which may be associated with different clinical and recovery characteristics.

Prism Adaptation Treatment

Participants received PAT once daily for ten days, using the procedure described in Chen et al. Each PAT session lasted 15 to 20 minutes.

Computerized Line Bisection: Where & Aiming Bias Assessment

Participants performed computerized line bisection prior to PAT. Sitting at a computer monitor, they bisected 32 horizontal lines (subtending 23.6° of visual angle) under normal and reversed viewing conditions. Lines appeared centrally, one at a time, and participants clicked on the line's center using a wireless mouse. Participants' direct view of their hand was occluded by a cardboard shelf. Thus, they needed to watch the monitor for visual feedback. Under normal viewing, the cursor on the monitor moved in the same direction as the mouse. Under reversed conditions, visual feedback was left-right reversed, such that rightward movements of the mouse resulted in leftward movements of the cursor and vice versa. This task has demonstrated research utility and construct validity to assess Where and Aiming bias in neglect patients, and healthy controls., Participants' line bisection error across 16 normal and reversed trials was averaged and fractionated into Where and Aiming components (mm equivalents) as follows:,,,,

$$\text{Normal Viewing Error} = \text{Where Bias} + \text{Aiming Bias} \quad \text{Eq. 1}$$

$$\text{Reversed Viewing Error} = \text{Aiming Bias} - \text{Where Bias} \quad \text{Eq. 2}$$

Neglect Assessment

Neglect was assessed with the BIT and CBS (via the Kessler Foundation-Neglect Assessment Process) at study entry (screening, session 1), re-assessed just prior to PAT (baseline, session 2), and then weekly thereafter for five weeks, for a total of six post-screening assessments. The BIT-Conventional is a paper-and-pencil test consisting of six sub-tests: line crossing, letter cancellation, star cancellation, figure/shape copying, line bisection and representational drawing (higher scores indicate better function). The CBS assesses neglect-specific functional impairment (e.g. dressing the left side of the body, eating from the left side of a plate). It was completed by occupational therapists, blind to the purpose of the study and reliability-trained by our research staff, who rated participants' performance for left-sided stimuli and actions (10 items, scored on a 0 to 3 scale, with *0* indicating *no neglect* and *3* indicating *severe neglect*). Lower scores indicate better function.

Data Analysis

As recently emphasized, a major translational block to valid neglect treatment research is the widespread use of statistical techniques that are inappropriate for analyzing longitudinal trajectories of improvement in heterogeneous subject groups for whom there is high within-subject intra-correlation of dependent measures. To avoid this pitfall, participants' recovery trajectories were analyzed with mixed linear modeling (MLM) using STATA/IC 12.1. The primary analytic goal was to determine whether classifying patients on the basis of Where and Aiming biases predicted neglect improvement following PAT (i.e., sessions two through seven). Thus, participants were coded as to whether they had a rightward Where bias (Where bias greater than zero) and whether they had a rightward Aiming bias. Participants' bias type was then categorized: isolated Where bias (n = 7), isolated Aiming Bias (n = 5), or both Where and Aiming biases (n = 12). Group equivalence was tested prior to treatment with non-parametric Kruskal-Wallis tests on the screening characteristics.

Estimating Spontaneous Recovery Rate

The analyses took into account the possible confounding effects of spontaneous recovery using an estimate of each participant's spontaneous recovery rate between the screening (session 1) and baseline (session 2) assessments. Session 1 occurred within 48 hours of participants' consenting and Session 2 just prior to PAT, with an average of 15 days between

(SD = 6.02). Separate spontaneous recovery rates on the BIT and CBS were calculated for each participant:

$$\text{Spontaneous recovery rate} = \frac{\textit{Difference In Neglect Score at Sessions 1 and 2}}{\textit{Number of Days Between Sessions 1 and 2}}$$

Higher values on this measure indicate greater per-day improvement between sessions one and two.

MLM Analyses

The MLM employed an unstructured covariance structure and maximum likelihood estimation, and it included participants' random intercepts and slopes. The F distribution with between-within denominator degrees of freedom was used to assess significance of fixed effects parameters.,

The predictors of theoretical interest were the effects of bias type and the bias type by session interaction. The covariates were participants' spontaneous recovery rate and its interaction with assessment session (two through seven). Preliminary analyses identified potential additional covariates by separately testing the ability of age, gender, days-post-stroke, lesion volume, and baseline deficit (as assessed at screening) to predict the CBS and BIT on their own. Variables that acted as significant predictors when entered on their own were introduced as potential covariates.

