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Dissociating neuro-cognitive component processes: voxel-based correlational methodology

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Abstract

Relating behavioural deficits to lesion site has long been an important tool for localising the brain bases of cognitive function. Voxel-based methods, based on statistical analyses of structural brain images, allow a major step forward in the effectiveness of this approach. These methods provide a fine-grained assessment of damaged tissue by assigning a continuous value to each voxel over the entire brain. This information, correlated with continuous behavioural data reflecting specific aspects of cognition, offers new opportunities for identifying the neural organisation underlying cognitive function. The research reported here demonstrates the ability of this correlational methodology to differentiate between the neuro-cognitive components involved in word recognition and lexical decision, providing an important new tool for directly linking brain areas to specific aspects of psychological performance.

Keywords: Neuro-cognitive component processes; Voxel-based correlational methodology; Lesion-deficit approach

1. Introduction

The lesion-deficit approach, whereby a patient's focal brain lesion is related to their behavioural deficit, has been important in developing accounts of the brain bases of cognition (Dronkers, 1996; Dronkers & Lundy, 1998; Damasio, Grabowski, Hichwa, & Damasio, 1996; Tranel, Damasio, & Damasio, 1997). Until the advent of functional imaging, this was one of the methods for determining the functional significance of specific brain regions and for investigating how cognitive processes are instantiated in cortical tissue. Although it remains widely used (Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000; Bates et al., 2003) the standard implementations of this approach have significant limitations.

One important issue concerns the methods used to assess cortical damage, which typically assume that there is a binary distinction between intact and damaged tissue. Across lesion-deficit studies a variety of different methods are used to determine the extent of the lesion, involving either manual tracing of the lesion or more automated methods (Bates et al., 2003; Damasio & Damasio, 1989; Lawrie & Abukmeil, 1998; Mega, Thompson, Toga, & Cummings, 2000). Irrespective of the specific technique used to assess the lesion, the purpose of the procedure is the same—to judge whether cortical tissue is damaged or intact. This all-or-none distinction fails to capture a much larger range of potentially informative gradations in degree of structural damage. Another limitation is that the analysis is typically confined to specific brain regions, with ROIs driven by lesion locations, rather than covering the entire brain. This makes it hard to detect properties of the overall functional network (Naeser, Gaddie, Palumbo, & Stiassny-Eder, 1990; Willmes & Poeck, 1993). Additionally, methodologies that depend on observer input for the delineation of a lesion are susceptible to problems of subjectivity and reproducibility.

Voxel-based methodologies, which involve voxel-by-voxel analyses of the entire brain, have the potential to avoid

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these problems. Whole brain analyses escape the limitations of analyses which are limited to specific brain regions and form the basis for a more comprehensive understanding of the neural system involved in a cognitive task. In addition, voxel-based methods can provide a more sensitive estimate of intact and damaged tissue by assigning a continuous signal intensity value to each voxel.

Another significant limitation of most lesion-deficit studies is the way in which a patient's behavioural deficit is assessed. Typically, this also involves making a binary decision as to whether or not a patient has an impairment on the basis of a set of behavioural scores (Adolphs et al., 2000), which provides a very coarse-grained estimate of the degree to which a patient's performance is impaired. A more accurate assessment of the relationship between damage and impaired performance is possible if we adopt a methodology in which both cortical damage and behavioural deficit can be assessed in a more graded manner. This can be achieved by correlating the continuous intensity value for each voxel with suitably continuous behavioural data, thereby increasing both the sensitivity and the statistical power of the analyses. Furthermore, this allows the use of more dynamic measures of cognitive function, such as reaction time performance in cognitive tasks, which allows the structural data to be related directly to variations in functional capacities. This in principle is capable of delivering a much more differentiated picture of which brain regions are critical to performance of which aspects of a cognitive task.

The research reported here constitutes a first trial of this new combination of continuous whole-brain voxel-based measures of structural integrity with continuous measures of dynamic cognitive performance. What the results reveal is a striking ability to differentiate between neurocognitive component processes, providing much more specific structure–function correlations than existing methods. To this end, we carried out a study which correlated the signal intensity of each voxel across the brains of 19 brain-damaged patients with their performance on a speeded lexical decision task.

