The Neural Substrates of Drawing: A Voxel-based Morphometry Analysis of Constructional, Hierarchical, and Spatial Representation Deficits

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Abstract

■ Deficits in the ability to draw objects, despite apparently intact perception and motor abilities, are defined as constructional apraxia. Constructional deficits, often diagnosed based on performance on copying complex figures, have been reported in a range of pathologies, perhaps reflecting the contribution of several underlying factors to poor figure drawing. The current study provides a comprehensive analysis of brain–behavior relationships in drawing disorders based on data from a large cohort of subacute stroke patients (n = 358) using whole-brain voxel-wise statistical analyses linked to behavioral measures from a complex figure copy task. We found that (i) overall poor performance on figure copying was associated with subcortical lesions (BG and thalamus), (ii) lateralized deficits with respect to the midline of the viewer were associated with lesions within the posterior parietal lobule, and (iii) spatial positioning errors across the entire figure were associated with lesions within visual processing areas (lingual gyrus and calcarine) and the insula. Furthermore, deficits in reproducing global aspects of form were associated with damage to the right middle temporal gyrus, whereas deficits in representing local features were linked to the left hemisphere lesions within calcarine cortex (extending into the cuneus and precuneus), the insula, and the TPJ. The current study provides strong evidence that impairments in separate cognitive mechanisms (e.g., spatial coding, attention, motor execution, and planning) linked to different brain lesions contribute to poor performance on complex figure copying tasks. The data support the argument that drawing depends on several cognitive processes operating via discrete neuronal networks and that constructional problems as well as hierarchical and spatial representation deficits contribute to poor figure copying. ■

INTRODUCTION

One of the fundamental human abilities is to represent objects in drawings—from rudimentary representations produced by children to sophisticated representation in art (Cavanagh, 2005). However, the reproduction of objects through drawing is a complex process, and it is widely accepted that it depends on an array of cognitive mechanisms including visual object recognition, routines of spatial coding and binding, attention, and planning. The relative contribution of these different mechanisms to drawing is not fully understood (for reviews, see Trojano, Grossi, & Flash, 2009; Grossi & Trojano, 1999); however, some insights into the complex underlying processes can be gleaned through the study of drawing impairments after brain damage. Constructional apraxia is defined as a lack of ability to accurately copy complex figure drawings, sketch (draw) objects, or assemble three-dimensional structures despite otherwise intact motor and perceptual skills (Grossi & Trojano, 1999; Hier, Mondlock, & Caplan, 1983a, 1983b; Kleist, 1934). These so-called "constructional" deficits are relatively common following brain damage including stroke and in progressive neurodegenerative disorders such as frontotemporal dementia, Parkinson disease, and Alzheimer disease (e.g., McKinlay, Grace, Dalrymple-Alford, & Roger, 2010; Trojano et al., 2009; Laeng, 2006; Cosentino, Jefferson, Chute, Kaplan, & Libon, 2004; Grossi et al., 2002; Ala, Hughes, Kyrouac, Ghobrial, & Elble, 2001; Kirk & Kertesz, 1991; Hier et al., 1983a, 1983b).

Constructional apraxia is often measured by figure copying tests, which can reveal patient shortfalls in (1) visuospatial abilities including shape processing and understanding the spatial relations between different components of objects, (2) executive abilities involved in planning drawing, and (3) attention to the overall extent and local aspects of a figure (e.g., Russell et al., 2010; Laeng, 2006; Gainotti & Tiacci, 1970; for a review, see Trojano et al., 2009). As deficits in the cognitive processes underlying these diverse abilities can contribute to constructional apraxia, it raises an important question of whether there is a unitary syndrome or rather a broad range of symptoms associated with different brain lesions.

As an alternative to viewing constructional apraxia as a unitary syndrome, some authors have argued that it

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might be more appropriate to describe "impaired drawing abilities" (Farah, 2003), which can stem from breakdowns in a number of different underlying processes. This argument is supported by the contrasting constructional symptoms that have been reported following brain lesions to the left versus right hemisphere (e.g., Trojano & Conson, 2008; Laeng, 1994, 2006; Trojano et al., 2004; Gainotti & Tiacci, 1970; Warrington, James, & Kinsbourne, 1966). For example, whereas patients with right hemisphere damage (RHD) frequently have problems with representing the distances and spatial relations between visual elements, patients with left hemisphere damage can have planning problems resulting in oversimplification and perseveration errors (Trojano & Conson, 2008; Gainotti & Tiacci, 1970). Furthermore, poor figure drawing abilities resulting from a variety of executive/planning problems have been reported in neurodegenerative disorders such as Alzheimer disease, frontotemporal dementia (frontal and temporal variant), and Parkinson disease affecting both anterior and posterior cortical regions as well as subcortical structures (McKinlay et al., 2010; Grossi et al., 2002; Ala et al., 2001; Kirk & Kertesz, 1991). It has also been noted that poor spatial scanning and representation can lead to poor reproduction of line drawings in patients with visual neglect (for an extensive review, see Behrmann & Plaut, 2001). In summary, the diverse neural substrates of constructional symptoms and their links to different functional problems suggest contributions from several underlying mechanisms in neurological disorders of drawing.

Constructional deficits following both left and RHD have been strongly associated with lesions within posterior parietal cortex (PPC; e.g., Caplan, 2006; Grossi & Trojano, 1999; De Renzi, 1997; Gainotti, 1985; Kleist, 1934). These neuropsychological findings have been confirmed by later functional neuroimaging studies in healthy controls. For example, Makuuchi, Kaminaga, and Sugishita (2003) demonstrated bilateral PPC activation in participants engaged in the drawing activity (based on a contrast between drawing and naming tasks; Makuuchi et al., 2003). Furthermore, Ogawa and Inui (2009) found that bilateral PPC activation was specifically linked to figure copying (reproducing by drawing) as opposed to line tracing (Ogawa & Inui, 2009). In each case, the functional neuroimaging studies (Ogawa & Inui, 2009; Makuuchi et al., 2003) have found activation within the intraparietal sulcus (IPS) and supramarginal gyrus along with other posterior parietal regions. Interestingly, RHD within both superior (including IPS) and inferior (including supramarginal gyrus) parietal lobule have been also associated (among other cortical regions) with the syndrome of egocentric spatial neglect (e.g., Chechlacz et al., 2010, 2012; Gillebert et al., 2011; Medina et al., 2009; Hillis et al., 2005; Mort et al., 2003; Vallar, Bottini, & Paulesu, 2003). Surprisingly, to date, the common and/or dissociable neural substrates of constructional deficits and neglect in figure copying have not been systematically examined.

