

A deficit of spatial remapping in constructional apraxia after right-hemisphere stroke

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Constructional apraxia refers to the inability of patients to copy accurately drawings or three-dimensional constructions. It is a common disorder after right parietal stroke, often persisting after initial problems such as visuospatial neglect have resolved. However, there has been very little experimental investigation regarding mechanisms that might contribute to the syndrome. Here, we examined whether a key deficit might be failure to integrate visual information correctly from one fixation to the next. Specifically, we tested whether this deficit might concern remapping of spatial locations across saccades. Right-hemisphere stroke patients with constructional apraxia were compared to patients without constructional problems and neurologically healthy controls. Participants judged whether a pattern shifted position (spatial task) or changed in pattern (non-spatial task) across two saccades, compared to a control condition with an equivalent delay but without intervening eye movements. Patients with constructional apraxia were found to be significantly impaired in position judgements with intervening saccades, particularly when the first saccade of the sequence was to the right. The importance of these remapping deficits in constructional apraxia was confirmed through a highly significant correlation between saccade task performance and constructional impairment on standard neuropsychological tasks. A second study revealed that even single saccades to the right can impair constructional apraxia patients' perception of location shifts. These data are consistent with the view that rightward eye movements result in loss of remembered spatial information from previous fixations, presumably due to constructional apraxia patients' damage to the right-hemisphere regions involved in remapping locations across saccades. These findings provide the first evidence for a deficit in remapping visual information across saccades underlying right-hemisphere constructional apraxia.

Keywords: parietal; spatial localization; saccade

Introduction

Severe deficits in constructional skills such as drawing, copying and building 3D structures are a common yet poorly understood outcome of hemispheric stroke (e.g. Hier *et al.*, 1983a; Grossi and Trojano, 1999), as well as neurodegenerative conditions such as cortical Lewy body disease, Parkinson's disease with dementia and Alzheimer's disease (e.g. Kirk and Kertesz, 1991; Ala *et al.*, 2001; Aarsland *et al.*, 2003; Mori *et al.*, 2000). First defined as constructional apraxia by Kleist in 1934, patients with this form of apraxia have no difficulty in making relevant individual movements but are unable to copy even simple drawings accurately.

The deficits seen in copying and drawing are diverse across patient groups, with striking differences in performance between focal lesion patients with right as opposed to left hemisphere damage (e.g. see Warrington *et al.*, 1966; Gainotti and Tiacci, 1970; Guerin *et al.*, 1999). Characteristic of the drawings of right-hemisphere patients with constructional apraxia are the lack of accurate spatial relations between components of objects and an incoherent, disjointed quality. However, damage to the left hemisphere produces qualitatively different drawing performance with an oversimplification of figures and a perseveration on items suggestive of planning deficits (Gainotti and Tiacci, 1970; Trojano and Conson, 2008 for a recent review of constructional deficits).

Indeed, the range of brain regions implicated and the dissimilarity of inter-group symptoms suggest that a unifying explanation for all constructional apraxia is unlikely to be forthcoming or otherwise useful (e.g. Gainotti, 1985; Vallar, 2007). In fact, it has been suggested that the term constructional apraxia be replaced by the more general description of 'impaired drawing or building' (Farah, 2003), thereby circumventing description of constructional problems as a unitary syndrome.

An additional factor limiting full understanding of these deficits is the involvement of a widespread network of brain areas in the cognitive, perceptual and motor processes required for accurate copying, drawing and construction (Trojano *et al.*, 2009). In order to comprehend these deficits fully, it is essential to examine patients who differ both in hemisphere damaged and symptom presentation separately, as the mechanisms involved are likely to be very different (Laeng, 2006). Precisely delineating the component, contributing impairment will be essential in order to resolve the exact mechanisms underlying constructional deficits after stroke.

Here, we examine the mechanisms that underlie constructional apraxia following right-hemisphere stroke. Constructional impairments are present acutely in a large proportion of such patients (Hier *et al.*, 1983a), often persisting after other impairments related to right-hemisphere insult, e.g. neglect, have resolved (e.g. Hier *et al.*, 1983b). The right-hemisphere region most strongly implicated in constructional skills is the parietal cortex, as damage here has been reliably found to lead to enduring constructional apraxia (e.g. Gainotti, 1985; Grossi and Trojano, 1999). Neuropsychological evidence of parietal involvement is supported by functional imaging studies of healthy individuals, which have highlighted parietal involvement in drawing from copying (e.g. Makuuchi *et al.*, 2003; Ogawa and Inui, 2009).

Copying performance in patients with right-hemisphere constructional apraxia reveals specific deficits in correctly replicating the spatial relationships of items in complex figures (Fig. 1). Patients do not necessarily fail to notice or copy individual elements and do not have distinctly lateralized impairments as in neglect, but rather the correct spatial relationships between items are lost and elements are transposed, almost piecemeal, to different positions or orientations. Previous attempts to quantify and understand these problems have often focused on analysing and understanding drawing and copying performance itself (e.g. Guerin *et al.*, 1999; Ferber *et al.*, 2007; Ogawa and Inui, 2009). Whilst this is entirely reasonable given that these are the impairments from which patients suffer, the large number of processes involved in copying might preclude precise analysis of the discrete cognitive functions affected. From Fig. 1, it is evident that some breakdown of spatial processing has occurred, but not why or what type of spatial processing has failed. In order to delineate precisely the deficit involved, here we examine whether a specific function of right parietal cortex—remapping of visual information when we move our eyes (see Duhamel *et al.*, 1992b; Heide *et al.*, 1995)—is impaired in patients with constructional apraxia.

Spatial remapping in the right parietal cortex

Despite the retinal position of the visual input changing every time we move our eyes, we perceive the world as stable. The visual system appears to encode information about the upcoming saccade (such as its direction and distance) to enable remapping of the old retinal location with respect to new eye positions (Matin, 1986; Bridgeman *et al.*, 1994). Evidence suggests that the parietal lobes (particularly the right in humans) are critical for this remapping of spatial position across saccades (e.g. Duhamel *et al.*, 1992b; Heide *et al.*, 1995; Heide and Kompf, 1998; Sapir *et al.*, 2004). The classic double-step paradigm, often used to assess spatial remapping processes, is adapted from neurophysiological

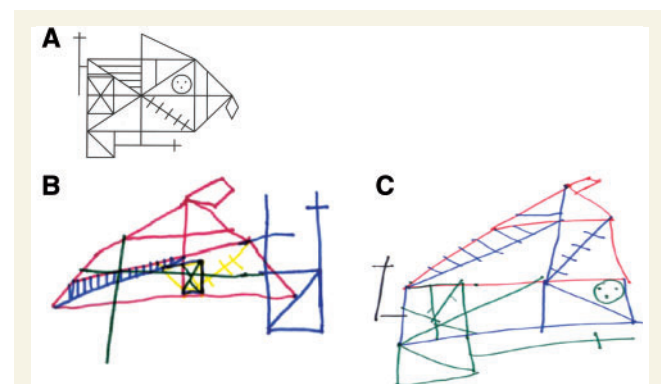


Figure 1 Constructional apraxic patients' performance in copying Rey–Osterrieth complex figure. (A) Original image. (B and C) Examples from two of the patients in this study. Colours indicate the order in which the patient drew different elements. The order colours were given to patients was red, blue, green and finally yellow in B and black in C.

experiments that have delineated areas of monkey cortex involved in remapping across eye movements (Duhamel *et al.*, 1992a).