We chose the lexical decision task because its component cognitive processes have been well studied and it is a task which has been used extensively to study both normal and abnormal word processing (Franklin, Howard, & Patterson, 1994; Jacobs, Graf, & Kinder, 2003; Marslen-Wilson, 1980; Rubenstein, Garfield, & Millikan, 1970). From a cognitive perspective, it is well-established that the lexical decision task consists of at least two different types of process (Carr & Pollatsek, 1985; Jacobs & Grainger, 1994): (a) the processing of the perceptual input and its rapid mapping onto lexical representations, thereby providing the basis for discriminating between words and non-words. (b) A set of decision processes that operate on the results of these mapping processes, and which require the listener to set a criterion for accepting a stimulus as a word or as a non-word. Depending on where listeners set their threshold, this will determine the proportion of hits (correctly identifying a word) and false alarms (incorrectly accepting a non-word as a word). These decision processes are usually assessed within the context of signal detection theory (Luce, 1986; Swets, 1996), which takes into account the relative rate of hits and false alarms, computing d' as a measure of sensitivity [$d' = z$[FA] $- z$[HIT]] and β as a measure of criterion-setting or response bias ($\beta = [(1 - \text{HIT})(1 - \text{FA})/(\text{HIT} \times \text{FA})]1/2$].

The lexical decision task has been used extensively with brain-damaged patients to determine the extent to which their word processing abilities are intact (Franklin et al., 1994; Milberg & Blumstein, 1981; Milberg, Blumstein, Giovanello, & Misiurski, 2003). However, no attempt has been made to relate the different components of the lexical decision task to specific sites of damage. Similarly, a number of functional imaging studies have used the lexical decision task as a means for exploring the neural basis of word processing (Devlin et al., 2002; Specht et al., 2003). These studies reveal that an extensive, primarily left lateralised, network of fronto-temporal brain regions is activated in this task. However, these studies were not designed to detect possible differences in the neural substrates for the different cognitive processes involved in word recognition and lexical decision. The question addressed by the present study is whether the correlational method provides a methodology for dissociating between different cognitive processes. To address this question we correlated signal intensity across the brains of a variety of brain-damaged patients with a variety of continuous behavioural measures derived from their performance on an auditory lexical decision task. We expected variations in performance to correlate with variations in signal intensity in areas of the brain important for the performance of the task, with different patterns potentially activated by the different components of the lexical decision task.

2. Method

2.1. Subjects

We selected 19 brain-damaged patients who had lesions in a variety of cortical sites due to various aetiologies (e.g. stroke, tumour excision, herpes encephalitis, semantic dementia) for this study. Patients were not selected on the basis of either their lesion location or their pattern of behavioural scores; the sole criteria for inclusion in the study were whether the patient: (a) had a T1 weighted 3D MRI scan, and (b) could perform the lexical decision task. All patients had scans and were tested in the study at least 2 years post-insult. The primary lesions for each patient were identified by means of an automated process which involved the comparison of single patient scan to a control group (Stamatakis & Tyler, 2003). The lesions identified in this way were turned into binary images, overlaid and the resulting lesion distribution is shown in Fig. 1. The purpose of Fig. 1 is to enable the reader to visualise the distribution of the primary lesions in this group of patients; it does not show damage that was