A further spatial deficit that can impact on copying performance is the ability to process local and global aspects of form (Kuschner, Bodner, & Minshew, 2009; McConley, Martin, Banos, Blanton, & Faught, 2006; Poreh & Shye, 1998). Neuropsychological data from brain-damaged patients, using both complex figure copying and the identification of hierarchical figures as well as functional neuroimaging and TMS studies in healthy controls, suggest some degree of functional lateralization of local and global form processing. Here, it has been argued that global form processing is mediated by the right hemisphere and that local feature processing is mediated by the left hemisphere (Mevorach, Humphreys, & Shalev, 2005; Fink et al., 1996; Lamb, Robertson, & Knight, 1989, 1990; Delis, Robertson, & Efron, 1986; Robertson & Delis, 1986; see Marshall & Halligan, 1995, for evidence of local processing mediated by the right hemisphere). For example, Fink et al. (1996) using PET have found that attention to global figures is associated with activation within the right lingual gyrus, whereas attention to local figures is linked to activation within the left inferior occipital cortex. Furthermore, TMS applied to temporarily disrupt the left PPC in right-handed healthy participants is linked to poor processing of local features (Mevorach et al., 2005). In neuropsychological patients, global versus local feature processing deficits have been associated with lateralized lesions to respectively the right (global) and left (local) TPJ and superior temporal gyrus (STG; Lamb et al., 1989, 1990). For example, Lamb et al. (1990), by using a simple task in which participants are asked to detect target letters occurring randomly at either the local or global level, have shown that patients with lesions to the right STG are more prone to global deficits and show local advantage, whereas patients with lesions to the left STG are more prone to local deficits and show global advantage. Although reported constructional deficits and other related cognitive impairments vary qualitatively in left and right hemisphere patients, attempts to dissect out different effects of left versus right hemisphere lesions on complex figure tasks have not been done systematically. In particular, to date, the common and/or dissociate neural substrates of core constructional deficits and local/global processing in figure copy task has not been examined.

In the current study, we examined the neuronal substrates of different processes contributing to poor complex figure copying, using data from a large group of subacute stroke patients (n = 358). By using neuroimaging and behavioral data from a large and not preselected stroke cohort, we were able to include in the study patients who differed in terms of symptoms, damaged areas, and affected hemisphere. This then allowed us to delineate different mechanisms, both in terms of separate cognitive components (impairments) and associated brain lesions underlying drawing disorders in stroke. Symptoms of constructional apraxia and other associated deficits were measured using the complex figure copy task from the Birmingham Cognitive Screen (BCoS) battery—a battery

developed to screen patients for a range of cognitive problems following stroke (Humphreys, Bickerton, Samson, & Riddoch, 2012). Like other complex figure copy tasks, performance on this test is likely to be susceptible to different aspects of constructional apraxia, unilateral neglect, and global/local feature processing (Humphreys et al., 2012). The study was based on whole-brain statistical analyses using voxel-based morphometry (VBM; Ashburner & Friston, 2000) to evaluate common structure–function relationships across the whole brain. The analyses treated all behavioral measures of performance on the figure copy test as continuous rather than as categorical scores, giving a better opportunity to tease apart the neural substrates of different constructional and associated cognitive impairments. Furthermore, the approach chosen here did not require us to select patients based on the anatomical characteristics of the lesion; rather, we included patients who had a wide range of lesions including right as well as left hemisphere cases. This avoided biasing the results based on priori assumptions about patients (e.g., confining the analysis to left hemisphere lesions so that the contribution of right hemisphere lesions is not assessed) and seems appropriate taking into account that constructional deficits have been reported following both left hemisphere damage and RHD. As the data were collected as a part of a large clinical trial carried out in the United Kingdom, we used computed tomography (CT) scans, which are routinely used in clinical practice. We have demonstrated that VBM analyses using CT scans can yield highly reliable and interpretable results (Chechlacz et al., 2012, 2013).

Our findings demonstrate that a single test measuring the performance of stroke patients on a complex figure copy test provides insights into the cognitive mechanisms of drawing and that distinct problems in the task are associated with contrasting brain regions. The results are discussed in relation to the neuroanatomy of constructional apraxia and the organization of brain networks associated with drawing.

METHODS

Participants

Patients were recruited from several stroke units across the West Midlands (United Kingdom) participating in the multicenter Birmingham University Cognitive Screen project (www.bucs.bham.ac.uk). Eight hundred seventy-three patients were given the BCoS cognitive assessment, designed to develop cognitive profiles for stroke survivors not contaminated by problems in neglect and aphasia (Humphreys et al., 2012). The behavioral data were only collected from patients who were physically stable, able to understand English, willing to perform the task, and had a concentration span of at least 60 min (judged by a multidisciplinary clinical stroke team). Clinical and demographic data, including CT scans, were obtained from the patients' clinical files. For the current study, we excluded patients whose CT scans were unavailable (n = 292). Furthermore, based on visual inspection of CT scans by two independent judges, we excluded patients who either had enlarged ventricles (n = 19) or poor-quality CT scans (n = 23) to prevent artifacts in the neuroimaging analyses. We also excluded patients who, because of severe motor deficits, could not complete the figure copy test (n = 181; see below for exclusion criteria). Three hundred fifty-eight stroke patients (160 men and 198 women; average age of 69.4 years, range = 26–93 years; see Table 1 for full demographic and clinical data) were included. All participants provided written informed consent in agreement with ethics protocols approved by the National Research Ethics Service: Essex 1 Ethics Committee.

Behavioral Measures

Cognitive Profile

Neuropsychological testing took place following stroke onset at the subacute phase (<3 months after stroke), and the average stroke to test interval was 23 days (±20.8, with 90% of patients being tested within 2 months and with 70% patients being tested within 1 month). The cognitive profile of each patient was derived using the BCoS (Humphreys et al., 2012), a 1-hr assessment composed of 23 tests within five broad cognitive domains: attention and executive functions, memory, language, praxis/control and planning of action, and mathematical/number abilities. The BCoS was administered in hospital settings. In the current study, we used one of the praxis domain subtests, BCoS complex figure copy task, to assess deficits associated with constructional apraxia. The BCoS visual extinction test has rudimentary measures of visual sensory loss based solely on trials where stimuli are presented unilaterally (Chechlacz et al., 2012, 2013). We used the visual sensory loss data from this test as a measure of the presence of visual field deficits. The BCoS also provides an assessment of the patient's awareness of their general setting and circumstance, that is, orientation measures, and these measures were used in the analyses to control for overall comprehension and for presence of anosognosia and somatoparaphrenia often associated with visuospatial symptoms (e.g., Gandola et al., 2012; Kortte & Hillis, 2009; Vallar & Ronchi, 2009). The full description of the task assessing visual sensory loss and the orientation measures is included in the supplementary material.

Complex Figure Copy Test

The BCoS complex figure consists of a rectangular box divided into three global rectangles. Within each of these rectangles are various local features, such as dots, diagonal lines, and arrows (see Figure 1A for details). Two criteria are used to determine whether patient could be tested on the task: (1) whether the patient was able to hold a pen and (2) whether the patient could make fluent

Table 1. Patient Details: Clinical and Demographic Data (n = 358, All Stroke Patients Included in the Current Study)

	Mean Value or Number of Patients	*SD*
Age in years	69.4	13.8
Sex (male/female)	160/198	N/A
Etiology (ISCH/BL)	328/30	N/A
Etiology (MCA/PCA/other)	167/35/156	
Lesion volume (mean/*SD*)[a]	50.1/70.6 cm^3	
BS	62.6/113.0 cm^3	
LHS	51.7/62.7 cm^3	
RHS	60.8/77.9 cm^3	
Handedness (right/left)	315 (61)/43 (14)[b]	N/A
Stroke, CT scan in days[c]	5.2	11.7
Stroke, BCoS in days[c]	23.0	20.8
Orient1[d]	7.6 (8)[e]	1.1
Orient2[d]	5.6 (6)[e]	0.8
Anosognosia: Orient3[d]	2.9 (3)[e]	0.3
BCoS Complex Figure Copy Test		
Complex figure: full score	35.7 (47)[e]	10.6
Left egocentric neglect score	0.6 (7)[e]	1.41
Right egocentric neglect score	0.2 (7)[e]	0.71
Relative position: whole figure score	20.2 (27)[e]	6.8
Relative position: left asymmetry score	0.6 (11)[e]	1.2
Relative position: right asymmetry score	0.8 (11)[e]	1.7
Local feature processing score	12.3 (14)[e]	2.9
Global feature processing score	5.3 (6)[e]	1.3

BL = bleed (hemorrhagic stroke); ISCH = ischemic stroke; MCA = middle cerebral artery stroke; PCA = posterior cerebral artery stroke; other = types of strokes other than MCA and PCA including the anterior cerebral artery area, BG, and thalamus (LSA and AChA territories of strokes) as well as the cerebellum; N/A = not applicable.

