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Integrity of medial temporal structures may predict better improvement of spatial neglect with prism adaptation treatment

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Abstract Prism adaptation treatment (PAT) is a promising rehabilitative method for functional recovery in persons with spatial neglect. Previous research suggests that PAT improves motor-intentional "aiming" deficits that frequently occur with frontal lesions. To test whether presence of frontal lesions predicted better improvement of spatial neglect after PAT, the current study evaluated neglect-specific improvement in functional activities (assessment with the Catherine Bergego Scale) over time in 21 right-brain-damaged stroke survivors with left-sided spatial neglect. The results demonstrated that neglect patients' functional activities improved after two weeks of PAT and continued improving for four weeks. Such functional improvement did not occur equally in all of the participants: Neglect patients with lesions involving the frontal cortex (n=13) experienced significantly better functional improvement than did those without frontal lesions (n=8). More importantly, voxel-based lesion-behavior mapping (VLBM) revealed that in comparison to the group of patients without frontal lesions, the frontal-lesioned neglect patients had intact regions in the medial temporal areas, the superior temporal areas, and the inferior longitudinal fasciculus. The medial cortical and subcortical areas in the temporal lobe were especially distinguished in the "frontal lesion" group. The findings suggest that the integrity of medial temporal structures may play an important role in supporting functional improvement after PAT.

Keywords Stroke rehabilitation · Prism adaptation · Unilateral spatial neglect · Catherine Bergego Scale · Voxel-based lesion-behavior mapping

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Introduction

Spatial neglect is a common consequence (30–70 %) of unilateral right brain damage (Fullerton et al. 1986; McGlone et al. 1997; Ringman et al. 2004; Stone et al. 1991), inducing an abnormal bias toward the right side during the information-processing stages of perception, representation, motor programming, or a combination of each (Halligan et al. 2003; Mesulam 1999). Therefore, individuals with this neurocognitive disorder manifest failure or slowness to orient attention or initiate action towards contralesional information in the external world (Heilman et al.

2012) or in mental imagery (Berti 2004; Bisiach et al. 1979). Spatial neglect is disabling (Barrett and Burkholder 2006), and patients are often impaired in self-care and social activities (Azouvi et al. 1996). Importantly, severity of spatial neglect at the acute stage adversely affects functional recovery (Appelros 2007; Cherney et al. 2001; Gillen et al. 2005), and persistent neglect symptoms are associated with poor functional performance in the chronic phase (Katz et al. 2000; Patel et al. 2003).

Prism adaptation treatment (PAT) is a promising rehabilitative method for functional recovery in persons with spatial neglect (Fortis et al. 2010; Frassinetti et al. 2002; Keane et al. 2006; Luaute et al. 2006a; Mizuno et al. 2011; Vangkilde and Habekost 2010). Several studies have shown that neglect improvement after PAT may last one to three months (Frassinetti et al. 2002; Mizuno et al. 2011; Serino et al. 2009). A single session of PAT usually involves 10 to 20 minutes of goal-directed arm movements with prism exposure (i.e., wearing a prism goggle). The treatment effect is observed *after* the prism exposure and is thus called "prism adaptation", which is behavioral changes observed when visuomotor coordinates represented in the neurocognitive systems have adapted to the prism-induced shift of the visual field (Redding and Wallace 2006). Accumulating evidence shows that PAT significantly ameliorates abnormal rightward bias in various paper-and-pencil tests (e.g., line bisection, target cancellation, visual search tasks, copying and drawing), in voluntary eye movements, and in detecting stimuli presented simultaneously in both right and left hemispaces (Angeli et al. 2004a, b; Berberovic et al. 2004; Farne et al. 2002; Fortis et al. 2011a; Ladavas et al. 2011; Maravita et al. 2003; Rossetti et al. 1998; Serino et al. 2006, 2009, 2007). However, some neglect patients' spatial bias improves more significantly than others' after PAT (Angeli et al. 2004b; Serino et al. 2006). Similarly, in rehabilitation research, some reported significant improvement in everyday activities (Fortis et al. 2010; Frassinetti et al. 2002; Keane et al. 2006; Mizuno et al. 2011; Vangkilde and Habekost 2010), and others observed no significant impact from PAT (Morris et al. 2004; Rousseaux et al. 2006; Turton et al. 2010). However, a recent review concludes that with sufficient treatment sessions (minimum of 10) and prism strength prism treatment is effective, on average (Kerkhoff and Schenk 2012). Nonetheless, some individual patients fail to respond, or respond to a lesser degree (e.g., Mizuno et al. 2011; Serino et al. 2009). Thus, individuals with spatial neglect differ in their responsiveness to PAT; this may be determined by the specific dysfunction in spatial cognitive information processing, or by other factors.

