Neuroimaging studies of the distributed semantic system and its disruption in disease

Catherine Jane Mummery
University College London

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This thesis investigates the neural correlates of semantic processing using a variety of language tasks while scanning normal subjects and patients with positron emission tomography. The aims were to (i) describe the general semantic network; (ii) investigate the internal architecture of semantic memory by examining variations in activation for different types of task or knowledge; (iii) study disruption of the network in patients with focal cognitive deficits.

In normals, the semantic network comprised the left anterior and inferolateral temporal lobe, inferior frontal lobe and temporo-parietal junction. Studies were performed to examine differential neural responses for categories of knowledge, and showed that the predominant segregation within the semantic system was due to knowledge type rather than due to object domain. The precise contribution of regions comprising the semantic network was explored using differing explicit and implicit semantic tasks.

Disruption of the semantic network was then investigated in patients with semantic dementia, who have a selective semantic associative deficit and anomia. Structural analysis showed a striking correlation between semantic deficit and degree of atrophy in the anterolateral temporal lobe. Functional analysis suggested that the anterior temporal lobes were being activated abnormally, possibly in an attempt to compensate for the damage, while the posterior inferior temporal lobe failed to activate despite being structurally intact. A patient with fronto-parietal lobe damage was also studied; results confirmed the importance of temporal regions for semantic processing and suggested that the inferior frontal lobe was not necessary for task performance.

The results suggest differential roles for regions within the distributed semantic system. For example, the anterior temporal lobe may act as a 'convergence' region, integrating multimodal representations into a unique concept. Secondly, results show that the conjunction of neuropsychology and neuroimaging allows more precise definition of the roles of regions involved in semantic processing.
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Chapter 1
General Introduction

1.1 OVERVIEW
Our current understanding of memory has evolved from the development of various conceptual dichotomies. Within long-term memory, a distinction between semantic and episodic subtypes was first drawn by Tulving (1972) on psychological grounds. Episodic memory was defined as the recollection of personally experienced episodes or events that were contextually and temporally specific. In contrast, semantic memory was defined as culturally shared, overlearned, and not temporally specific, initially thought of as no more than a mental lexicon: a store of the meaning of words. This early definition of semantic memory has since been expanded to include meaning of concepts in general, both abstract and concrete; in short, our repository of knowledge. To illustrate the difference in types of long term memory an example may be useful: remembering what you ate for Christmas lunch last year depends on episodic memory systems, whereas knowing that Christmas is a religious holiday draws on semantic memory. Semantic memory and episodic memory must to some degree interact: all experience must be understood at some level, and all knowledge must be acquired at some point in time. To go back to the initial example, at some point in time (i.e. at an event) one must have learned what ‘Christmas’ means.

The semantic memory system is also closely interlinked with language processing, being the central cognitive domain in understanding the meaning of a sentence or a single word. While linguistic processes such as auditory/visual input processing, phonological/featural analysis, lexical access, phonological/orthographic retrieval, articulation/writing, and syntactic processing are essential to reading a book or holding a conversation, comprehension of the conversation/text is obviously the pivotal process required for success. At a more fundamental level, the understanding of the meaning of concepts is necessary for survival. For example, it is vital that the meaning of a red traffic light is known for an appropriate (and safe) response to be made. The perception of the colour red only changes behaviour when ‘red’ is known to mean ‘stop’. This example also makes the point that the semantic system cannot function in isolation, but interacts with perception – the percept must be seen as ‘red’ in order for the correct response to occur. A colour-blind person would be just as unable to respond appropriately as an individual with a semantic deficit.
The importance of interactions between processes such as semantic memory and perception has been highlighted in attempts to investigate semantic memory. Tasks designed to tap semantic memory can yield sub-normal performance due to impairments in other processes that interact with semantic processing such as visual perception or speech production. The principle adopted for evaluating semantic memory in patients has therefore been to measure performance on a variety of tasks with different perceptual and motor requirements (e.g. Hodges et al, 1992; Hodges and Patterson, 1995). Consistently poor performance throughout the semantic battery of tests is taken to indicate semantic memory impairment. Extrapolating from this, the work presented here attempts to examine the functional anatomy of semantic processing from several differing perspectives, aiming to converge on the brain regions that are critical for semantic processing across modalities and tasks. This is not a purely phrenological approach. If one assumes that complex cognitive processes are widely distributed throughout the brain, there must be critical regions where these processes converge, in Damasio’s terms ‘convergence regions’ (Damasio and Damasio, 1994) or in Mesulam’s parlance ‘transmodal areas’ (Mesulam, 1998).

To summarise, the issue of where and how the brain represents knowledge about the world is a topic of continuing debate in cognitive neuroscience. Semantic memory is an integral part of both long-term memory and language processing, themselves complex, multi-faceted cognitive processes involving a number of interactive systems. Using neuroimaging, this thesis aims to delineate some of these critical regions within semantic memory, and to relate them to intact and disordered processing, using normal controls and patients with a selective semantic deficit in semantic processing.