We predicted that participants with Aiming bias would experience more improvement. Thus, the Aiming Only and Aiming+Where groups were expected to improve more than the Where Only group (i.e., a bias type by assessment session interaction). If this interaction were observed, planned orthogonal contrasts of the linear recovery trajectories would specifically test the hypothesis: one contrast comparing the two groups with Aiming bias to the Where Only group, and a second comparing the Aiming Only to the Aiming+Where group.

Lesion Mapping

Participants underwent standard clinical radiological exams (MRI and/or CT). Lesions were evaluated by selecting brain scans showing the greatest lesion extent. Lesion borders were manually mapped from clinical scans onto transverse brain images in MRIcro and then transposed to the standard brain template using a combination of MRIcro and Montreal Neurological Institute space. A "double-strain" lesion mapping method was performed. Three technicians, blind to patients' behavioral classifications, manually mapped out individual lesions, followed by conferencing with an independent neurologist to ensure accuracy. Lastly, two-dimensional MRIcro maps were transformed to three-dimensional maps (voxel of interest format) using MRIcron. Lesion location was identified using an anatomical checklist and lesion volume (voxels) was calculated from the lesion map. The normalized lesion images were used for subsequent group overlap in MRIcro.

RESULTS

Participant Characteristics

See Table 1 for participant characteristics at screening and Figures 1 to 3 for their lesion maps. The groups differed in average age, with Where Only older than both Aiming Only (p = .019) and Aiming+Where (p = .018) participants, who did not differ (p = .752). The groups also differed in their Aiming and Where bias, as expected.

MLM Predicting CBS

CBS scores were positively skewed and non-normal [joint test of normality in skewness and kurtosis: χ^2 *(2)*=9.33, *p*<.009]. Taking the square-root transform improved the distribution's shape [χ^2 *(2)*=2.79, *p*=.248]. Therefore, all analyses were performed with the square-root transformed CBS. For ease of interpretation, figures reflect CBS scores transformed back into their original scale.

CBS scores showed high within-subject correlation across sessions [intra-class correlation coefficient (ICC) of 0.67]. The preliminary MLM analyses to identify potential covariates revealed that both age (*p* = .008) and baseline CBS (*p* < .001) predicted average CBS performance across assessment sessions two through seven, while gender (*p* = .630), days-post-stroke (*p* = .539), and lesion volume (*p* = .171) did not. Thus, age and baseline deficit were entered as covariates into the main analysis. Additionally, because residual diagnostics revealed heteroskedasticity among the different bias types, the MLM employed a residual covariance structure that allowed different variances for each bias type.

Results of the analysis are depicted in Table 2. Consistent with our hypothesis, there was a bias type by session interaction (Figure 4). Planned contrasts showed that the Aiming Only and Aiming+Where participants differed significantly from the Where Only, *z*= −2.60, *p*=.009, but not from each other, *z*= −1.02, *p*=.306. Aiming Only participants had the steepest linear recovery, *β*= −0.56, *b*= −0.41, *SE*=.17, *CI*:−0.73,−0.08, *z*= −2.44, *p*=.015, while Where Only participants had a slope that did not differ from zero, *β*= −0.11, *b*= −0.08, *SE*=.17, *CI*:−0.42,0.24, *z*= −.52, *p*=.516. Participants with Aiming+Where bias had an intermediate slope, *β*= −0.41, *b*= −0.30, *SE*=.16, *CI*:−0.61,0.01, *z*= −1.89, *p*=.058. These results support our hypothesis: participants with a rightward Aiming bias showed greater improvement with PAT.

There were also main effects of baseline CBS and spontaneous recovery rate on the average CBS score across all sessions (Table 2). Participants with poorer CBS scores at screening tended to have poorer CBS scores averaged over sessions two through seven. Participants with greater recovery before PAT tended overall to have better CBS scores across assessments two to seven. The lack of significant interaction between spontaneous recovery rate and session indicates that spontaneous recovery, as assessed prior to the treatment, did not predict change after PAT.