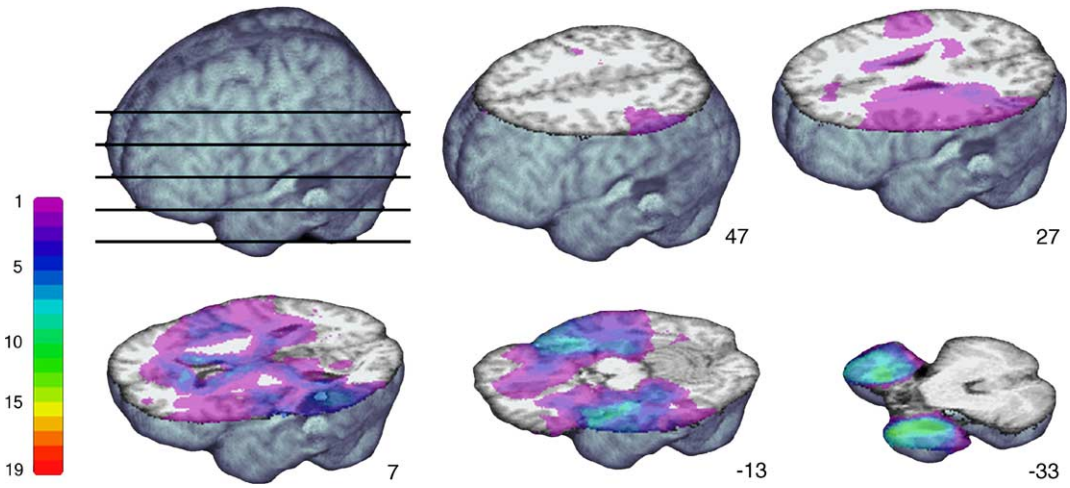

Fig. 1. Representative axial slices showing lesion frequency distribution, (as detailed in the colour bar) in the 19 patients included in the analyses described here. The lesions are superimposed on the mean patient T1 weighted image. The numbers on the right hand side of each panel indicate Talairach *z* planes in mm. The patient group consisted of patients with the following aetiologies: semantic dementia, herpes simplex encephalitis, cerebral infarcts, tumour excisions, partial lobectomy and resection due to epilepsy.

below the statistical threshold used in the lesion analysis. The data shown in Fig. 1 was not used in the correlational analysis described in the paper; for that analysis we used signal intensity values across the entire brain without segregating the brains into damaged and intact tissue. All patients were right-handed native speakers of English, ranging in age from 25 to 67 (mean = 52, S.D. = 14). Written informed consent was obtained from each patient.

2.2. Stimuli and experimental design

The stimuli consisted of 80 real words and 80 non-words. The words were all morphologically simple (e.g. *cloth*, *horse*) and relatively high familiarity (mean familiarity = 540, S.D. = 37; Coltheart, 1981). The stimuli were recorded by a native English speaker and the words and non-words were randomly ordered into a playlist. Subjects were presented with one stimulus every 3 s and instructed to press one key if the stimulus was a word and a second key if it was a non-word. They were encouraged to respond quickly but accurately. Reaction times were measured from word-onset and errors were recorded.

2.3. Correlational analysis

T1 weighted MR scans were obtained for each patient. The first pre-processing step involved spatially normalising the images to the MNI template provided by SPM99 (Wellcome Institute of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk). The presence of abnormalities/lesions can compromise spatial normalisation (Brett, Leff, Rorden, & Ashburner, 2001; Stamatakis, Wilson, & Wyper, 2001) but this problem can often be resolved by utilizing weighting in the form of masks in order to exclude the lesion during nonlinear normalization (Brett et al., 2001) or by penalizing unlikely deformations (Ashburner et al., 1998, 1999). In the current study, the spatial normalization involved both linear (12 affine transformations i.e. translations, rotations, zooms and shears in *x*, *y*, and *z* directions) and nonlinear ($7 \times 8 \times 7$ basis functions) transformations. High regularization was used to constrain the nonlinear part of the algorithm and effectively penalize unlikely deformations associated with the presence of lesions (Ashburner & Friston, 1999). We visually inspected each image to assess whether the spatial normalisation was successful by comparing the spatial location of homologous regions in the template and the patient images. The spatial normalisation procedure did not generate satisfactory results in three images which we subsequently renormalised successfully by utilising weighting in the form of binary masks (Brett et al., 2001; Mort et al., 2003) to exclude lesions from the nonlinear parts of the calculation.

The lesion distribution figure (Fig. 1) was produced by comparing each patient to a group of controls as explained in Section 2.1. These comparisons produced significant results (reduction in signal intensity) in areas already identified by experienced radiologists as lesions. The preprocessing used for this comparison was identical to the one used for the correlation method, suggesting that the spatial normalisation worked correctly.