The following sections discuss previous research into semantic processing, reviewing the history of the lesion deficit model (Section 1.2), the localisation of lesions causing semantic deficits (Section 1.3), and findings from neuroimaging (Section 1.4). I then explore the theoretical accounts of within-semantic organisation (Section 1.5) and the relationship between semantic and episodic memory (Section 1.6). Finally, the research rationale for this thesis is detailed (Section 1.7).
1.2 THE LESION DEFICIT MODEL AND COGNITIVE NEUROPSYCHOLOGY

1.2. A History of the lesion deficit model

The lesion deficit model equates the site of a lesion to lost function. A closely related discipline is cognitive neuropsychology, which models cognitive processes from neuropsychological deficits. Language was the first higher cognitive function to be associated with a neural basis, using the lesion deficit model. Broca (1861) described a dissociation between ‘the faculty of articulate language’ (speech production), impaired in his patients, and language understanding (speech comprehension), which he contended remained intact in patients with frontal lesions. Wernicke (1874) observed the complementary disorder in patients with aphasia following temporoparietal damage, and proposed a theoretical framework for language representation involving two centres, an anterior centre sustaining articulatory images of words, and a posterior region involved in auditory images of words. Three types of aphasia were predicted, resulting from anterior lesions (‘Broca’s aphasia’: poor output, preserved comprehension), posterior lesions (‘Wernicke’s aphasia’: preserved output, poor comprehension) and lesions to the white matter (arcuate fasciculus) linking the two centres (‘conduction aphasia’).

Several years later, Lichtheim (1885) refined this model, proposing a third element – ‘concept centres’, the original prototype of the semantic system (Figure 1.1). Disruption to connections between motor images and the concept centre resulted in ‘transcortical motor aphasia’; disruption to connections between auditory images and the concept centre resulted in ‘transcortical sensory aphasia’.

**Figure 1.1:** *Schematic representation of Lichtheim’s model showing hypothetical disconnection syndromes*

![Schematic representation of Lichtheim's model showing hypothetical disconnection syndromes](image)

- **Disconnection Syndromes**
  - CA: Conduction Aphasia
  - TMA: Transcortical Motor Aphasia
  - TSA: Transcortical Sensory Aphasia
This classical model of language organisation, based on individuals with aphasia secondary to cerebral infarction, was further refined in subsequent years (e.g. Geschwind, 1971), but for a long time there was little change to this extremely important and influential model.

In cognitive neuropsychology, the dichotomy between perception and meaning was first made by Lissauer (1890), suggesting two stages in the organisation of visual recognition, the ‘apperceptive’ stage and the ‘associative’ stage. In the past hundred years, many cases have been documented of selective difficulty with comprehension and relatively preserved perception. This can be in any modality: visual, auditory or tactile. For example, patients may be unable to comprehend a spoken word, but are able to repeat it (Vignolo, 1969). The first prominent description of such selective deficits, which explicitly related them to semantic memory, was by Warrington (1975), who reported three patients with progressive degenerative brain disease. These cases had progressive anomia and impaired word comprehension, while general intellectual function, other linguistic functions, perceptual and spatial skills, and problem solving were relatively preserved. In fact, a similar pattern had been described in Japan several decades earlier under the label of “gogi” (word-meaning) aphasia (Sasanuma and Monoi, 1975). More recently, an increasing number of patients have been reported with similar deficits, and the term semantic dementia has been coined to convey the nature of the progressive cognitive deficit involved (Snowden et al, 1989; Hodges et al, 1992). This is described in more detail below in the description of patients with semantic deficits (Section 1.4).

1.2B Limitations

Until recently, the primary tool in the investigation of language and memory was patient (lesion) data. Lesion data informs us about i) putative brain location of a cognitive function; ii) the dissociability of functions within the living brain. However, both conclusions, if arrived at in isolation, are fundamentally limited.

1.2.B.1 Limitations of lesion deficit model

While it is intuitively attractive to equate a focal structural deficit with cognitive deficit, there are difficulties with correlating performance on a given task with the site of a lesion.

(i) Damage following brain insult is often widespread, or in multiple areas, seldom conforming to functionally homogeneous systems.
(ii) The cognitive deficit in a patient is usually complicated involving more than one process.

(iii) Cognitive processes may have a widely distributed anatomical representation (Goldman-Rakic, 1988) and a lesion which interrupts a whole process may occupy only a small part of the network sustaining that process. One therefore requires additional methods of examining the functional deficit in patients with a focal brain lesion.

1.2.B.2 Limitations of cognitive neuropsychology
The tacit assumption made from observing dissociations between cognitive functions was that the neural mechanisms underlying the processes involved were also modular or separate to some extent. For example, dissociations found in patients with semantic deficits for knowledge of animate and inanimate concepts led to the hypothesis that semantic memory was organised in a modular or categorical fashion, with regions dedicated to differing concept types (some still adhere to a similar view, e.g. Caramazza (1998)).

However, in recent years, the advent of new techniques has provided further information on the nature of processes involved in language. Connectionist modelling has recently challenged the ‘dissociation = modularity’ assumption by showing that dissociations can be modelled in a distributed system without dissociable mechanisms, but rather by interactions between multiple networks that support specific processes (e.g. McClelland and Rumelhart, 1985; Plaut and Shallice, 1993). This has led to a revolution in the conceptualisation of language and other higher cognitive functions. Modern language theorists now increasingly use connectionist models to explain and predict the deficits found in patients. For example, Devlin et al (1998) used a computational model to simulate the category specific semantic deficits found in patients with Alzheimer’s disease, and presented evidence supporting a distributed model of semantic memory with topographical organisation of types of features, but not of specific categories. In a similar way, Small et al (1995) used neural networks to show that, if objects are encoded in terms of their features, categorical information emerges without any explicit memory for categories.
The double dissociation is therefore still an invaluable methodological tool for establishing the sub-components of complex skills, but converging evidence from other methods is required for a fuller interpretation. Of course, dissociation at a featural (or micro-featural) level still underpins connectionist modelling. However, the advantage of such an approach is that it allows modelling of brain processes in a distributed manner, with dissociations being emergent rather than categorical.

1.3 LOCALISATION OF LESIONS CAUSING A SEMANTIC DEFICIT

The lesion deficit model has shown that dissociations within semantic memory and other language/memory functions exist, suggesting separable neural substrates underpinning semantic processing. Detailed examination of patients with selective semantic deficits can lead to the localisation of regions thought to be necessary for semantic processing. There now follows a description of patients with such a deficit, due to different disorders.