The mechanism of PAT is to alter directional bias in visually guided, goal-oriented movement (Redding and Wallace 2006; Serino et al. 2006), but the locus of the mechanism in the visuospatial information processing stream is debatable. Recently, two independent studies found that PAT reduces motor-intentional "aiming" bias rather than perceptual-attentional "where" bias in persons with spatial neglect (Fortis et al. 2011a; Striemer and Danckert 2010), suggesting that the visuomotor neural networks associated with motor-intentional spatial systems are critically involved in prism adaptation (see also Fortis et al. 2011b). In Fortis et al.'s study (2011a), five right-brain-damaged stroke survivors with spatial neglect underwent two days of PAT with one 15-min session per day. Before and after PAT, Fortis et al.'s participants performed a computerized line bisection task, bisecting lines in both a natural viewing and a left-right reversed viewing condition. This technique allows one to determine whether a person's spatial bias is primarily from the perceptual-attentional or motor-intentional spatial system (Na et al. 1998; Schwartz et al. 1997) and to quantify perceptual-attentional and motor-intentional spatial bias separately (Barrett and Burkholder 2006; Chen et al. 2009, 2011; Garza et al. 2008). Fortis et al. found that motor-intentional "aiming" bias improved in all participants after PAT but there was no systematic change in perceptual-attentional "where" bias (Fortis et al. 2011a). Similar results were reported by Striemer and Danckert (2010), who studied three right-brain-damaged neglect participants performing line bisection (manually marking the center of a horizontal line) and landmark tasks (judging whether a horizontal line was segmented in half or one segment was longer than the other) before and after a 10-min session of PAT. While the line bisection task has both perceptual and motor components, the landmark task is a primarily perceptual task. Performance in line bisection improved after PAT, but performance in the landmark task did not (Striemer and Danckert 2010). Results from both studies are consistent with the hypothesis that PAT increases the propensity to initiate action towards the contralesional hemispace and thus primarily acts to improve spatial movement preparation, rather than primarily influencing spatial perception. Such improvement in motor-intentional function may be observed in multiple effector systems, including movements of the eyes (Angeli et al. 2004a), arms (Frassinetti et al. 2002), and whole body (Jacquin-Courtois et al. 2008; Keane et al. 2006).

Since behavioral changes after PAT are observed primarily in the motor-intentional function, the frontal cortex may play a crucial role in prism adaptation. The frontal cortex is critically involved in the production of voluntary action (Lau et al. 2004; Moore et al. 2003; Rushworth 2008) and is the hub of the networks for the motor-intentional "aiming" spatial system (Ghacibeh et al. 2007; Maeshima et al. 1997; Na et al. 1998; Tegner and Levander 1991; Verdon et al. 2010). For example, using repetitive transcranial magnetic stimulation (rTMS) and the previously mentioned technique for separating perceptual-attentional and motor-intentional bias in line bisection, Ghacibeh et al. (2007) found that rTMS on the right middle frontal gyrus induced rightward "aiming" spatial bias in healthy adults. In a recent voxel-based lesion-symptom mapping study of neglect patients, motor-exploratory deficits were found to be significantly correlated with dorsolateral prefrontal lesions (Verdon et al. 2010). Since lesions in the frontal cortex may impair motor-intentional functions, patients with frontal lesions may have less capacity than patients without frontal lesions in adapting to the prism-induced visuomotor coordinate changes for voluntary action, and consequently patients without frontal lesions may demonstrate greater functional improvements after PAT.

Alternatively, patients with frontal lesions may demonstrate greater functional improvements after PAT. Given that PAT may primarily improve motor-intentional, but not perceptual-attentional, spatial deficits (Fortis et al. 2011a; Striemer and Danckert 2010), neglect patients with frontal lesions, who likely have motor-exploratory impairments (Verdon et al. 2010), may have a better or more observable response to PAT than patients without frontal lesions, whose spatial errors may not be motor-intentional in origin. The effectiveness of PAT in these patients with frontal lesions may be mediated by intact medial and posterior feedback-dependent networks implicitly monitoring self-movement, in a stimulus-driven (bottom-up) fashion, facilitating re-alignment and recalibration of visuomotor coordinates during and after PAT (Aimola et al. 2011; Luaute et al. 2006a).

The primary goal of the present study was to examine the two opposing hypotheses regarding whether frontal lesion involvement predicts greater or poorer functional improvement after PAT in right-brain-damaged neglect patients. Although these hypotheses focused on the frontal cortex, we recognized the potentially critical contribution of other cortical and subcortical structures in adapting to prisms. Luaute et al. (2006b) used positron emission tomography (PET) to investigate the functional neural network associated with neglect improvement in five right-brain-damaged patients after one PAT session. The areas that significantly changed activation levels after PAT included cortical (the left temporo-occipital and medial temporal cortices) as well as subcortical areas (the left thalamus) (Luaute et al. 2006b). This result indicates a possible contribution from the intact hemisphere, and suggests the critical roles of these regions in adapting to prisms. However, with the very small sample (n=5) studied after only one PAT session, Luaute et al.'s result may not be generalized to other neglect patients demonstrating functional improvement after a more conventional course of multiple PAT sessions over a longer period of time. Thus, our second goal was to investigate whether the integrity of certain cortical or subcortical structures may be critical to functional improvement in 21 neglect patients who received 10 sessions of PAT over two weeks and were followed up for neglect assessments in functional activities once a week for 4 weeks after PAT.

Functional improvement was assessed with the Catherine Bergego Scale (CBS) (Azouvi et al. 1996). The CBS directly measures neglect-related limitation on everyday activities (Ting et al. 2011), has significantly higher sensitivity to detect spatial neglect than paper-and-pencil tests (Azouvi et al. 1996, 2003, 2002), and produces scores highly correlated with conventional functional assessments such as the Functional Independent Measure and the Barthel Index (Azouvi et al. 2006, 1996; Goedert et al. 2012; Qiang et al. 2005). Of the existing 28 standardized assessments, the CBS is the only one assessing performance in personal (on the body or body part), peri-personal (within arm's reach) and extra-personal spaces (beyond arm's reach), capturing the heterogeneity of the neglect disorder (Menon and Korner-Bitensky 2004). Therefore, the CBS has been considered the functional outcome measure in many recent studies of PAT and other treatments for spatial neglect (Ertekin et al. 2009; Fortis et al. 2010; Keane et al. 2006; Luukkainen-Markkula et al. 2009; Mizuno et al. 2011; Samuel et al. 2000; Staubli et al. 2009; Turton et al. 2010). In the present study, functional improvement was defined by CBS improvement over time. Specifically, we used lesion localization to examine the ability of frontal lesions to predict functional improvement after PAT and used voxel-based lesion-behavior mapping (VLBM) to identify the intact regions that may mediate the PAT effect on functional improvement.