[a]Mean lesion volume provided for the entire group and by stroke laterality: BS = bilateral stroke; LHS = left hemisphere strokes; RHS = right hemisphere strokes.

[b]The number in brackets indicates patients who performed the task with nondominant hand.

[c]Interval between stroke onset and CT scan or cognitive assessment based on BCoS.

[d]BCoS-derived assessment of the patient's awareness of their general setting and circumstance, that is, orientation measures (Orient1, orientation measure assessing personal information; Orient2, orientation measure assessing time and space awareness).

[e]Mean score across the entire group of patients; the number in brackets indicates maximum score for a given test.

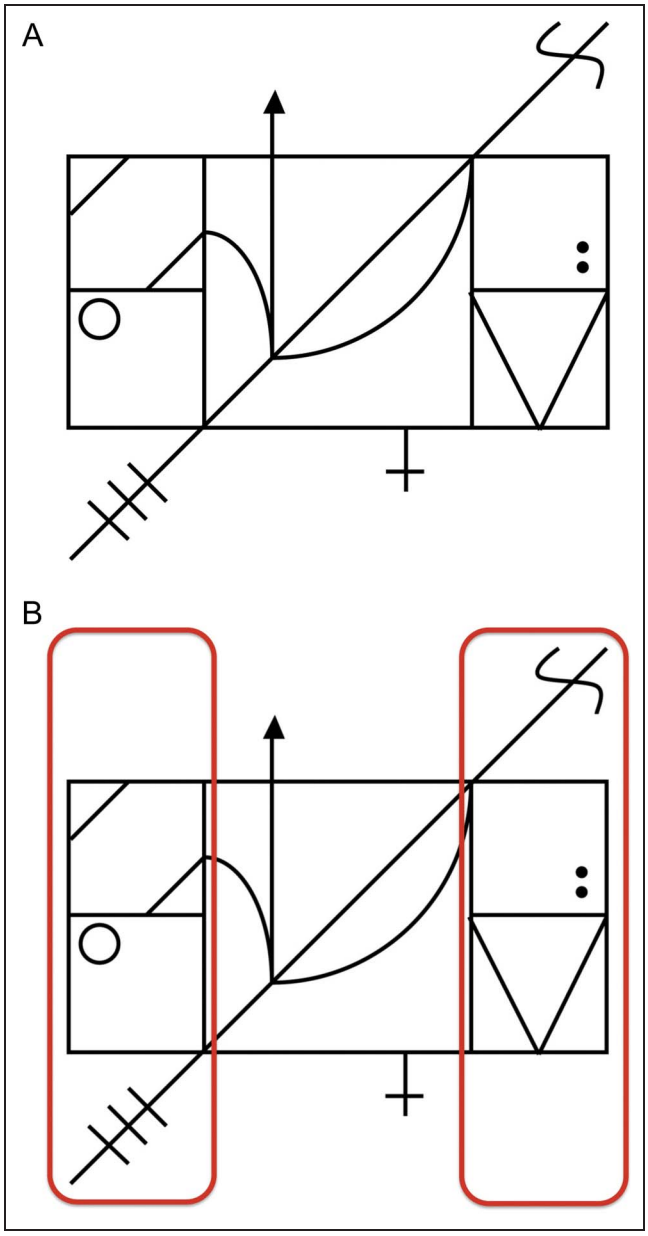

Figure 1. BCoS complex figure copy task. Following the instruction, "I will show you a figure. Please copy the figure the best you can," the complex figure drawing (A) is presented to the patient in the top half of an A4 page. Each patient is given a maximum of 5 min to complete the task. In the original task (Humphreys et al., 2012), performance is scored based on the presence (1 point each), shape/proportion (1 point each), and placement (1 point each) of five left elements (diagonal end/three bars, rectangle, horizontal bar, double oblique bars/parallel, and circle), five right elements (diagonal end/one curved line, rectangle, horizontal bar, double oblique/triangle shape, and double dot), and five middle elements (arrow, right curve, left curve, middle cross, and main diagonal line). In addition, the presence and shape/proportion of the middle square is assigned 2 points, thus giving the maximum achievable score of 47 points for the completed task. (B) Example of the modified scoring on the BCoS complex figure copy test. To examine lateralized deficits, each end rectangle was evaluated on the presence of seven elements (left rectangle: diagonal end/three bars, circle, horizontal bar, top square, bottom square, top left diagonal bar, and the parallel bar below it; right rectangle: left and right lines of the triangle shape, double dot, horizontal bar, top square, bottom square, and right diagonal end/one curved line with an "S" shape).

marks/lines on paper. The complex figure was presented to the patient in the top half of an A4 page, and the patient was asked to draw an exact copy of the image underneath the original. Patients were given a maximum of 5 min to complete the task. Following the BCoS manual, once the figure has been copied, performance was scored according to whether the visual elements were present (1 point each), the correct shapes were represented (1 point each), and whether the elements were assigned their correct position (1 point each), with the maximum achievable score being 47 points (see Figure 1A for full details of scoring). An overall score of less than 44 points (age group of <64 years), 43 points (age group of 65–74 years), and 37 points (age group of >75 years) can be considered indicative of a deficit, based on the cutoff scores (less than fifth percentile) derived from a group of elderly control participants with no history of neurological diseases (n = 100; Humphreys et al., 2012).

The BCoS figure contains a middle square plus two additional rectangles to the left and right with several smaller features inside, and thus, the scoring of copying performance can be adapted to evaluate patient ability to replicate spatial relationships between various elements of the figure (see Figure 1). Furthermore, all individual features are symmetrically organized, that is, the number of individual elements to the left is equal to the number of elements to the right, and thus, scoring can provide an easy measure of lateralized deficits with respect to the midline of the viewer (egocentric neglect). Finally, the figure is composed of both global and local features, allowing for the analysis of errors with global features (e.g., the central square) and local features (e.g., the right double dots). As this study aimed to examine various visual and spatial deficits associated with drawing disorders, we used such modified scoring methods to measure these different deficits as described below.