During the double-step procedure, two sequential saccadic targets are presented and extinguished before the participant commences the eye movement towards the first target. The result of this manipulation is that the second saccade must take into account the changed retinal position of the second target's location in order to make an accurately directed saccade commensurate to the correct spatiotopic position. Experiments using this paradigm have suggested that patients with parietal damage fail to make accurate second saccades as they do not correctly update the position of the second target.

Duhamel *et al.* (1992b) demonstrated that a patient with damage to right parietal regions could remap retinal position correctly only if the first saccade target appeared on their ipsilesional side, but that the patient consistently failed to make an accurate second saccade if the first target was on the contralesional side of space. Heide *et al.* (1995) confirmed this result with a larger group of patients with right parietal stroke. These authors describe this pattern of decrement as demonstrating that failed mechanisms in the damaged right cortex are unable to remap the retinotopic location of the second target once a saccade has been initiated into impaired hemispace.

Related studies in neurologically healthy populations using functional MRI have confirmed the parietal cortex as being critically involved in tasks involving spatial updating across saccades (e.g. Tobler *et al.*, 2001; Merriam *et al.*, 2003) and transcranial magnetic stimulation over posterior parietal cortex appears to disrupt this remapping process as transaccadic changes become more difficult to detect (Chang and Ro, 2007). Recently, Vasquez and Danckert (2008) confirmed the dominance of the right hemisphere in spatial remapping processes as they examined performance in neurologically healthy individuals when they were required to make judgements after remapping locations overtly (with eye movements) or covertly (without eye movements). Participants' performance was significantly worse when they were required to remap into right visual space, suggesting inferior remapping processes in the left hemisphere.

The importance of the right parietal cortex and the failure of some accounts of visuospatial neglect to account for all the features of the syndrome led Pisella and Mattingley (2004), in a theoretical paper, to propose that impairments in spatial remapping processes underlie many deficits in neglect. For example, they suggest that the mislocation of items presented on the contralesional side is not adequately explained by purely attentional accounts of neglect, as these stimuli can often be briefly perceived but are then incorrectly attributed to the ipsilesional side of space (Di Pellegrino and De Renzi, 1995). Highly relevant to this research, they emphasized that neglect patients often transpose elements from the contralesional side of the figure onto the ipsilesional side whilst they copy (see Halligan *et al.*, 1992).

The proposed involvement of spatial remapping impairments in visuospatial neglect was recently directly assessed (Vuilleumier *et al.*, 2007). These investigators were able to demonstrate that patients with neglect suffer from a failure to remap correctly the spatial location of a to-be-remembered target when they moved their eyes. However, this deficit was particularly strong when they

were required to move their eyes towards the ipsilesional side of space. That is, making a saccade towards the 'intact' visual field actually disrupted memory for the correct spatial location of the previously seen item *more* than if they moved their eyes contralesionally.

This directional impairment contrasts with neglect patients' performance in the double-step tasks discussed earlier. They exhibited a remapping of a saccade plan that was consistently less accurate if the first eye movement was made into contralesional space (Duhamel *et al.*, 1992b; Heide *et al.*, 1995). In contrast, Vuilleumier and colleagues (2007) proposed that different processes are involved in the two types of task: one concerned with oculomotor programming (over milliseconds) and another with maintaining correct representations of spatial locations when we move our eyes (over seconds and minutes). This distinction is supported by neurophysiological studies by Colby *et al.* (1995).

Vuilleumier *et al.*'s proposal (2007) is that when their patients encoded an object's location at fixation and then moved their eyes ipsilesionally—to the right in these patients—the retinotopic representation of the initial location they were fixating was remapped to the left of the new fixation point. Thus, it would have been necessary to preserve this leftwards remapped position in the neurons of the right parietal cortex. As this is the area damaged in these patients with neglect, this maintenance of spatial location would be severely impaired after any rightwards eye movement.

The lesions of patients with neglect participating in the study of Vuilleumier and colleagues (2007) are similar to those typically seen in patients with right-hemisphere constructional apraxia. As figure copying requires precise integration of information across multiple eye movements, we sought to investigate whether patients with constructional apraxia might suffer from impairments in this process. According to this account, deficits observed in patients with constructional apraxia could reflect a loss of spatial information gained from previous fixations, leading these patients to be unable to correctly represent spatial relations of items whilst copying.

A recent neurophysiological study explicitly linked impairments in constructional apraxia in a study of single cell recordings in monkeys performing a construction task (Chafee *et al.*, 2007). These authors demonstrated that neurons in posterior parietal cortex selectively maintain the correct spatial relationships between elements of objects in the visual scene, regardless of any changing relationship of the elements' position to the viewer. Such a mechanism would support the remapping processes that help maintain stable visual percepts in the healthy brain and, as the authors assert, are likely to be critical in the problems suffered by right-hemisphere patients with constructional apraxia (see also Averbeck *et al.*, 2009).

Accordingly, we have examined here whether patients with constructional apraxia are selectively impaired in the ability to remap spatial location information across saccades, as well as exploring whether any remapping impairment is specific to direction of saccade sequence. Our novel paradigms investigate whether patients with right-hemisphere constructional apraxia have problems in maintaining spatial location information over intervening saccades, or even just one saccade. The direction of

single saccades or saccade sequence might be critical, as previous research has found conflicting results. Some researchers have reported that patients with similar lesions are worse when making saccades in a contralesional direction—i.e. left for these patients (Duhamel *et al.*, 1992*b*)—while others demonstrated greater deficits when saccades are in an ipsilesional direction (Vuilleumier *et al.*, 2007). Furthermore, it is important to assess whether any remapping impairments correlate with level of constructional impairment in right-hemisphere stroke patients, as indexed by standard neuropsychological tests.

The paradigms outlined here will examine a possible key deficit that might contribute to constructional apraxia, a common disorder associated with stroke and several neurodegenerative conditions (e.g. Ala *et al.*, 2001; Aarsland *et al.*, 2003), which has received relatively little experimental scrutiny.

Experiment 1

Methods

Participants

Eight right-hemisphere patients with constructional apraxia aged 31–68 years (mean 57.5 years) were tested. These were compared to seven patients without constructional apraxia, also suffering from lesions in their right hemisphere (non-constructional apraxia). The non-constructional apraxia group were aged 45–75 years (mean 57 years). Patients with constructional apraxia were inpatients at the Fondazione Santa Lucia Neuro-Rehabilitation Hospital in Rome, Italy. They had suffered their stroke on average 5 weeks prior to entering Santa Lucia's research programme. Four of the right-hemisphere control patients without constructional apraxia were also from this patient

pool, whilst the other 4 were recruited from a research program at The National Hospital for Neurology and Neurosurgery. A group of eight neurologically healthy volunteers also participated in the saccade studies (age range: 56–70 years, mean age: 62 years). Brain lesions, imaged by CT or MRI, were reconstructed with MRICro software (<http://www.sph.sc.edu/comd/rorden/micro.html>), plotted with the use of a graphics tablet (WACOM Intuos A4). Figure 2 displays lesion plots for the patient groups.