1.3.A Semantic dementia

As discussed above, the first description of a progressive brain disorder with selective deficit in semantic memory was by Warrington (1975). The patients reported had deficits in both word meaning and in understanding the meaning of non-verbal concepts. This enormously influential paper put semantic disorders on the map, and precipitated a burgeoning body of research into the architecture of semantic memory. Subsequently, the term 'semantic dementia' was coined to describe such patients (Snowden et al., 1989; Hodges et al., 1992). The three cases studied by Warrington would have fallen under the same rubric.

The syndrome of semantic dementia results in a loss of the conceptual database (semantic memory) underlying language usage. Though the most apparent early deficits may be in the domain of language, all abilities requiring access to conceptual knowledge are typically affected. The impairment appears strikingly restricted to lexico-semantic processing. Syntactic and phonological processes are largely uncompromised, at least until late in the course of the disease (Breedin et al, 1994; Hodges et al, 1994). Furthermore, in contrast to more common and more global dementing conditions, particularly Alzheimer’s disease, patients with semantic dementia have relatively preserved episodic memory (at least for recent events: Graham and Hodges, 1997; Hodges and Graham, 1998), especially when non-verbal tests of episodic memory are
used (Snowden et al, 1996). Patients achieve average or even superior scores on tests of visuospatial skills, frontal executive functions and problem solving which do not require comprehension of specific semantic concepts. Two points are noteworthy – the relative sparing of other language functions, and the relative sparing of other memory functions.

The regions of most prominent atrophy in semantic dementia are thought to be in anterolateral temporal cortex, especially the temporal pole, inferior and middle temporal gyri (Hodges and Patterson, 1996; Snowden et al, 1996). Coregistration of SPECT and MRI imaging (Breedin et al, 1994) has suggested the importance of the inferior temporal gyrus in particular. This syndrome therefore not only presents with a focal cognitive deficit restricted to the semantic domain, but also with restricted neuroanatomical abnormality on structural imaging. One major aim of this thesis was to investigate how the structural deficit affects the functional profile, and how the two correlate, using an observer independent technique to define the affected regions more precisely than has been possible using manual methods. To my knowledge, this has not been studied previously.

The degree of selectivity seen in semantic dementia, in terms of cognitive function and structural damage, is unusual in lesion studies. Even so, there is subtle evidence from these patients that the semantic deficit interacts with other cognitive processes. For example, a study of patients with semantic dementia has suggested that the intactness of meaning has direct implications for the integrity of phonological word forms, without disrupting the individual elements of phonological representation (Patterson et al., 1994). This hypothesis supports an interactive model of language processing. Secondly, while semantic dementia patients show relatively intact episodic memory, the dissociability between the two forms of long-term memory is not completely clear cut. An observed feature of patients with semantic dementia is that their conversation focuses exclusively on personally relevant topics, raising the possibility that autobiographical experience may contribute to the preservation of concept meaning (Snowden et al, 1995), or at least interact with semantic memory (Hodges and Graham, 1998). These two examples highlight the importance of considering a complex cognitive process such as semantic memory in conjunction with closely related processes.
1.3.B. Other causes of semantic memory impairment

Loss of semantic knowledge has been reported secondary to other aetiologies. Patients who recover from Herpes Simplex Viral Encephalitis (HSVE), a devastating form of acute necrotising brain infection, show a severe semantic disorder. All suffer from anomic aphasia. However, 10/11 of the reported cases in a review by Alexander (1997) also had significant episodic memory impairments (the exception was a case of De Renzi et al (1987) who had good day-to-day memory). Structural imaging of patients post-HSVE reveals evidence of severe damage to medial temporal lobe structures and inferior temporal neocortex (Pietrini et al, 1988; Sartori and Job, 1988; Silveri and Gainotti, 1988; Sartori et al, 1993). Testing these patients is notoriously difficult, given the degree of amnesia often shown. This lack of selectivity in cognitive impairment makes claims of semantic deficit localisation somewhat tenuous.

Another cause of semantic deficit is posterior cerebral artery infarction, which affects the inferior and medial temporo-occipital regions, and produces a variety of semantic, lexical and visual deficits. Damasio et al (1996) reported a group of such patients, with semantic deficits and temporal lobe damage. Alexander et al (1989) argued that stroke patients with the syndrome of transcortical sensory aphasia, in whom semantic knowledge is impaired, have cortical or white matter lesions that isolated the left posterior association regions. Again, these lesions rarely cause selective deficits to semantic memory, often producing concurrent episodic memory impairment, plus visual recognition deficits, leading to difficulties with task performance interpretation.

Finally, a case has been reported of selective semantic memory impairment post cardiac arrest and consequent cerebral hypoxia (Alexander, 1997). This patient showed hypoperfusion of bilateral posterior association regions, particularly in the inferior temporal lobes and temporoparietal regions, left greater than right. Both this case and those with posterior cerebral artery infarction suggest the temporal and temporoparietal association regions are important in semantic processing, though this conclusion must be interpreted with caution for the reasons described above.

It seems, from the existing patient data, that there is converging evidence for the involvement of the inferolateral temporal and temporoparietal regions in semantic processing. However, as mentioned earlier, it is important that lesion data is not
interpreted in isolation; correlation of lesion and functional deficit is important in ascertaining the regions involved in semantic processing.

**1.4 FINDINGS FROM NEUROIMAGING**

Functional neuroimaging offers several advantages over the lesion deficit model. Firstly, one can observe brain activity non-invasively in normal subjects. Secondly, the technique is not limited to the damaged part of the brain, and can therefore identify cortical function at a systems level, allowing the investigation of functional deficits in the absence of structural damage.

