Letters to the Editor

Using SPM normalization for lesion analysis in spatial neglect

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Traditionally, the neglect syndrome has been associated with damage to the right inferior parietal lobule (IPL) and the right temporoparietal junction (Heilman et al., 1983; Vallar and Perani, 1986). Thus, it was surprising when a recent study found that the centre of lesion overlap covered the right superior temporal gyrus and planum temporale, suggesting that the superior temporal cortex rather than the inferior parietal lobule is the critical substrate for spatial neglect in humans (Karnath et al., 2001). In that study, the authors used a new tool for lesion analysis (MIRcro; www.mricro.com), which allows more precise lesion localization than ever before. Lesions are mapped manually on a T1-weighted template MRI that is aligned with stereotaxic space (Rorden and Brett, 2000). The template scan provides various anatomical landmarks for precisely plotting the size and localization of the lesion. Moreover, automatic three-dimensional rendering of the lesion data derived from the transverse slices is available (Rorden and Brett, 2000). This reduces significantly the uncertainty brought in by the paper-and-pencil procedures used in previous anatomical studies on spatial neglect (Heilman et al., 1983; Vallar and Perani, 1986).

In a recent article by Mort et al. (2003), the authors noted that the lesions in the study of Karnath et al. (2001) were still demarcated by hand onto standard template images. To overcome this limitation, Mort et al. (2003) used a lesion analysis method that did not rely on the manual transfer of lesions to standard template slices, employing a technique in which the location of the lesion is drawn directly onto the patient’s own MRI scan, and both the scan and the lesion shape are then mapped into stereotaxic space using an automated normalization process (Brett et al., 2001). This procedure avoids the need for the investigators to make (observer-dependent) decisions based on a limited number of slices. Although the investigator still has to delineate the boundary of the lesion manually, he or she can do this directly on the MRI images of the individual patient rather than searching for common landmarks on the patient’s scan and the template scan. Combining all slices produces a lesion region of interest (ROI) for each patient. Using SPM (http://www.fil.ion.ucl.ac.uk/spm/), this ROI is normalized together with the patient’s individual MRI to the appropriate template MRI distributed with SPM. Using this automated normalization protocol, the study of Mort et al. (2003) came to the conclusion that the most critical brain region associated with neglect in the territory of the middle cerebral artery is the angular gyrus on the lateral surface of the IPL.

To determine whether the discrepancy in findings between the studies of Karnath et al. (2001) and Mort et al. (2003) is due to the different lesion analysis protocols used in the two studies, we investigated a new sample of 15 patients with acute right-hemisphere ischaemic strokes consecutively admitted to our neurology department, and used the automated MRI normalization protocol for lesion analysis outlined above.

Unlike our earlier study (Karnath et al., 2001), the present study did not exclude subjects showing hemianopia in addition to spatial neglect. We excluded only those patients who had no cortical involvement, i.e. who showed subcortical lesions confined to the basal ganglia or to the thalamus. Neuropsychological testing and criteria for spatial neglect were identical with the procedure carried out in our previous studies (Karnath et al., 2001, 2002). All patients showed clinically manifest, severe spatial neglect (letter cancellation, mean left 6.9, mean right 19.1; Bells test, mean left 2.3, mean right 8.3; copying task, 47.4% omissions on average). The patients’ mean age was 62 years and 14% had additional hemianopia. All patients gave their informed consent to participate in the study, which was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Unlike Mort et al. (2003), who used T1-weighted MRI scans obtained in the post-acute stage about 2 months after the infarct, we used T2-weighted fluid-attenuated inversion-recovery (FLAIR) and diffusion-weighted (DWI) imaging at the time of stroke when the patients showed severe spatial neglect. While FLAIR images provide high sensitivity for acute cerebral infarcts, DWI has proved to be particularly

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sensitive for the detection of hyperacute infarcts and shows high accuracy in predicting final infarct size (Brant-Zawadzki et al., 1996; Noguchi et al., 1997; Ricci et al., 1999; Schaefer et al., 2002). Accordingly, we used DWI within the first 48 h after stroke (five patients) and FLAIR sequences when imaging was conducted 48 h or later after the stroke (ten patients). The mean time since lesion was 4.4 days (SD = 5.1) for all subjects.

Figure 1 shows the overlay plots for the group of patients with spatial neglect. The number of overlapping lesions is illustrated by colour-coding, with frequency increasing from violet (n = 1) to red (n = 15). The lesion overlap centred on the superior temporal gyrus, the insula and the operculum. It continued into the pre- and postcentral gyri, middle temporal gyrus and putamen. The present data, obtained from a new sample of neglect patients, thus clearly argue against the traditional view that the IPL and right temporoparietal junction are the critical substrates for spatial neglect in humans.

Therefore, we believe that the protocols used for lesion analysis do not explain the discrepant findings of Mort et al. (2003) and Karnath et al. (2001). Instead, we suspect that the different criteria used for selecting patients might be responsible for the conflicting conclusions. While our neglect patients in the previous as well as the present study all had a severe bias in cancellation, about one-third of the sample studied by Mort et al. (2003) was normal or close to normal in cancellation. These patients rather showed a bias in line bisection. What is the problem with using these different selection criteria?

Line bisection and cancellation are the two most popular tasks traditionally used to diagnose the neglect syndrome. Thus, one would expect that performances on these two tasks would show a strong correlation. However, there are now many studies demonstrating that the performances appear to dissociate from each other. For example, Ferber and Karnath observed that line bisecting is unimpaired in 40% of patients who exhibit clear spatial neglect on conventional clinical measures, such as spontaneous exploration, posture, behaviour on the ward, copying, clock-drawing, etc., whereas the cancellation task is a very sensitive measure for this disorder (Ferber and Karnath, 2001). In other words, performance in line bisecting does not reflect the characteristic behavioural disorders observed when patients with spatial neglect are admitted to a neurology department following a right hemisphere infarct. This observation should not be interpreted as suggesting that poor performance on the line bisection task is not clinically important in its own right: it certainly suggests a profound spatial deficit. However, line bisection and cancellation obviously do make different cognitive demands. It is thus possible that the two tasks not only measure different aspects of performance but also are linked to different cortical circuits.

Indeed, empirical evidence for the assumption that different types of brain damage might impair performance on these two tasks has been reported previously (Binder et al., 1992). The authors examined 34 patients with right hemisphere stroke. They found no significant correlation between performance on the line bisection and cancellation tasks: while some patients showed deficits on each task, performance on one task did not predict performance on the other task. Interestingly, when they made overlay plots of the patients’ brain lesions, they observed that patients who showed abnormal line bisection tended to have posterior lesions. In contrast, patients who were specifically impaired on the cancellation task showed more anterior damage. This finding has important implications for the current dispute regarding the neuroanatomical basis of spatial neglect. In the present as well as our recent anatomical study, patients were selected on the basis of two cancellation tasks and a number of clinical measures, and explicitly not on their performance on the line bisection task. This is different from the study of Mort et al. (2003), which included one-third of the middle cerebral artery patient sample on the basis of deficient line bisection behaviour despite accurate performance in the cancellation task. From the work of Binder et al. (1992), one can expect that studies that select patients on the basis of line bisection errors will tend to report more posterior lesions.
compared with studies in which performance on this task is not considered. This conclusion does seem to explain some of the different findings regarding the anatomy of spatial neglect seen in the recent studies of Mort et al. (2003) and Karnath et al. (2001).

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References