A T₁-weighted template consisting of 12 axial slices was used to demarcate the lesions for constructional apraxia and non-constructional apraxia patients. As shown in Fig. 2A, the area of maximum overlap was in white matter, extending superiorly and posteriorly towards the temporoparietal junction, (see red region circled on Fig. 2A—Talairach coordinates 36, –31, 24). Lesions of patients without constructional apraxia solely affected deep white matter and did not encroach upon cortical areas. Subtracting the lesions of non-constructional apraxia from constructional apraxia patients reveals regions specific to these patients in the white matter adjacent to the temporoparietal junction, extending anteriorly to the insula (see yellow regions in Fig. 2C). The anatomy presented here is given for completeness, but the principal purpose of the present experiment was to investigate whether there is a deficit of spatial remapping across saccades in constructional apraxia.

Diagnosis of constructional apraxia was made with administration of the Rey–Osterrieth Complex Figure (Boston Qualitative Scoring System, 1999) and the Block Design task from the Wechsler Adult Intelligence Scale III (2002). A normalized percentile rank was obtained for each participant in these tasks and those scoring 'below average' to 'severely impaired' were categorized as having constructional apraxia (see Table 1 for participants' scores on these tasks). Patients within the hospital unit undergo regular screening for visuospatial neglect [a battery of tasks is used, which includes letter cancellation, line bisection, reading aloud, examination of more subtle perceptual problems with the Wundt–Jastrow test (e.g. Paolucci *et al.*, 1996) and examination of personal neglect]. None of the patients revealed

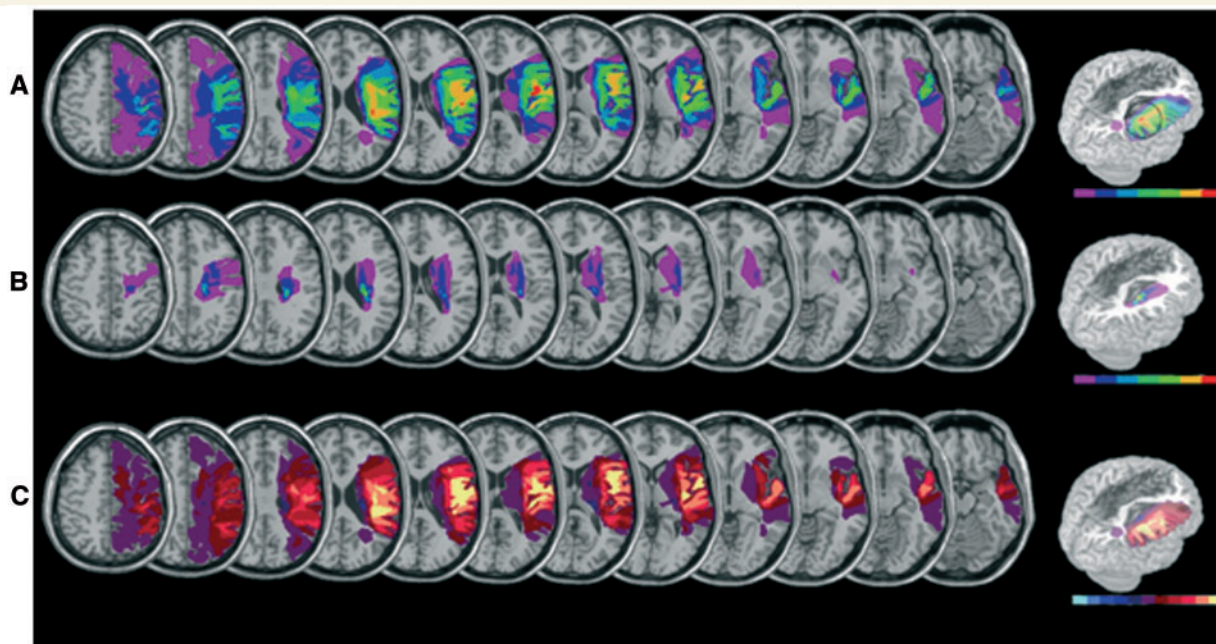


Figure 2 Lesion overlaps and subtractions of all patients. (A) constructional apraxia patient group, (B) non-constructional apraxia patient group, and (C) maps showing constructional apraxia lesions minus non-constructional apraxia. Yellow indicates areas most damaged in patients with constructional apraxia and that were not damaged in the non-constructional apraxia group.

Table 1 Patients' performance on Rey–Osterrieth complex figure and block design from Wechsler Adult Intelligence Scale

Patient	Rey figure t-score	Rey figure percentile	Block design scale score	Block design percentile
Constructional apraxia				
1	31	3	5	5
2	<20	1	4	2
3	<20	1	4	2
4	<20	1	3	1
5	35	7	7	16
6	<20	1	2	1
7	36	8	5	5
8	<20	1	2	1
Non-constructional apraxia				
1	54	66	8	25
2	49	46	6	9
3	49	46	7	16
4	65	93	10	50
5	55	69	10	50
6	65	93	7	16
7	47	38	8	25

neglect clinically at the time of testing. The lesions seen in these patients with constructional apraxia suggest that it is likely some of them might have suffered from neglect immediately after their stroke, and it remains possible that analysis of reaction times might perhaps reveal that some of these patients are slower to respond to stimuli on the contralesional side. However, detailed screening revealed that the patients with constructional apraxia fulfilled the clinical diagnosis of constructional apraxia and not of visuospatial neglect. All participants gave written informed consent according to the Declaration of Helsinki. The study was approved by both the hospital and university research ethics committees.

Procedure

All tasks were programmed with Psycscope software (Cohen *et al.*, 1993) run from a Macintosh G4 laptop computer attached to a large view monitor (width 41 cm). Participants sat approximately 50 cm from the computer screen. We used a 2 × 2 experimental design. Observers made judgements about the spatial location or form of a checkerboard pattern, either with or without intervening saccades. In all experiments, participants viewed two presentations of the checkerboard and had to judge whether it had moved (vertical) position in the position judgement conditions, or whether the pattern had altered in the pattern judgement conditions. In the saccade conditions, they made intervening saccades between seeing the first and second checkerboard, while in the no-saccade condition they maintained fixation during a delay. Detection of vertical displacement was chosen for a number of reasons. First, healthy participants have been shown to suffer differential inaccuracies in detection of lateral movement according to the direction of their saccades, i.e. their judgement is biased by the direction of the saccade (e.g. see Bridgeman, 1995; Ross *et al.*, 2001). Additionally, patients with unilateral brain injury might have a response bias when making left or right judgements after right-hemisphere damage, e.g. saying right more often than left. Finally, these parietal patients may also suffer from some disorientation in making left versus right decisions. Each trial began with a

small central fixation cross, presented for 1000 ms (Fig. 3). The cross was immediately followed by the appearance of a pattern constructed from a 3 × 5 checkerboard consisting of black and white squares (width of checkerboard was 1.7° of visual angle and height was 2.9°). Black and white elements were randomly placed in this checkerboard, with certain constraints. For example, there was a 3:2 ratio of black to white in half of the checkerboards and 3:2 white to black in the others (this split meant that overall amount of black to white could not guide participants as to whether the pattern had changed or not in the pattern task outlined below).

The checkerboard was displayed at or around screen centre. There were five possible starting positions. One of these was positioned at screen centre and the other four locations overlapped this position somewhat but were shifted by 0.9° out to each of the imaginary four sides of a checkerboard in this central position. The first checkerboard was presented for 500 ms. After this, it disappeared to be replaced on the screen by a small letter 0.4° across (H, L, M or N).