The authors of a recent lesion study in spatial neglect successfully used masking to spatially normalize images with lesions (Mort et al., 2003). The analysis involved lesion tracing on both spatially normalised images and images that had not been normalised and by comparing results the authors established that their findings were not influenced by spatial normalisation (Mort et al., 2004).

We decided against using non-uniformity correction in the pre-processing because a recent assessment of six widely used non-uniformity correction algorithms arrived at the conclusion that each algorithm produced different results with none of the algorithms performing ideally under all the experimental conditions manipulated (Arnold et al., 2001). Ad-

ditionally we did not segment the images into grey and white matter since this procedure often fails when brains contain large lesions (Stamatakis & Tyler, 2003).

The spatially normalised images were subsequently skull stripped by masking them with the brain mask provided in SPM99 in order to exclude the skull from the analysis, and smoothed with a 10 mm Gaussian kernel. We used smoothing to account for small-scale variations in individual's sulcual and gyral anatomy and to increase the signal to noise ratio (Friston, 1994). For this analysis we correlated four behavioural measures for each patient with signal intensity in each voxel across all the scans. Covariate analyses were carried out in the context of the general linear model (Friston et al., 1995) as implemented in SPM99. For this analysis we entered four behavioural measures and correlated each measure with each voxel across all the scans. In separate analyses we correlated signal intensity with each patient's (a) mean reaction time (RT in ms) for the words, (b) mean non-word RT, (c) measure of d', and (d) measure of β. Patient age and global mean signal for each scan were included in each analysis as confounding covariates. We used global mean from each scan to account for systematic differences in signal intensity values across the scans. Since lesioned areas present lower signal intensity than equivalent tissue in control T1 scans (Stamatakis & Tyler, 2003) we expected relationships between low signal intensity and poor performance in neuropsychological tests to become apparent with this method. Statistical results are reported at cluster levels and were corrected for multiple comparisons.

