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# Lesion Sites Associated with Allocentric and Egocentric Visuospatial Neglect in Acute Stroke

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## Abstract

Visuospatial neglect is a disorder that can often result from stroke and is characterized by an inability to attend to contralesional stimuli. Two common subtypes include allocentric (object-centered) neglect and egocentric (viewer-centered) neglect. In allocentric neglect, spatial inattention is localized to the contralesional side of an object regardless of its relative position to the observer. In egocentric neglect, spatial inattention is localized to the contralesional side of the individual's midline. The neuroanatomical correlates of each subtype are unknown. However, recent work has suggested that damage to temporal, inferior parietal, and occipital areas may result in allocentric neglect and that damage to frontoparietal areas may result in egocentric neglect. We used voxel-based lesion-symptom mapping (VLSM) to compare lesion location to behavioral performance on the conventional six subtests of the Behavioral Inattention Test (BIT) in 62 subjects with acute right hemisphere ischemic stroke. Results identified an anatomical dissociation in lesion location between subjects with neglect based on poor performance on allocentric tests (line bisection, copying, and drawing tasks) and on egocentric tests (star, letter, and line cancellation). VLSM analyses revealed that poor performance on the allocentric tests was associated with lesions to the superior and inferior parietal cortices, and the superior and middle temporal gyri. In contrast, poor performance on the egocentric tests was associated with lesions in the precentral gyrus, middle frontal gyrus, insula, and putamen. Interestingly, the letter cancellation test and average performance on egocentric tests were associated with frontal and parietal lesions. Some of these parietal lesion locations overlapped with lesion locations associated with allocentric neglect. These findings are consistent with suggestions that damage to temporal and parietal areas is more associated with allocentric neglect and damage to frontal lobe areas is more associated with egocentric neglect.

**Key words:** allocentric; Behavioral Inattention Test; egocentric; spatial neglect; stroke; voxel-based lesion symptom mapping

## Introduction

The study of visuospatial neglect after stroke has been instrumental in identifying brain areas important for visuospatial attention (Corbetta and Shulman, 2011; Karnath and Rorden, 2012). Classically, an individual with visuospatial neglect fails to attend to stimuli located in his or her visual space contralateral to the side of their lesion (Heilman et al., 2000). For example, following right hemisphere brain lesions, individuals may not make eye contact with people on their left, may only shave the right side of their face, or only eat the food on the right half of their plate (Driver and Vuilleumier, 2001). Previous research has found that the presence of visuospatial neglect is predictive of greater impairment in sensorimotor function and cognition (Katz et al., 1999), lower scores on activities of daily living measures (Jehkonen et al., 2000), and longer hospital stays (Gillen et al., 2005).

Evidence suggests that visuospatial neglect is a heterogenous disorder that comprises several subtypes of visuospatial deficits (Adair and Barrett, 2008; Binder et al., 1992; Buxbaum et al., 2004). Allocentric (object-centered) neglect has been described as a failure to perceive the contralesional side of an individual stimulus regardless of its position or location in space (Driver and Halligan, 1991). In contrast, egocentric (viewer-centered) neglect refers to inattention to any stimuli located in the space contralesional to the individual's midline (Arguin and Bub, 1993; Karnath and Rorden, 2012).

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Some evidence from behavioral and imaging studies suggests that allocentric and egocentric forms of neglect are closely related (Yue et al., 2012), with both resulting from injury to the temporoparietal junction (Chechlacz et al., 2012b), including the superior temporal and supramarginal gyri (Rorden et al., 2012). Molenberghs and Sale (2011) have also suggested that lesions to the angular gyrus of the right hemisphere are involved in both types of neglect.

In contrast, other groups have found a clear dissociation in the neuroanatomical representation of allocentric and egocentric neglect (Committeri et al., 2004; Marsh and Hillis, 2008; Molenberghs et al., 2012). Injury or dysfunction of the intraparietal sulcus (Ptak et al., 2012), superior temporal gyrus (Hillis et al., 2005), and occipital lobe (Vossel et al., 2011) have all been associated with allocentric neglect. More anterior lesion locations, including the superior and middle frontal gyri (Grimsen et al., 2008; Verdon et al., 2010), superior temporal gyrus (Chechlacz et al., 2010), and inferior parietal cortex (Hillis et al., 2005; Medina et al., 2009), have been associated with egocentric neglect.

Overall, the neuroanatomical origins of allocentric and egocentric neglect are still not well defined. Some studies describe shared neuroanatomy (Rorden et al., 2012; Yue et al., 2012), while others suggest a separation of neuroanatomy (Verdon et al., 2010). The variety of tests used to classify these different neglect symptoms may add to the inconsistencies between studies (Saj et al., 2012). In this study, we used voxel-based lesion-symptom mapping (VLSM) (Bates et al., 2003) to identify the relationship between lesion location after stroke and behavioral performance on the Behavioral Inattention Test (BIT) (Wilson et al., 1987). The BIT is a validated clinical test of visuospatial neglect containing line bisection, cancellation, and drawing tasks, which is commonly used after stroke (Bozzali et al., 2012; Jehkonen et al., 2000; Koch et al., 2012). Karnath and Rorden (2012) have recently suggested that line bisection biases are likely associated with allocentric (object-centered) neglect and cancellation biases are associated with egocentric (viewer-centered) neglect.