Alternate Explanations for CBS Improvement

Although the a priori criterion for inclusion of potential covariates was that they independently predict CBS over assessment sessions, post-hoc analyses were performed to exclude the alternate explanations that potential group differences in age or lesion volume accounted for the differential improvement among the bias types. An MLM with the effects of age, bias type, session, and the bias type by session and age by session interactions, revealed a non-significant age by session interaction (p=.508), but significant bias type by session interaction (p=.050), with slopes for each bias type similar to those in the main analysis. Thus, the differential improvement we observed for the bias types cannot be attributed to age-related changes: Age did not predict improvement across assessments, but controlling for age-related improvements, bias type continued to predict improvement across the assessments.

A similar MLM tested for the effects of lesion volume. The lesion volume by session interaction did not reach significance (p=.133), but the bias type by session interaction did (p=.003), with slopes for each bias type similar to those observed in the main analysis. Thus, the differential improvement observed for the bias types cannot be attributed to lesion-volume related improvements in CBS scores.

MLM Predicting BIT

Preliminary analyses revealed that BIT scores were significantly non-normal [joint test of normality in skewness and kurtosis: $\chi^2(2)$=16.34, p<.001]. No transformation improved the shape of the distribution. Therefore, analyses of the BIT employed bootstrapped estimates of the standard errors. A limitation of this method is that it does not allow for modeling of random slopes (only random intercepts).

As with the CBS, there was high within-subject correlation of BIT scores (ICC=0.91). Preliminary MLM analyses to identify potential covariates identified only baseline BIT as a significant predictor of averaged BIT performance (p<.001), while gender (p=.355), days-post-stroke (p=.082), lesion volume (p=.597), and age (p=.142) did not. Although age did not significantly predict BIT scores on its own, because of baseline age differences, it was included as a covariate in the main analysis.

Contrary to the hypothesis, bias type failed to predict differences in linear improvement across assessment sessions on the BIT, (p=.551 for the bias type by session interaction). However, there was a significant linear effect of session, β=0.50, b=10.029, SE=3.96, p<.001, indicating that, as a group, participants BIT scores improved after PAT. There was also a trend on the quadratic effect of session, β= −0.35, b= −.767, SE=.390, p<.10. Similar to the CBS, there were effects of baseline status and spontaneous recovery rate: Participants with better screening BIT scores had better BIT throughout, β=0.90, b=0.856, SE=0.098, p<.001. Likewise, participants with better spontaneous recovery between sessions one and two had higher scores across the assessment sessions, β=0.44, b=9.532, SE=1.852, p<.001. Furthermore, spontaneous recovery in BIT did not predict change across sessions two through seven, β=0.03, b=0.127, SE=.263, p=.567.

GENERAL DISCUSSION

It's been previously argued that sorting patients from neglect treatment studies into groups based on their specific neglect characteristics may be useful for predicting treatment response. Here, we predicted that patients with Aiming deficits would experience greater recovery after PAT than those with isolated Where deficits. Participants' performance on the CBS is consistent with this hypothesis: Participants with Aiming bias had steeper recovery trajectories than did those without Aiming bias. Furthermore, participants with isolated Where spatial deficits failed to show improvements. These results are consistent with prior work demonstrating that PAT improved Aiming, but not Where, spatial dysfunction.

While Where and Aiming spatial biases predicted different patterns of recovery on the CBS, they did not do so for the BIT, a paper-and-pencil test of neglect. It is possible that the CBS may be more sensitive to detect neglect (and neglect improvement), especially body-based, motor-exploratory or functional deficits, as compared to paper-and-pencil tests.[,] Consistent with this argument, the quadratic component on assessment session approached significance for the BIT, but not CBS. This pattern suggests those with Aiming deficits were still improving on the CBS, but that participants' improvement on the BIT was plateauing. In their Cochrane review, Bowen and Lincoln contended that evaluating functional outcomes may be critical in determining neglect treatment value, a view consistent with our results.