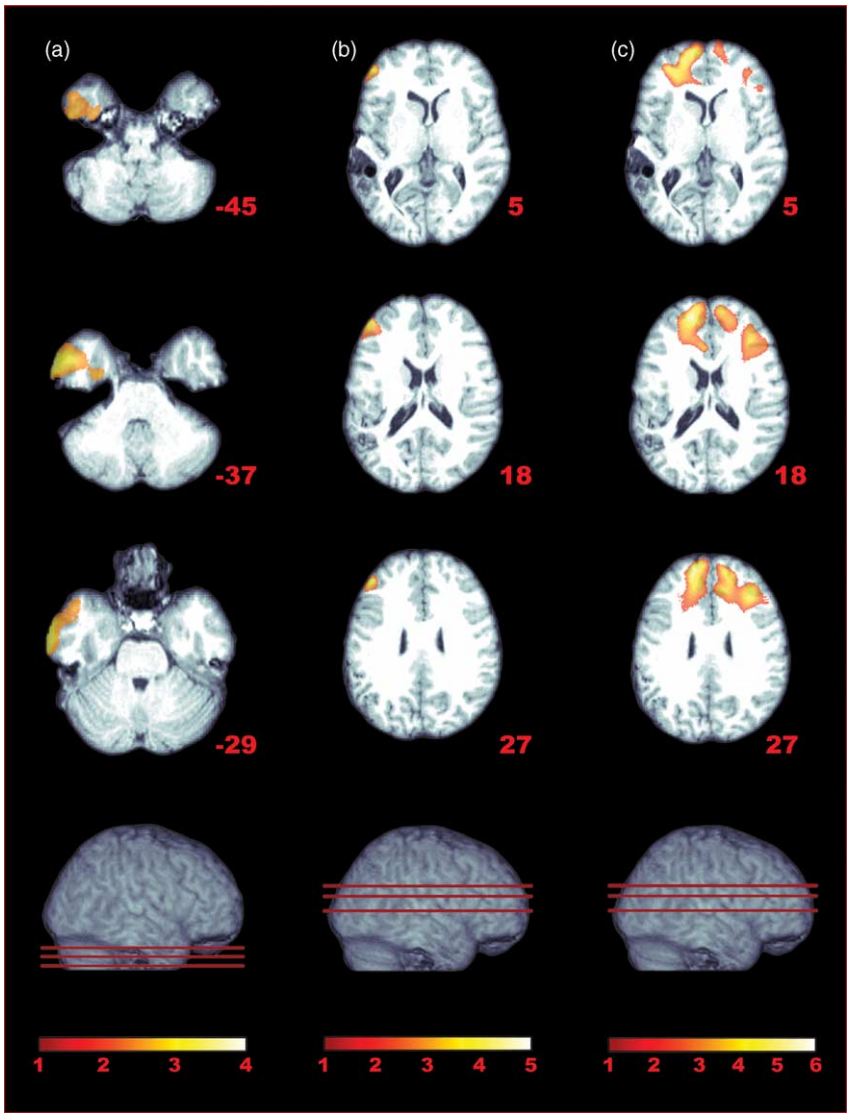

Fig. 2. Representative axial slices showing T1 signal correlations with RTs to real words (column a), d' measure (column b) and β (column c). The correlations are superimposed on the mean patient T1 weighted image and slices are shown in neurological convention where left = left. Talairach z values (mm) are shown in the right hand corner of each panel. The colour bars indicate strength of correlation (voxel level T values).

3. Results

We report cluster level *P*-values corrected for multiple comparisons with peak voxel *z* scores (*P*, *z*). The first set of analyses looked at the primary behavioural data generated by the tasks—the average speed and accuracy of the patients' lexical decision responses. Reaction-times (RT) to real words correlated negatively ($P = 0.0001$; $z = 3.68$) with signal intensity in a large area of the left anterior temporal cortex including the temporal pole, and the superior, inferior and middle temporal gyrus extending into the fusiform gyrus and the parahippocampal gyrus (peak in BA 20; see Fig. 2a). Fig. 3a plots the distribution of each individual at the peak voxel. Since longer RTs reflect increasing difficulty of processing, these results suggest that damage to these left temporal regions, implicated by some investigators in semantic processing (Devlin et al., 2002; Mummery et al., 1999), is associated with increased difficulty in processing the meaning of words. RTs to non-words were negatively correlated ($P = 0.0001$; $z = 3.78$) with signal intensity in essentially the same regions of left inferior and middle temporal cortex (BA21, 20). RTs to real words and non-words did not correlate with signal intensity in the right temporal cortex even though this is damaged in a similar number of patients as shown in Fig. 1. The fact that signal intensity in overlapping left temporal regions correlates with real and non-word RTs is consistent with neuroimaging data showing that real words and non-words activate similar regions of temporal cortex (Binder et al., 2000; Specht et al., 2003). This suggests that listeners attempt to map speech sounds onto meaning irrespective of whether they are hearing real words or non-words, consistent with current theories of spoken word recognition (Marslen-Wilson, 1987), and with the view that the lexical decision task typically involves access to word meaning (Balota, Ferraro, & Connor, 1991; James, 1975; Tyler, Voice, & Moss, 2000).

A second set of analyses, based on simple percent error for words and non-words produced no significant correlations with signal intensity for either the real word or non-word error rates, suggesting that raw error rate does not provide a sensitive measure of the cognitive processes involved in the lexical decision task. In contrast, derived measures, based on signal detection analyses of error patterns (hits and misses), proved much more informative, and correlated with quite different cortical areas from those that correlated with RTs. The d' measure positively correlated ($P = 0.055$; $z = 4.18$) with an area of the left anterior prefrontal cortex centering on the lateral anterior middle frontal gyrus, BA 10, and extending superiorly into the middle frontal gyrus, indicating that a reduction of signal intensity in this region is associated with a decrease in sensitivity (see Fig. 2b). The contribution of each patient to this effect is shown in Fig. 3b, where we plot each individual's scores at the peak voxel. The β, reflecting response bias correlated negatively with signal intensity in BA10 ($P < 0.0001$; $z = 4.35$), but in more medial regions than was the case for d' and in both the left and right hemispheres (see Figs. 2c and 3c). At a lower threshold, this activation