We hypothesized that subtests of the BIT measuring allocentric deficits (line bisection, figure and shape copying, and representational drawing) would be associated with different stroke lesions from those subtests measuring mainly egocentric processing (star, letter, and line cancellation tests) (Karnath and Rorden, 2012). More specifically, we hypothesized that damage to inferior parietal brain regions would be observed in subjects with allocentric neglect (Verdon et al., 2010) and damage to superior temporal and frontal regions would be observed with egocentric neglect (Chechlacz et al., 2010; Medina et al., 2009).

## Materials and Methods

### *Subjects*

Individuals with right hemispheric stroke (9.0 ± 6.3 days poststroke [mean ± SD]) were recruited from the Foothills Medical Centre or the Dr. Vernon Fanning Center in Calgary, Alberta, Canada. Inclusion criteria were as follows: first ever right hemisphere ischemic stroke, able to follow commands for assessment, and older than 18 years of age. Subjects were excluded if they had a history of prior stroke, other neurological conditions, or a stroke located in the brainstem or cerebellum. All subjects provided informed consent before participating in the study. Ethics were approved by the University of Calgary Research Ethics Board.

### *Clinical assessments*

Clinical assessments were performed by an experienced study physician or therapist. The Chedoke-McMaster Stroke Assessment (CMSA) Impairment Inventory for the upper extremities was completed to identify arm and hand motor function (Gowland et al., 1993). The Functional Independence Measure (Keith et al., 1987) was administered to determine the subject's functional abilities.

The presence and extent of visuospatial neglect were assessed using the conventional six subtests of the BIT. Subjects were diagnosed as having visuospatial neglect if they scored less than 130 points of a possible 146 (Halligan et al., 1991). The six conventional subtests of the BIT were each completed using a pen and paper, and are outlined below.

Line bisection. Three horizontal black lines (20.32 cm long, 1 mm thick) were presented in a staircase manner on the page. The subject was instructed to mark the midpoint of each line. The maximum score of nine was achieved if the subject marked within 12.75 mm of the true midpoint for all three lines (Halligan et al., 1991). Percent accuracy was determined using the following equation:

$$\text{Percent accuracy} = 100\% - \left[\frac{(\text{true midpoint} - \text{measured right section})}{\text{true midpoint}} \times 100\right]$$

The measured right section is the average distance from the right end of the line to the subject's mark (Molenberghs and Sale, 2011; Schenkenberg et al., 1980). For those subjects who, on average, bisected the line leftward from the true midpoint (therefore, receiving a negative percent deviation score), the percent deviation was added to 100%. This was done so that no subject received a score greater than 100%. These percent accuracy scores were used for the VLSM analysis.

Figure and shape copying. A four-point star, a cube, and a daisy were arranged on the left side of the page. The subjects were cued to look at/identify each object and draw a replica on the right side of the page. Next, on a separate sheet of paper, three geometric shapes were presented along the top of a page and the subject was required to replicate the shapes in the space below. Scores ranged from zero to four, with scores based on omissions or gross distortions of any major contralesional component of the objects (Halligan et al., 1991).

Representational drawing. Subjects were asked to make a line drawing of a clock face (including the numbers and setting of the hour and minute hands), a person, and a butterfly. Scoring was defined by omissions or gross distortions of any major contralesional component of the objects. The maximum score was three (Halligan et al., 1991).

Line crossing. Seven columns of small lines in random orientations were arranged across the page. The examiner first demonstrated the nature of the task by crossing out two lines in the central column. Subjects were then asked to cross out all the lines they saw (total 36 targets, 4 targets in the central column were excluded from scoring).

Letter cancellation. Five rows of 34 uppercase letters were presented in random order on the page. Subjects were asked to cross out all the Es and Rs observed in each row (20 targets were located on each half of the page).

Star cancellation. Fifty-four small star targets (8 mm) were arranged amid distracters of larger stars (14 mm), letters, and words. The examiner first crossed out two stars located on the midline of the page (excluded from scoring). Subjects were then asked to cross out all the small stars that he/she observed (27 stars were located on each half of the page).

The Center of Cancellation (CoC) software program (Rorden and Karnath, 2010) (www.mricron.com/cancel/) was used to score the line, letter, and star cancellation subtests from the BIT. The CoC measures the center of mass for all cancelled targets, which is used to generate a normalized score for each subject's test based on leftward or rightward biases in target omissions. The CoC score ranges from −1 (only the leftmost target is detected) to +1 (only the rightmost target is detected). For all three cancellation tests, the CoC score (instead of the overall number of targets detected) was used for the VLSM analysis. Total score from the BIT was analyzed using VLSM.

Spearman correlations were performed on the six subtests of the BIT and a Bonferroni-corrected ($\alpha = 0.05$, $N = 6$) alpha level of $p < 0.00238$ was used to correct for multiple comparisons. Comparisons between clinical measures and demographics were performed using unpaired t-tests, chi squared tests, or Fisher's exact tests where appropriate.

