

Monitoring and the Controlled Processing of Meaning: Distinct Prefrontal Systems

David J. Sharp, Sophie K. Scott and Richard J.S. Wise

MRC Clinical Sciences Centre, Cyclotron Unit, Hammersmith Hospital, London W12 0NN, UK

Distinct prefrontal regions are specialized for the controlled processing of semantic information. We have dissociated components of this system used in semantic decision-making across different perceptual conditions. Nineteen subjects were presented with auditory word sequences, on which they made semantic or syllabic decisions, while neural activity was measured using PET. Contrasting the semantic with syllabic tasks, there was activation within left rostral prefrontal cortex (RPFC) when the stimuli were presented as clear speech, reducing when the stimuli were presented in acoustically degraded form. In contrast, activation of the right dorsolateral prefrontal cortex (DLPFC) was observed with the degraded stimuli, an effect that inversely correlated with accuracy on the task. We have thus demonstrated two prefrontal systems where activity is differentially modulated by the 'quality' of information held in working memory. This dissociation is likely to represent an alteration in the type of cognitive operations employed during task performance, where left RPFC is activated during extensive semantic elaboration and right DLPFC is recruited as the monitoring demands, associated with items held in working memory, increase. The function of these separate systems is integrated during the performance of verbal problem-solving tasks although they are differentially sensitive to stimulus degradation.

Introduction

In circumstances where there is ambiguity about a required task, about the identity of a stimulus or about the selection of a response, then the involvement of prefrontal cortex (PFC) becomes increasingly important (Fuster, 1998). Prefrontal damage may result in a subject being unable to cope with ambiguity, resulting in arbitrary or inflexible responses (Burgess *et al.*, 2000; Elliott *et al.*, 2000; Manes *et al.*, 2002; Stuss and Levine, 2002). Intact prefrontal function is thus essential for the control of action when the correct response is not necessarily obvious.

A major role of the PFC involves the maintenance, manipulation and monitoring of information held within working memory (Goldman-Rakic, 1987; Fuster, 1998), processes important for the resolution of lexical ambiguity (Miyake *et al.*, 1994b). Evidence suggests that these complex functions are served by different PFC regions (D'Esposito *et al.*, 2000). Studies of non-human primates and functional neuroimaging work in humans suggest an organization within posterior PFC regions along a ventral-dorsal dimension (Petrides, 1995; Owen, 2000; Rowe and Passingham, 2001). It is proposed that ventrolateral PFC (VLPFC) is specialized for the strategic mapping of semantic stimuli onto representations, the controlled retrieval of these representations into working memory and the maintenance of information within working memory (Petrides, 1995; Owen, 2000). In addition, dorsolateral PFC (DLPFC) is specialized, through its interaction with VLPFC, for

the subsequent monitoring, manipulation and active selection of maintained information. In non-human primates, lesions within DLPFC produce specific deficits in monitoring information held within working memory (Petrides, 2000) and in humans, neural activity within DLPFC increases when the monitoring demands associated with mnemonic retrieval increase (Henson *et al.*, 1999, 2000). The information that is temporarily retrieved into working memory is selected from a much larger store of long-term memories held within regions caudal to PFC. Such a role requires the rapid, dynamic updating of information within working memory (O'Reilly *et al.*, 2002).

In addition to the ventral-dorsal distinction found in posterior PFC regions there exists also a major rostral-caudal organization within the frontal lobes (Fuster, 1998). Rostral PFC (RPFC) regions exhibit distinct cytoarchitectonics and neural connectivity (Barbas *et al.*, 1999), and in general, in functional neuroimaging studies, rostral prefrontal regions are activated during complex reasoning and problem-solving tasks (Christoff and Gabrieli, 2000; Kroger *et al.*, 2002). A number of different proposals have been made about the cognitive processes localized to left RPFC [i.e. medial BA 8/9 and frontal pole (BA 10)]. These include the context-dependent representation of, and choice between, multiple alternative responses (Scott *et al.*, 2000b, 2003), the need to represent a number of variables in parallel (Kroger *et al.*, 2002), the need to produce self-referential (Gusnard *et al.*, 2001) or self-initiated thought (McGuire *et al.*, 1996), to maintain multiple goal contingencies (McGuire *et al.*, 1996), to process information about intentions, i.e. theory-of-mind (Gallagher *et al.*, 2000) and to evaluate both externally (Zysset *et al.*, 2003) and internally generated information (Christoff and Gabrieli, 2000).

This study of PFC function addressed the effects of perceptual degradation across two different tasks, enabling a separate analysis of PFC involvement in both. The tasks we employed were performed on either clear or distorted speech. One task, semantic decision-making, required the retrieval of associative knowledge about the meaning of the words, with individual decisions dependent on different aspects of semantic relatedness between word triplets. The baseline task was to relate the number of syllables within each word of a triplet, and indicate which pair had the same number of syllables. Therefore, this study investigated the impact of perceptual distortion upon distinct prefrontal neural systems contributing to the executive control of semantic processing, a question that has theoretical and practical implications for the study of the involvement of PFC in the recovery from, and rehabilitation of, aphasic stroke.

We predicted a dissociation of the neural responses to task (semantic and syllable decision-making) and stimulus type

between left RPFC and right DLPFC, identifying two separate prefrontal systems associated with different aspects of the task demand. The first system would be associated with complex problem solving and be maximally active in conditions where the semantic identity of heard words was clear, allowing extensive semantic elaboration between stimuli to take place (left RPFC). The second system would be associated with processes increasingly engaged as decisions are made in degraded perceptual conditions. Perceptual degradation leads to increased uncertainty about the information held within working memory and its relationship to current task demand (right DLPFC). This system would thus be implicated in additional processes, including monitoring operations, recruited when the information held in working memory is of reduced quality.

Materials and Methods

Subjects

Nineteen right-handed, normal volunteers (seven females), aged between 37 and 83 years, gave informed, written consent for the study. All had English as their first language. Prior testing demonstrated that they were capable of hearing the stimuli clearly. The studies were approved by the Administration of Radioactive Substances Advisory Committee (Department of Health, UK) and the research ethics committee of The Hammersmith Hospital.