Lateralized Deficits with Respect to the Midline of the Viewer (Egocentric Deficits)

Patients can make drawing errors by omitting elements on one side of the figure in spatial positions defined relative to the midline of the viewer (e.g., stemming from egocentric neglect). To capture this, we scored each of the end rectangles in the complex figure based on the presence/omission of each element (giving 7 points for the left rectangle and 7 points for the right rectangle). Asymmetry scores were calculated by evaluating whether patients missed more features from the left side of the figure (left asymmetry) or more features from the right side of the figure (right asymmetry) to depict spatially selective copying deficits. The asymmetry scores indicate whether a patient missed more items on the left or right. If the patient missed more items on the right, the difference between the number of detected left and detected right items would generate a right asymmetry score and a left asymmetry score of 0 (and vice versa if the patient missed more items on the left). Both left and right asymmetry scores were entered into statistical models used in the VBM analyses.

Relative Position Scoring

Patients with constructional apraxia often show deficits in correctly replicating the spatial relationships between different elements in target figures, and these deficits may be independent of deficits associated with neglect (e.g., they may not be spatially lateralized; see Halligan, Marshall, & Wade, 1992). To reflect the representation of relative spatial positions, each patient's performance was rated using three different measures: the placement (correct position and orientation) of individual features in the whole figure (27 points), the placement of individual features within the left side of the figure (11 points), and the placement of features within the right side of the figure (11 points). The last two measures were used to calculate asymmetry scores. The whole-figure relative positioning scores as well as the left and right asymmetry measures were entered into statistical models used in the VBM analyses.

Global/Local Processing

Finally, we measured the reproduction of global and local aspects of the complex figure.[1] For this, global features were defined as the larger parts of the figure and included the middle square, the left rectangle, the right rectangle, the left double bar (inside the top left square), the right triangle, and the long main diagonal line. Local features were defined as details that further refined the figure. The local features included the top left diagonal bar, the parallel bar below it, the left horizontal bar, the left circle, the left diagonal end/three parallel bars, the left curve (inside the middle square), the arrow, the right curve (inside the middle square), the cross, the right double dot, the right side of the triangle, the left side of the triangle, the right horizontal bar, and the right diagonal end/curved line ("S" shape). Participants were graded according to whether each global or local feature shape was present. The actual shape of the feature and the placement of the figure were not taken into account in this analysis. Participants could score 6 points on the global processing measure and 14 points on the local processing measure, and scores were entered into the statistical model used in the VBM analyses.

Neuroimaging Assessment

For all 358 patients included, CT scans were acquired as part of routine clinical assessment following stroke and hospital admission. The average time between the stroke and the CT scan acquisition was 5.2 days (±11.7 days,

with 82% of cases within a week). The neuroimaging data were acquired using the following scanners: Siemens Sensation 16, GE Medical System LightSpeed 16, and LightSpeed Plus. The CT images covered the whole brain with an in-plane resolution of 0.5×0.5 mm^2 and a slice thickness varying between 4 and 5 mm. Thus, in comparison with a typical MR structural scan (T1- or T2-weighted images), the CT scans used in the current study had double in-plane resolution (along the x and y axes) but poorer ventral–dorsal resolution (along the z axis). We have shown that, despite such limitations of CT scans, it is feasible to conduct VBM analyses using clinically acquired CT scans (Chechlacz et al., 2012). Specifically, we demonstrated that neural correlates of egocentric versus allocentric neglect examined using clinical CT scans were in direct agreement with findings from a separate study (different patient population) based on high-resolution structural and diffusion scans (MRI study: Chechlacz et al., 2010; CT study: Chechlacz et al., 2012).

Image Preprocessing

All the CT scans were preprocessed using SPM8 (Wellcome Department of Cognitive Neurology, London, United Kingdom) as described (Chechlacz et al., 2012, 2013). Briefly, the images were first realigned manually along the anterior–posterior commissural axes and then normalized (Ashburner & Friston, 2003) to an in-house CT template. Next, we used the unified segmentation algorithm as implemented in SPM8 (Ashburner & Friston, 2005) with six standard tissue class priors indicating the probability of finding expected signal sources of gray matter (GM), white matter (WM), cerebrospinal fluid, fat, bone, and air (i.e., six different tissues classes), at each voxel of the image. As the CT scans were acquired following stroke, to account for the presence of any abnormal tissue, we also included an additional, seventh tissue class corresponding to the lesioned tissue based on a previously described modified segmentation protocol (Seghier, Ramlackhansingh, Crinion, Leff, & Price, 2008). The probability for an abnormal voxel (lesioned voxel) within the GM and WM was estimated based on the ratio between average lesion size (computed for 160 patients; Chechlacz et al., 2012) and the GM plus WM voxels (Chechlacz et al., 2012, 2013). Furthermore, we constrained the classification of GM and WM to each being based on a single Gaussian (normal) distribution, whereas two Gaussian distributions were used to model the intensities in the abnormal tissue class. This last procedure was used to account for any possible inhomogeneity of the abnormal tissue. Finally, the segmented GM and WM images were smoothed with a 12-mm FWHM Gaussian filter to accommodate the assumption of random field theory used in the statistical analysis (Worsley, 2003). The choice of intermediate smoothing of 8- to 12-mm FWHM was shown to be optimal for lesion detection and further analysis of segmented images (e.g., Chechlacz et al., 2012, 2013; Leff et al., 2009; see Seghier et al., 2008; Stamatakis & Tyler, 2005, for discussion and technical details). The quality of the segmentation and normalization procedures was assessed for each patient. The preprocessed GM images were further used in the analyses to determine voxel-by-voxel relationships between brain damage and deficits associated with constructional apraxia (see below).

VBM

In the current study, we employed random effects analyses within the general linear model framework (Kiebel & Holmes, 2003) to compute correlations between the behavioral measures of deficits associated with constructional apraxia as measured by BCoS complex figure copy test and GM lesions. We used the full factorial design to generate five models testing for (1) overall deficits associated with figure copying including the full (overall) BCoS figure copy score as the main covariate, (2) lateralized omissions with respect to the midline of the viewer (egocentric deficits) including both left and right asymmetry scores as main covariates, (3) global/local processing deficits including global and local processing scores as main covariates, (4) overall relative positioning deficits including the placement score for elements within the whole figure as the main covariate, and (5) the relative positioning of left and right elements including the left and right position asymmetry scores as main covariates.

To control for potential confounding factors, we included the following covariates in all analyses: age, gender, handedness, time from stroke to neuropsychological testing, time from stroke to scan, the type of stroke (ischemia or hemorrhage), and three orientation measures assessing the patient's awareness of their general setting and circumstance. In all statistical models, we included measures of left and right asymmetry scores based solely on the unilateral trials from the visual extinction test as separate covariates to reduce the spurious effects of the presence of sensory impairments/visual field defects that could affect performance on the complex figure test. Finally, the size of the lesion visible on the CT scan (lesion volume) was rated for each patient from 0 to 5, where 0 = *no visible lesion*, 1 = *small/precise lesion (up to 5 cm^3)*, 2 = *one fourth of the hemisphere (up to 100 cm^3)*, 3 = *one half of the hemisphere (up to 250 cm^3)*, 4 = *two thirds to three fourths of the hemisphere (up to 450 cm^3)*, and 5 = *a lesion encompassing the entire hemisphere*. This information was then added as a covariate to all statistical models. We validated this categorical estimation of lesion size based on the actual lesion volume computed from reconstructed lesion maps of 160 stroke patients (see Chechlacz et al., 2013).