### *Imaging and lesion analysis*

Each subject underwent magnetic resonance imaging (MRI, $n = 47$) or computed tomography (CT, $n = 15$) according to the standard acute stroke protocol at the Foothills Medical Centre. Consistent with previous research using acute neuroimaging (Becker and Karnath, 2010; Verdon et al., 2010), the lesion location was identified by marking directly on the $T_2$-weighted fluid-attenuated inversion-recovery (FLAIR) images by trained researchers (J.M.K., S.E.F.) using MRIcron software for subjects with MRI images (Rorden et al., 2007); www.mricro.com. Considering that some scans were obtained within 24 h of stroke onset, lesion delineation was guided by diffusion-weighted images collected at the same time. Each axial slice (3 mm) of the FLAIR image was directly marked to obtain a volume of

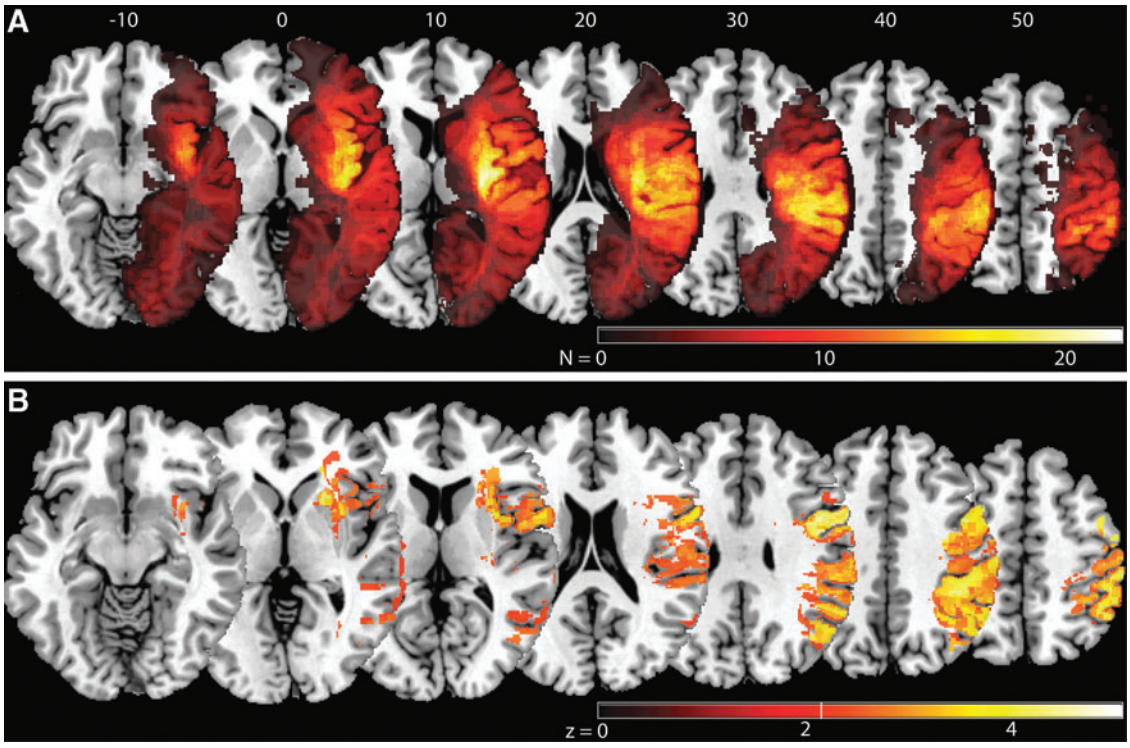


**FIG. 1.** **(A)** Lesion overlap comparison of all 62 subjects with right hemisphere damage. MNI z-coordinates are displayed above slices. Color bar indicates number of subjects (N) with lesion locations at that respective color, with red indicating fewer overlapping lesions and white indicating more overlapping lesions at that voxel. Higher concentration of lesions was observed in the middle cerebral artery territory. **(B)** Voxel-based analysis of the Behavioral Inattention Test. Only voxels that survived a correction for multiple comparisons ($p = 0.05$, FDR corrected. $z$-value $\geq 2.12$) are displayed. Scale bar indicates the significance level, and white bar indicates FDR threshold. Voxels in red indicate lower significance, and voxels in white indicate higher significance. FDR, false discovery rate; MNI, Montreal Neurological Institute.

interest (VOI) for each individual, indicating the area of damage due to ischemia. Lesion locations for all subjects were verified and corrected when necessary by a trained stroke neurologist (J.A.D.). The FLAIR images and subjects' VOI were normalized to the Montreal Neurological Institute (MNI) template using the normalization algorithm available in SPM8 (www.fil.ion.ucl.ac.uk/spm) (Baier et al., 2010). A FLAIR template brain was used (Winkler et al., 2012). A cost-function masking approach was used to prevent distortions in warping damaged tissue during this normalization process (Brett et al., 2001). For those subjects who had only CT imaging available, the lesion location was demarcated directly on the $T_1$-weighted MNI template brain available in MRIcron (Kalenine et al., 2010). Final normalized lesion locations for all subjects were verified and corrected when necessary by trained researchers (J.M.K., S.E.F.), blinded to subject's clinical scores, to ensure accuracy before VLSM analysis.

VLSM (Bates et al., 2003) was used to statistically identify which regions of the brain, when damaged by stroke, were significantly associated with behavioral deficits. Unpaired *t*-tests were performed at each voxel, comparing performance on the BIT subtests between subjects with and without damage involving that voxel. In this study, *t*-tests were confined to only those voxels damaged in at least five subjects, corresponding with previously established thresholds (Barbey et al., 2014; Herbet et al., 2014; Mengotti et al., 2013). BIT subtest scores were compared with voxel damage using the Non Parametric Mapping (NPM) software program (Rorden et al., 2007) distributed with MRIcron. The statistical values for each voxel were then visualized by presenting them as a statistical map on the MNI template brain corrected for multiple comparisons using a false discovery rate (FDR) correction ($p < 0.05$) (Barbey et al., 2012; Benjamini and Hochberg, 1995; Chechlacz et al., 2010).