**1.4.A Early results**

Pioneering work by Petersen et al (1988) investigated the anatomical areas engaged by visual and auditory word processing by comparing blood flow during different word tasks. A hierarchical technique was used, with conditions being visual fixation (baseline), silent word viewing, reading aloud and verb generation. To isolate semantic processing, verb generation was compared to reading aloud. Activation was seen in the left dorsolateral prefrontal cortex and anterior cingulate. It was concluded that the left prefrontal cortex was associated with semantic processing, a result conflicting with evidence from the lesion studies discussed above.

Subsequently, two further neuroimaging studies were performed, investigating language processing, producing rather different results. Wise and colleagues (1991) compared verb generation to heard nouns with rest and found evidence suggesting that left posterior temporal regions were involved in semantic processing. Demonet et al (1992) used a monitoring task to compare phonological processing with semantic processing and found activation of posterior and inferolateral temporal regions for semantic processing. Both of these studies found frontal activity as well as the temporal activation, but in additional regions to those seen by Petersen et al. (1988). These findings, amongst others, have resulted in a vigorous and ongoing debate concerning the roles of frontal and temporal regions in semantic processing.

**1.4.B Limitations of early PET studies**

The studies by Petersen et al (1988), Wise et al (1991), and Demonet et al (1992) reached differing conclusions, and it is important to understand why these differences occurred. A
major limitation of early PET studies involved task analysis. Task analysis is the decomposition of a task into the component cognitive and sensori-motor processes whose existence is inferred on the basis of neuropsychological, psychophysiological and psychophysical studies. Petersen et al (1988) assumed differences between verb generation and repetition were due to semantic processing only. However more detailed task analysis would include additional processes such as lexical search, attention, and willed action.

Secondly, the use of subtraction methodology has several pitfalls, especially when investigating higher cognitive functions such as language (see Methods, section 2.5.A). The main limitations are (i) implicit processing in baseline tasks due to the highly interactive nature of the system; (ii) extra processes modulating processing in the earlier process i.e. an interaction between the ‘active’ and ‘baseline’ task.

A further difficulty was that the focus of attention was placed on the ‘wrong’ regions. According to lesion studies, the perisylvian regions (e.g. superior temporal gyrus) are crucial to phonological processing, and the extrasylvian regions (e.g. inferior temporal gyrus) are crucial for intact semantic processing (see section 1.3). Early imaging studies, where visualisation of inferior regions of the extrasylvian cortex were compromised, focussed on perisylvian activation during semantic tasks.

Finally, the value of neuroimaging as a tool for understanding cognition and the brain has been criticised for being inconsistent. For example, in studies of phonological processing, doubts have been expressed about the validity of conclusions drawn because of early variability in location of regions thought to be involved in the same function (Sergent et al, 1992; Poeppel, 1996). However, as the experimental database expands, findings increasingly overlap, and provide new insights not only into which regions are involved in certain cognitive processes, but how these regions are involved (Fiez and Petersen, 1998).

1.4.C More Recent Imaging Findings
Since the early studies, imaging techniques have become increasingly sophisticated, due to factors such as increased sensitivity of cameras, wider field of view allowing greater brain coverage, the advent of fMRI, and development of more refined experimental
paradigms, with emphasis placed on more detailed task analysis. Increasingly convergent results have been reported concerning the regions implicated in the language system, providing support for theories involving a distributed system.

Several functional imaging studies have now shown a widely distributed network of mainly left-lateralised regions involved in language processing, involving both perisylvian and extra-sylvian regions (e.g. Wise et al, 1991; Demonet et al, 1992; Mummery et al, 1996; Pugh et al, 1996; Vandenberghe et al, 1996; Binder et al, 1997b; Price et al, 1997), despite employing several different semantic tasks (e.g. semantic categorisation; associative semantic judgements; semantic category fluency) and stimuli presented in several different modalities (pictures of objects; spoken words; written words). An example of the network of regions activated for several studies is shown in Figure 1.2. This depicts the left and right hemisphere in 3D, with regions of significant activation for semantic judgement (on words or pictures) versus visual size judgement (on words or pictures) shown in red/yellow. This task was subsequently adapted and used to investigate activation in patients with semantic dementia. It is described in greater detail in Chapter 8, section 8.3.

**Figure 1.2:** The common semantic network (for words and pictures) using a semantic associative task and PET (from Vandenberghe et al, 1996)

![Figure 1.2](image)

The general consensus on regions involved in semantic processing is now changing. The temporal regions are thought to be critical to semantic processing. In addition, it has been proposed that while regions of the prefrontal cortex are clearly activated for semantic
tasks, the function of these regions might be executive rather than the site of semantic memory (Thompson-Schill et al., 1997; Fiez, 1997). This point is discussed further in relation to our own findings in the general discussion (Chapter 10, section 10.4.B).

While such results have been groundbreaking in terms of delineating a system for semantic processing, we know from lesion data that the regions activated in such a network are differentially involved in specific types of language processing. What is needed is a resolution between the widely distributed network seen for tasks such as word generation, the multiple cognitive components involved, and the remarkably focal deficits seen in patients with lesions restricted to one part of that network. In order to address this issue, this thesis uses data from both patient and normal studies in parallel to converge upon a solution. Details of the studies are given in Sections 1.7.B and 1.7.C.

1.5 WITHIN SEMANTIC ORGANISATION

There is a vigorous ongoing debate in the neuropsychological literature over the internal organisation of the semantic system. Dissociations observed in patients have led to varying theoretical standpoints on the organisation of language processing, two examples of which are illustrated in Figure 1.3.

Figure 1.3: Models of two differential accounts of the organisation of language. Figure 1.3.A depicts the multiple semantic systems model (Beauvois, 1982). Figure 1.3.B depicts the single semantic system, as described by Riddoch et al (1988).