We only report results that showed significant effects at $p < .001$ cluster-level corrected for multiple comparison with the amplitude of voxels surviving of $p < .001$ uncorrected across the whole brain and an extent threshold of 800 mm^3 (>100 voxels). The brain coordinates are

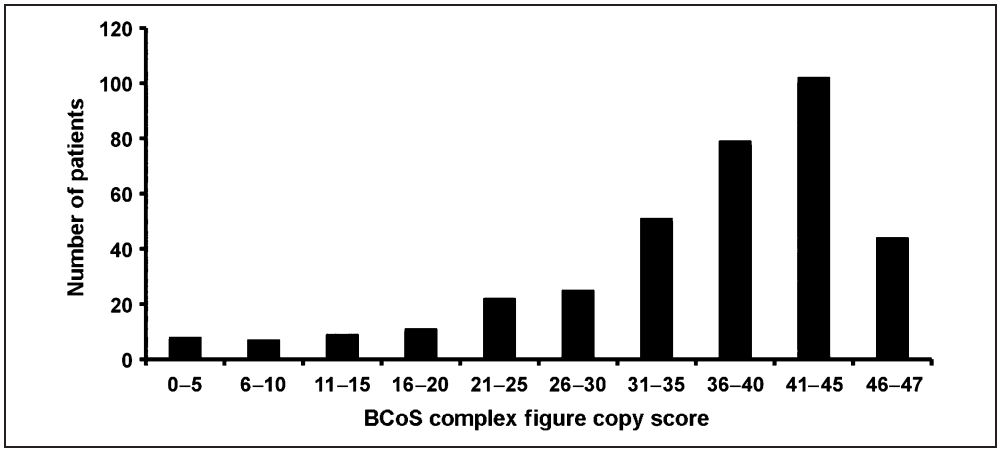

Figure 2. BCoS complex figure copy task: distribution of the full (overall) scores in the patients included here (n = 358).

presented in standardized Montreal Neurological Institute space. The anatomical localization of the lesion sites associated with constructional apraxia was based on the anatomical automatic labeling toolbox (Tzourio-Mazoyer et al., 2002), the Duvernoy Human Brain Atlas (Duvernoy, Cabanis, & Vannson, 1991), and the Woolsey Brain Atlas (Woolsey, Hanaway, & Gado, 2008).

RESULTS

Behavioral Findings

Table 1 presents the demographic and clinical data for all patients included in the current study as well as a summary of the behavioral findings with respect to the different measures used in the VBM analyses. The overall performance on BCoS complex figure copy test is illustrated in Figure 2 presenting distributions of full (overall) score on the task in the studied group of patients.

Neuroimaging Findings

Our VBM analyses based on the general linear model aimed to determine whether different aspects of performance on the BCoS complex figure copy test were associated with damage to discrete neuroanatomical substrates. Please note that Supplementary Figure 1 illustrates the lesion distribution for all 358 stroke patients (i.e., the overlap of the lesion maps for all patients in the study as defined by the semiautomated lesion detection algorithm; see supplementary material).

Neural Substrates of Overall Deficits

We first investigated the relationships between overall deficits on the complex figure test and GM lesions. We found that damage within subcortical structures including the putamen and caudate, and extending into the thalamus within the right hemisphere, was associated with overall poor figure copying (see Table 2 and Figure 3). As these findings were somewhat puzzling, we sought to determine whether the results reflected true correlates of deficits in figure copying or perhaps resulted from confounding influences from other symptoms (as fractionated below), that is, lateralized omissions and deficits in representing the global and/or local properties of the figures. To do this, we repeated the analysis based on a statistical model that included the overall BCoS complex figure score along with scores reflecting these other deficits. Again, we found that overall poor figure copy performance was associated with subcortical damage within the BG and the thalamus (see Supplementary Figure 2).

Neural Substrates of Omission Errors

We found that left omissions in figure copying were associated with lesions within the right inferior parietal

Table 2. GM Substrates of Overall Deficits in BCoS Complex Figure Copy Task (Based on the Overall Task Score)

	Cluster Level		*Voxel Level*	*Coordinates*			
Model	p_{FWE}	*Size*	*z Score*	*x*	*y*	*z*	*Brain Structure (Location)*
Full score	.000	1212	5.47	21	−7	12	Right putamen
			4.50	22	−19	9	Right thalamus
			4.20	27	−4	27	Right caudate

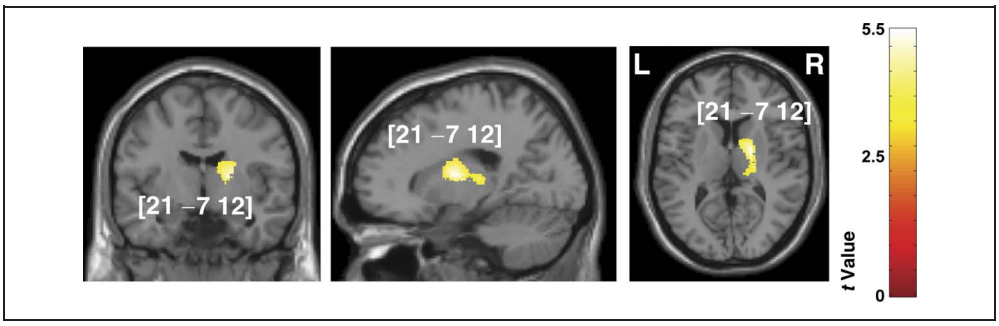

Figure 3. Neural substrates of overall deficits in the BCoS complex figure copy task: VBM GM analysis based on total scores. The lesioned areas associated with overall deficits in the figure copying task are colored according to the level of significance in the VBM analysis, where brighter colors represent higher *t* values. The numbers in brackets indicate peak MNI coordinates.

lobule (damage within both supramarginal and angular gyri) and the right middle frontal gyrus (Table 3; Figure 4). We did not observe any brain regions significantly correlated with right omission errors in the complex figure copy.

Neural Substrates of Relative Position Errors

Our further analysis examined lesions associated with deficits in reproducing the spatial relationships between the features in the complex figure. Overall relative position errors were associated with damage to the right insula and the left lingual gyrus extending into the calcarine sulcus (Table 4; Figure 5A). Errors in positioning left-side features were associated with RHD to the angular gyrus, putamen, and lingual gyrus (Table 4, Figure 5B). In contrast, errors in positioning right-side features were associated with damage within both hemispheres including the right middle temporal gyrus (MTG) and inferior temporal gyrus (ITG), the right angular gyrus, the right IPS, the right insula, the left precuneus, and the left ITG partly extending into the MTG (Table 4, Figure 5C).

Neural Substrates of Global/Local Processing Deficits

Finally, we examined neural substrates of deficits in processing local versus global features. Local feature processing deficits were associated exclusively with left hemisphere damage to the calcarine cortex extending into the cuneus and precuneus, the insula, the TPJ, and the left cerebellum (see Table 5 and Figure 6A). In contrast, global feature processing deficits were associated exclusively with RHD to the MTG extending into the ITG (Table 5, Figure 6B).