Methods

Participants

After providing informed consent, the participants were enrolled from an inpatient rehabilitation hospital. Twenty one consecutive right-brain-damaged stroke survivors with spatial neglect were included in the present study, meeting the criteria of having a first stroke in the right cerebral hemisphere within the previous 60 days, no lesion in the left hemisphere, no history of other neurological or psychiatric disorders, no uncorrected ocular disorders (e.g., near-sightedness or cataract), and having the presence of left-sided spatial neglect (CBS > 0). The participants consisted of 10 males and 11 females, all right-handed, aged from 30 to 89 years old (M=62, SD=15.6), and screened for spatial neglect 9 to 48 days post stroke (M=24.0, SD=10.0). At screening, participants were also assessed with the Behavioral Inattention Test (BIT) for assessing spatial neglect using paper-and-pencil tasks (Wilson et al. 1987), the Barthel Index (BI) for assessing independence in self-care and mobility (Mahoney and Barthel 1965), and the Mini

Mental State Examination (MMSE) for examining global cognitive function (Folstein et al. 1975). In addition, hemianopia screening revealed hemianopia of the left visual field in three participants.

With participants' authorization, all clinical scans were obtained from participants' acute care hospitals and viewed from digital media on compact discs (CDs). Clinically available scans closest to the baseline neglect assessment, on average 15.0±7.9 days in between, were used for identifying lesions. Inspection of the brain scans confirmed that none of the participants' lesions involved brain areas or structures in the left hemisphere. These scans were used for the lesion mapping and localization analyses (described in the next section). There were 13 participants with frontal lesions and 8 participants with no frontal lesions. Table 1 summarizes characteristics of the "frontal lesion" group and the "no frontal lesion" group.

Lesion mapping and localization

A "double-strain" method was performed: First, lesions were mapped from clinical images (CT or MRI) to a standard template, and second, a neurologist-technician conference was held for evaluating the accuracy of the map. Specifically, two trained technicians, blinded to patients' behavioral symptoms and study rationale, manually mapped out individual lesions on a transverse plane of the standard brain image provided in MRIcro® (Rorden and Brett 2000). Lesion extent was determined by selecting the brain scans that showed the greatest extent of brain injury. Lesions were drawn on rotated templates and then realigned with stereotaxic Montreal Neurological Institute (MNI) space to overlay them on standard brain templates. A lesion map was then transformed into MRIcron®-based lesion volumes. The size of the lesioned regions of a given patient was then standardized as the volume (cm^3) of the lesioned region in the standard brain. The VLBM analysis was performed with the MRIcron's built-in nonparametric mapping software (Rorden et al. 2007).

During each hour-long neurologist-technician conference, the technicians discussed 3 or 4 lesion maps with the independent neurologist specialized in neuroradiology. The purpose of such conference was to evaluate the accuracy of the lesion maps individually and decide whether a map needed revision. An anatomical checklist was then used to determine lesion involvements in cortical areas (frontal, temporal, parietal, occiptical, and insula) and subcortical locations (gray and white matters). Specifically for the subcortical lesion location, the gray matter was marked as lesioned if a lesion was located in any of the thalamus, the caudate, the putamen, the globus pallidus, or the subthalamus, and the white matter was marked if a lesion was found in the internal capsule, the external capsule, the centrum semiovale, the corona radiata, or the periventricular white matter. Table 2 summarizes the lesion locations and sizes for each participant.

Procedures

Figure 1 illustrates the timeline of the study course including 7 assessment sessions and 10 sessions of the prism adaptation treatment (PAT). In an assessment session, the participants' occupational therapists administered the CBS to assess spatial neglect in functional activities. The assessment occurred via direct observation for 30 to 60 minutes with most of the time observing the behavior during a meal. The outcome was quantified in 10 items: limb awareness,

Table 1 Characteristic summary of the "frontal lesion" and the "no frontal lesion" groups

	"Frontal lesion" group			"No frontal lesion" group			p
	M	Med	SD	M	Med	SD	
Age (years)	56.6	58	15.7	69.6	66	12.4	.055
Days post stroke	23.7	21	8.6	19.3	16	11.9	.110
BIT	75.1	67	42.6	61.5	32.5	50.9	.663
CBS	19.1	20	6.4	21.9	24	7.8	.373
MMSE	24.4	26	4.6	21.0	19.5	5.2	.110
Barthel Index	32.7	30	17.5	19.4	15	19.5	.074
Lesion volume (cm^3) *	168.1	181.1	94.7	63.6	35.7	50.3	.010
SRR	.34	.43	.69	.21	.31	.42	.690
VP prism aftereffect (cm)	−1.6	−1.3	2.7	−1.4	−1.3	6.4	.651
P prism aftereffect (cm)	−2.4	−1.7	4.6	1.1	2	5.5	.205

Abbreviation: *BIT* Behavioral Inattention Test, *CBS* Catherine Bergego Scale, *MMSE* Mini Mental State Examination, *SRR* spontaneous recovery rate (CBS change per day during baseline period); *P prism aftereffect* proprioceptive prism aftereffect, *VP prism aftereffect* visual-proprioceptive prism aftereffect, *M* mean, *Med* median; *SD* standard deviation