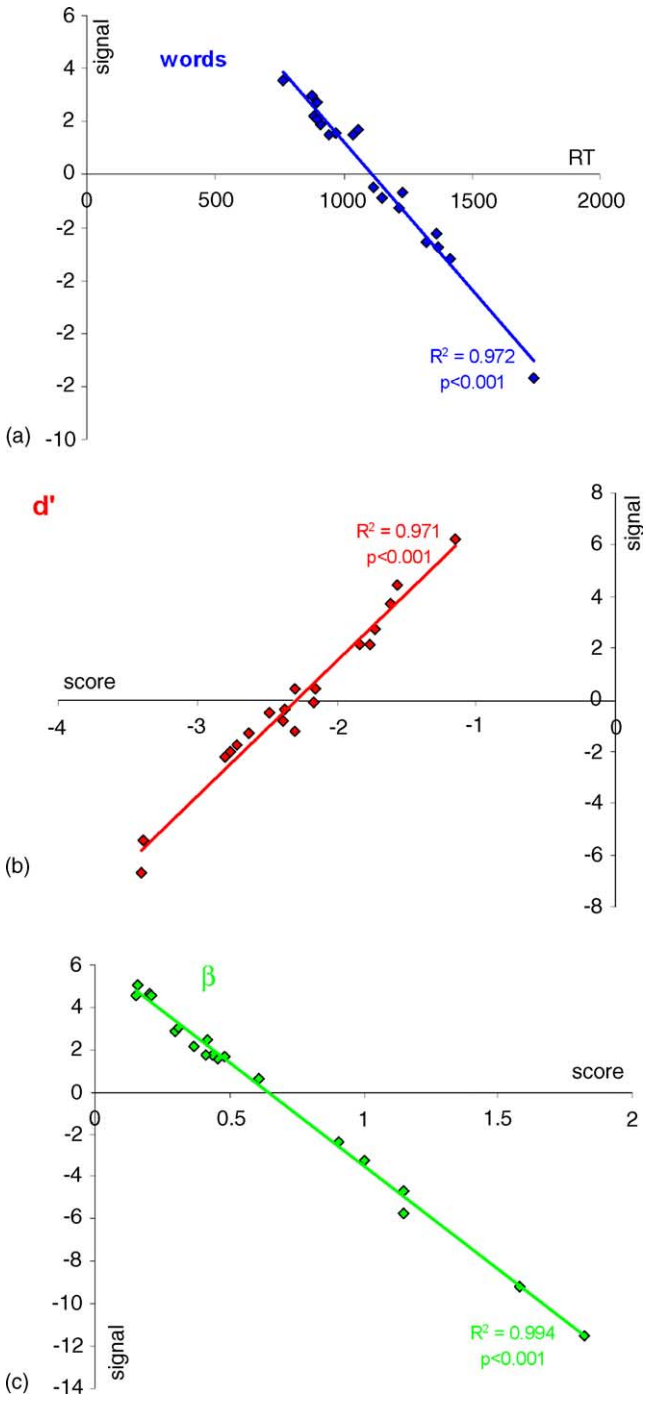

Fig. 3. Scatter plots of intensity values from every patient's scan, after they have been corrected for global mean differences and scaled, plotted against (a) reaction times to real words (b) d' measure and (c) β at the peak voxel in each case.

overlapped on the left with the lateral regions which correlated with d'. The role of the anterior prefrontal cortex in cognition has been investigated in many neuroimaging studies, but continues to be unclear. It has long been claimed to be involved in aspects of memory for verbal materials (e.g. Fiez et al., 1996; McDermott, Jones, Peteren, Lageman, & Roediger, 2000; Rugg, Henson, & Robb, 2003), but its spe-

cific role in memory processes is unresolved. Some recent neuroimaging research has implicated these regions in semantic decision making (Sharp, Scott, & Wise, 2004), and other work has suggested that the anterior prefrontal cortex is primarily activated in conditions where subjects make decisions and choose responses under conditions of uncertainty (Elliot, Dolan, & Frith, 2000). Given that d' and β measure accuracy in the context of uncertainty, the finding that they are associated with the integrity of cortical tissue in area BA10 fits well with this account of the role of this region in cognitive processing.