## Results

### *Subject demographics*

Demographics and clinical assessment scores are displayed in Table 1. A total of 62 right hemisphere ischemic stroke patients were recruited for this study. The sample consisted of 48 males and 14 females with a mean age of 63.5 years. The mean time between stroke onset and imaging was 2.1 days (CT = 3.2, MRI = 1.7 days), and the mean time between stroke onset and assessment was 9.0 days. Visual field deficits were identified in 12 subjects (11 left hemianopsia, 1 left upper quadrantanopsia). Of those subjects with visual field deficits, nine were classified as having visuospatial neglect. A total of 21 subjects were classified as having visuospatial neglect defined by a BIT score of less than 130 (Halligan et al., 1991). All neglect subjects were right handed. Table 2 shows Spearman correlations between the conventional subtests of the BIT across the whole study sample (subjects with and without neglect). The copying task was significantly correlated with representational drawing, line bisection, and overall BIT score. The letter cancellation task was significantly correlated with line bisection, line cancellation, and overall BIT score. The overall BIT score was significantly correlated with all tasks except line cancellation. Table 3 shows Spearman correlations between subtests of the BIT for only those subjects with neglect. Only letter cancellation performance was significantly correlated with line cancellation and BIT score.

### *Lesion overlap*

Figure 1A displays a simple overlay map of the lesions of all subjects ($N = 62$), illustrating the distribution of right brain damage in this study. Voxels are colored along a gradient from red to white, with red indicating fewer overlapping lesions and white indicating more overlapping lesions at that voxel. Across all subjects, we saw a higher lesion frequency

Table 1. Demographic Information and Clinical Scores for Subjects With and Without Neglect

| | *Neglect* (n = *21*) | *No neglect* (n = *41*) | *Unpaired* t-*test* (*df* = *60*), *unless specified* |
|---|---|---|---|
| Age in years | 65.7 (47–86) | 62.4 (25–87) | $p = 0.360$ |
| Gender (M/F) | 18/3 | 30/11 | Chi-square (df = 1), $p = 0.35$ |
| Handedness (R/L/Mixed) | 21/0/0 | 38/2/1 | Chi-square (df = 2), $p = 0.45$ |
| Imaging (MRI/CT) | 11/10 | 28/5 | |
| Lesion volume ($cm^3$) | 84.9 (0.73–266.2) | 28.0 (0.24–167.8) | $p = 0.001$ |
| Days from stroke to imaging | 2.2 (0–7) | 2.0 (0–12) | $p = 0.417$ |
| Days from stroke to assessment | 9.9 (2–25) | 8.5 (1–24) | $p = 0.731$ |
| Stroke territory[a] (MCA/PCA/ACA/Ant Cho) | 18/5/2/0 | 36/4/2/1 | |
| BIT score (/146) | 101.1 (61–128) | 140.5 (132–146) | $p = 2.5 \times 10^{-15}$ |
| CMSA (1/2/3/4/5/6/7) | | | |
| Affected arm | (1/2/1/1/10/4/2) | (4/2/3/2/5/7/18) | $p = 0.285$ |
| Affected hand | (2/1/0/1/9/8/0) | (5/1/4/1/12/10/8) | $p = 0.928$ |
| FIM score (max = 126) | 83.3 (41–122) | 103.4 (62–126) | $p = 0.001$ |

[a]Four subjects had strokes in more than one arterial territory.

Data are presented as mean (range).

ACA, anterior cerebral artery; Ant Cho, anterior choroidal artery; BIT, Behavioral Inattention Test; CMSA, Chedoke-McMaster Stroke Assessment; CT, computed tomography; FIM, Functional Independence Measure; LA, left arm; LH, left hand; MCA, middle cerebral artery; MRI, magnetic resonance imaging; PCA, posterior cerebral artery; RA, right arm; RH, right hand.

Table 2. Spearman Correlations ($r$ Values) Between Subtests of the Behavioral Inattention Test in Total Sample ($N=62$)

| | *Copy* | *Draw* | *Line Bis.* | *Star Can.* | *Letter Can.* | *Line Can.* |
|---|---|---|---|---|---|---|
| Drawing | 0.499[a] | 1 | | | | |
| Line Bis. | 0.499[a] | 0.243 | 1 | | | |
| Star Can. | −0.347 | −0.169 | −0.264 | 1 | | |
| Letter Can. | −0.352 | −0.106 | −0.428[a] | 0.372 | 1 | |
| Line Can. | −0.060 | 0.030 | −0.029 | 0.230 | 0.422[a] | 1 |
| BIT | 0.671[a] | 0.560[a] | 0.470[a] | −0.596[a] | −0.370[a] | −0.248 |

[a]Significant at a Bonferroni-adjusted alpha level of 0.00238.
Bis, bisection; Can., cancellation.

in the middle cerebral artery territory ($n=54$), centered around the insula and frontoparietal areas. Lower lesion frequency was seen in the thalamus as well as the frontal lobe in the anterior cerebral artery territory.

### *VLSM analysis*

The results of the VLSM analysis for the overall BIT score are displayed in Figure 1B. Lesions significantly associated with poor BIT score included the anterior putamen and insula, pre- and postcentral gyri, as well as the posterior parietal cortex. Interestingly, lesions to the superior temporal gyrus were not significantly associated with poor overall BIT scores. Significant voxels in this map were present on the edge of the temporal lobe. Due to concerns that this might be due to artifact, we performed a supplementary analysis with a lower statistical threshold ($z \geq 1.28$, $p=0.10$) applied (Supplementary Fig. S1;Supplementary Data are available online at www.liebertpub.com/brain) and found that the voxels in the underlying cortex and white matter were below the initial (FDR)-corrected statistical threshold. Additionally, given the larger lesion volumes observed in individuals with visuospatial neglect (Table 1), we conducted a logistic regression analysis using lesion volume as a regressor (Supplementary Fig. S2). Lesions to the anterior putamen, precentral gyrus, and parietal cortex were again associated with poor BIT performance, but not the postcentral gyrus. Results of the VLSM analysis for the allocentric tasks (line bisection, figure and shape copying, and representational drawing) are displayed in Figure 2. Results of VLSM analysis for the egocentric tasks (star cancellation, letter cancellation, line cancellation) are displayed in Figure 3. Damaged voxels that were associated with significant behavioral deficits are presented on a color gradient scale, increasing in significance from red to white.