Study Design

A 2×2 factorial design was employed with brain activation measured using positron emission tomography (PET). On line recordings of responses and reaction time (RT) were made. Two tasks were involved that used different arrangements of the same words presented as either clear or distorted speech:

Semantic Decision – Subjects were asked a standard question at the start of each scan, i.e. ‘which of the second two words has most in common with the first word in terms of its meaning?’. They then made semantic decisions on heard word triplets presented during the course of each scan (e.g. ‘beach, island, mountain’). The triplets were selected on the basis of a pilot study on 10 normal subjects who did not subsequently participate in the scanning study. This study was used to identify word triplets for the semantic task where there was at least 90% agreement on the ‘correct’ response.

Syllable Decision – Subjects were asked a standard question at the start of each scan, i.e. ‘which of the second two words has the same number of syllables as the first word?’. They then made decisions based on the number of syllables within heard word triplets presented during the course of each scan (e.g. ‘hammer, tool, trailer’). This is an unfamiliar task and it was predicted, on the evidence of a previous study, that it would take at least as long for the subjects to respond in this task as in the semantic decision task (Scott *et al.*, 2001). As with the semantic decision task, word triplets were only chosen for presentation when the pilot data demonstrated agreement on the choice in at least 90% of subjects.

Clear and Noise-vocoded Stimuli

Subjects made the semantic and syllable decisions on stimuli presented either as clear speech (SemSp and SyllSp) or as eight-channel noise-vocoded speech (8-VoCo) (SemVoCo and SyllVoCo) (Shannon *et al.*, 1995), spoken by a female speaker of British English. The method of constructing noise-vocoded speech is described in the original publication and in our previous publication that investigated temporal lobe activity in response to intelligible and unintelligible speech (Shannon *et al.*, 1995; Scott *et al.*, 2000a). After such manipulation, 8-VoCo sounds like a harsh whisper, but it can be understood after a brief period of training. For the purposes of this study, training consisted of a single session, immediately prior to scanning. The subjects heard 54 single, 8-VoCo words and were scored on the accuracy of their repeti-

tion of these words. The period of training was adjusted until each subject was repeating with >50% accuracy (range 55.3–85.6). Thus, the word triplets formed from 8-VoCo remained subjectively and objectively more ‘difficult’ to comprehend than the triplets formed from clear speech.

PET Scanning

Subjects were scanned on a Siemens HR++ (966) PET camera operated in high-sensitivity 3D mode. Sixteen scans were performed on each subject, with the room darkened and the subjects’ eyes closed. The dependent variable in functional imaging studies is the haemodynamic response: a local increase in synaptic activity is associated with increased local metabolism, coupled to an increase in regional cerebral blood flow (rCBF). Water labelled with a positron-emitting isotope of oxygen ($H_2^{15}O$) was used as the tracer to demonstrate changes in rCBF, equivalent to changes in tissue concentration of $H_2^{15}O$. The resolution of the technique meant that the activity at the level of neural systems (i.e. local populations of many millions of synapses) was observed.

Analysis involved relating changes in local tissue activity (normalized for global changes in activity between scans) to the behavioural task. Thirteen stimuli were presented in each block with a new stimulus occurring every 6 s and the onset of the block timed to start 15 s before the arrival of radiolabelled water in the brain, and covering the critical measurement period of rapid build-up of tracer in the brain over 30 s. Pacing of stimuli was required to maintain a constant rate of stimulus presentation across scans and subjects. After measured attenuation correction, images were reconstructed by filtered back projection (Hanning filter, cut-off frequency 0.5 Hz).

Data Analysis

SPM99 software (Wellcome Department of Cognitive Neurology, Queen Square, London: <http://www.fil.ion.ucl.ac.uk/spm>) was used to realign the individual PET scans. These were then spatially transformed (normalized) into standard MNI (Montreal Neurological Institute) stereotactic space (Evans *et al.*, 1993). This transformation allowed comparisons across individuals to be made. The scan data were then smoothed using an isotropic 16 mm, full-width half-maximum Gaussian kernel to account for individual variation in gyral anatomy found within prefrontal cortex (Rajkowska and Goldman-Rakic, 1995) and to improve the signal-to-noise ratio. Specific effects were investigated using appropriate contrasts and covariates to create SPMs of the *T* statistic (which were subsequently transformed into *Z* scores). We used a blocked ANCOVA with global counts as confound to remove the effect of global changes in perfusion across scans.

The following analyses were performed:

- A contrast of the semantic tasks with their respective baseline syllable judgement tasks, i.e. [(SemSp – SyllSp) + (SemVoCo – SyllVoCo)]. This was the main effect of task, demonstrating the distributed system involved in decision-making based upon associative knowledge about the individual words in each heard triplet. The peak voxel statistical threshold was set at $P < 0.05$, corrected for analyses across the whole volume of the brain. The spatial extent threshold was set to include only clusters of >10 voxels.
- A contrast of decision-making upon degraded stimuli with those made upon clear stimuli over both task conditions, i.e. [(SyllVoCo – SyllSp) + (SemVoCo – SemSp)]. This revealed the main effect of stimulus degradation, demonstrating the distributed system recruited during decision-making upon distorted stimuli, in addition to that involved in decisions made upon clear stimuli. The peak voxel statistical threshold was set at $P < 0.05$, corrected for analyses across the whole volume of the brain. The spatial extent threshold was set to include only clusters of >10 voxels.
- The interaction of task (semantic or syllable decision-making) with stimulus type (normal speech or noise vocoded speech) was investigated by performing the following two contrasts: [(SemSp – SyllSp) + (SyllVoCo – SemVoCo)] and [(SyllSp – SemSp) + (SemVoCo – SyllVoCo)].
- Planned comparisons of the direct contrast between the two semantic conditions were carried out, i.e. (SemSp – SemVoCo) and (SemVoCo – SemSp). As there was an *a priori* hypothesis about the role

of the left superior frontal gyrus (SFG) during semantic decision-making, a mask was created to include the whole of the left SFG and the statistical threshold for activations within this region was set at $P < 0.05$, corrected for the volume of the mask. For all other activations within PFC, the threshold was set at $P < 0.05$, corrected for the total volume of PFC.