The data underscore the importance of finding a match between cognitive mechanisms targeted by a treatment and patients' cognitive impairments. However, classifying patients requires an assessment that identifies specific information-processing deficits. Thus, the findings here support substituting modality-specific cognitive assessment for the generic, composite cognitive screening tools, typically employed in many health outcome studies. Such classification may be important for identifying not only which patients will respond positively to a treatment, but may help clarify the negative impact of treatment for sub-groups of patients: Treatments improving function in one brain-behavior system may simultaneously adversely affect other neuroanatomic systems.[,]

Neural Mechanisms

Where and Aiming spatial deficits may be supported by dissociable neuroanatomic systems. Heilman and colleagues,[,] first proposed an Aiming, motor-intentional set of neglect deficits critically linked to lesions affecting frontal, rather than parietal cortex, and affecting subcortical regions. Subsequent reports partially supported an association between motor-intentional impairment and damage to anterior dorsolateral prefrontal and subcortical sites.[–] However, Aiming motor-intentional deficits were also reported in association with parietal and temporal cortical lesions.[–] Similarly while, Where, perceptual-attentional impairment was frequently associated with damage to posterior parietal or temporal cortical regions,[–,] this form of impairment has also been associated with more anterior lesions.

The small sample size within the groups of the current study precluded systematic analysis of the lesion-behavior associations. Nonetheless, Figures 1 through 3 illustrate that even within groups showing similar behavioral deficits, there was much variety in the lesion locations. Where and Aiming function are each likely supported by a network of interacting brain areas.– Damage in any one of the component areas of the network may result in Where or Aiming deficits. Previously, we demonstrated a complex association: frontal lobe lesions that spared medial temporal sites, including the basal ganglia, predicted better PAT response in spatial neglect. That study did not analyze participants' pattern of spatial deficits, but suggests that analyzing both lesioned and spared regions may be necessary to understand neuroanatomic PAT response predictors. Ideally, future research will include larger groups of patients having a range of representative lesions, in order to assess neuroanatomic-behavioral correlations.

Conclusions and Implications for Clinical Trials

The results of the current study suggest patients with spatial neglect and Aiming spatial biases may experience the most benefit from treatment with prism adaptation therapy (PAT). PAT may be ineffective in improving function for patients with isolated perceptual-attentional Where bias. While neglect severity and lesion location also mediate response to prism adaptation,, these factors are commonly considered when designing clinical trial research investigating rehabilitations for these patients. However, since other neglect treatments also target specific spatial neglect deficits, classifying deficits using modality-specific measures may be an important part of any trial intending to obtain the most valid, applicable, and valuable results for neglect care. Aiming spatial neglect also adversely affects motor function and self-care measures. Thus, in the future it may be appropriate for biological stroke treatment trials enrolling diverse patient groups to consider stratification of patients based on initial classification of spatial processing deficits.