Figure 1.3.A
While there are several differences between these two models, the critical difference from the point of view of this thesis is that the semantic system is held to be unitary in the Riddoch et al (1988) model (Fig 1.3.B), whereas in Fig 1.3.A (Beauvois, 1982), the semantic system is multiple, consisting of a verbal and visual subsystem.

1.5.A Modality specificity

The modular systems seen in Figure 1.3.A were initially postulated to explain the modality specific deficits observed in patients. For example, Warrington and McCarthy (1987; 1994) have reported a series of cases whose degree of success on semantic tasks depended on the modality of presentation (pictures versus words). They postulated four different meaning systems i.e. visual and verbal systems for living things and artefacts, arguing that the relatively late acquisition of language results in a conceptual system for words that is distinct from object knowledge. This proposal is contested by other theorists, (e.g. Riddoch et al, 1988; Caramazza et al, 1990), who argue instead for a single, all-purpose meaning system, and interpret modality effects as arising either from selective deficits in pre-semantic input systems or from differences in the information inherent in pictures and words.

Support for the latter view comes from functional neuroimaging. Vandenberghhe et al (1996) found evidence for considerable overlap in the brain areas activated in semantic
judgements on words and on pictures, activating a common distributed set of left lateralised frontal and temporal regions for both modalities. The authors suggested that 'when primates acquired language, a pre-existing object-recognition system could have been adapted to attribute meaning to nouns'. As this thesis is based on experimental work utilising words as stimuli almost exclusively, this evidence for commonality across modalities is extremely important in terms of the generalisability of the findings.

1.5.B Category specificity
One of the most popular topics in neuropsychology, and one that has so far resisted all attempts to resolve it, is that of category specificity. The importance of this topic lies in the potential for explanation of the internal structure of semantic memory. I will now briefly review the theoretical positions held regarding category specificity.

Studies of patients with brain damage suggest that specific brain regions may be differentially involved in representing/processing certain categories of conceptual knowledge. It has been suggested, for example, that patients may have selective preservation of superordinate category information (Warrington, 1975), or that their understanding of abstract terms may be superior to that of concrete terms (Warrington, 1975; Warrington and Shallice, 1984).

1.5.B.1 Patient data supporting animate-inanimate dissociation
The most thoroughly documented conceptual distinction is between the domain of living things (including animals, fruits, and vegetables), on the one hand, and manmade artefacts (such as tools, household objects, vehicles, etc) on the other. There are now numerous reports of patients, most with bilateral inferomedial temporal lobe damage secondary to HSVE, with significantly impaired semantic performance on living things relative to artefacts (Warrington and Shallice, 1984; Basso et al, 1988; McCarthy and Warrington, 1988; Pietrini et al, 1988; Sartori and Job, 1988; Silveri and Gainotti, 1988; Farah et al, 1991; Hillis and Caramazza, 1991; Silveri et al, 1991; Funnell and Sheridan, 1992; Hart and Gordon, 1992; Sartori et al, 1993; De Renzi and Lucchelli, 1994; Damasio et al, 1996; Funnell and De Mornay Davies, 1996; Forde et al, 1997; Tranel et al, 1997). However, cases exist with the opposite pattern (i.e. a deficit for artefacts relative to living things: Warrington and McCarthy, 1987; Hillis and Caramazza, 1991; Sacchett and Humphreys, 1992; Tippett et al, 1996; Caramazza and Shelton, 1998).
1.5.B.2 Theoretical Accounts

Debate continues as to whether these category-specific effects reflect neural implementation of categories directly, or some more basic properties of brain organisation. Appendix 1 shows a schematic representation of the various explanations of semantic category-specific deficits (from Caramazza, 1998).

1.5.B.2.1 Categorical

The most transparent account suggests a categorical organisation of semantic information in the brain; that is, living things and artefacts might be so genuinely different that neural implementation of knowledge about the two domains is anatomically separated. This is reminiscent of the traditional neurological approach to functional specialisation, where dissociations are assumed to be due to separable neural substrates. For example, Caramazza and Shelton (1998) argue that there is an innate disposition for the recognition of animals and plants, a capacity essential to the survival of the species. As artefact recognition must depend on other (uncommitted) neural mechanisms, impairments involving non-living things arise as a secondary consequence of the innate specialisation for living things, not as a result of special representational requirements for artefacts (see also Laiacona et al, 1993).

There are problems with this model, however. In particular, it fails to address the issue of how artefact-specific deficits come about, with sparing of animate knowledge. It also fails to address the specific deficits certain patients have in types of knowledge, as opposed to category type (e.g. Silveri and Gainotti, 1988).

1.5.B.2.2 Reductionist

a) Artefactual

It has been suggested that the dissociation might reflect a bias in some variable (such as familiarity) that inherently favours everyday artefacts, and indeed not all of the apparent reports of a deficit for living things have survived stringent stimulus matching (Funnell and Sheridan, 1992; Sartori et al, 1994). There are however some compelling demonstrations of this dissociation based on careful stimulus selection. Furthermore, the existence of cases with the opposite pattern (see above) rules out any simple familiarity imbalance as an explanation of a selective living-things impairment. In addition, in the
Hillis and Caramazza case (1991), the identical set of test materials elicited opposing patterns of performance in different patients.

b) Emergent Property
An alternative and now more widely accepted account argues that there are substantial differences in the types of semantic features that constitute the core meaning of instances of these two broad categories. This school of thought owes more to the connectionist accounts of semantic organisation, e.g. Allport (1985), see Figure 1.4. In this type of account, the semantic system is thought of as a giant distributed net where certain regions tend to be specialised for different process types. In the example below, the representation of ‘telephone’ includes representation of the noise it makes, its sensory features, how it is used, where it might be found etc.