VLSM of line bisection, copying, and drawing. Rightward deviations in line bisection (Fig. 2A) were associated with lesions to the middle and superior temporal gyri as well as inferior and superior parietal cortices. Interestingly, the middle and inferior occipital gyri were also significantly associated with rightward deviation on line bisection. Poor performance on the copying task was significantly associated with damage to the middle occipital gyrus, angular gyrus, postcentral, and superior parietal cortex (Fig. 2B). Significant voxels were located around the edge of the temporal cortex for the copying task (Fig. 2B), similar to the overall BIT (Fig. 1B). Again, we conducted a supplementary analysis, which shows the surrounding areas as just below the FDR statistical threshold (Supplementary Fig. S3). Poor performance on the representational drawing task was associated with damage to the postcentral, supramarginal, and angular gyri (Fig. 2C, MNI z-coordinates 30 and 40). This was in addition to the superior parietal cortex and superior and middle temporal gyri. Logistic regression analysis with lesion volume as a regressor demonstrated largely the same areas as being significantly associated with poor performance on these tasks Supplementary Fig. S4). Interestingly, significant voxels in the superior and middle temporal gyri were mostly lost after considering lesion volume.

VLSM of star, letter, and line cancellation. Left-sided omissions on the star cancellation task corresponded to damage in the anterior aspect of the putamen, the insula, the precentral gyrus, and posterior aspect of the middle frontal gyrus (Fig. 3A). Left-sided omissions on the letter cancellation task were significantly associated with lesions to anterior

Table 3. Spearman Correlations ($r$ Values) Between Subtests of the Behavioral Inattention Test in Subjects with Neglect ($N=21$)

| | *Copy* | *Draw* | *Line Bis.* | *Star Can.* | *Letter Can.* | *Line Can.* |
|---|---|---|---|---|---|---|
| Drawing | 0.541 | 1 | | | | |
| Line Bis. | 0.285 | 0.104 | 1 | | | |
| Star Can. | 0.051 | 0.537 | 0.271 | 1 | | |
| Letter Can. | 0.042 | 0.329 | 0.000 | 0.591 | 1 | |
| Line Can. | 0.033 | 0.258 | 0.016 | 0.587 | 0.737[a] | 1 |
| BIT | 0.174 | −0.050 | −0.090 | −0.728 | −0.660[a] | −0.494 |

[a]Significant at a Bonferroni-adjusted alpha level of 0.00238.