In saccade tasks, this letter was either on the left or the right periphery of the screen (15° from the centre). Pilot testing confirmed that the letter stimuli could not be identified without being fixated. In no-saccade control conditions, letter stimuli appeared in the same position as the black-and-white pattern it replaced (Fig. 3). Regardless of condition, letter stimuli remained on the screen until participants had verbally responded as to the letter's identity.

During analysis, trials were deleted if letter identity had been reported incorrectly (this occurred in less than 1% of trials across participants). The letter disappeared as soon as participants' responses were entered onto a button pad. The second black and white checkerboard pattern then appeared on the screen, remaining until the participant's verbal response. In different blocks, participants performed judgements on either the spatial location of the checkerboard or the pattern within it.

Position judgement tasks

In these tasks, the second presentation of the checkerboard could shift vertically with respect to the position of the original presentation. Specifically, the second pattern could be presented in a position slightly higher (1.4°) or slightly lower (same distance) than the original pattern. These shifts of position occurred on 50% of the trials. Subjects responded as to whether the second pattern was in the identical position as the first or had moved; they were not required to describe the direction of any movement.

Participants were presented with two possible versions of the position judgement task. One required an intervening two-saccade sequence between first and second pattern presentation (with the letter stimulus that had to be read out aloud appearing towards the periphery, necessitating one saccade out to identify the letter and then another saccade back), and another version with no intervening saccades (letter stimuli appeared in the centre, at fixation).

Pattern judgement tasks

In these tasks, participants were informed that the second checkerboard might change in pattern with respect to the first. Changes consisted of a previously white square becoming black or one of the original black squares becoming white. Observers were asked to respond whether the second pattern was the same or different from the first. Changes occurred in 50% of the trials and were equally likely to take place on the right or the left columns of the 3 × 5 pattern. No changes took place in the middle column.

Participants again completed a version of the pattern judgement task either with an intervening two saccade sequence, or without intervening saccades.

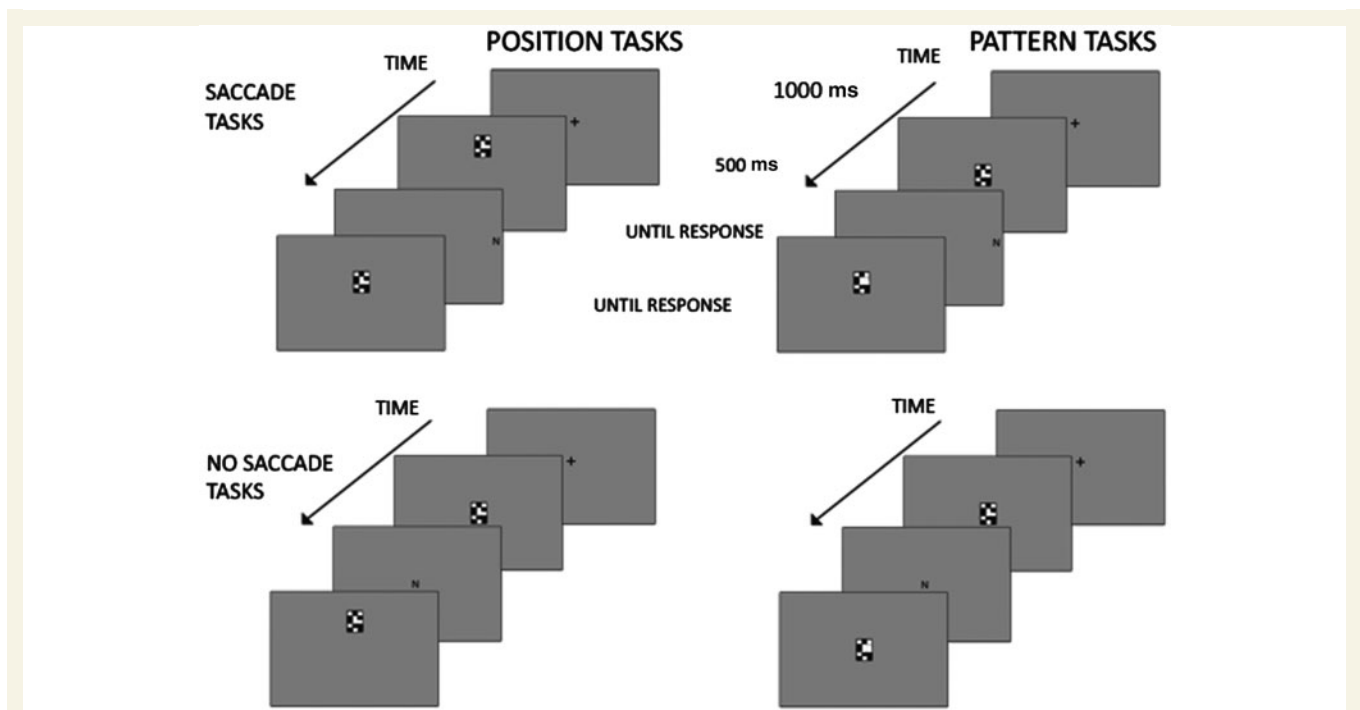


Figure 3 Schematic outline of experimental paradigms from Experiment 1. Position tasks shown in left column with pattern tasks on right. Saccade conditions shown in top row and no-saccade in the bottom row.

There were separate blocks (each of 50 trials) for the pattern and position tasks and for the saccade conditions. As a result, patients completed four different tasks: pattern judgement with or without intervening saccades, and position judgement, with or without intervening saccades (Fig. 3). Each patient completed two blocks of each condition, finishing the study in approximately three 45 min sessions. Neurologically healthy controls only completed the saccade conditions for 2 blocks each of the pattern judgement and the position judgement tasks (due to uninformative ceiling performance in no-saccade conditions).

Two experimenters were present throughout testing. One sat facing participants behind the computer monitor with the response button box, enabling them to cancel trials in which participants did not make the correct saccades or made additional eye movements and to enter the participants' verbal responses (letter identity and whether second pattern was the same or not). The other experimenter started each block, explained the task and observed whether the participant appeared to understand task requirements. The use of two experimenters, the size of the peripheral letters and the large saccades required to complete the task established that eye movements were made accurately and that any trials with additional saccades or incorrect identification of the letter were removed. A similar task with these patients and head mounted eye tracking equipment was originally piloted. Unfortunately, due to the length of this paradigm, this equipment was not tolerated during the pilot and no useful data were obtained.

Results

Analyses across groups

Analyses of task performance were conducted using d' -prime (sensitivity) data. The d' value was calculated for each participant for each condition in order to produce a value less susceptible to bias.

Table 2 Means and standard deviations of d' sensitivity scores for all participants of Experiment 1

	CA patients	Non-CA patients	Healthy controls
Saccade			
Position judgement	0.664 (0.469)	2.119 (0.345)	2.946 (0.812)
Pattern judgement	1.18 (0.722)	1.742 (0.327)	2.305 (0.545)
No saccade			
Position judgement	1.869 (1.206)	2.977 (0.571)	N/A
Pattern judgement	1.208 (0.764)	2.284 (0.583)	N/A

CA = constructional apraxia; non-CA = non-constructional apraxia. Data are split by group (patients with constructional apraxia, patients with non-constructional apraxia and healthy controls) and gives the mean d' score of each group for each task (position and pattern judgement) and each eye movement condition (saccade or no saccade).