Figure 1.4: Allport’s (1985) model of the accessing of semantic representations in word comprehension.

![Diagram of semantic system](image)

Early protagonists of this view included Warrington and McCarthy (1987), who proposed that experience governing the acquisition of information has influenced the regions critical to retrieval of information about a concept, for example sensory features for animals, functional features for tools. If living things are distinguished primarily by their perceptual (mainly visual) features whilst artefacts are more specified by functional/associative attributes (how an object is used, where it is found, etc.), then the
observed category effects may result from selective disruption to neural regions specialised for these two types of featural information. Similar accounts, based on principles of distributed neural networks, focus on differences between the domains in degree and pattern of intercorrelation between different elements of our knowledge about an object (Devlin et al., 1998; Durrant-Peatfield et al., 1997; Gonnerman et al., 1997; McRae et al., 1997). These accounts propose that the semantic system is organised in terms of featural representation. For example, authors such as Small et al (1995) and Devlin et al (1998) showed that category specific effects can be produced by lesioning a network model of the semantic system involving no explicit categories, but featural description alone.

Much of the patient data supports such a view. For example, Farah and McClelland (1991) asked subjects to quantify the properties (visual or functional) that figured in dictionary definitions of living and man-made things. Visual descriptors featured more heavily in the definitions of living things (see also Gainotti et al., 1995; Garrard et al., 1998; Saffran and Schwartz, 1994; Warrington and Shallice, 1984). This formulation accounts for anomalies such as preserved knowledge of body parts in animate deficit (Saffran and Schwartz, 1994), a biological category where functional properties are salient, and poor knowledge of musical instruments and gems, two inanimate categories where sensory attributes are particularly relevant (e.g. Warrington and Shallice, 1984).

If the 'living things' deficit reflects a loss of perceptual knowledge, patients who demonstrate this pattern should have particular difficulty with the perceptual properties of objects. This has been investigated in a number of patients. Consistent with this conceptual division are reports of deficits in perceptual relative to associative knowledge (Silveri and Gainotti 1988). Moss, Tyler and Jennings (in press) investigated patient SE, an HSVE patient with a mild impairment on living things. Performance on a property judgement task was comparable to that of controls, with the exception of performance on perceptual properties of living things. SE was also tested using a priming paradigm, on tasks comparing the effects of visually and non-visually related primes, as well as unrelated primes, performing lexical decision for words representing living and non-living things. The patient’s priming data was similar to that of the controls, except for perceptual primes for living things, where the priming manipulation proved ineffective. However, there are patients whose performance is inconsistent with such accounts. For
example, Caramazza and Shelton (1998) found that a patient with category-specific deficits for living things was equally impaired with visual and functional attributes of living things, and equally unimpaired with both attribute types of non-living things.

Others suggest that the theoretical accounts proposed so far have been over-simplistic. Coltheart et al (1998) suggested that the different forms of selective semantic impairment may be classified into three general classes: semantic-category selective, modality-of-input selective, and semantic-attribute selective. They described a patient who was unable to access visual semantic attributes in semantic memory, whereas he could access semantic attributes relevant to other sensory modalities, and could also access non-perceptual semantic attributes, independent of modality of input and of semantic category. They suggested that their data supports an organisation of the semantic system where subsystems exist for perceptual-attribute knowledge, one for each of the different perceptual modalities, plus a subsystem where non-perceptual knowledge is represented, which in turn is categorically organised into semantic categories such as ‘animate’.

It is by no means clear at this stage whether these various explanations constitute mutually exclusive hypotheses about the conceptual basis of the category distinction, nor whether each leads to testable predictions about neuroanatomical differences underlying the effect.

1.5.C Localisation of lesions in category specificity

When one examines the localisation of lesions causing category specific deficits, the relationship between neuropsychological disorder and cerebral distribution of lesions shows some consistencies (for reviews see Saffran and Schwartz, 1994; Gainotti et al, 1995).

Impaired knowledge of animate categories compared to manmade artefacts has been reported in patients with substantial damage to the anterior inferior temporal lobes. The typical cause of the brain insult is HSVE (e.g. Warrington and Shallice, 1984; Silveri and Gainotti, 1988). Damage in such patients is usually bilateral and particularly affects the medial temporal regions (though lateral areas can also be affected). Animate specific deficit has also been observed post cerebral infarction. Damasio et al (1996) studied 30 patients with specific naming deficits and focal lesions, and showed that animal naming
was impaired by anterior ventral temporal lesions. Less commonly focal temporal lobe
degeneration has produced animate specific deficit (Basso et al, 1988; Breedin et al,
1994; Cardebat et al, 1996). However, disproportionate impairment on living things is not a consistent feature of the ‘semantic dementia’ syndrome, under which label these latter patients would fit. Damage in semantic dementia tends to be most severe in the infero-lateral parts of the anterior temporal lobe, with relative sparing of the medial temporal lobe. Animate deficits therefore tend to arise after focal damage to the anterior inferior temporal lobes, most consistently associated with more medial temporal lobe damage, and occur in a ‘selective’ context in that other language processes are relatively spared.

In contrast, impaired performance for inanimate objects has usually arisen through acute vascular insult. This tends to affect language areas of the left hemisphere extensively, especially fronto-parietal lobes, and is associated with a global or nonfluent aphasia. In other words, the cognitive impairment in these patients is usually relatively unselective (e.g. Warrington and McCarthy, 1987). There are two exceptions to this localisation: firstly Hillis and Caramazza’s (1991) patient, whose lesion involved the left temporal lobe and basal ganglia; secondly the patient group described by Damasio et al (1996), in whom impaired naming of tools correlated with posterior ventral temporal lesions extending to the temporo-occipito-parietal junction. These two studies showed a much more localised region of damage than usually described in such patients.