*p<.05 with two-tailed Mann–Whitney U tests comparing the two groups

Table 2 Locations and size of lesion in the right brain

ID	Image Type	Cortical lesion location					Subcortical lesion location		Lesion volume (cm^3)
		Frontal	Temporal	Parietal	Occipital	Insula	GM	WM	
1	MRI		x	x		x		x	25.57
2	CT	x	x	x		x	x	x	226.56
3	CT	x	x			x			71.12
4	MRI	x	x	x		x	x	x	205.08
5	MRI	x	x	x		x	x	x	181.12
6	MRI	x						x	42.06
7	CT	x	x	x		x	x	x	230.26
8	CT			x	x			x	117.47
9	CT		x	x		x		x	112.51
10	CT	x	x	x		x	x	x	281.92
11	MRI	x		x			x	x	126.13
12	MRI					x	x	x	41.79
13	MRI	x			x		x	x	55.52
14	MRI					x		x	14.96
15	CT	x	x	x	x			x	306.91
16	CT		x	x		x	x	x	139.19
17	CT		x	x			x	x	27.61
18	MRI		x				x	x	29.69
19	MRI	x		x	x	x		x	88.52
20	CT	x	x	x		x		x	284.77
21	CT	x		x				x	85.11

Abbreviations: *GM* gray matter including thalamus, caudate, putamen, globus pallidus, and subthalamus, *WM* white matter including internal capsule, external capsule, centrum semiovale, corona radiata, and periventricular white matter. Presence of a lesion is marked "x"

personal belongings, dressing, grooming, gaze orientation, auditory attention, navigation, collisions, eating, and cleaning after meal (Chen et al. in press). For each item, a score of 0 (no neglect) to 3 (severe neglect) was given, and the total score ranged from 0 to 30. Thus, higher scores on the CBS indicate more severe neglect. In a PAT session, an examiner independent of participants' rehabilitation care conducted the prism adaptation procedure. Participants received PAT for two weeks, five sessions per week, one session per day.

Baseline period (prior to PAT) Within 48 hours after enrolling into the study, participants were assessed for severity of spatial neglect in functional activities, quantified with the CBS (Assessment 1). On the first day of the PAT, before the PAT started, participants were assessed for spatial neglect again (Assessment 2). Therefore, during the baseline period, participants were assessed two times, yielding an estimate of their spontaneous recovery rates, calculated as:

$$\text{Spontaneous recovery rate(SRR)} = \frac{(\text{CBS at Assessment 1} - \text{CBS at Assessment 2})}{\text{Days between Assessment 1 and Assessment 2}}$$

A positive SRR indicates a decrease in the CBS score (indicating an increasing improvement in function) and a negative value indicates an increase in the CBS score (indicating an increasing deficit in function).

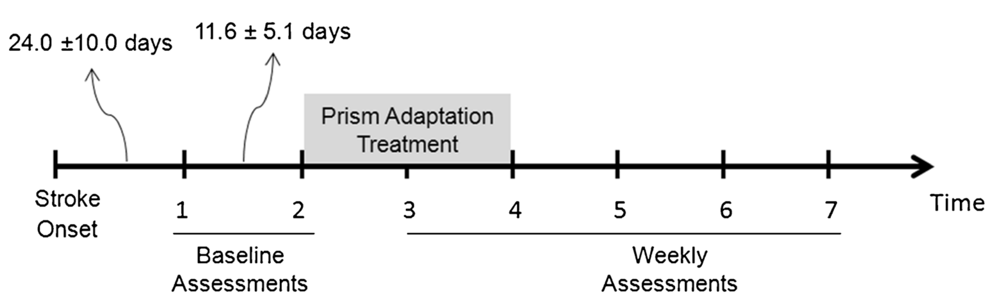

Fig. 1 Study time line. After Assessment 2, the interval between each tick is a week. The gray bar indicates two weeks of the prism adaptation treatment

Prism Adaptation Treatment (PAT) In each PAT session, participants wore a goggle of wedge prisms (Bernell Deluxe Prism Training Glass, 20-diopter, Mishawaka, Indiana, USA) for approximately 15 minutes. The prisms displaced the visual field horizontally rightward by 12.4 degrees of visual angle, and the goggle provided an opaque frame to block distraction from peripheral visual stimuli. With the prisms on, participants used a pen to bisect 60 horizontal lines printed on a letter-sized sheet of paper (27.9×21.5 cm) placed on a table. Each line, 24.1 cm, was presented aligned with the participant's body center, 31.0 cm to the right, or 31.0 cm to the left of the participant. The line location was pseudorandom. Participants' view of the starting point of their arm movement was blocked by an occluding shelf, which allowed a view of only the distal portion of the arm movement.

Immediately prior to and immediately after the first PAT session, participants were tested for the ability to adapt to prisms with and without visual input. This included two pointing tasks. In the visual-proprioceptive pointing task, participants extended their arm and index finger to point to the target at the arm-reaching distance, in one of the three locations (center, 31.0 cm to the right and to the left of the participant) at their shoulder level; their arm movements and the final position of their finger were blocked from their view. Each location repeated twice in the visual-proprioceptive pointing task. In the proprioceptive pointing task, participants were blind-folded and required to extend their arm and index finger to point straight ahead from the center of their chest; this task repeated 10 times. The pointing error was measured in cm with the rightward error coded positive and leftward negative. Following suggestions of previous research that prism aftereffects may decay within 60 seconds (Fernandez-Ruiz et al. 2004), the present study computed the aftereffect using the first three trials of each pointing task, comparing post-prism to pre-prism errors.

Functional Assessments during and after PAT As illustrated in Fig. 1, the participants were assessed with the CBS before, during, and after PAT. See Baseline Period for Assessments 1 and 2. On the first day of the second PAT week, spatial neglect was assessed (Assessment 3). Afterwards, participants were assessed once a week for four weeks (Assessments 4 to 7). To examine functional improvement specifically related to spatial neglect, the outcome measures of the present study were the CBS scores from Assessments 2 to 7.