DISCUSSION

The current study provides compelling evidence that several separate cognitive mechanisms contribute to the poor performance of stroke patients on complex figure copying and that these contrasting mechanisms are associated with different lesions. This is in direct agreement with the idea that drawing depends on several cognitive processes operating via discrete neuronal networks (for reviews, see Trojano et al., 2009; Grossi & Trojano, 1999). Specifically, we found that, although overall poor performance on figure copying was associated with subcortical lesions (the BG and thalamus), the lateralized deficits with respect to the midline of the viewer were associated with lesions within the posterior parietal lobule, whereas spatial positioning errors across the entire figure were associated with lesions within visual processing areas (the lingual gyrus, calcarine cortex, and precuneus) as well as the insula. Furthermore, we found that, whereas global processing deficits were associated with damage within the right MTG, deficits in local feature processing were linked to left hemisphere lesions within the calcarine cortex (extending into the cuneus and precuneus), the insula, and the TPJ. The study provides the first comprehensive analysis of brain–behavior relationships in drawing disorders based on data from a large cohort of subacute stroke patients (n = 358) using behavioral measures derived from a single task and the

Table 3. GM Substrates of Lateralized Deficits with Respect to the Midline of the Viewer

	Cluster Level		*Voxel Level*	*Coordinates*			
Model	p_{FWE}	*Size*	*z Score*	*x*	*y*	*z*	*Brain Structure (Location)*
Left egocentric neglect	.000	600	4.17	62	−51	33	Right IPL (angular and supramarginal gyri)
	.000	157	3.74	30	−9	31	Right MFG

IPL = inferior parietal lobule; MFG = middle frontal gyrus.

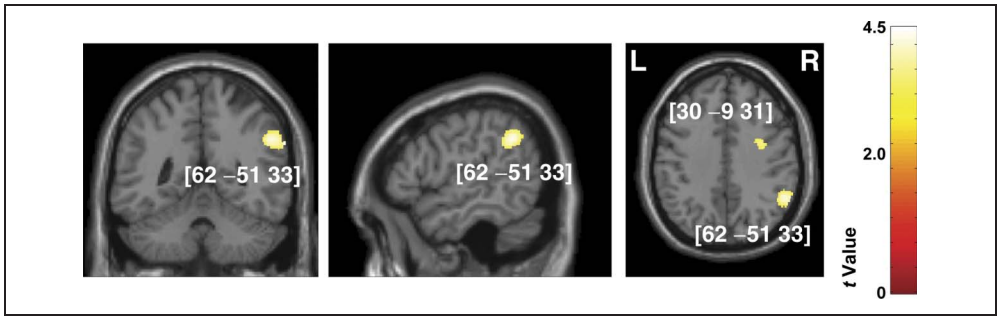

Figure 4. Neural substrates of lateralized deficits in the BCoS complex figure copy task. Lesions associated with poor performance on the figure copy task (lateralized deficits) representing left egocentric neglect symptoms. The lesioned areas are colored according to the levels of significance in the VBM analysis, where brighter colors represent higher *t* values. The numbers in brackets indicate peak MNI coordinates.

whole-brain voxel-wise statistical analyses (VBM; Ashburner & Friston, 2000).

BCoS Complex Figure Copy Task and Constructional Apraxia

The Rey–Osterrieth complex figure has traditionally been used to diagnose constructional apraxia (Osterrieth, 1944; Rey, 1941). A number of different errors are typically noted (Lezak, 1995). Specifically, patients may produce distorted copies (e.g., elements are transposed to different locations) and impoverished drawings (missing elements; Smith, Little, Nowinski, & Walker, 2009; Lezak, 1995). In the current study, we used the BCoS complex figure copy (Humphreys et al., 2012), which is simplified in relation to the Rey–Osterrieth complex figure, making it easier to use as a part of the clinical diagnosis in subacute stroke. The organization of the BCoS figure also enables the examiner to derive several different measures assessing not only constructional problems but also lateralization of performance and the reproduction of global and local elements (see Figure 1; Humphreys et al., 2012). As we discuss below, these properties have advantages for dissociating components of constructional problems from other associated deficits. As a result, the data acquired here using the BCoS figure allowed us to provide evidence that figure drawing depends on several cognitive processes operating via discrete neuronal networks and also that constructional

Table 4. GM Substrates of Relative Position Errors

	Cluster Level		*Voxel Level*	*Coordinates*			
Model	p_{FWE}	*Size*	*z Score*	*x*	*y*	*z*	*Brain Structure (Location)*
Relative position: whole figure score	.000	462	3.43	42	21	−8	Right insula
	.000	144	3.33	−18	−60	0	Left lingual gyrus extending into the calcarine
Relative position: left asymmetry score	.000	672	4.15	48	−70	37	Right angular gyrus
			4.04	58	−60	31	
	.000	180	3.59	32	−4	−8	Right putamen
	.000	180	3.45	18	−58	−5	Right lingual gyrus
Relative position: right asymmetry score	.000	421	5.54	63	−54	7	Right MTG
	.000	230	5.38	56	−51	−24	Right ITG (posterior part)
	.000	2.27	5.34	−48	0	−42	Left ITG (anterior part)
	.000	450	5.25	−12	−73	48	Left precuneus
	.000	112	5.06	42	26	−18	Right insula
	.000	495	4.39	44	−60	40	Right angular gyrus
	.000	160	4.24	36	−78	31	Right IPS
	.000	182	4.03	50	−64	16	Right MTG extending into MOG

MOG = middle occipital gyrus.