The localisation of lesions producing category specific deficits (animate deficits produced by bilateral anteromedial temporal damage and inanimate deficits produced by left temporo-parietal, and possibly frontal, lobe damage) supports some form of principled division within the semantic system. However, while this could take the form of regions specific to animate objects or to artefacts, the data could equally well be explained by damage affecting regions supporting sensory or functional featural representation in line with connectionist accounts of semantic organisation (Shallice, 1988). A direct test of these alternative hypotheses can be investigated at a systems level with functional neuroimaging.
1.5.D **Neuroimaging findings in category specificity**

There is now an accumulating body of neuroimaging data on the issue of category specificity. Several recent studies have shown differential activation for performance on tasks with different categories of objects in normal subjects. Results of these studies are summarised in Appendix 2 (see also chapter 4, section 4.1).

1.5.D.1 **Animate versus Inanimate**

The direct comparison of words or pictures denoting animate and inanimate objects while performing the same task has tended to produce small activation differences. Perani et al (1995) used a same-different judgement on pictures of animals and tools. Martin et al (1996) asked subjects to name pictures of animals or tools. Both Perani et al (1995) and Martin et al (1996) showed activation more for animate objects in medial occipital regions. Notably, these observations were seen in studies using picture stimuli rather than auditory stimuli with intrinsic word generation, or words presented visually, and it seems likely that some or all of this apparent discrepancy in outcome relates to presentation modality. Damasio et al (1996) combined functional and lesion data to examine regions differentially involved in naming pictures of animals and tools. In the activation study, they found more activation for animate objects in anterior ventral temporal regions, correlating with their lesion study (see section 1.5.C).

There is considerable consistency in the differential activation for inanimate more than animate across studies. Experiments employing either picture naming or verbal fluency for semantic categories have produced greater activation for artefacts in left posterior temporal or temporo-parietal areas (Damasio et al., 1996; Martin et al., 1996; Mummery et al., 1996; Cappa et al, 1998) and also in a left inferior frontal region (BA 44/6) (Grabowski et al., 1997; Martin et al., 1996; Cappa et al, 1998; Perani et al, 1995). However, a study by Perani et al. (1995), involving same-different judgements on pictures of animals or tools rather than a naming task, revealed left medial frontal activity for tools, but no posterior temporal locus (see Appendix 2). Martin et al (1996) found a similar medial frontal region was more active for animate objects relative to inanimate objects.
1.5.D.2 Perceptual versus associative/functional knowledge

Even fewer studies have examined differential activation for the type of knowledge retrieved about a concept. This is obviously an important topic, given that the current balance of theoretical opinion favours functional segregation of types of knowledge rather than categorical representation. The studies that have examined this are represented in Appendix 3. Martin et al. (1995) asked subjects to imagine either a perceptual attribute of an object (its colour) or a functional attribute (the object’s typical action). The ‘perceptual’ condition produced enhanced activation in the ventral temporal lobe (left lateralised when stimuli were words, bilateral when pictures were used) while the ‘functional’ condition revealed increased activity in the left posterior middle-temporal region. Vandenberghe et al (1996) compared real-life size and associative knowledge, and found no significant differences. In addition to the study described in Chapter 4, one other study has examined differences due to both category and type of knowledge in the same experiment (Cappa et al, 1998). Cappa et al (1998) compared visual knowledge for words denoting animals and tools to a letter detection control task for pseudo-words. They found that differences seen for type of knowledge retrieved were more prominent than those seen for category. Specifically, living versus nonliving activated the right middle frontal gyrus and right fusiform gyrus; nonliving versus living activated the left inferior temporal cortex (BA 21/37), left supramarginal gyrus, right superior temporal gyrus and right thalamus. Visual versus associative judgement activated bilateral brain regions including the supramarginal gyrus, middle frontal gyrus, precentral gyrus, inferior temporal cortex (BA 37/20) and anterior cingulate. Associative versus visual judgement activated the posterior cingulate cortex.

It is worth commenting that, in the literature on both selective category deficits in patients and regional brain activation in normal individuals, there are often substantial differences between studies in the nature of stimulus materials, tasks, or both. Such diversity is not surprising, and indeed should eventually assist progress towards a full characterisation of the relevant phenomena; but at present, when so little of the experimental parametric space has been explored, these major differences tend to impede neat comparisons and summaries. As noted above, many of these studies were performed using pictures. It is obviously important to examine the semantic system using words, as picture stimuli may lead to pre-semantic differences in processing causing differential activation that is not
directly due to semantic processing. The studies described in this thesis have therefore always used words as stimuli, either instead of, or in addition to picture stimuli.

1.6 THE RELATIONSHIP BETWEEN SEMANTIC AND EPISODIC MEMORY

In section 1.1, the perceived dichotomy between episodic and semantic memory was described. This is not, however, a generally accepted fact, but rather a theoretical standpoint, adhered to by some (e.g. Tulving, 1972) but contested by others. According to some theorists (Baddeley, 1976, 1992; Cermak, 1984; Squire and Knowlton, 1995), semantic memory is merely an overlearned episodic memory, which has become context free. In other words, the two subtypes are seen by some as extremes of one spectrum of information acquisition. However, the existence of patients with impairments in either episodic or semantic memory alone argues that the two systems are at least partially separable on neuropsychological grounds. Patients with a specific deficit in semantic memory provide one dissociation (Warrington, 1975; Snowden et al, 1989; Hodges et al, 1992). The existence of patients with the reverse finding, i.e. isolated impairment in episodic memory with preserved semantic knowledge (Scoville and Milner, 1957; Vargha-Khadem et al, 1997) completes the double dissociation, making the 'separability argument' much more convincing (Tulving and Markowitsch, 1998).