- Comparisons of the direct contrast between the two syllable conditions were carried out, i.e. (SylSp - SylVoCo) and (SylVoCo - SylSp). The peak voxel statistical threshold was set at $P < 0.05$, corrected for analyses across the whole volume of the brain. The spatial extent threshold was set to include only clusters of >10 voxels.
- A final set of analyses used percentage accuracy of decision-making as a covariate of interest to identify neural regions where activity was predicted by accuracy of decision-making. Whole-brain analyses were carried out separately for the combined semantic (SemSp and SemVoCo) and syllable (SylSp and SylVoCo) scans. There was no *a priori* hypothesis about the location of correlations, and the threshold was set at $P < 0.05$, corrected for the volume of the whole brain. An additional analysis was performed to investigate whether performance in the four individual conditions predicted activity within right DLPFC. Data were extracted from the peak voxel within right DLPFC, functionally defined from the contrast of decision-making on degraded versus clear speech stimuli (see contrast 3). The slope of the regression of percentage accuracy upon neural activity, for this right DLPFC voxel, was determined for each individual. A one-sample *t*-test was then performed on the regression slopes to assess group significance.

Results

Behavioural Performance

The behavioural results are summarized in Table 1. Due to loss of data, behavioural results were available for only 18 of the 19 subjects. Errors were classed as incorrect responses according to either the criterion of responses established in the pilot study (at least 90% agreement) or due to a failure to respond during the 6 s interval between the end of presenting one stimulus and the start of presenting the next. During scanning, semantic and syllable decisions on clear speech were >90% accurate for all subjects with no significant difference between the two conditions. There was a main effect of stimulus type with more errors made upon vocoded stimuli [$F(1,17) = 51.2, P < 0.0005$]. A significant interaction between task and stimulus type was observed [$F(1,17) = 34.0, P < 0.0005$], with performance on the vocoded semantic task more impaired relative to clear speech than on the syllable task (see Table 1). This interaction was expected, as even single-channel noise-vocoded speech (the amplitude-time envelope of speech filled with white noise, similar to signal correlated noise) retains some of the syllabic structure of the

original speech signal in the absence of any intelligibility (Rosen, 1992).

A main effect of stimulus type on RT was observed [$F(1,17) = 15.7, P = 0.001$] with slower responses for vocoded stimuli. A main effect of task on RT was also seen [$F(1,17) = 9.1, P = 0.008$], with responses to semantic decisions longer than to syllable decisions. There was no interaction between task and stimulus type (see Table 1).

Imaging Results

The Main Effect of Task (Fig. 1)

The main effect of semantic decision-making, when contrasted with syllable decision-making, demonstrated a predominantly left-lateralized system (Fig. 1). The most extensive region activated was within RPFC, extending along the medial half of the left superior frontal gyrus, i.e. dorsally from Brodmann areas (BA) 8, through BA 9 and as far ventrally as the frontal pole (BA 10). Activity was also present in VLPFC which merged with that present in rostral superior temporal cortex. In one of our previous studies on decisions based on word meaning, peaks within the left IFG and rostral left temporal cortex were more clearly distinguished (Scott *et al.*, 2001). Additional activations were observed in the left fusiform gyrus, in the inferior parietal lobe and in both left and right cerebellar hemispheres.

The Main Effect of Stimulus Type (Fig. 2)

Contrasting semantic and syllable decisions made upon degraded stimuli with those made upon clear stimuli demonstrated the main effect of degrading the stimuli (Fig. 2). This contrast revealed a right-lateralized prefrontal system with peaks of activation observed in the right DLPFC and VLPFC (BA 9 and 47). Activation was also observed in the superior temporal gyrus lateral to primary auditory cortex. No regions survived correction for multiple comparisons in the reverse contrast of clear decisions versus degraded stimuli.

Task By Condition Interactions

No significant regions of activation were observed with either of the interaction analyses.

The Effect of Degraded Stimuli on Semantic Decision-making (Fig. 3)

When considering the prefrontal responses to the semantic conditions alone, there was a clear regional difference of activation observed during decisions based on clear and degraded speech. Directly contrasting the scans of semantic decision-making upon clear stimuli with those made upon vocoded stimuli revealed greater activity within the left rostral PFC (BA 8) during semantic decisions made upon clear speech (Fig. 3). This activation was observed within a task-specific region of PFC, i.e. one activated by the main effect of semantic decision-making relative to the baseline of syllable decision-making. Conversely, increased activation was observed within right DLPFC (BA 9), left orbitofrontal (OFC) cortex (BA 10) and right insular during semantic decision-making upon degraded stimuli. Greater activation for degraded semantic decision-making was observed in regions previously identified in the main effect of stimulus type and not within task specific PFC. The presence of a common activation within right DLPFC for both semantic and syllable decision-making upon degraded stimuli potentially explains the absence of these regions from

Table 1

Reaction time and mean accuracy as percentage of accurate total responses (SEM)

Condition	RT (ms)	Accuracy %
Clear speech		
Syllable decision	4193 (131.7)	91.1 (1.6)
Semantic decision	4295 (118.4)	90.9 (1.9)
Vocoded speech		
Syllable decision	4340 (109.7)	86.7 (2.0)
Semantic decision	4562 (115.9)	73.2 (2.4)