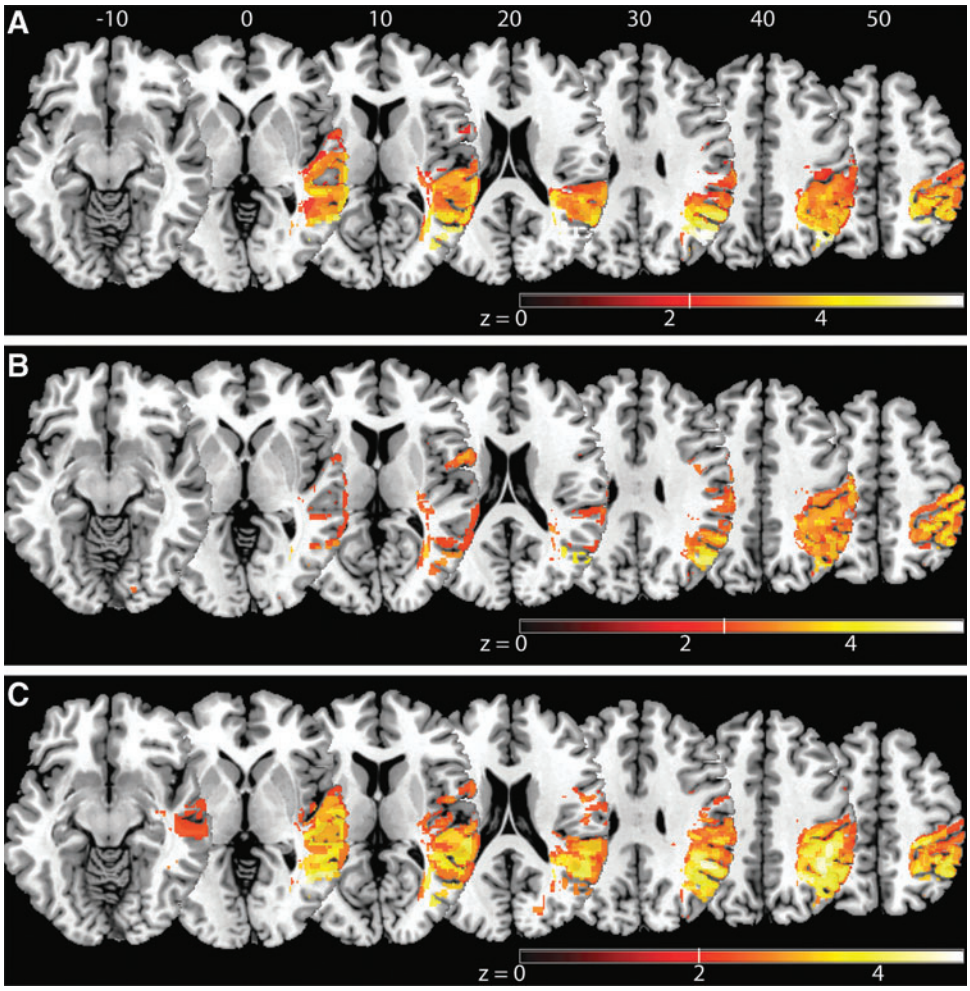


**FIG. 2.** VLSM analysis for line bisection **(A)**, figure and shape copying **(B)**, and representational drawing **(C)**. All voxels displayed have survived a correction for multiple comparisons ($p = 0.05$, FDR corrected). MNI z-coordinates are displayed at the top of the figure. Scale bars indicate the significance level, and white bars indicate FDR thresholds. Voxels in red indicate lower significance, and voxels in white indicate higher significance. **(A)** Decreased accuracy on the line bisection task was significantly associated with lesions to the superior and inferior parietal cortices, superior and middle temporal gyri, and inferior occipital gyrus (threshold, $z \geq 2.13$). **(B)** Poor performance on the figure and shape copying task was associated with damage to the postcentral gyrus, posterior parietal cortex, and inferior and middle occipital gyri (threshold, $z \geq 2.25$). **(C)** Poor performance on representational drawing was associated primarily with lesions to postcentral gyrus, posterior parietal cortex, and superior/middle temporal gyri (threshold, $z \geq 2.01$). VLSM, voxel-based lesion-symptom mapping.

putamen, insula, the posterior aspect of the middle frontal gyrus, pre- and postcentral gyri, and posterior parietal cortex (Fig. 3B). Finally, left-sided omissions on the line cancellation task were associated with lesions to the anterior putamen, insula, precentral gyrus, and posterior aspect of the middle frontal gyrus (Fig. 3C). Logistic regression analysis using lesion volume as a regressor demonstrated that many of the same areas were significantly associated with poor performance on the star and letter cancellation tasks (Supplementary Fig. S5). Logistic regression on the line cancellation task could not be performed due to insufficient heterogeneity in task performance.

VLSM of normalized allocentric and egocentric tasks. An average allocentric versus egocentric statistical map was derived from the average of the z-transformed scores for each individual task across all subjects (Fig. 4). The average of the line bisection, copying, and drawing tasks produced an overall allocentric score. The average of the star, letter, and line cancellation tasks produced an overall egocentric score. Figure 4 shows VLSM analysis for the average allocentric and egocentric scores. Allocentric deficits (red voxels) were associated with lesions to the superior and middle temporal gyri, parietal cortex, and superior occipital cortex. Egocentric deficits (green voxels) were associated with lesions to putamen, insula, and precentral gyrus. Overlap between these neglect types (yellow voxels) was observed in the pre- and postcentral gyri and posterior parietal cortex.

## Discussion

This study used VLSM to investigate brain regions associated with performance on the BIT following acute right