Results

Characteristic comparison between groups

Baseline measures are summarized in Table 1. Two-tailed Mann–Whitney U tests revealed that the "frontal lesion" group and the "no frontal lesion" group did not differ in days post stroke at Assessment 1, when the two groups showed no statistical difference in age, spatial neglect severity measured with the paper-and-pencil test (BIT) or with performance in functional activities (CBS), global cognitive function (MMSE), or self-care and mobility (BI). However, the "frontal lesion" group had a significantly larger lesion volume than the "no frontal lesion" group, $p=.010$. The group comparison also showed that the two groups were not statistically different in spontaneous recovery rate (SRR; Table 1).

One-tailed Wilcoxon signed rank tests were performed to examine whether each group showed significant leftward prism aftereffects. In the visual-proprioceptive pointing task, the "frontal lesion" group's leftward prism aftereffect reached significance, $z=-1.65$, $p=.050$, but the "no frontal lesion" group's did not, $z=-.51$, $p=.306$. In the proprioceptive pointing task, the "frontal lesion" group's leftward prism aftereffect approached significance, $z=-1.63$, $p=.051$, but the "no-frontal lesion" group's did not, $z=.51$, $p=.306$. However, the "frontal lesion" group and the "no frontal lesion" group did not significantly differ from each other in visual-proprioceptive or proprioceptive prism aftereffects ($p=.651$ and .205 respectively; also see Table 1).

Presence of frontal lesions vs. Functional improvement after PAT

To test whether patients with frontal lesions showed better or poorer improvement trajectory after PAT (independent of spontaneous recovery), scores of the CBS from Assessment 2 to Assessment 7 were examined with a multilevel modeling (MLM) analysis using maximum likelihood estimation and an unstructured covariance matrix. Specifically, the MLM included 1) the random effects of participant intercepts and slopes, 2) fixed effects of predictors including spontaneous recovery rate (SRR), presence of frontal lesions, assessment session, and all of the two-way and three-way interaction terms from these three factors, and 3) fixed effects of covariates including age, age by assessment session interaction, days post stroke, and lesion volume. A covariate was selected via the following procedure: We assessed each of the potential covariates (age, days post stroke, MMSE, Barthel Index, and lesion volume) to see if it significantly predicted CBS scores on its own. Then we tested the inter-correlations among those covariates that significantly predicted CBS scores on their own, to assess for potential problems with multi-collinearity. When multiple covariates were highly correlated, we chose a single covariate from that correlated set. Therefore, age, days post stroke, and lesion volume were included, but MMSE and Barthel Index were not because they were highly correlated with age. Note that in addition to having SRR as a predictor, we included the interaction term of age by assessment session to add a statistical control for any age-related changes over time (namely, age-dependent recovery of spatial neglect). We report all the fixed effects in Table 3 and, in the text below, describe effects reaching significance ($p<.05$). Figure 2 depicts the recovery trajectories of the "frontal lesion" and "no frontal lesion" groups.

With the intraclass correlation of .60, the MLM showed that participants' intercepts and slopes were negatively correlated, $b=-.93$ $SE=.05$, 95 % CI [−.99, −.71], indicating that participants with more severe neglect experienced less improvement over the course of the study. The interaction between presence of frontal lesion and session was significant, $F(1, 82)=6.97$, $p=.010$. None of the other predictors showed an effect approaching or reaching significance. Importantly, none of the interaction terms that involved spontaneous recovery rate (SRR) showed a statistically significant effect. Age was the only one covariate effect reaching significance, $F(1, 14)=11.11$, $p=.005$, suggesting that participants with older age had more severe neglect (higher CBS) on average over the assessment sessions. Importantly, the results of this MLM analysis indicate that independent of spontaneous recovery prior to the treatment, age, age-related change over time, days post stroke, and lesion volume, the "frontal lesion" group's functional improvement of spatial neglect was significantly greater than that of the "no frontal lesion" group after the PAT (see Fig. 2).

Inspection of the marginal linear slopes, from Assessment 2 to Assessment 7, for the "frontal lesion" and "no frontal lesion" groups revealed that the "frontal lesion" group's linear improvement was significantly different than zero, $b=-1.98$, $SE=.30$, 95 % CI [−2.57, −1.38], $p<.001$, while that of the "no frontal lesion" group was not, $b=-.34$, $SE=.43$, 95 % CI [−1.17, .50], $p=.426$. This indicates that the "frontal lesion" group's daily functions related to spatial neglect improved approximately at a rate of 2 points per week on the CBS; however, the "no frontal lesion" group's did not demonstrate a significant outcome change after the PAT over the course of the study.

Spared regions for mediating PAT effects

Given that the presence of frontal lesions predicted better functional improvement after PAT independent of spontaneous recovery and age-related changes, we explored which brain areas likely provide the capacity to mediate the PAT effect, using the techniques of lesion overlapping and voxel-based lesion-behavior mapping (VLBM). Figures 3a and b respectively show the lesion overlaps of the 13 "frontal lesion" and 8 "no frontal lesion" participants. In the "frontal lesion" group, the highest lesion overlap fell in the insula, the transverse temporal gyrus, the rolandic operculum (superior and central temporal areas), and the parietal supramarginal gyrus (Fig. 3a). In the "no frontal lesion" group, the most common lesion regions were in the medial temporal areas and the posterior limb of the internal capsule (Fig. 3b).