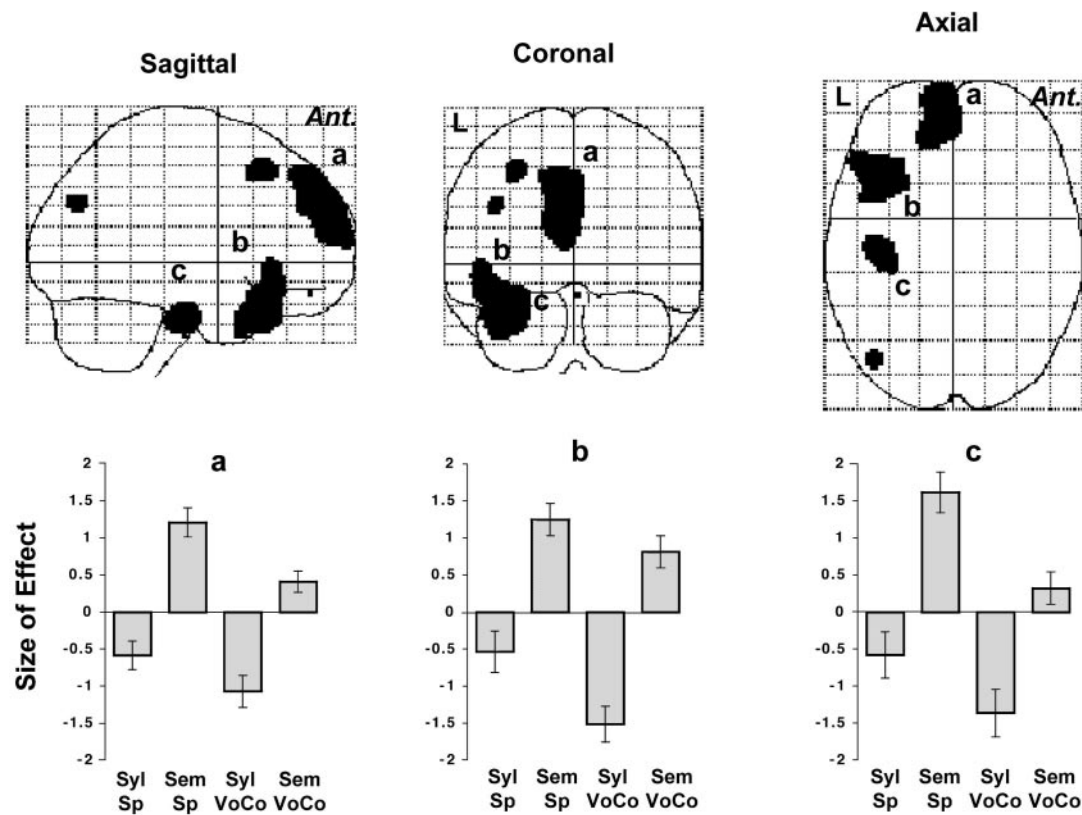


Figure 1. Statistical parametric maps of the main effect of semantic decision [(SemSp – SyllSp) + (SemVoCo – SyllVoCo)] displayed as sagittal, coronal and axial projections. The threshold was set at 0.05 corrected excluding clusters with a spatial extent of <10 voxels. The locations of the peak voxels are: (a) left rostral PFC (BA 9) –4 52 40 ($Z = 7.54$), (b) left VLPFC (BA 47) –32 22 –26 ($Z = 7.08$) and (c) left fusiform gyrus (BA 20) –38 –18 –30 ($Z = 5.52$). Coordinates of the peak voxels are in the stereotaxic space of the Montreal Neurological Institute (MNI), implemented in SPM 99. Plots of the mean effect size for each condition \pm SEM are shown for (a) left rostral PFC (b) left VLPFC and (c) left fusiform gyrus. Units of effect size are relative to whole-brain mean activity values and represent the percentage change of whole-brain activity produced by each condition.

the main effect analysis of task and suggests that the right DLPFC forms part of a neural system recruited as perceptual difficulty increases. There was no evidence that activity in the left VLPFC was significantly modulated by degrading the speech signal.

The Effect of Degraded Stimuli on Syllable Decision-making

No regions survived whole-brain correction for the direct contrasts of syllable decision-making in either clear or degraded perceptual conditions. However, when a less conservative threshold ($P < 0.001$ uncorrected) was employed, the contrast of syllable decision-making on degraded versus clear speech stimuli revealed activation with a peak within right DLPFC ($x = 38$ $y = 52$ $z = 28$), close to the peak activation for the overall main effect of degraded speech decision-making. Peaks of activation were also observed in bilateral pars opercularis and right planum temporale. No significant activation was observed for the reverse contrast of syllable decision-making on clear speech versus degraded speech stimuli.

The Effect of Performance during Decision-making (Fig. 4)

The accuracy of semantic decisions predicted neural activity within right DLPFC. Whole-brain analysis showed a significant negative correlation between percentage accuracy on semantic decision-making and activation within right DLPFC

(BA 10) (Fig. 4). The reverse contrast revealed activation within right posterior brain regions, which included the right superior parietal lobe and right fusiform gyrus. To assess further the significance of the observation that declining accuracy predicts neural activity within right PFC, an additional analysis was performed that used the regression slopes of accuracy upon neural activity taken from the right DLPFC. Data were extracted from the peak voxel within right DLPFC from the correlational analysis of accuracy. A one sample t -test was then performed on individual's regression slopes which revealed a significantly negative slope across the group ($t = 4.459$, $d.f. = 17$, $P = 0.002$, two-tailed).

Whole-brain analysis performed using syllable decision-making accuracy as a covariate of interest revealed no regions significantly correlated with performance when whole-brain correction ($P < 0.05$) was employed. Using a less conservative threshold ($P < 0.001$ uncorrected), a negative correlation between percentage accuracy and activation was observed within right PFC in the region of the pars opercularis and a positive correlation observed within the right orbitofrontal cortex.

A further analysis was performed to investigate whether performance in decision-making predicted neural activity specifically within the right DLPFC region that was activated in the main effect of stimulus type (i.e. decision-making on degraded versus clear speech stimuli). Data were extracted