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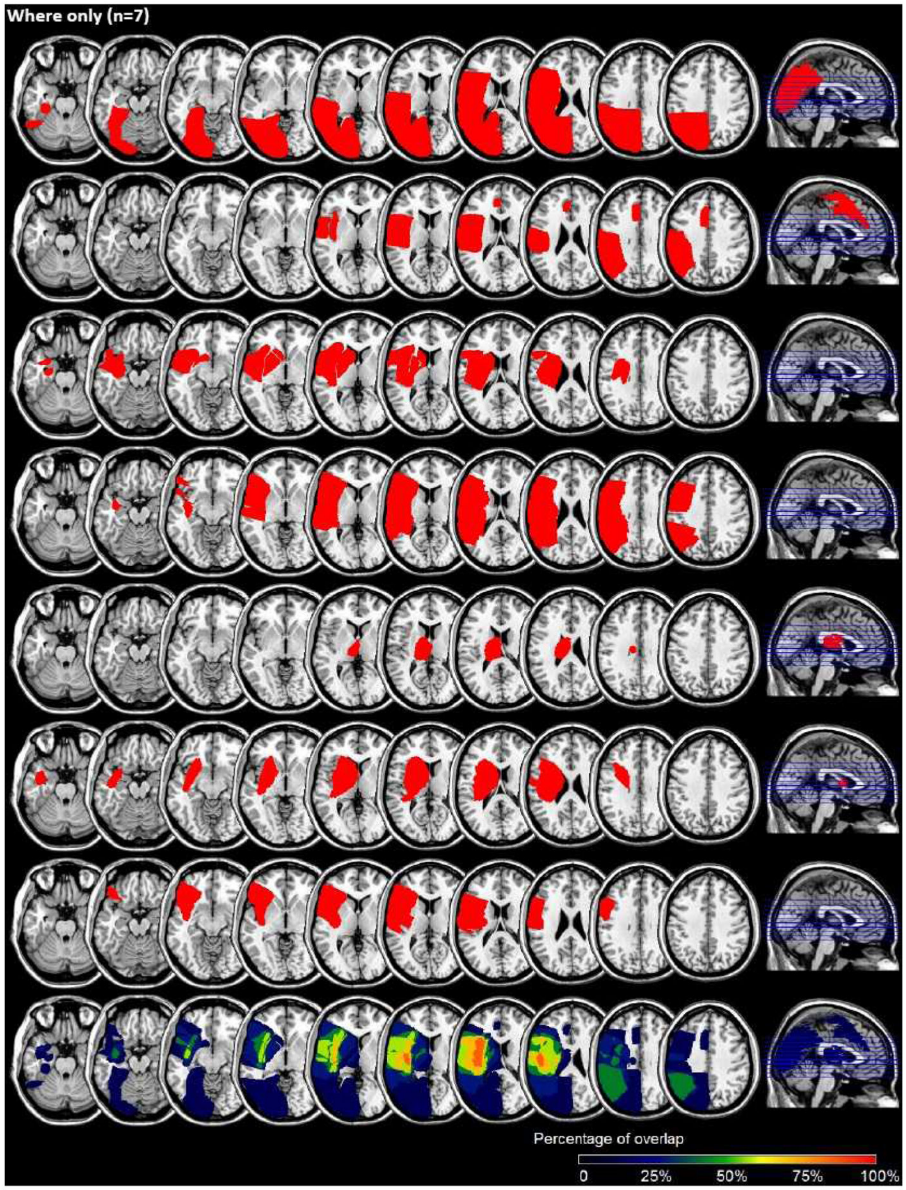

Figure 1.
Individual lesions (rows 1–7) and group overlap (row 8) for Where Only participants ($n = 7$).