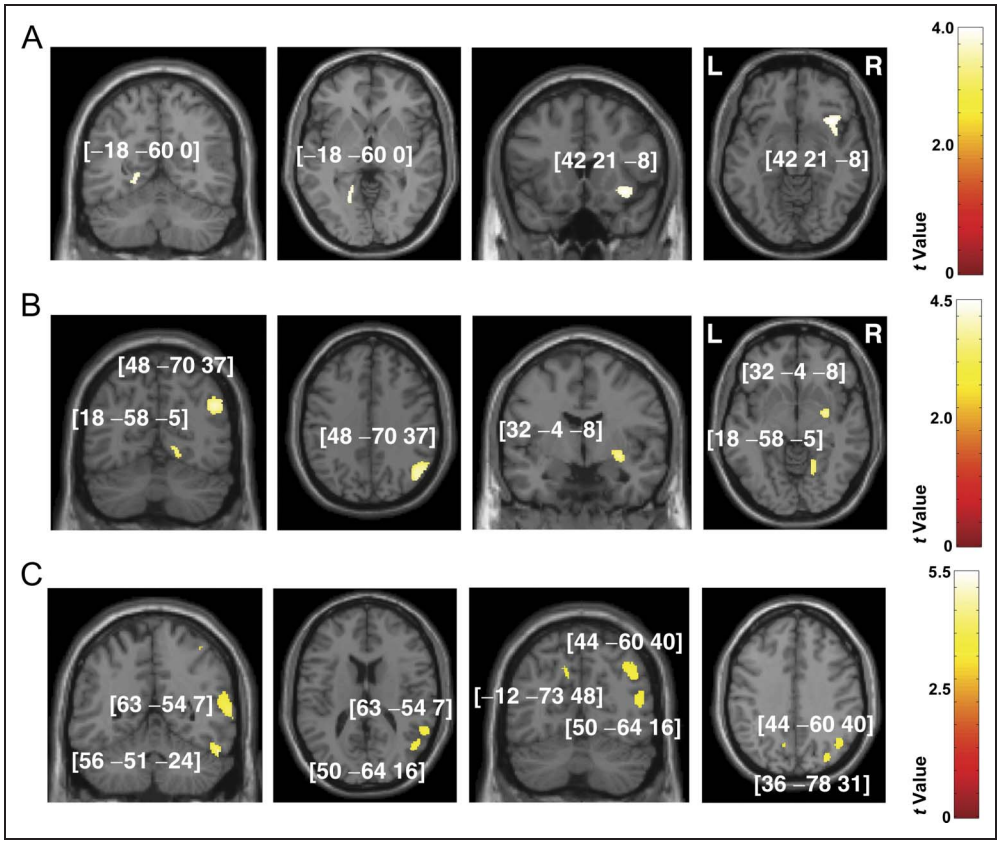

Figure 5. Neural substrates of relative position errors in BCoS complex figure copy task. (A) Lesions associated with deficits in replicating the spatial relationships between individual features based on the measure for the whole copied figure. (B) Lesions associated with errors in the relative positioning of left and (C) right elements within the BCoS complex figure test. In A–C, the lesioned areas associated with deficits in figure copying are colored according to the level of significance in the VBM analysis, where brighter colors mean higher *t* values. The numbers in brackets indicate peak MNI coordinates.

problems as well as hierarchical and spatial representation deficits contribute to poor figure copying.

Neural Substrates of Deficits in BCoS Complex Figure Copy Task

Rather than linking overall deficits in drawing to damage within parietal cortex (Trojano & Conson, 2008; Vallar, 2007; Caplan, 2006; Laeng, 1994, 2006; Trojano et al., 2004; Grossi & Trojano, 1999; De Renzi, 1997; Gainotti, 1985; Gainotti & Tiacci, 1970; Critchley, 1969; Warrington et al., 1966; Kleist, 1934), our results point to associations with right hemisphere subcortical lesions within the putamen, caudate, and thalamus. Although the BG have been traditionally associated with motor control, a large body of evidence suggests their involvement in a diverse set of cognitive processes including visual perception, spatial working memory, and executive functions (for a comprehensive review, see Brown, Schneider, & Lidsky, 1997). fMRI studies with normal participants also indicate that drawing is linked to increased activation of the putamen (Makuuchi et al., 2003), whereas the caudate has been linked to motor control, planning movement sequences, and goal-directed behavior (Grahn, Parkinson, & Owen, 2008, 2009; Jankowski, Scheef, Huppe, & Boecker, 2009; Li, 2000). These studies, together with our findings, suggest that damage to the BG and thalamus may cause a problem in planning movement sequences, which impacts on copying complex figures.

Table 5. GM Substrates of Global and Local Processing Deficits

	Cluster Level		*Voxel Level*	*Coordinates*			
Model	p_{FWE}	*Size*	*z Score*	*x*	*y*	*z*	*Brain Structure (Location)*
Local feature processing	.000	811	4.61	−14	−64	18	Left calcarine extending into the cuneus and precuneus
	.000	925	4.21	−38	11	3	Left insula
	.000	292	3.88	−2	−21	−42	Left cerebellum
	.001	112	3.44	−46	−34	22	Left TPJ
Global feature processing	.000	296	3.93	64	−36	−12	Right MTG

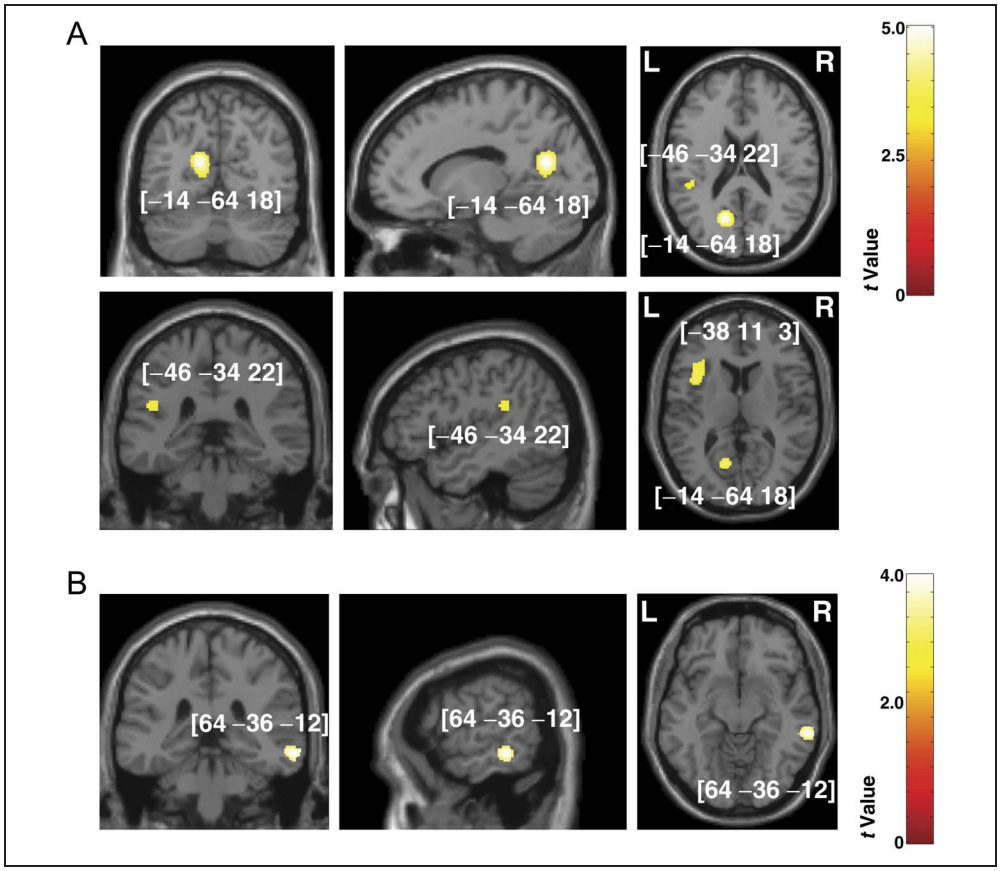

Figure 6. Neural substrates of global and local processing deficits in the BCoS complex figure copy task. (A) Lesions associated with deficits in representing local features. (B) Lesions associated with deficits in representing global features. In both A and B, the lesioned areas are colored according to the level of significance in the VBM analysis, where brighter colors mean higher *t* values. The numbers in brackets indicate peak MNI coordinates.

One account of these links between poor performance on BCoS figure test and damage to the caudate, putamen, and thalamus is that they might disrupt neuronal loops connecting cortical regions concerned with spatial representation (e.g., in parietal cortex) and motor planning (e.g., in premotor cortex). Thus, lesions to these regions disrupt the connections required to translate the spatial codes for the complex figure into appropriate motor action, and this results in overall poor performance on BCoS figure test. It is noteworthy that these lesions were not related to other aspects of performance, including the lateralization of errors, consistent with the BG and thalamic lesions affecting some more general factor in drawing.