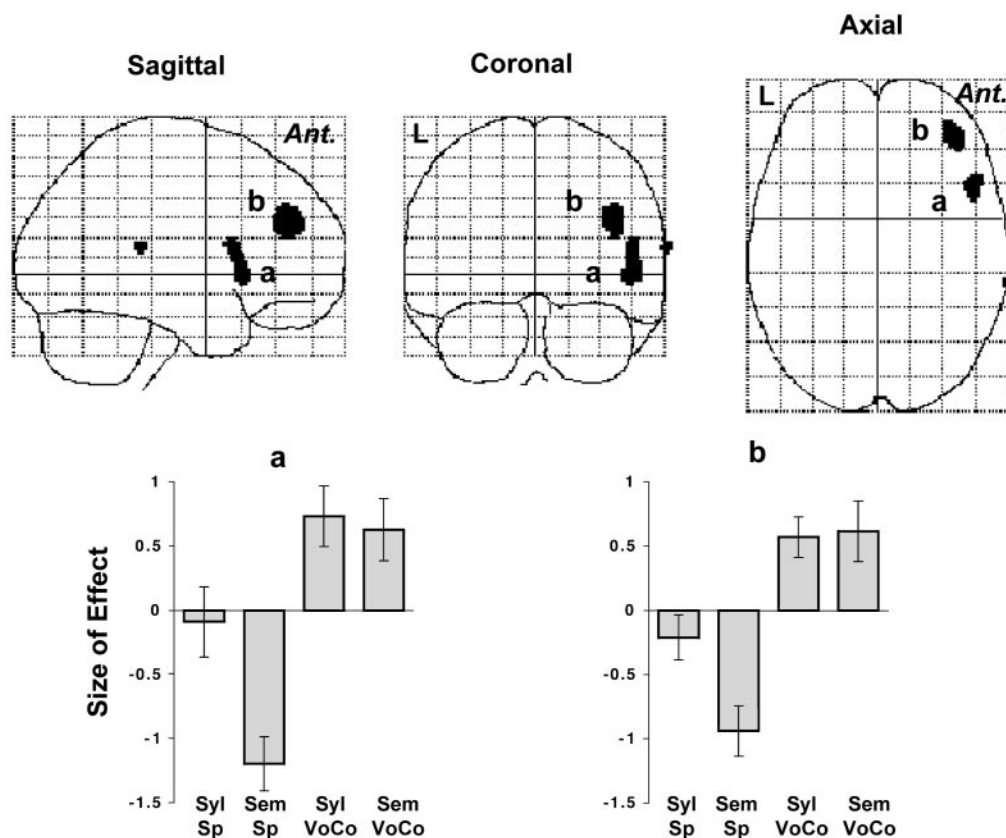


Figure 2. Statistical parametric maps of the main effect of vocoding speech $[(\text{SylVoCo} - \text{SylSp}) + (\text{SemVoCo} - \text{SemSp})]$ displayed as sagittal, coronal and axial projections. The threshold was set at 0.05 corrected excluding clusters with a spatial extent of < 10 voxels. The locations of the peak voxels are: (a) right VLPFC (BA 47) $-50\ 18\ 0$ ($Z = 4.8$) and (b) right DLPFC (BA 9) $40\ 42\ 30$ ($Z = 5.02$). Plots of the mean effect size for each condition \pm SEM are shown for (a) right VLPFC and (b) right DLPFC. Units of effect size as for Figure 1.

from the peak of activation within right DLPFC and individual slopes of regression calculated for percentage accuracy upon neural activity (both combined across perceptual conditions for semantic and syllable decisions and for each of the four separate conditions). One-sample t -tests were performed on the resulting sets of regression slopes. A significantly negative slope was identified between the combined semantic performance and neural activity ($t = 4.61$, $d.f. = 17$, $P < 0.0001$). There was no significant relationship between combined syllable accuracy or the individual conditions and activity within right DLPFC.

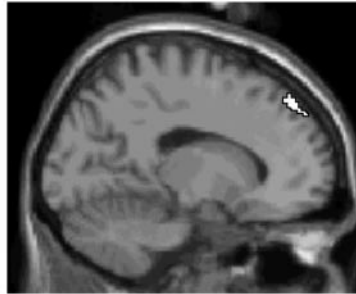
Discussion

This study investigated the effect of increasing perceptual degradation on the prefrontal cortical (PFC) neural system involved in the controlled processing of semantic memory. The semantic task, relative to another based on the sound structure of the stimulus words, was associated with activation of a widely distributed, predominantly left-lateralized, system, which included an extensive region in left RPFC. Noise-vocoding the stimuli resulted in a significant reduction in the activity within left RPFC (BA 8). In contrast, perceptual degradation resulted in greater activity in a separately distributed prefrontal system, consisting of right DLPFC (BAs 9 and 46) and parts of left OFC (BA 10). Within right DLPFC there was a strong correlation between neural activity and decreasing accuracy in the choices made upon degraded speech stimuli.

The clear speech semantic and syllable tasks were balanced for low level perceptual and motor processing demands and had similar working memory loads associated with maintenance of information during decision-making. However, the type of information actively retrieved into working memory differs (semantic or phonological representations) and the potential computational complexity of decisions based on ambiguous semantic relationships is much greater than those based on unambiguous syllabic sound structure. Activation of left ventrolateral PFC (BAs 45/47) has been observed previously during the controlled retrieval of semantic information into working memory (Owen, 2000; Wagner *et al.*, 2001b) and this interpretation of VLPFC function is compatible with the activation observed within left VLPFC in the current study. Activation of left RPFC has been observed during various types of complex decision-making (Goel *et al.*, 1997; Scott *et al.*, 2003; Zysset *et al.*, 2003) and the computational complexity of semantic relative to syllabic decision-making is likely to explain the activation observed in this region in this study.

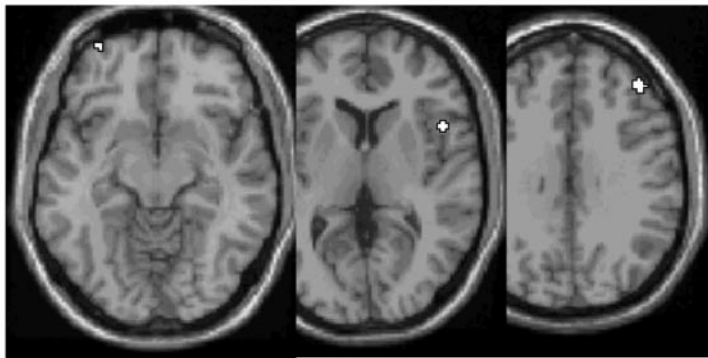
Clinical neuropsychological (Burgess *et al.*, 2000; Metzler, 2001; Ferstl *et al.*, 2002; Manes *et al.*, 2002), functional neuroimaging (e.g. D'Esposito *et al.*, 2000; Scott *et al.*, 2000b), and non-human primate research (e.g. Petrides, 2000), suggest that the PFC is integral to the control of complex choices, and that different prefrontal regions mediate distinct aspects of this control. In humans, the controlled processing of semantic knowledge is impaired by damage to the PFC. For example, left PFC lesions produce abnormalities in the lexical priming