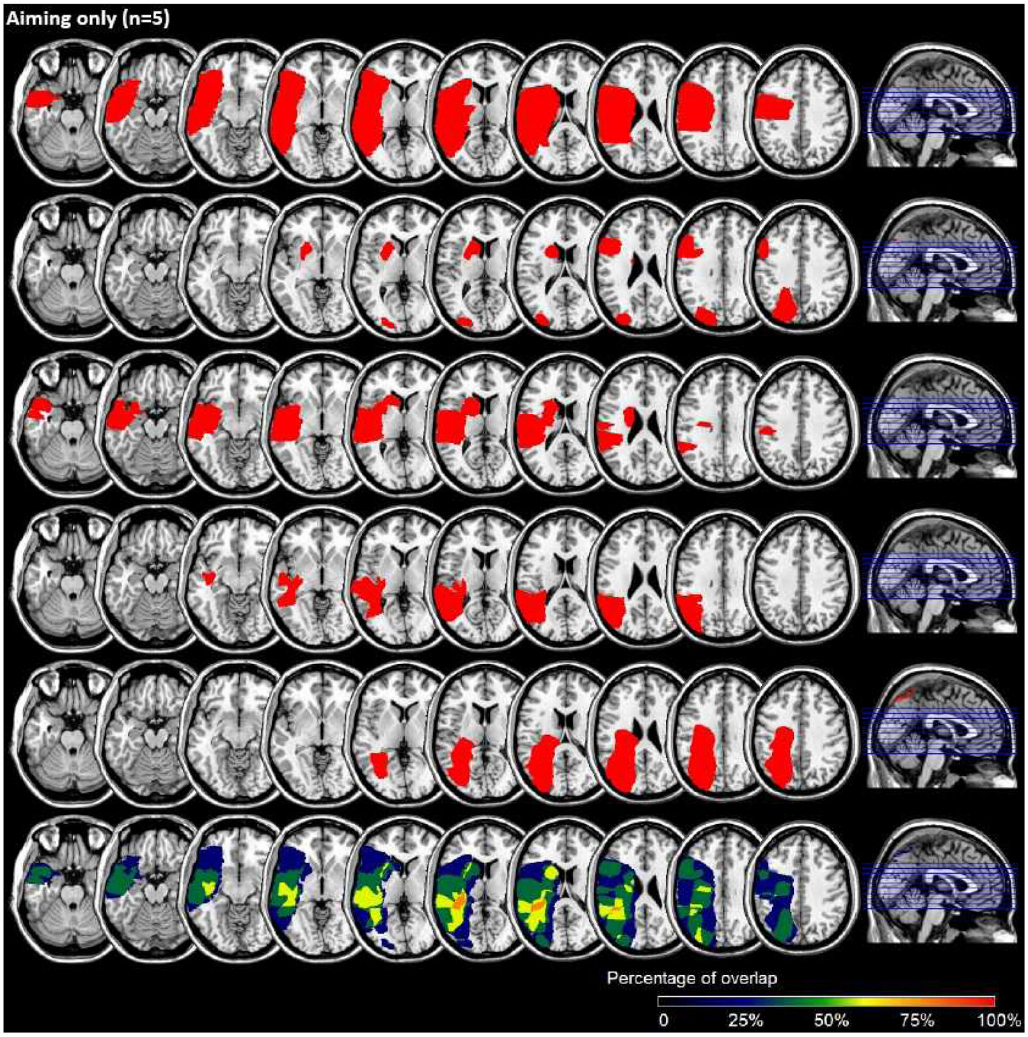

Figure 2.
Individual lesions (rows 1–5) and group overlap (row 6) for Aiming Only participants (n = 5).

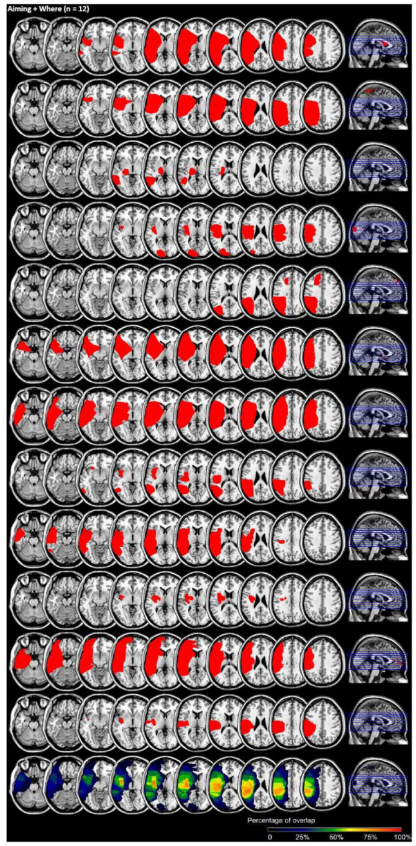

Figure 3.

Individual lesions (rows 1–12) and group overlap (row 13) for Aiming+Where participants (n = 12).