Table 2 gives the means and standard deviations while and Figs 4a and 4b show line graphs of these data.

An ANOVA was conducted to assess whether performance differed between the patient groups across Task types (position judgement versus pattern judgement) and Eye movement conditions (saccades versus no saccades). This ANOVA revealed a main effect of Task between patient groups [$F(1, 13) = 5.558, P > 0.05$]; no main effect of Eye movement condition between these groups [$F(1,13) = 0.077, n.s.$] and no three-way interaction (Group \times Task \times Eye movement condition), although this did approach significance, [$F(1,13) = 3.635, P = 0.079$]. This ANOVA indicates that both patient groups suffer from an impaired performance in the two tasks when they must move their eyes.

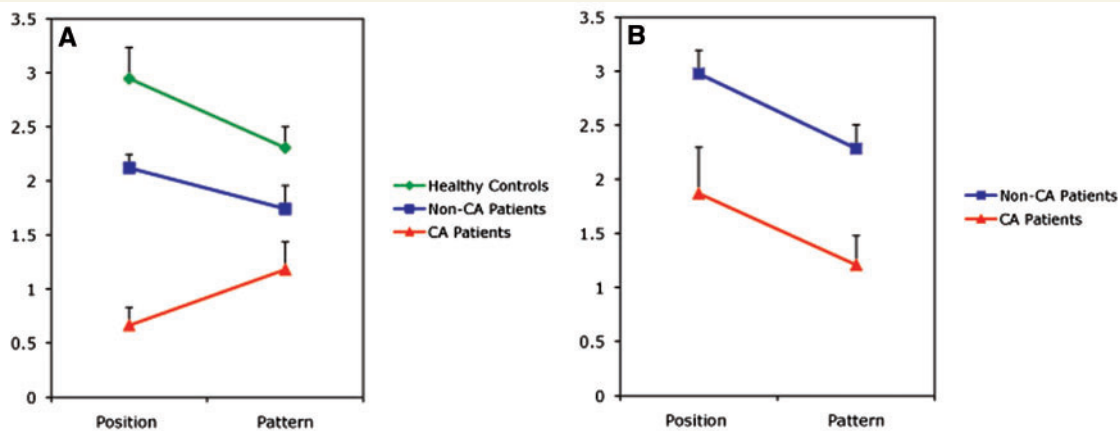


Figure 4 Overall sensitivity to change in Experiment 1. Means and standard error bars of all participants' d' data. (A) Data for saccade tasks split according to group (constructional apraxia patients—red line; non-constructional apraxia patients—blue line; healthy controls—green line). Task type (position versus pattern) is given along the horizontal axis. (B) Data from non-saccade tasks split according to patient groups and following the same colour coding as A. Constructional apraxia = constructional apraxia; non-constructional apraxia = non-constructional apraxia.

However, examination of Figs 4a and 4b demonstrates that, despite non-constructional apraxia patients' performance falling in saccade conditions, their pattern of response in saccade tasks remains similar to that of healthy controls. That is, both these groups are worse in the pattern task when they move their eyes, compared to when they must make position judgements. This is in sharp contrast to the performance of patients with constructional apraxia in the two tasks when they move their eyes. These patients instead appear severely impaired when they move their eyes and judge whether the stimuli have moved—a task that remains comparatively straightforward for the two control groups. As a result, and to enable full understanding of the deficit from which the constructional apraxia group suffer, analysis was then carried out separately for saccade tasks and non-saccade tasks.

Sensitivity to position versus pattern changes with intervening saccades

To assess differences between participant groups and performance during position judgements versus pattern judgements when there were intervening saccades (Fig. 4a), an ANOVA was carried out with the within-subjects factor of Task (position judgement versus pattern judgement) and between-subjects factor of Group (constructional apraxia, non-constructional apraxia, healthy controls). This revealed a significant difference in Task performance between Groups [$F(2,20) = 8.68, P < 0.01$]. To determine whether performance significantly differed between patient groups for pattern versus position judgements, an additional ANOVA was carried out with the two Patient groups: constructional apraxia and non-constructional apraxia. This demonstrated no main effect of Task but critically a significant interaction between Task (pattern versus position) and Patient group [$F(1,13) = 13.71, P < 0.01$]. Thus, patients with constructional apraxia were less accurate in position judgements whilst non-constructional apraxia patients were actually more accurate in that task.

t -tests confirmed that, in saccade tasks, patients with constructional apraxia were particularly poor in the position judgement task as they were significantly worse than non-constructional apraxia in this task [$t(13) = -6.75, P < 0.0001$] but importantly not in the pattern judgement task [$t(13) = -1.89, n.s.$].

Sensitivity to position versus pattern changes without saccades

Turning to performance in the no-saccade conditions (see in Fig. 4b), an ANOVA comparing Task (position versus pattern judgement) with Patient group (constructional apraxia versus non-constructional apraxia) demonstrated a significant main effect of Task, with position judgements being better than pattern ones [$F(1,13) = 15.19, P < 0.01$]. However, unlike for saccade tasks, there was no significant interaction between Task by Group [$F(1,13) = 0.009, n.s., P = 0.93$] in the no-saccade conditions. Thus the pattern of performance between groups was similar when no eye movements were required.

Analyses within groups

Constructional apraxia patients

To examine these effects further, we next looked at performance within the constructional apraxia group. A two-way within-subjects ANOVA involving Task (position versus pattern judgements) and Eye movement condition (saccades or no saccades) revealed a main effect of Eye movement condition [$F(1,7) = 9.267, P < 0.05$], no main effect of Task [$F(1,7) = 0.197, n.s., P = 0.670$] but crucially a significant interaction between these two factors [$F(1,7) = 13.098, P < 0.01$]. Paired-sample t -tests were carried out to investigate this relationship. The critical comparison here is whether patients with constructional apraxia are significantly worse in judging whether the stimulus changed position when they moved their eyes.

Results demonstrated that this was the case [$t(7) = -2.758, P < 0.05$]. Patients with constructional apraxia were significantly

impaired when judging whether the second pattern moved when they made intervening saccades, compared to performance for a pattern judgement task. Patients with constructional apraxia were actually significantly better in making position judgements compared to pattern judgements when they were not required to move their eyes [$t(7) = 2.491$, $P < 0.05$].

Furthermore, if we compare the saccade versus non-saccade conditions for each task in turn, the analysis reveals that while intervening eye movements on the pattern task do not significantly impair performance [$t(7) = -0.139$, n.s.], they do in the position judgement task [$t(7) = -3.97$, $P < 0.001$].