(A) Clear vs Vocoded



(C) Vocoded vs Clear

X=-15

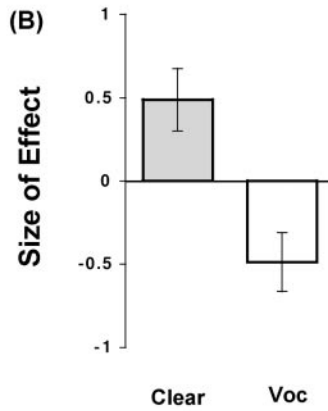


Z=-10

Z=6

Z=32

(B)



(D)

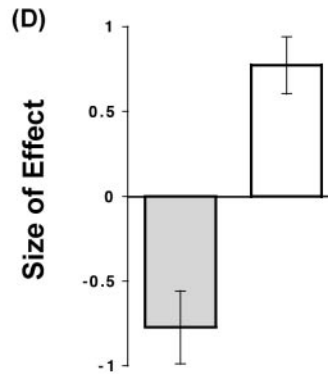
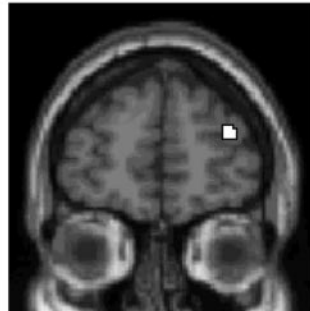
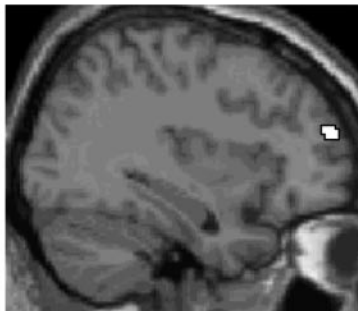


Figure 3. Statistical parametric maps of the direct contrast of semantic decision-making on clear and vocoded speech (A) (SemSp – SemVoCo) and (C) (SemVoCo – SemSp). The threshold was set at 0.05 corrected excluding clusters with a spatial extent of <10. A small volume correction was employed in (A) using a region of interest incorporating the whole of the left superior frontal gyrus. The locations of the peak voxels are: (A) left rostral PFC (BA 8) –12 50 48 ($Z = 3.94$), (C) right DLPFC (BA 9) 44 40 32 ($Z = 5.12$), right insular cortex 44 14 8 ($Z = 4.78$) and left orbitofrontal cortex (BA 10) –32 62 –8 ($Z = 4.64$). Plots of the mean effect size for each condition \pm SEM are shown for (B) left rostral PFC and (D) right DLPFC. Units of effect size as for Figure 1.

(A)



(B)

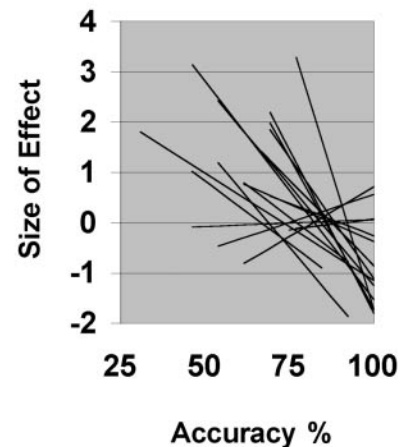


Figure 4. (A) Statistical parametric maps of the inverse correlation between rCBF and percentage accuracy. The threshold was set at 0.05 corrected excluding clusters with a spatial extent of <10 voxels. (B) Individual subjects regression lines of effect size as a function of accuracy taken from the peak voxel within right DLPFC (BA 10) 36 54 20 ($Z = 5.05$). Units of effect size as for Figure 1.

of ambiguous, but not unambiguous words, suggesting a deficit in the selection of context-appropriate meanings (Metzler, 2001) with the same type of lesions also producing abnormalities in the judgement of semantic coherence across

sentences (Ferstl *et al.*, 2002). Medial prefrontal lesions have been shown to produce deficits in the planning of action (Burgess *et al.*, 2000) which, importantly, are not simply a function of the size of the prefrontal lesion (Manes *et al.*,

2002). In contrast, lesions to the prefrontal cortex leave intact the representations of semantic knowledge, which appear to be represented in a distributed system caudal to prefrontal cortex (Martin and Chao, 2001; Sylvester and Shimamura, 2002).

In terms of the tasks used in this study, a difference in the degree to which the left rostral prefrontal region might be involved can be determined. While making judgements about the sound structure of acoustic stimuli is demanding, the choice is unambiguous and the dimension along which that choice is made, i.e. ascertaining the number of syllables within each word, is constant. In contrast, choices made on the basis of semantic features can involve comparisons potentially made along multiple dimensions of meaning, resulting in a choice that may be inherently ambiguous in nature. The contribution of PFC to the semantic task is dependent on the degree to which the target and probe words are linked by shared semantic associations (Wagner *et al.*, 2001b). For example, deciding whether *clown* is more closely related to *lion* or *giraffe* requires manipulation of long-term associative knowledge in relation to the specific task requirement and a choice made by identification of a single associative feature, namely location, i.e. the circus.

As a result of these complexities and ambiguities, the number of interacting variables that must be represented, in parallel, to enable accurate performance is much larger for semantic than for syllable decision-making. The contrast of these two decision-making tasks demonstrated that RPF, localized to the medial part of the left SFG, is involved when representing the relations between multiple items of recalled information held within working memory in the context of a specific task demand, and informing selection of the appropriate response.