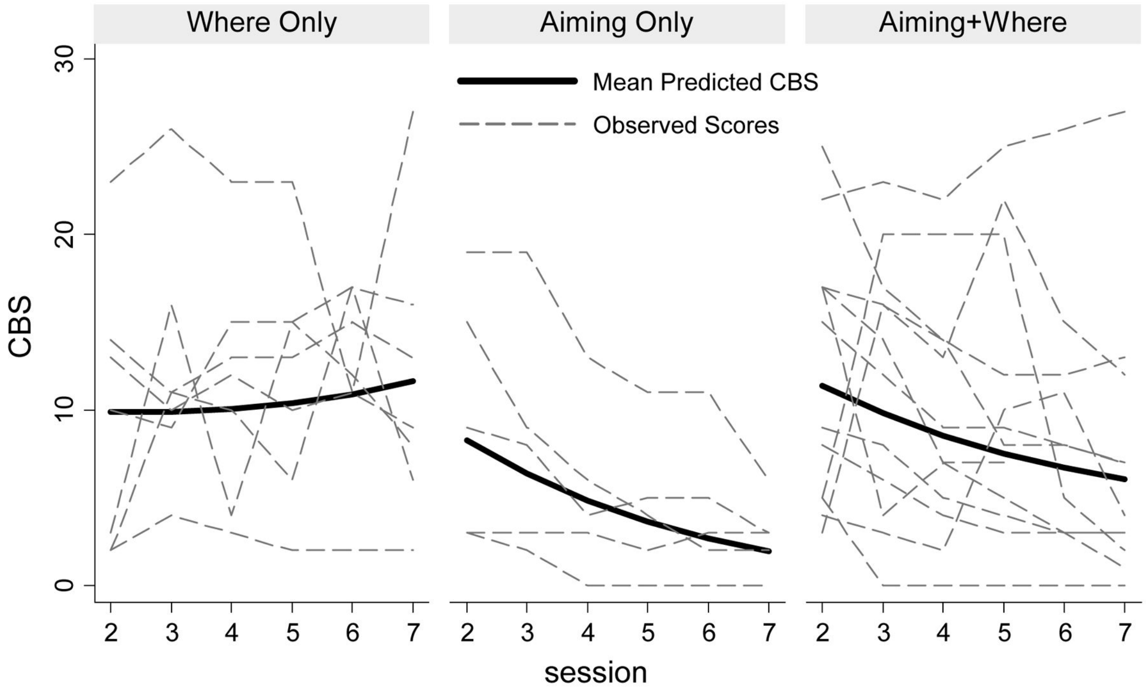

Figure 4.

Participants' observed CBS scores (dashed lines) and average model predicted CBS scores (thick, solid lines) across assessment sessions for each of the three bias types. One week separated each session. Assessment session 2 occurred just prior to prism treatment. One week of prism treatment occurred between sessions 2 and 3 and another between sessions 3 and 4. Lower scores indicate better performance (less severe neglect).

Table 1

Median participant characteristics at screening as a function of bias type.

	Bias Type			
	Where Only (*n*=7)	**Aiming Only (*n*=5)**	**Aiming+Where (*n*=12)**	***p*-value**
Age	77.00 (10.00)	58.00 (19.00)	56.00 (15.50)	0.024
Gender	1 F/6 M	1 F/4 M	5 F/7 M	0.394
Days-post-stroke	40.00 (12.00)	39.00 (8.00)	32.00 (16.50)	0.730
Lesion Volume (cc)	106.3 (119.42)	99.76 (84.33)	120.20 (180.25)	0.171
Hemianopia	*n* = 0	*n* = 0	*n* = 3	0.180
CBS	10.00 (12.00)	9.00 (12.00)	12.00 (12.00)	0.528
CBS Spontaneous Recovery Rate	0.54 (0.51)	0.00 (0.25)	0.31 (0.54)	0.104
BIT	113.00 (42.00)	104.50 (43.50)	112.00 (79.50)	0.275
BIT Spontaneous Recovery Rate	0.54 (1.98)	0.43 (2.31)	1.41 (1.99)	0.367
Aiming Continuous	−5.15 (10.53)	4.81 (18.58)	9.38 (6.85)	< 0.001
Where Continuous	8.26 (18.23)	−9.70 (13.30)	6.67 (42.83)	0.003

Note: Cells reflect medians with interquartile range in parentheses. Days-post-stroke is the days-post-stroke at start of prism treatment. Higher scores on the CBS indicate more severe neglect. Lower scores on the BIT indicate more severe neglect. Aiming and Where continuous values in mm. *p* values refer to the results of Kruskal-Wallis tests, with the exception of that for gender and hemianopia, which refer to a chi-square test of independence.

Table 2

Fixed effect predictors and covariates for predicting the square-root transformed CBS across assessment sessions two through seven.

	β	*b*	*SE b*	*95% CI*	*F*(df1, df2)	*p*
Predictors						
Session - Linear	−0.15	−0.113	0.178	−0.46, 0.24	F(1,112)=0.40	0.528
Session-Quadratic	0.17	0.014	0.016	−0.02, 0.05	*F*(1,112)=.072	0.398
Bias Type					*F*(2,18)=1.95	0.171
Bias Type X Session					*F*(2,112)=3.66	0.028
Covariates						
Age	0.19	0.015	0.009	0.00, 0.03	*F*(1,18)=2.95	0.103
Baseline Deficit	0.77	0.836	0.113	0.62, 1.06	*F*(1,18)=55.15	< 0.001
Spontaneous Recovery Rate	−0.51	−1.72	0.510	−2.72, −0.73	*F*(1,18)=11.46	0.003
Rec Rate X Session	0.13	0.091	0.127	−0.16, 0.34	*F*(1,112)=0.51	0.477

Note. Parameters tested with *F* distribution using between-within degrees of freedom. Group-level parameter estimates for significant categorical predictors are provided in the text.