4. Discussion

The results presented here show that different cortical regions are associated with different cognitive components of the lexical decision task. The mapping of sound onto meaning, as reflected in speed of response, is associated with left anterior temporal regions, whereas accuracy of responding, as reflected in d' and β, is associated with anterior prefrontal regions. Moreover, those regions that show significant correlations with different aspects of the lexical decision task overlap considerably with the cortical areas activated in functional imaging studies using the lexical decision task. This consistency helps to validate these new correlational techniques in delineating the neural basis of different cognitive components. For example, studies investigating the cortical regions involved in semantic processing, using both spoken and written words, report activations in inferior anterior and middle temporal cortex, particularly in the LH (Devlin et al., 2002; Specht et al., 2003; Zahn et al., 2000). However, due to susceptibility artefacts in anterior inferior regions of the temporal cortex using fMRI, it is only in activation studies using PET that we can see the most anterior parts of the temporal cortex, including the poles (e.g. Devlin et al., 2002). Given the limitations of fMRI in this respect, correlational analyses of the type described here clearly have an important role to play in investigating the brain bases of semantic processing.

The anterior prefrontal cortex has been shown to be activated in tasks involving semantic decision-making (e.g. Sharp et al., 2004; Scott, Lerff, & Wise, 2003), and has been claimed to be part of the neural network involved in chosing between alternative lexical semantic representations. It has also been studied extensively in the context of the processes involved in memory. There is general agreement that this region is involved in retrieval processes, but there no clear consensus beyond that. Tulving and co-workers have claimed that the anterior prefrontal cortex, while being involved in retrieval processes, is insensitive to the nature of the task and to the types of retrieval cues used (Lepage, Ghaffar, Nyberg, & Tulving, 2000), while Rugg et al. argue that it is indeed sensitive to these variables (Rugg et al., 2003). This latter research suggests that the anterior prefrontal cortex is involved in modulating retrieval processes according to task demands, and specifically retrieval success. The anterior prefrontal cortex has also been claimed to be involved in retrieval strategies (Wagner, 1999) while research by Ranganath, Johnson, & D'Esposito, 2000 focuses more on the commonalities and differences in the role of this region in working memory and long term memory. Whatever the specific functions of the anterior prefrontal cortex in memory and decision-making processes, the present results suggest that it plays a role in word recognition, presumably in modulating the retrieval of lexical and semantic representations.

The correlational method as described here represents an advance on other studies which select patients on the basis of their lesion location or their behavioural deficit. Any selection on this basis brings with it a priori assumptions about behavioural impairment and about the relevance of specific lesion sites to specific behaviours, thereby restricting the possible set of associations to those included in the analysis and making it impossible to determine whether other brain regions are also involved. Here we demonstrate that it is possible to obtain meaningful correlations even when no a priori assumptions are made about lesion location or behavioural deficit, and patients are not pre-selected on this basis.

In summary, we have presented data, using a correlational technique involving two continuous variables—signal intensity and behavioural measures—showing that the method is remarkably sensitive to the different components of a complex cognitive task. The advantage of using continuous measures is that they increase the range of data that are entered into the correlation and this may account for the degree of sensitivity shown here. At the same time, the method we have described here avoids some of the limitations of the traditional lesion-deficit approach. Lesion–behaviour correlations of the type described here, which correlate continuous behavioural measures of specific, theoretically-motivated aspects of cognitive functions with detailed voxel-by-voxel signal intensity across the entire brain offer the possibility of a more detailed and accurate analysis of the neural mechanisms involved in language and cognition. In addition, they are highly complementary to functional neuro-imaging results because they allow stronger inferences about the causal roles of the structures involved.

Acknowledgements

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