To examine the lesion difference between the two groups, VLBM was performed using the Liebermeister quasi-exact test yielded a z score for each voxel of the entire brain (Rorden et al. 2007). Using the cutoff threshold of 5 % false discovery rate, the result generated a map of voxels that obtained z scores ranging from 1.73 to 2.67. These voxels indicated the regions that were not only intact in the "frontal lesion" group but also statistically differentiable from the "no frontal lesion" group. Two general areas emerged from the VLBM analysis as shown in Fig. 4a: medial temporal cortical and subcortical regions ($z=2.19$–2.67), and Fig. 4b: the medial temporal gyrus ($z=1.73$–2.25), the superior temporal area ($z=1.73$), the anterior transverse temporal area ($z=1.73$), and the inferior longitudinal fasciculus (ILF; $z=1.73$). With a more conservative cutoff threshold (1 % false discovery rate), only the red-colored areas (the medial temporal cortical and subcortical regions) in Fig. 4a surpassed the significance ($z=2.57$–2.67). Results of the VLBM suggest that the integrity of the medial cortical and subcortical areas in the temporal lobe plays an important role in supporting functional improvement after PAT.

Table 3 Fixed effects on CBS scores from assessment 2 to assessment 7

Dependent Variable: CBS score		*b*	*SE b*	95 % CI	*F*(df1, df2)	*p*
Predictors	Presence of frontal lesions	−.06	3.88	−7.67, 7.55	*F*(1,14)=.0002	.988
	Assessment session	1.31	1.23	−1.10, 3.71	*F*(1,82)=1.14	.290
	SRR	−9.40	6.65	−22.43, 3.63	*F*(1,14)=2.00	.179
	Frontal × Assessment *	−1.51	.57	−2.63, -.39	*F*(1,82)=6.97	.010
	Frontal x SRR	7.74	7.50	−6.95, 22.43	*F*(1,14)=1.07	.320
	SRR x Assessment	.85	1.04	−1.19, 2.89	*F*(1,82)=.67	.416
	Frontal x SRR x Assessment	−.45	1.15	−2.71, 1.81	*F*(1,82)=.15	.696
Covariates	Age *	.38	.12	.16, .61	*F*(1,14)=11.11	.005
	Age x Assessment	−.03	.02	−.06, .002	*F*(1,82)=3.21	.077
	Days post stroke	.04	.08	−.12, .20	*F*(1,14)=.26	.621
	Lesion volume	.01	.01	−.01, .03	*F*(1,14)=1.21	.290

The *p* value is corresponding to the F distribution. Abbreviation: SRR, spontaneous recovery rate; Frontal, presence of frontal lesion

*$p<.05$

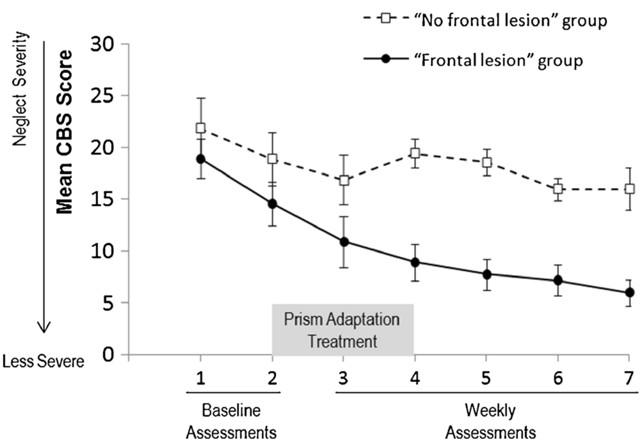

Fig. 2 CBS improvement trajectories for participants with and without frontal lesion involvement. Dots are means; error bars are standard errors.

Discussion

The present study demonstrated that neglect patients' functional activities improved after two weeks of PAT and continued improving for at least four weeks. Such functional improvement did not occur equally in all of the participants: Neglect patients with lesions involving the frontal cortex experienced significantly greater functional improvement than did those without frontal lesions. More importantly, integrity of the medial temporal cortical and subcortical structures may support functional improvement in the "frontal lesion" group after PAT. It is important to note that the difference in the improvement of the "frontal lesion" and "no frontal lesion" groups was significant even controlling for spontaneous improvements observed between the two baseline sessions and when controlling for any age-related changes. The notable improvement in the "frontal lesion" group is underscored by the fact that this group actually had larger lesions than did the "no frontal lesion" group.

Some research has demonstrated that the reduction of left neglect with prism adaptation is related to the visual-proprioceptive or proprioceptive prism aftereffects (Fortis et al. 2010; Frassinetti et al. 2002; Sarri et al. 2008). Our data also showed a similar relation. The fact that the "frontal lesion" group showed a significant visual-proprioceptive prism aftereffect is consistent with the result that this group improved significantly after PAT. Likewise, that the "no frontal lesion" group showed no significant aftereffect is also consistent with the result that this group did not demonstrate significant improvement after PAT. Taken together with the VLBM result, it is possible that the temporal medial cortical-subcortical region, which was significantly spared in the "frontal lesion" group, mediates the visuomotor adaption to the prism and in turn results in detectable prism aftereffects. Nonetheless, we acknowledge that the mechanism is unclear on how the presence of aftereffects or the magnitude of the aftereffect may account for neglect improvement, functional change, or long lasting effect after PAT (Newport and Schenk 2012; Sarri et al. 2008). In addition, prism aftereffects are not always predictive of PAT treatment effect (Dijkerman et al. 2003; Ladavas et al. 2011; Serino et al. 2007).