Control participants

To explore task performance in control participants, similar analyses were first conducted with the non-constructional apraxia patient group. ANOVA revealed main effects of task and eye movement condition but importantly no interaction between these factors [$F(1,6) = 29.983$, $P < 0.01$; $F(1,6) = 10.012$, $P < 0.05$; $F(1,7) = 1.073$, n.s. $P = 0.340$, respectively]. The lack of interaction here reveals that performance in the pattern and the position task in this group is not differentially affected by making eye movements. This is in contrast to patients with constructional apraxia, whose performance became much worse when they were required to move their eyes in the position task. Comparable t -tests were also conducted to examine performance in the position and pattern tasks with or without making saccades. Non-constructional apraxia patients, unlike patients with constructional apraxia, were significantly better in the position task in both conditions [saccade task $t(6) = 2.634$, $P < 0.05$; non-saccade task $t(6) = 3.245$, $P < 0.05$]. Despite the non-significant interaction revealed in the ANOVA, a further t -test was carried out to confirm that non-constructional apraxia patients could not be described as suffering from a greater impairment across eye movements than patients with constructional apraxia. It was necessary to check that their performance in the pattern task when they moved their eyes did not significantly fall (as patients with constructional apraxia do not suffer a significant fall in performance in those conditions). This t -test revealed that the difference in performance for this group in the pattern task between the saccade and no-saccade conditions was also non-significant [$t(6) = -2.02$, n.s.]. Data from healthy controls in the saccade studies also showed them to be significantly more accurate in position judgements [$t(7) = 2.426$, $P < 0.05$]. Note that both control groups had less difficulty in judging position changes across saccades compared to judging pattern changes. This was in sharp contrast to the profound impairment shown by patients with constructional apraxia in judging whether the patterns moved when they were required to make eye movements.

Correlation with level of constructional problem

The analyses above demonstrated that patients with constructional apraxia had a deficit in perceiving position shifts across two intervening saccades. This pattern of impairment contrasts to the performance of right-hemisphere stroke patients without constructional apraxia and healthy participants: both these control groups showed greater difficulty in the pattern judgement task.

To examine whether performance on the position judgement task is critical to constructional apraxia, these patients' scores in

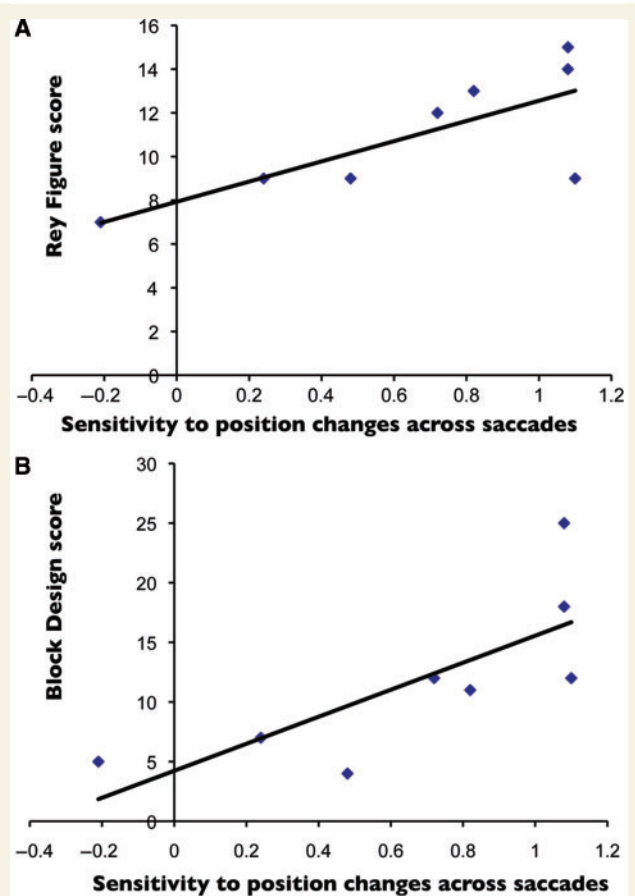


Figure 5 Regression graphs for correlation analysis of Experiment 1. (A) Rey–Osterrieth figure score correlation with sensitivity to position changes across saccades. (B) Block design score correlation with sensitivity to position changes across saccade.

the Rey–Osterrieth complex figure and in the Block Design task were compared to performance in the position task with eye movements (Fig. 5). Patients with constructional apraxia show a particular difficulty in judging spatial position across saccades and so it is important to assess whether they show a correlation between experimental task and clinical constructional test performance. Analysis on only these patients revealed there to be a correlation between both Rey–Osterrieth figure scores and Block design scores with position judgement across saccades ($r = 0.75$, $P < 0.05$ and $r = 0.76$, $P < 0.05$ for Rey and Block design, respectively; Fig. 5).

Sensitivity to changes according to direction of saccade sequence

Does the direction of initial saccade make a difference to performance? Note that in the present study, a saccade in both possible directions is made in each trial so the search for any direction-related impairment in Experiment 1 concerns the order of the sequence, i.e. whether the saccade is first to the right and then leftwards to centre, or vice versa.

Examination of the data (Fig. 6 and Table 3) reveals that the two control groups have an equivalent level of performance in both directions for both saccade and no-saccade tasks (blue and

green bars). In contrast, the patients with constructional apraxia (red bars), who were particularly poor in the position judgement task, were worse when the first saccade was to the right. ANOVA within the constructional apraxia group revealed a main effect of Task [$F(1,7) = 6.637$, $P < 0.05$], near significant main effect for direction of initial saccade [$F(1,7) = 4.949$, $P = 0.06$] and critically an overall interaction between the Task and Direction of first saccade [$F(1,7) = 5.908$, $P < 0.05$].

t -tests were conducted to investigate this interaction. These revealed that there was no direction-specific difference in performance during the pattern judgement task [$t(7) = 1.207$, n.s., $P = 0.266$] but patients with constructional apraxia were significantly more accurate in the position judgement task when their first saccade was to the left [$t(7) = 2.494$, $P < 0.05$].

In contrast, neither the non-constructional apraxia group nor the healthy controls showed any significantly different performance in relation to the direction of their first saccade. Within non-constructional apraxia analysis, there were no main effects and no interaction [$F(1,6) = 4.185$, n.s. $P = 0.09$; $F(1,6) = 0.466$, n.s. $P = 0.52$; $F(1,6) = 4.649$, n.s. $P = 0.074$, respectively]. Despite the non-significant interaction, there is arguably a possible trend revealed in these patients' performance. Also, when viewing the

blue bars in Fig. 6, there is a slight drop in the non-constructional apraxia group performance when they first saccade rightwards in the position task. To examine this further, t -tests were carried out to examine any direction-specific effects in this group. However, these t -tests confirmed that performance according to direction of the first saccade did not approach significance in either the position task or the pattern task [$t(6) = 1.25$, $P = 0.26$ and $t(6) = 0.02$, $P = 0.98$, respectively] in non-constructional apraxia patients. There was a similar pattern in the data from neurologically healthy controls. They did have a main effect of task but none of direction of first saccade and no interaction [$F(1,7) = 15.417$, $P < 0.01$; $F(1,7) = 0.017$, n.s. $P = 0.9$; $F(1,7) = 0.194$, n.s. $P = 0.673$, respectively].

Patients with constructional apraxia therefore demonstrated a bidirectional deficit in the position judgement task, being worse than both control groups if the first saccade is to the left or right. However, unlike either control group, they demonstrated a significantly greater impairment in the position task when they first saccade towards the right.

The directional bias is intriguing and is similar to the pattern of performance shown in Vuilleumier *et al.*'s neglect patients (2007). Because two intervening saccades were made in our task and that of Vuilleumier *et al.* (2007), it is important to investigate whether the directional bias might also be present in a paradigm involving only one saccade. Thus, an additional study was carried out to determine performance for single intervening saccades to the left or right with some of the patients tested in Experiment 1.