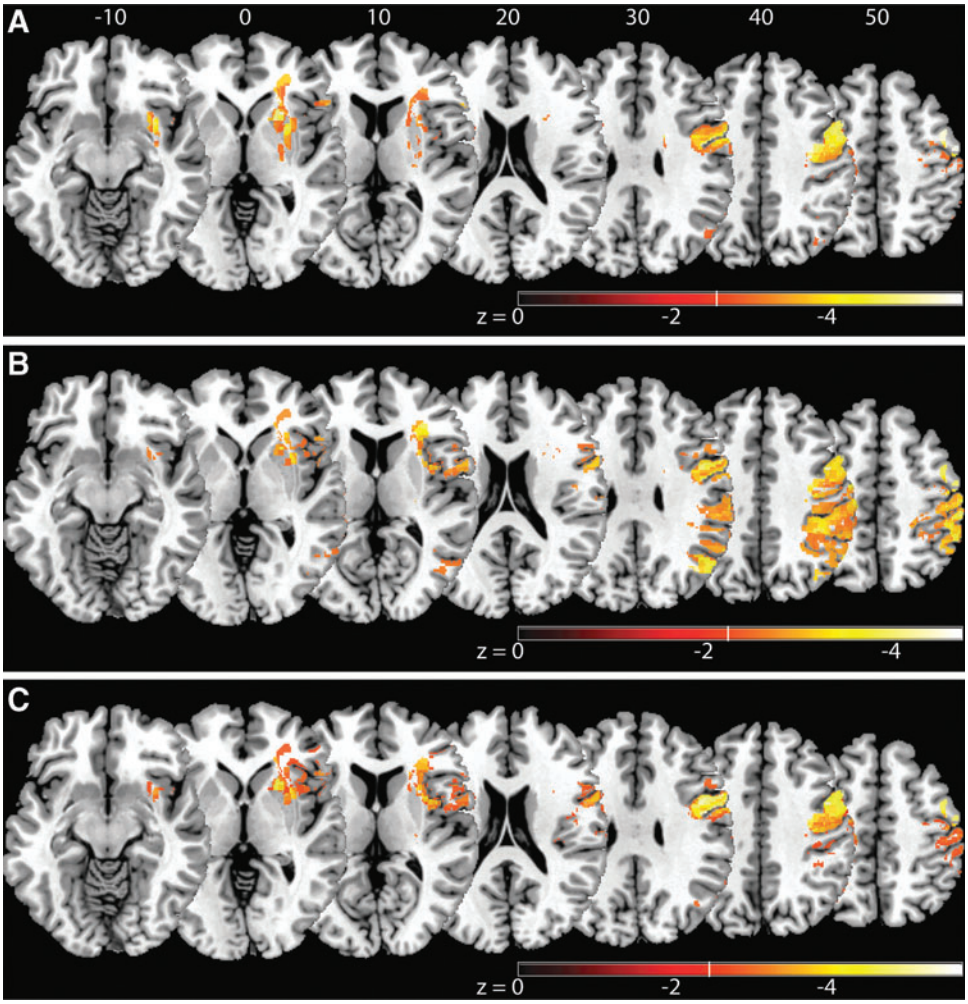


**FIG. 3.** VLSM analysis for star cancellation **(A)**, letter cancellation **(B)**, and line cancellation tasks **(C)**. All voxels displayed have survived a correction for multiple comparisons ($p = 0.05$, FDR corrected). MNI z-coordinates are displayed at the top of the figure. Scale bars indicate the significance level, and white bars indicate FDR thresholds. Voxels in red indicate lower significance, and voxels in white indicate higher significance. **(A)** Left-sided omissions on the line cancellation task were predominantly associated with lesions to the middle frontal gyrus, precentral gyrus, and putamen with a few voxels in posterior parietal cortex (threshold, $z \leq -2.61$). **(B)** Left-sided omissions on the letter cancellation task were associated with lesions to the middle frontal gyrus, precentral gyrus, anterior insula, putamen, and the posterior parietal cortex (threshold, $z \leq -2.34$). **(C)** Left-sided omissions on the star cancellation task were associated with lesions to middle frontal gyrus, precentral gyrus, anterior insula, and putamen (threshold, $z \leq -2.47$).

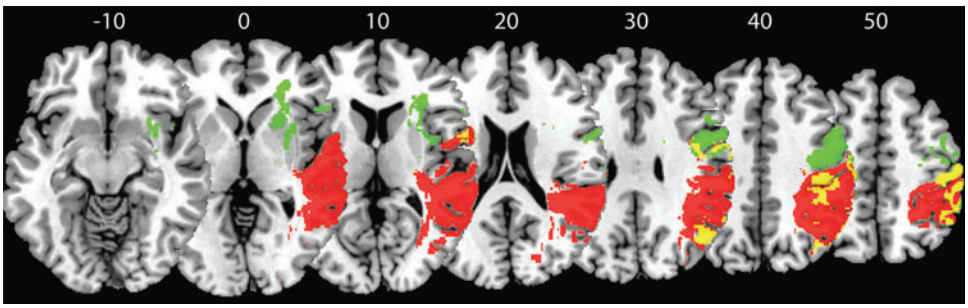


**FIG. 4.** VLSM analysis of average z-transformed scores for allocentric and egocentric tasks. Lesion locations associated with allocentric neglect (red), egocentric neglect (green), and overlap between the two (yellow) are presented. Only voxels that survived an FDR-corrected threshold ($z \geq 1.99$ for allocentric, $z \leq -2.47$ for egocentric) are shown. MNI z-coordinates are presented at the top of the figure.

hemisphere ischemic stroke. Consistent with previous research (Hillis et al., 2005; Medina et al., 2009; Ota et al., 2001), we found that lesions to frontoparietal structures and subcortical structures were significantly associated with poor performance on cancellation tasks, while lesions to parietal and temporal lobes were associated with poor performance on line bisection, copying, and drawing tasks.

The BIT is a validated and commonly used clinical tool to determine the presence or absence of neglect following stroke (Halligan et al., 1991). Since the development of the BIT by Halligan et al. (1991), other authors have suggested that cancellation tests measure egocentric neglect, while line bisection, copying, and drawing tasks measure allocentric neglect (Karnath and Rorden, 2012; Medina et al., 2009). While it is often possible to behaviorally separate these two subtypes of neglect, the underlying neuroanatomy responsible for these deficits is highly debated.

To the point that one can behaviorally separate subtypes of neglect on clinical assessments, we examined the relationship between the performance on the conventional subtests of the BIT by looking at correlations between subtests in subjects with neglect (Table 3). Only the letter cancellation task was significantly correlated with the line cancellation task and overall BIT score. This is a somewhat unexpected finding, given that there appears to be overlap of the brain areas responsible for many of the individual tasks on the VLSM maps within those tasks that are considered either allocentric or egocentric. This finding is likely due to heterogeneity in the behavioral scores of the neglect subjects and the somewhat smaller sample size. Future studies may wish to consider the inter-relationships of the performance of these tasks across a larger sample.

These VLSM results suggest that the critical lesion areas associated with performance on allocentric tasks are the superior and middle temporal gyri, the middle occipital gyrus, as well as the superior and inferior parietal cortices. These findings are consistent with previous studies that have also attributed damage to posterior brain regions to allocentric neglect (Chechlacz et al., 2010, 2012a; Hillis et al., 2005; Medina et al., 2009; Verdon et al., 2010). The superior parietal lobule, however, has not commonly been observed in previous lesion analysis studies. A study by Vossel et al. (2011) showed the parieto-occipital regions, including the superior parietal lobule, as well as the middle frontal gyrus were significantly associated with deficits in a line bisection task. Involvement of the right superior parietal cortex in a landmark task has also been observed in healthy subjects (Fink et al., 2000). The superior temporal gyrus, which we also found to be significantly associated with allocentric neglect, has previously been found to be involved in object-centered exploratory search behavior (Ellison et al., 2004). This may explain the involvement of the superior temporal lobe with these object-based perceptual tasks as well.