The right posterior parietal lesions that have been reported in previous studies with constructional apraxia patients are thought to produce deficits in drawing abilities associated with different aspects of spatial coding. Notably, damage within the parietal cortex has been also linked to egocentric neglect (e.g., Chechlacz et al., 2010, 2012; Gillebert et al., 2011; Medina et al., 2009; Hillis et al., 2005; Mort et al., 2003; Vallar et al., 2003), and this may or may not affect the ability of patients to evaluate spatial distances and the relations between objects even when the elements are detected. Specifically, although egocentric neglect is usually diagnosed using performance in complex figure copying based on the omission of elements on the contralesional side of the figure defined in terms of the viewer's midline, it can also be expressed in the spatial misplacement of elements (Halligan et al., 1992). However, the deficits in correctly replicating the spatial relationships between different elements traditionally associated with constructional apraxia are often independent of deficits associated with neglect (e.g., they may not be spatially lateralized or persist after neglect symptoms have resolved; Hier et al., 1983a, 1983b).

Consistent with previous studies examining the neuroanatomy of egocentric neglect (see, e.g., Chechlacz et al., 2010, 2012; Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010; Medina et al., 2009; Hillis et al., 2005; Mort et al., 2003; Vallar et al., 2003), we observed that left-side poor performance (as measured by the number of replicated elements) was associated with lesions within the right inferior parietal lobule (damage within both supramarginal and angular gyri) and the right middle frontal gyrus. However, when we performed analyses using errors in the relative position of individual features of the complex figure, that is, indicating problems in replicating spatial relationship between elements of the copied figure, we found that lesions to the right insula were associated with overall poor performance on tasks measuring the relative positions of copied features in the whole BCoS figure (although this was also linked to lesions of the left lingual gyrus extending into the calcarine cortex). Previous studies have mainly linked RHD to

problems in spatial mapping—particularly in the ability to evaluate distances and the spatial relations between objects (Laeng, 1994; Gainotti & Tiacci, 1970). Although these studies have emphasized the role of the right parietal cortex, the presence of lesions extending into the right insular cortex has been noted in cases of poor spatial mapping in constructional apraxia (Russell et al., 2010). The lesions within the right insula have also been connected to the heterogenous visuospatial symptoms of the neglect syndrome (for a review, see Corbetta & Shulman, 2011). Nevertheless, all these findings are somewhat surprising, and they do not match the standard understanding of the role of insular cortex as being functionally linked to auditory, sensorimotor, pain, taste, and emotional processing (for a recent comprehensive review, see Jones, Ward, & Critchley, 2010).

Importantly, the lingual gyrus has been associated with processing the spatial relations between different features by Riddoch and Humphreys (1987), who reported a case study of an agnosic patient with bilateral lesions affecting the inferior ventral cortex, including the lingual gyrus (patient HJA; Allen, Humphreys, & Bridge, 2007; Riddoch, Humphreys, Gannon, Blott,4 & Jones, 1999; Riddoch & Humphreys, 1987). Interestingly, although HJA was able to perform imagery tasks based on single objects or object parts, he had difficulty on tasks requiring judgments about the spatial relations between multiple local parts of objects. Furthermore, the lingual gyrus has been associated with a role in visual working memory (e.g., de Fockert, Rees, Frith, & Lavie, 2001; Courtney, Ungerleider, Keil, & Haxby, 1996, 1997). Thus, we suggest here that disrupted visual working memory undermines constructional apraxia patients' ability to keep in mind the spatial relationships between features, causing them to inaccurately copy complex figures.

When we next specifically examined the lesions linked to errors in the relative positioning of left versus right elements, we found that left-side errors were associated with RHD to the angular gyrus, putamen, and lingual gyrus. On the other hand, right-side errors were associated with damage within both the left and right hemisphere including the right MTG and ITG, the right angular gyrus, the right IPS, the right insula, the left precuneus, and the left ITG partly extending into the MTG. These findings are consistent with the role of the right PPC (along with the insula) in spatial mapping across both sides of space, along also with the role of the lingual gyrus and precuneus in spatial working memory (Russell et al., 2010; Allen et al., 2007; Cavanna & Trimble, 2006; de Fockert et al., 2001; Riddoch et al., 1999; Courtney et al., 1996, 1997; Laeng, 1994; Riddoch & Humphreys, 1987; Gainotti & Tiacci, 1970). Furthermore, the bilateral temporal regions linked to poor performance here (middle and inferior temporal cortices) have been indicated in controlling various visuospatial tasks, including local and global processing (see below; Doyon & Milner, 1991; Lamb et al., 1989, 1990).

Our final analyses examined the neural substrates of poor performance with respect to the reproduction of local and global features of the figure. Local feature processing errors were associated exclusively with left hemisphere damage to the calcarine cortex extending into the cuneus and precuneus, the insula, and the TPJ, along with the left cerebellum. On the other hand, poor reproduction of global features was associated exclusively with RHD to the MTG extending into the ITG. These results support previous work linking the left hemisphere to local feature processing (see Fink et al., 1996; Lamb et al., 1989, 1990) and the right hemisphere to global feature processing (see Doyon & Milner, 1991; Lamb et al., 1990). Importantly, our findings provide direct neuroanatomical evidence that deficits in local versus global processing can be measured by the performance on BCoS complex figure copying task (Humphreys et al., 2012), and this task is sensitive enough to separate these deficits from other constructional symptoms. Our findings support the notion that visual processing errors are one of the potential mechanisms underlying drawing and copying deficits and subserved by cortical regions outside PPC. This is in agreement with earlier studies (Kuschner et al., 2009; McConley et al., 2006; Poreh & Shye, 1998) showing that global/local processing deficits are detrimental to drawing abilities in different patient groups.

Methodological Considerations

We have demonstrated that clinically acquired CT scans can be successfully used to conduct lesion-symptom mapping based on VBM (Chechlacz et al., 2012, 2013). However, there are several methodological issues that should be considered. One is that, although CT scans have some advantages (including, e.g., reduced field strength inhomogeneities and clear biological meaning of the signal), they also have obvious limitations such as reduced resolution relative to MRI scans. However, we would like to note here that our image segmentation and normalization methods worked well with clinical CT scans and there were no problems in image interpolation and resampling. Furthermore, the large sample size in this study (n = 358) enabled us to gain power even from the analysis of lower resolution images. Second, we would like to note that CT scans (similar to standard anatomical MRI scans such as T1 and FLAIR frequently and traditionally used in lesion-symptom mapping studies) fail to detect cortical dysfunction within regions that are structurally intact but that have inadequate cortical perfusion (see Ticini, de Haan, Klose, Nagele, & Karnath, 2010; Hillis et al., 2005; Karnath et al., 2005), and thus, we cannot exclude the possibility that, for some of our patients, our analysis missed dysfunctions that potentially contributed to the cognitive deficits. Finally, it should be noted that, in the current study, our brain–behavior relation analyses were limited to understanding the GM substrates of deficits associated with poor performance on complex figure

copying. It is plausible that these deficits may also result from WM disconnections, and further analyses are needed to clarify this. For example, we suggested earlier that the disconnection of neuronal loops connecting cortical regions concerned with spatial representation and motor planning is a plausible explanation of the deficits in figure copying resulting from damage to the caudate, putamen, and thalamus. Therefore, WM analyses could provide direct evidence that subcortical lesion disrupts such neuronal loops.

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Note

1. Specifically, global features were defined as contributing to the larger layout of the figure, that is, based on being either larger features and composed of different elements (local features) or having smaller local features located inside them. Local features were defined as details that further refine the figure but are not essential for its identification as a whole, that is, based on being smaller and simpler elements or part of global features.

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