The PAT improved spatial neglect in "frontal lesion" group during the treatment, and the improvement continued for at least four weeks in the present study. This finding is consistent with a recent report (Mizuno et al. 2011). Similar to the present study, Mizuno et al.'s study (2011) examined the treatment effect of 2 weeks of PAT on acute stroke survivors with spatial neglect (stroke onset < 3 months) in an inpatient rehabilitation hospital. The authors assessed functional improvement immediately after the treatment

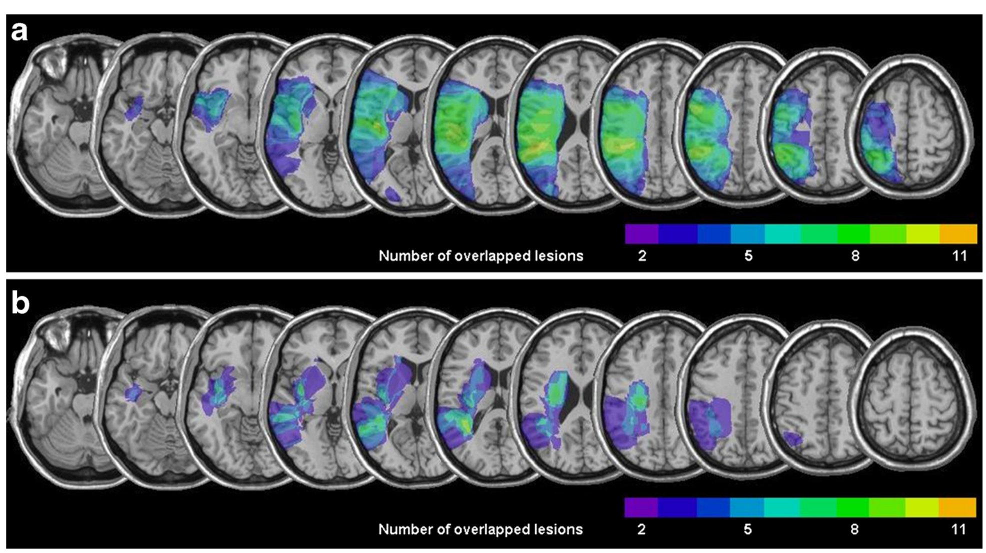

Fig. 3 Comparison of lesion maps of the "frontal lesion" and "no frontal lesion" groups. The maps are presented with the right hemisphere showing on the left. The number of overlap = 1 is not presented **a**. Participants with frontal lesion involvement; the "frontal lesion" group (n= 13). **b**. Participants without frontal lesion involvement; the "no frontal lesion" group (n=8)

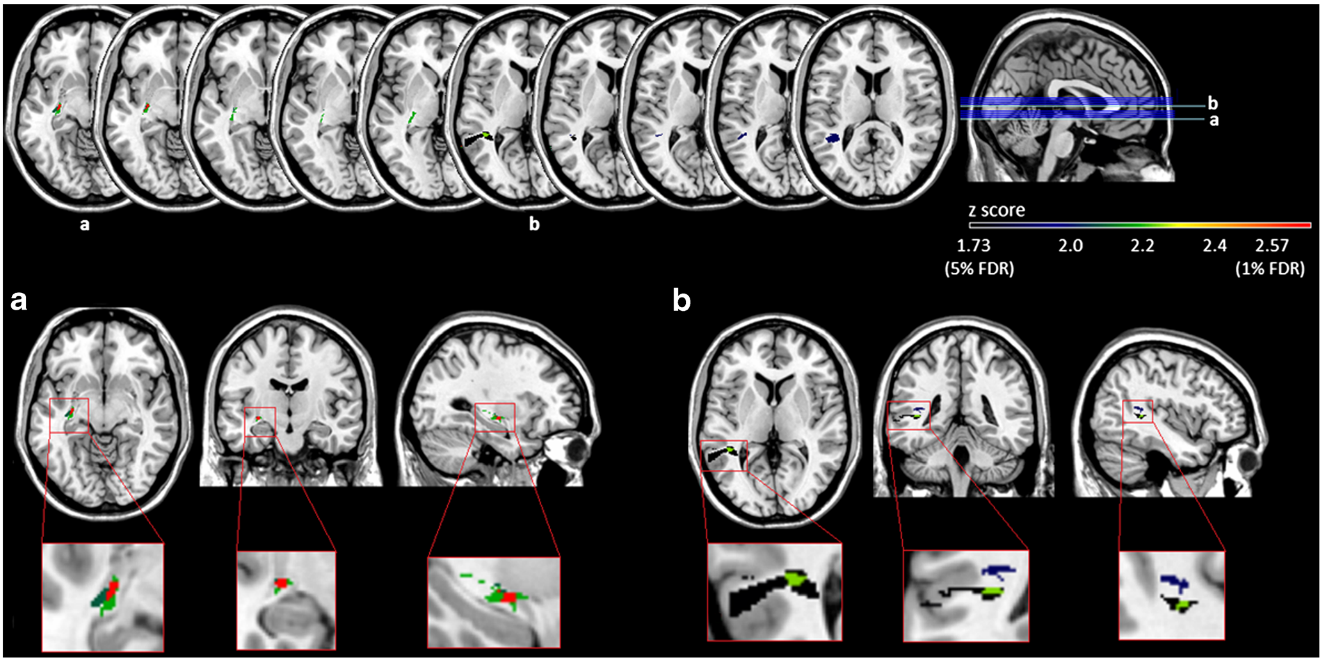

Fig. 4 Result of the voxel-based lesion-behavior mapping (VLBM). The color codes are the z scores that survived the 5 % false discovery rate cut-off threshold. These regions were not only intact in the "frontal" group but also significantly differentiable from the "no-frontal" group. The axial, coronal, and sagittal views of slides *a* and *b* (see the upper right corner) are displayed with selected zoom-in images. Abbreviation: FDR, false discovery rate

and right before the participants were discharged from the hospital. They found continuous functional improvement, on average, 95 days after PAT, especially in patients with milder spatial neglect at baseline. In the present study, controlling for changes between baselines, we found continuous improvement in the "frontal lesion" group. It is possible that at the acute stage post stroke, PAT facilitates functional recovery in stroke survivors who are capable to respond to prism adaptation. At a relatively chronic stage, PAT also improves daily functions in stroke survivors with spatial neglect (Vangkilde and Habekost 2010), and the treatment effects last reportedly 5 weeks to 6 months (Fortis et al. 2010; Frassinetti et al. 2002; Serino et al. 2007).