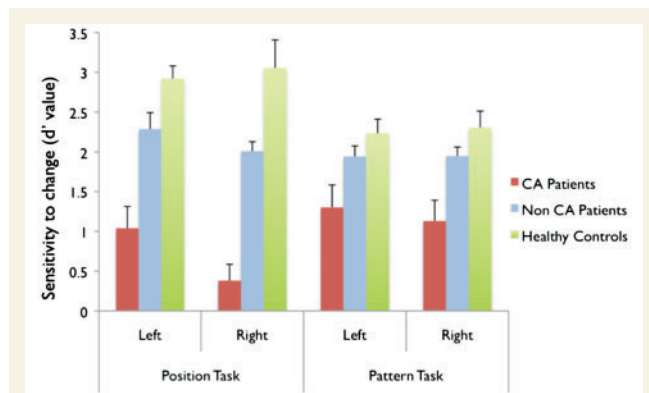


Figure 6 Sensitivity to changes according to direction of first saccade in Experiment 1. Means and standard error bars of all participants' d' data. Data are split according to task (position versus pattern) and direction of first saccade (left versus right). Sensitivity of patients with constructional apraxia can be seen by examination of the red bars, the non-constructional apraxia patients' performance is given in blue and the healthy controls' data are shown in the green bars. CA = constructional apraxia; non-CA = non-constructional apraxia.

Experiment 2

Methods

Participants

Eight patients from the original study took part in this direct examination of the effect of saccade direction. Five of these patients suffered from constructional apraxia and three did not (non-constructional apraxia). All were inpatients at the Fondazione Santa Lucia Rehabilitation Hospital.

Procedure

The method used was an adaptation of the position judgement saccade task as described above. An initial black-and-white checkerboard pattern, identical to those used in Experiment 1, was presented at or around screen centre for 500 ms. This pattern then disappeared and

Table 3 Means and standard deviations of d' sensitivity scores according to direction of first saccade for all participants of Experiment 1

Task	Saccade direction	CA patients	Non-CA patients	Healthy controls
Position judgement	Left	1.039 (0.768)	2.286 (0.549)	3.054 (0.448)
	Right	0.380 (0.579)	2.009 (0.317)	2.921 (1.001)
Pattern judgement	Left	1.300 (0.802)	1.943 (0.348)	2.234 (0.505)
	Right	1.130 (0.802)	1.947 (0.302)	2.304 (0.593)

CA = constructional apraxia; Non-CA = non-constructional apraxia. Note that data are only included from the saccade conditions of both tasks (position and pattern judgement). These have been split according to direction of the first saccade of the sequence (left versus right). Means are given for the d' scores of all three groups (constructional apraxia patients, non-constructional apraxia patients and healthy controls).

Table 4 Means and standard deviations of d' sensitivity scores for all participants of Experiment 2 split according to participant group (patients with either constructional apraxia or non-constructional apraxia) and the direction of the saccade required (left versus right)

Subject group	Left saccade	Right saccade
CA patients	3.096 (1.455)	2.502 (1.099)
Non-CA patients	3.697 (0.440)	3.873 (0.236)

CA = constructional apraxia; Non-CA = non-constructional apraxia.

reappeared, after a brief 200 ms blank, on either the left side of the screen or on the right side (the distance from centre was the same as that between the near centre first stimuli and peripheral letters in the first study). The patient's task was to respond verbally as to whether the second appearance of the pattern was at the identical vertical position as the first, or whether it had shifted up or down.

The experimental situation was identical to the first study with the patient seated approximately 50 cm from the screen and two experimenters present; one recording responses and monitoring eye movements and the other setting up each block. Two blocks of 50 trials were run on each participant, all within one session.

Results

Examination of the mean d' scores for the two patient groups across the direction conditions (right versus left saccade) suggests that patients with constructional apraxia remain much worse in judging the relative height of a stimulus even after they make a single rightward saccade (Table 4). An ANOVA was carried out on these data with the within-subjects factor of Saccade direction and the between-subjects factor of Patient group. Even in this relatively small sample, the ANOVA revealed a significant interaction between Saccade direction and Patient group [$F(1,6)=8.09$, $P<0.05$]. Further analysis of these data with unrelated sample t -tests revealed that during left directed saccades performance is equivalent between the groups [$t(5.1)=-0.86$, n.s.], right saccades are required patients with constructional apraxia are significantly worse [$t(4.6)=-2.66$, $P<0.05$]. If we examine the data for each group separately, a paired samples t -test on the data for patients with constructional apraxia confirmed that these patients are significantly less accurate in judging spatial location after a rightwards saccade to their ipsilesional hemifield [$t(4)=3.38$, $P<0.05$].

By contrast, the difference in performance between saccade directions in non-constructional apraxia patients does not approach significance [$t(2)=-0.943$, n.s.]. Thus, even this single saccade task demonstrates a deficit in spatial remapping which is worse for rightward saccades in patients with constructional apraxia.

General discussion

The studies outlined in this article provide evidence that a critical mechanism underlying constructional apraxia following right-hemisphere stroke is a failure to remap spatial information correctly across saccadic eye movements. There has previously

been no direct analysis of the involvement of this process in this common and poorly understood disorder, which can follow both stroke (Hier *et al.*, 1983a) and several neurodegenerative conditions (Ala *et al.*, 2001; Aarsland *et al.*, 2003).

Our first experiment demonstrated that patients with constructional apraxia have a specific impairment in correctly remembering spatial location information when they must move their eyes. This impairment did not appear to extend to pattern information, as accuracy in the condition where participants judged a pattern change did not reveal a significant difference between patients with constructional apraxia and other right-hemisphere patients without this disorder (Fig. 4).

When no saccades were necessary, constructional apraxia patients' performance became equivalent to that of the other groups as they were less accurate in judging the pattern information. Vital to our assertion that these impairments underlie right-hemisphere constructional apraxia, performance in the position judgement task correlated strongly with overall constructional impairment as measured by two standard neuropsychological tests (Fig. 5).

Importantly, the first experiment revealed that constructional apraxia patients' ability in judging location was significantly worse after they had first made a saccade towards the right. This was not a general impairment as their performance was equivalent for both saccade sequences in the pattern judgment task. Experiment 2 was conducted in order to investigate this directional deficit more thoroughly and to establish that the impairment in Experiment 1, during the right-to-left saccade sequence, is not a result of an impaired contraversive second saccade. We were able to confirm that patients with constructional apraxia have greater difficulty in a task involving the remapping of a memory trace for original location when they make a single saccade rightwards.

This is a surprising result as many investigators have previously suggested that right parietal patients' deficits are most prominent when they must make a first saccade in either a contraversive direction or into the contralesional hemifield (e.g. Duhamel *et al.*, 1992b; Heide *et al.*, 1995; Heide and Kompf, 1998). However, we are not assessing spatial remapping of programmed saccade metrics but rather the remapping of a memory trace of the original position. Each trial in the paradigm outlined here took place over several seconds not milliseconds, as is usual in the classic double step paradigm. The assertion here is that the reason for the greater impairment when eyes are moved into ipsilesional space is that the original position of the stimulus at fixation is now in a contralesional position relative to the new fixation (the new fixation being on the peripheral letters in Experiment 1 and on the second pattern stimulus in Experiment 2).