Although the left SFG and frontal pole have been observed previously in other studies of decision-making based upon verbal semantics (Binder *et al.*, 1999; Scott *et al.*, 2003; Zysset *et al.*, 2003) this region is not solely recruited by tasks that involve semantic reasoning. Thus left RPF has been activated in sound source decision-making (Scott *et al.*, 2000b) and inductive versus deductive reasoning (Goel *et al.*, 1997). This region has also been shown to be activated in a recent study that used progressive, multiple, step-wise change in visual patterns to vary the relational complexity of decision-making requiring subjects to complete the progression by selecting one pattern from among distracter patterns (Kroger *et al.*, 2002). The left SFG activation was at a site indistinguishable from that observed in the other verbal studies. Although the authors of this study chose a different interpretation for the function of the left medial SFG, placing the result in the perspective of the rest of the functional neuroimaging literature suggests that this rostral prefrontal region behaves as an amodal cognitive system facilitating complex, attribute-rich reasoning (Barnard, 1998). Thus, it may operate when relating external stimuli that have no long-term mental representations [e.g. the abstract visual patterns (Kroger *et al.*, 2002)] as well as when inferring relationships that are dependent upon the recall of internal mnemonic representations, as in this study.

Increasing perceptual degradation in presented stimuli will influence the amount and type of information held within working memory. In the extreme case, failure to identify any word within a triplet will have resulted in no recall of associative knowledge into working memory. Therefore, the reduc-

tion of activity in RPF in response to degraded stimuli corresponds to a reduction in potential relational processing and not to task difficulty, which increased with the 8-VoCo stimuli (as reflected in reduced percentage accuracy and longer RTs). The lack of a direct association between increasing PFC activation and increasing task difficulty is unusual. Increasing task difficulty is usually (Duncan and Owen, 2000) although not always (Bor *et al.*, 2003) associated with increasing PFC activation, a relationship demonstrated across many different cognitive domains. For example, a number of previous studies have investigated the effects that degrading perceptual visual stimuli have on PFC activation during decision-making (Grady *et al.*, 1996; Barch *et al.*, 1997). In these studies, increasing task difficulty secondary to perceptually degraded stimuli was associated with increases in activation within the PFC. In terms of cognitive processing, interpreting the significance of neural activity related to increasing task difficulty can be particularly difficult. The dissociation of increasing task difficulty from RPF activation in our study is important because it allows a distinction to be made between cognitive processes associated with semantic decision-making, which are emphasized in clear perceptual conditions, from those more general aspects of executive function recruited as task difficulty increases.

In contrast to left RPF, activation observed within right DLPFC was greater for decision-making performed upon degraded than on clear speech stimuli. Activations within this region have been observed in many previous neuroimaging studies (Duncan and Owen, 2000). As we discuss above, the interpretation of such activations, associated with increases in task difficulty and seen across many different cognitive domains, can be problematic. However, insights into the significance of the right DLPFC seen in the current study can be drawn from studies of working and episodic memory.

Verbal working memory is known to be sensitive to low-level perceptual factors. For example, verbal span is influenced by many aspects of the perceptual presentation of stimuli such as their rhythm, the presence of distracting background sounds and the suffix effect (Hitch *et al.*, 1996; Beaman and Morton, 2000; Jones *et al.*, 2000). Thus, when heard words are degraded the cognitive resources recruited to enhance the accuracy of choices would be expected to increase. Evidence from lesion studies in non-human primates (Petrides, 1991, 2000), structural connectivity analysis (Petrides and Pandya, 1994) and neuroimaging studies (D'Esposito *et al.*, 1998; Henson *et al.*, 1999, 2000; Rowe and Passingham, 2001; Wagner *et al.*, 2001a) supports the proposal that a ventral-dorsal hierarchical organization exists within the PFC in which DLPFC is involved in monitoring and manipulating information maintained within VLPFC.

Studies of episodic memory retrieval provide a description of the nature of these monitoring operations relevant to the current study. In Burgess and Shallice's model of episodic retrieval, an important component of a multistage process is the existence of a 'memory editor' whose role is to monitor retrieved information to assess first its relevance to current task demands and second whether the information is sufficient to allow a response (Burgess and Shallice, 1996). Evidence for localization of this type of monitoring operation to right DLPFC comes from two event-related fMRI studies showing that activity within this region was modulated by monitoring demands associated with judgements made during an episodic

memory task (Henson *et al.*, 1999, 2000). In the first study, monitoring demands associated with recognition memory judgements were manipulated by varying whether decisions did or did not require reference to the spatio-temporal context of words presented in a previous study episode. In the second study, subjects' confidence in recognition memory judgements were used to predict activity on correct responses within right DLPFC. In both cases, right DLPFC activity was increased when decisions were associated with greater monitoring demands, i.e. where reference to the spatio-temporal location of words was required and where subjective confidence in decision-making was low.

In the context of the current study, decisions made upon vocoded speech stimuli were both more difficult (longer RTs and more errors) and less familiar (subjects had one pre-training session and repetition scores were not at ceiling) suggesting a requirement for greater monitoring. By analogy to the 'memory editor' described for episodic memory, monitoring processes involved in verbal decision-making would be expected to determine whether the information currently held in working memory (i.e. representations of associative knowledge or phonological sound structure) is relevant to the current task (i.e. semantic or syllabic decision-making) and whether this information is sufficient to allow a choice to be made. The involvement of these monitoring processes to individual decisions is related to the 'quality' of information retrieved into working memory. For example, where unambiguous lexical semantic representations are retrieved following the presentation of clear speech stimuli, we would expect low involvement of the right DLPFC because deciding on the relevance of retrieved information to current task demand and whether the information is sufficient to allow a decision is likely to be straightforward. In contrast, when perceptual degradation leads to incomplete retrieval or noisy lexical semantic information held within working memory we would expect higher activity within right DLPFC due to increased difficulty deciding on the relevance and sufficiency of retrieved information for decision-making. The observed increase in activation of right DLPFC during both semantic and syllable decisions made upon vocoded stimuli is hence compatible with increasing demands placed on an amodal system engaged in situations where the relationship between information held in working memory, task demand and response selection is unclear.