Furthermore, we observed differences in VLSM results between the allocentric tasks (Fig. 2A–C). The figure and shape copying task shows areas in the middle and inferior occipital gyri as being significant lesion locations associated with deficits in this task, while the middle and superior temporal gyri appear to be more significant for performance on the drawing task. Interestingly, Ogawa and Inui (2009) found an increased activation of the middle occipital gyrus and fusiform gyrus on a copying task when compared with a drawing from memory task in a group of healthy volunteers assessed using fMRI. The greater involvement of the occipital lobe during the copying task in this sample may be explained by increased visual processing requirements during a visually guided drawing task versus a memory guided drawing task (Ferber et al., 2007).

Results from the VLSM analysis of the egocentric tasks showed the precentral gyrus, middle frontal gyrus, insula, and putamen as associated with poor performance (Fig. 3). For the letter cancellation task (Fig. 3B), the postcentral gyrus and posterior parietal cortex were also significantly associated with poor performance. Previous work has shown that damage to anterior and subcortical regions is related to egocentric neglect (Binder et al., 1992). However, the significance of the involvement of posterior parietal cortex is less clear. These results are also supported by a lesion study performed by Grimsen et al. (2008). They performed a subtraction analysis with 21 right hemispheric stroke subjects and found that egocentric neglect was associated with lesions to the middle and inferior frontal gyri and precentral gyrus. Verdon and colleagues (2010) performed VLSM with 80 right hemisphere stroke subjects (55 with neglect symptoms) and found that egocentric spatial biases were highly related to lesions in the dorsolateral prefrontal cortex. These frontal lobe regions are known to be involved in visual attention and eye movements (Schall, 2004) and have previously been associated with visual selection of targets among distracters (Schall, 1999).

The regions associated with allocentric and egocentric neglect likely form a network of attention structures interconnected by white matter tracts. Karnath and colleagues have suggested that the superior/middle temporal cortex, inferior parietal lobule, and ventrolateral prefrontal cortex are part of a perisylvian network of spatial attention (Karnath et al., 2009; Karnath and Rorden, 2012) essential for processes involved in spatial orientation. Considering that these results show an anatomical dissociation between allocentric and egocentric deficits, it may be possible that the temporoparietal and frontal lobe regions are interconnected, but responsible for different aspects of this attention network (i.e., object-centered and viewer-centered spatial representations, respectively).

In contrast, behavioral and anatomical similarities between allocentric and egocentric spatial processing have been recently reported by Rorden et al. (2012) who found a strong behavioral and anatomical association between egocentric and allocentric neglect. Their VLSM results from a sample of 24 subjects (unknown number with neglect) revealed overlapping lesion locations associated with both allocentric and egocentric neglect in the temporal parietal region, tested using a modified version of the gap detection task (Ota et al., 2001). Another study by Yue et al. (2012) looked at 110 right hemisphere stroke subjects assessed using the traditional gap detection test (Ota et al., 2001). They found overlapping regions associated with egocentric and allocentric neglect in the superior temporal gyrus, middle temporal gyrus, and lenticular nucleus. In this study, results implicate largely separate anatomical structures associated with egocentric and allocentric visuospatial processing, with some overlap between neglect subtypes in the superior parietal lobe (Fig. 4). The implication here is that the separation of allocentric and egocentric neglect is likely not as distinct as traditionally thought. The variety of tests used to classify different neglect symptoms may be one

of the biggest contributors to the heterogeneity of results that are observed between studies (Saj et al., 2012).

Interestingly, these results do not implicate lesions to the superior or middle temporal gyri as significantly associated with egocentric spatial neglect, contrary to previous neglect studies (Chechlacz et al., 2010; Medina et al., 2009; Rorden et al., 2012). Additionally, while the logistic regression analysis showed largely the same lesion sites as being associated with allocentric and egocentric neglect compared with the VLSM analysis (Supplementary Figs S2, S4, and S5), for the allocentric tasks, the significance of lesions to the superior and middle temporal cortices was reduced or lost. These results are surprising, considering many lesion analysis studies show the superior temporal gyrus as one of the most important areas associated with neglect symptoms (Buxbaum et al., 2004; Karnath and Rorden, 2012).

We acknowledge that the study sample size is a limitation, and while it is larger than other similar studies (Molenberghs and Sale, 2011; Vossel et al., 2011), it is still relatively small ($N=21$ with neglect, $N=62$ total). Additionally, given the acute nature of the clinical neuroimaging, some of the scans (FLAIR and CT) may have slightly underestimated the lesion size. This is because lesion boundaries can still be somewhat in a state of flux during the first week poststroke, leading to slight potential underestimation of these lesion volumes of interest.

## Conclusion

The results of this study agree with the concept that visuospatial neglect is a heterogeneous syndrome that occurs as a result of multiple distinct lesion locations. These findings suggest that damage to different areas of the brain can produce dissociable deficits in visuospatial attention. Specifically, we observed that lesions to parietal and superior temporal regions were associated with deficits in line bisection, copying, and drawing tasks (allocentric), while lesions to the inferior frontal gyrus, insula, putamen, and superior parietal cortex were associated with deficits in cancellation tasks (egocentric). Thus, poor performance on allocentric and egocentric visuospatial task processing is linked with lesion locations that are largely dissociable.

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## Author Disclosure Statement

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