The posited contralesional position of the critical representation is then lost or degraded because of damage to the right parietal lobe (Vuilleumier *et al.*, 2007). Figure 7 provides a schematic of the mechanism we propose to underlie the deficit. Note that the spatial component of the representation appears to be critical as maintenance of a representation of non-spatial pattern information was not significantly impaired.

These studies are consistent with the findings of Vuilleumier *et al.* (2007) who revealed similar impairments in remapping of spatial location information within patients with visuospatial

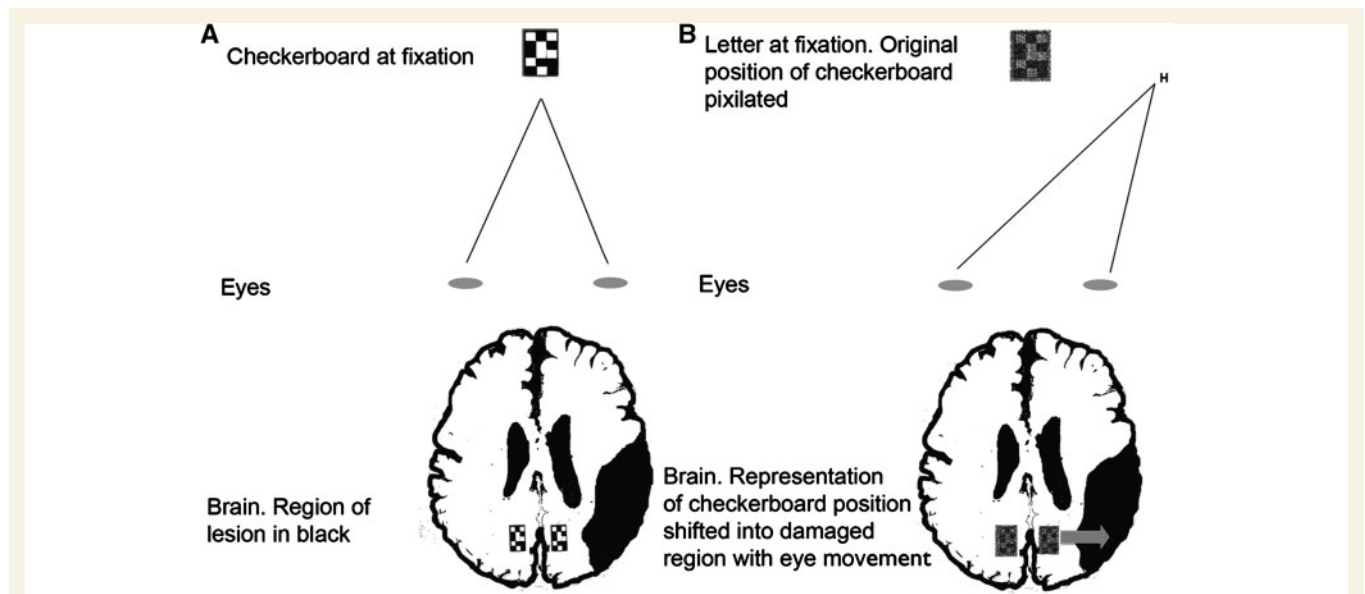


Figure 7 Schematic figure of suggested events involved in spatial remapping during the current experiments. In (A), the participant's eyes are fixating straight ahead at the checkerboard pattern. In (B), the observer shifts gaze towards the letter at the right periphery of the screen. The previous position of the checkerboard is now to the left of the new eye position. If memory for retinotopic locations is localized in the contralateral hemisphere (for example, in posterior parietal cortex), the representation of the remembered position of the checkerboard would shift into the damaged region of right hemisphere, thereby leading to a degraded memory of its spatial location.

neglect. However, they did not study right-hemisphere stroke controls, nor did they examine the effects of single leftward versus rightward saccades. Here we have extended the remapping paradigm to patients who do not suffer from neglect although they have damage to similar brain regions. Our results show that spatial remapping defects are not neglect-specific, since none of our patients with constructional apraxia had clinically demonstrable neglect. Moreover, the findings reported in Experiment 2 show that deficits can be observed even after a single ipsilesional saccade. The existence of these impairments in patients with constructional apraxia without the lateral bias of neglect raises a number of important questions concerning functions of the right parietal cortex and of the visuospatial neglect syndrome.

First, it appears that spatial remapping deficits can contribute to both neglect and constructional apraxia, but their relative contribution to each of these disorders remains to be established. Combinations of deficits—spatial and non-spatial—appear to exist in the neglect syndrome (Husain and Rorden, 2003), with the exact combination varying across patients (e.g. Buxbaum *et al.*, 2004). Second, it will be important to determine whether saccades are critical to these remapping deficits. Future studies might investigate possible differences in remapping these memory traces covertly—with attention shifts—rather than overtly with saccades. A recent study suggests a greater burden in location judgements for healthy individuals when they covertly shift attention between stimuli as compared to when they move their eyes (Vasquez and Dankert, 2008). Finally, to what extent are the remapping impairments reported here related to the deficit in spatial working memory recently established as a feature of neglect (Pisella *et al.*, 2004; Malhotra *et al.*, 2005; Mannan *et al.*, 2005; Ferber and Dankert, 2006)? Certainly the preservation of a

memory trace of location position across eye movements must involve spatial working memory processes, but presumably working memory was also involved in our non-saccade condition, for which the pattern of results was very different.

This being the case, these studies provide further evidence that any spatial working memory 'store' is likely to be in parietal cortex but that additional processes are involved when we move our eyes and possibly when we shift our attention. These additional processes probably involve the shift of spatial memory representations to different neuronal populations when any eye movement is made (Vuilleumier *et al.*, 2007), and possibly with covert shifts of attention. It will be important to understand the links between attention and spatial remapping processes for this has implications not only for patients but also for visual processes in the healthy brain, as attention and spatial remapping together lead to perception of a stable visual world (Berman and Colby, 2009).

Worthy of mention is the relationship between constructional apraxia and visuospatial neglect. Many patients with constructional apraxia might fulfil the criteria for neglect diagnosis immediately after their stroke but these neglect symptoms often resolve (e.g. Hier *et al.*, 1983a,b). However, constructional apraxia is dissociable from neglect and is a specific clinical syndrome, in that it describes a set of commonly co-existing symptoms, i.e. deficits on construction tasks. Vitaly, these deficits are not lateralized to one side (as otherwise a diagnosis of neglect would also be made). Additionally, constructional apraxia does not necessarily have to be associated with previous neglect or in fact right-hemisphere lesions at all. Conversely, not all patients with recovered neglect eventually suffer from constructional apraxia. As a result, constructional apraxia can be detected after neglect has resolved but there is no evidence that it is always a persistent symptom after neglect;

moreover, it can be diagnosed in some patients who have not suffered from neglect. Both neglect and constructional apraxia comprise several cognitive components, but they may also share some of these, including the remapping disorder elucidated here.

The studies in this article provide a platform for understanding the mechanisms underlying constructional apraxia in patients with right-hemisphere damage. Rather than directly assess performance on a drawing task alone, one of the key processes that is likely to be critical for copying from a figure has been directly probed. This approach has revealed that an important deficit in right-hemisphere constructional apraxia may be in maintaining spatial information across eye movements.

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