The engagement of this type of monitoring during decision-making may lead to a number of different outcomes (Burgess and Shallice, 1996; Henson *et al.*, 2000). Information already obtained may be used to inform choice, the subjective confidence of which may increase following the monitoring process. Alternatively, if information is inadequate for a confident decision, further strategic 'mediator' operations may be engaged to improve the chance of a success or simply to allow any decision to be made. These could take a number of different forms, for example, further attempts to retrieve relevant semantic information or the involvement of problem solving routines to allow 'mediation' between conflicting choices

This interpretation of our results is supported by the behavioural results and by the correlation observed between behavioural performance and neural activity within right DLPFC. Decisions made upon degraded stimuli were associated with increased RTs, suggesting that the working memory

component of these decisions involved a prolonged period of monitoring. In the context of the high accuracy of decision-making made upon clear stimuli (>90%), decreased accuracy when decisions were made upon degraded stimuli indicates a failure of semantic elaboration or syllabic comparison in a proportion of these trials. The increase of neural activity in right DLPFC with decreasing accuracy provides further support for the role of the right DLPFC in the control of processing as task difficulty increases, compatible with a role for this region in the monitoring of information held within working memory. This result of correlating decreasing accuracy with activity may, to some extent, be restating the result from contrasting degraded with clear stimuli, because accuracy decreases with decisions made upon degraded stimuli. However, the result from correlating activity with behaviour emphasizes the role for the right DLPFC that we have outlined above. Similar levels of activation are observed within right DLPFC for both the degraded conditions despite differences in performance, which may reflect a complex relationship between performance monitoring demands and activation of DLPFC. If response in right DLPFC linearly increased with increasing monitoring demands and these demands were accurately reflected by percentage accuracy then one would predict an increased level of activation in right DLPFC. However, neither of these assumptions may be true, which makes the lack of activation difference between tasks difficult to interpret

The dissociation shown in PFC regions recruited during semantic decision-making in varying perceptual conditions is thus likely to represent a change in the nature of task performance, with a shift in the type of cognitive operations employed in an attempt to maximize performance. When no perceptual degradation is present and clear lexical semantic information is held in working memory, the requirement to represent multiple semantic variables in parallel and thus allow accurate semantic comparison recruits regions within the left SFG and frontal pole. When the 'quality' of the lexical semantic information held in working memory falls as a result of reduced intelligibility of heard stimuli, the involvement of cognitive operations enabling monitoring of this information increases, producing increased neural activation within right DLPFC. We hypothesize that these two systems are to some extent independent of one another. Thus the processing of lexical semantic information can only proceed accurately when full sound to meaning mapping has occurred (RPFC), whereas increased monitoring is involved when the sound to meaning mapping is degraded (DLPFC). Consistent with this, the increasing activity in right DLPFC with decreasing performance is not complemented by an inverse relationship in left RPFC with accuracy.

In the comparison of degraded against clear speech decision-making, activation was also observed within the right superior temporal gyrus (STG) lateral to primary auditory cortex. This may reflect the increased auditory perceptual demands associated with verbal decisions made upon degraded speech stimuli. Attentional modulation of right STG activation has been observed previously in neuroimaging studies (Wise *et al.*, 1999; S.K. Scott *et al.*, submitted for publication) and this may reflect the top-down attentional modulation of auditory cortex during decision-making in 'difficult' perceptual conditions.

The observation that distinct PFC regions are recruited during semantic decision-making in conditions of varying

intelligibility has important implications for the interpretation of neuroimaging studies of recovery and rehabilitation following aphasic stroke. Previous studies of the distribution of prefrontal activity in recovering patients with focal left hemisphere damage have described activation within right PFC, contralateral to that observed in normal subjects (Weiller *et al.*, 1995; Rosen *et al.*, 2000; Blasi *et al.*, 2002). One interpretation of such a shift in activation pattern is that, following brain damage, the neural structure responsible for a particular cognitive operation is lateralized or relocated to intact neural tissue. Our study demonstrates that this cannot be inferred from changing patterns of activation within PFC, particularly when performance is not matched between patient and control groups. Changes in the nature of cognitive operations occurring as a result of changes in the difficulty and/or automaticity of processing associated with the task, are at least as likely to account for observed patterns of neural activation observed in these studies.

Aphasic stroke frequently results in ambiguity in the lexical semantic identity of heard speech. It has been proposed that the degree of resulting comprehension deficit is influenced by individual variations in the contribution of working memory to language comprehension (Miyake *et al.*, 1994a) which becomes less automatic in nature. Patients with comprehension deficits following temporal lobe damage often have intact PFC (Selnes *et al.*, 1983) and following left middle cerebral artery infarctions, which cause the majority of comprehension deficits, the left RPF is almost always left undamaged because of its distinct vascular supply (the anterior cerebral artery). The recovery from and response to rehabilitation in patients following aphasic stroke is thus likely to be, at least in part, dependent on the ability of this intact PFC to actively influence language processing through the instantiation of working memory processing. Intact PFC which is able to interact with posterior brain structures will allow ambiguous lexical semantic information to be held in working memory, represented in a rapidly updateable form and monitored for its relation to current conversational context. This active control of speech comprehension following aphasic stroke is likely to facilitate the extraction of the maximum semantic content from ambiguous percepts produced following temporal lobe damage.

In summary, we have shown a dissociation between PFC regions activated in two types of verbal decision-making made in differing perceptual conditions, likely to represent a change in the type of cognitive operations employed to maximize task performance. During semantic decision-making activation within left rostral prefrontal cortex is prominent when stimuli are presented clearly but reduces when degraded stimuli are used. In contrast, activation of a distinct neural system, which includes right DLPFC, is shown when decisions are made upon degraded speech stimuli. Left RPF is activated during many types of complex decision-making and we propose that this region is involved in the representation in parallel of multiple features (e.g. semantic) of the stimuli in relation to the current task demand. This is a computational requirement for many complex cognitive operations including the extensive semantic elaboration required in our task. In contrast, when reduced or degraded information is available, distinct PFC regions, including right DLPFC, are recruited that are thought to enable the information maintained within working memory to be monitored more closely.

Notes

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Address correspondence to Dr David Sharp, MRC Cyclotron Unit, Hammersmith Hospital, London W12 0NN, UK. E-mail: david.sharp@ic.ac.uk.

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