Few studies have investigated the relation between lesion location and the PAT effect on spatial neglect. Serino et al. (2006) used a very similar PAT procedure to the one described in the present study and found that lesions involving the occipital lobe were associated with poor treatment effects (Serino et al. 2006). However, in the present study, we did not completely replicate these results as we did not find that areas in the occipital lobe play a critical role in functional improvement after PAT. A post hoc MLM (with the same model structure described in Results but with presence of occipital lesions replacing presence of frontal lesions) revealed no statistical significance of "the presence of occipital lesion by assessment session" interaction on functional improvement, $F(1, 82)=.55$, $p=.460$. In addition, inconsistent with our findings, Serino et al. provided no evidence that frontal lesion involvement was associated with PAT effects (Serino et al. 2006). It is important to note that in the present study, only 4 of the 21 participants had any lesion involvement of occipital cortex and those that did had only a small portion of this region involved in the lesion (see Fig. 3), but in the Serino et al.'s study, 11 of the 14 participants had frontal lesions. The discrepancy in findings between the present study and Serino et al.'s may also result from different outcome measures. Serino et al. (2006) used the Behavioral Inattention Test (BIT; Wilson et al. 1987), and we used the CBS. The former is a paper-and-pencil test in peri-personal space, and the latter is a functional assessment in the personal, peri-personal, and extra-personal space. While the BIT may be primarily sensitive to perceptual-attentional bias, the CBS assesses functional activities involving perceptual-attentional as well as motor-exploratory spatial systems (Goedert et al. 2012). While occipital lesions might predict poor PAT treatment effect, Serino et al. (2006) also did not report a neural correlate for better PAT treatment effect, making it difficult to generate a definitive hypothesis for the neural mechanism underlying neglect improvement after PAT. Therefore, the current finding provides new evidence to the field of neglect rehabilitation research in seeking the best candidates to benefit from PAT: neglect patients who have no lesion in the medial temporal lobe. Specifically, a bottom-up network, which subserves visuomotor adaptation to the prism-induced visual shift and consequently mediates functional improvement, may critically involve the medial temporal cortical and subcortical areas.

Although areas in the medial temporal lobe are often considered regions supporting the perceptual-attentional spatial system (Corbetta et al. 2005), it is possible that independent of dorsal cortical activity, the medial temporal cortical and subcortical structures form part of a non-geniculocortical pathway to the deep superior colliculus (Lovejoy and Krauzlis 2010), supporting mulitisensory integration, allocentric-egocentric remapping (Berman and Wurtz 2010), and eye-hand movement disparity (Lunenburger et al. 2001). Further, the medial temporal cortex is associated with viewing and reacting to stimuli presented in extra-personal space (Vuilleumier et al. 1998; Weiss et al. 2000), which is critical for navigation (Previc 1998; Weniger et al. 2010). The medial temporal areas are also associated with allocentric spatial representation and memory (Shrager et al. 2007; Verdon et al. 2010). Thus, neglect patients with the integrity of this brain region may be able to transform prism-induced visual information resulting in a relatively accurate representation of the body-environment relation and extra-personal space for navigation and spatial memory.

Using a more liberal analysis threshold (5 % vs. 1 % false discovery rate), the present findings also suggest that areas in the superior temporal gyrus (STG) and the inferior longitudinal fasciculus (ILF) may be involved in functional improvement after PAT. The STG plays a crucial role in spatial neglect (Golay et al. 2008; Karnath et al. 2004, 2009). The STG is responsible in various stages of visuospatial perception and representation. Lesions to the anterior STG may be associated with egocentric neglect while lesions to the posterior STG are related to allocentric neglect (Chechlacz et al. 2010; Hillis et al. 2005). The ILF mediates the fast transfer of visual information from the extrastriate visual areas in the occipital lobe to the anterior temporal regions and parahippocampal gyri (Catani et al. 2003). Recently, Voinesko et al. (2012) reported its association with visuomotor dexterity. The ILF, together with the non-geniculate pathway between the superior colliculus and temporal structures, may be important pathways for rapid visuomotor processing in an implicit, spatial exploratory memory network. Patients with damage to the hubs or pathways in this network may not demonstrate prism adaptation or experience-dependent learning after PAT.

The present study provides new evidence potentially accounting for neurocognitive mechanisms of PAT effects, however there are a number of limitations. Because individuals with lesions involving the medial cortico-subcortical networks may suffer from more severe neglect symptoms (Rengachary et al. 2011; Verdon et al. 2010) and likely develop chronic spatial neglect (Karnath et al. 2011), it is possible that the integrity of the medial temporal structures mediates not only PAT effects but also response to other neglect treatments, or that these regions provide critical support for neural or chemical plasticity in spontaneous recovery. Participants in the present study received the PAT within two months post stroke, and received routine occupational and physical therapies during the course of the study. Although we assessed and statistically controlled for spontaneous recovery, we acknowledge that the rate of spontaneous recovery may not stay the same over time, and varied spontaneous recovery rates may affect the effectiveness of PAT. Further research including large, diverse groups of stroke survivors exposed to different types of therapies are needed to confirm whether patients with intact medial temporal cortical and subcortical areas, STG, and ILF may benefit most from PAT, or whether these people may also recover better spontaneously or as a result of other treatment approaches.

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