The picture is of course more complicated than a simple division between these two types of long term memory. It has often been noted anecdotally that patients with selective deficit in semantic memory frequently refer to self-relevant information when attempting to retrieve semantic information. For example, when asked to define 'dog' a patient might reply 'dog...dog... I walk it every morning'. Such statements suggest an interaction between semantic memory and autobiographical memory. The nature of such an interaction is under debate (see Snowden et al, 1995, 1996; Hodges and Graham, 1998).

Recently, evidence has accumulated supporting an alternative dichotomy in long-term memory. Interest is developing as to whether memories for personal events differ from public events in terms of representation or organisation (Baddeley, 1992). The concept of autobiographical memory has been introduced to refer to personally relevant memories, which may be further divided into personal episodes (what did you do last Christmas) and personal semantics (whether you are married or not) (Kopelman et al, 1989).
First, I will briefly examine the lesion data evidence on episodic versus semantic memory deficit. At first glance there is considerable consistency in localisation of lesions. Patients with medial temporal lobe damage, in particular involving the hippocampal formation, show selective episodic deficits (e.g. Scoville and Milner, 1957; Vargha-Khadem et al, 1997). Patients with lateral damage appear to suffer more from semantic deficits (Hodges et al, 1992; Snowden et al, 1996). A recent review (Nadel and Moscovitch, 1997) has examined the existing data on autobiographical memory, public events, personal and general semantics, and concluded that within the temporal lobe, medial lesions and lateral lesions are associated with differing deficits, the medial lesions causing more severe deficit on autobiographical memory. However, direct comparison of the two subtypes of long term memory is remarkably sparcely represented in the literature, and when it has been examined (e.g. De Renzi et al, 1987) the self relevance and temporal specificity of memory have often been confounded. As a consequence, the instantiation of self-relevant and nonself relevant memory, and episodic and semantic memory at a neural level is as yet unclear (Nadel and Moscovitch, 1997).

To summarise, it seems that a full theoretical understanding of long-term memory will have to incorporate consideration of the interaction between episodic and semantic representations, and the importance of self-relevance. As yet, there has been little functional data examining such an interaction.

1.7 RESEARCH RATIONALE AND SPECIFIC HYPOTHESES

1.7.A General Aims of Thesis

Previous research on semantic memory has focussed on two broad issues:

a) theoretical psychological questions, such as the relationship between semantic and other language functions, the relationship between semantic and episodic memory, the internal structure of semantic memory;

b) more neurological issues, such as the neural basis of semantic memory and its disruption in disease processes.
As can be seen from the brief review of the literature on semantic memory, while we have come a long way in the attempt to understand the organisation of semantic processing, the data has engendered many more issues and hypotheses than it has resolved. It would be naïve to attempt an integration and resolution of these issues in a doctorate thesis. I have therefore chosen to focus on one methodology to investigate the organisation of the semantic system, namely functional imaging, in an attempt to address questions such as category specificity and interaction with other cognitive systems in a more direct way. Secondly, I will use varying experimental paradigms to highlight critical regions in semantic processing. Neuroimaging can add to the debate concerning language and memory organisation, by revealing the interactions and interdependence of brain regions, as well as the functional dissociability of functions in normals and patients (Price et al, 1998; Nobre and Plunkett, 1997).

As described above, many of the early imaging studies investigating language found a wide network of regions activated and were unable to disentangle the specific roles of such regions with the tasks used, despite psychological studies showing convincing dissociations. However, the increased sophistication of both imaging techniques and experimental paradigms have created the possibility of fractionating complex cognitive processes. In a multidisciplinary approach, one hopes to overcome the limitations of each type of methodology by combining several types, using convergence of findings to increase the probability of accuracy.

This thesis firstly uses functional imaging to explore the relationship between semantic memory and other functions, and the internal organisation of semantic memory. By comparing the findings in normals and patients, the aim is to show the neurophysiological changes underlying the disruption of semantic processing.

1.7.B. Study of semantic processing in normals
The initial aim of this thesis was to study the neural substrates of semantic memory in normals, converging upon common semantic areas in the brain. Chapters 3 to 6 explore four different types of dissociation prevalent in the neuropsychological literature.
1.7.B.1 Within semantic organisation

Building on the dissociation that has been found between performance on letter and category fluency using selective interference tasks (Martin et al., 1994), Chapter 3 used positron emission tomography in a group of normals to test the hypothesis that ‘semantically driven’ category fluency and ‘phonologically driven’ initial letter fluency would be more reliant on temporal and frontal lobe regions respectively. Secondarily, this study investigated whether retrieval of animate and inanimate object names would involve different regions of the word retrieval network. A key finding described in Chapter 3 was that there was differential activation for animate and inanimate name retrieval within the temporal regions activated more for semantically driven fluency. Chapter 4 tests the specific hypothesis that this difference could have been due to differential weighting on sensory and associative attributes of these concepts, rather than modular neural instantiation of categories per se. We directly examined the regional activation seen for animate and inanimate categories, and for sensory and associative attributes of these object categories.

While Chapter 4 showed an extensive network of regions involved in semantic processing, consistent with previous data, both Chapters 3 and 4 used explicit semantic tasks. It is important to distinguish between regions involved in explicit access to semantic memory, and those involved in implicit access. Regions activated in an explicit task and not an implicit one could be involved in the voluntary retrieval of information, rather than semantic processing per se. Regions commonly activated for both explicit and implicit tasks should be involved in semantic processing itself, or the semantic store. Experiment 5 therefore used an implicit measure of semantic processing, semantic priming, and found that the anterior and inferior temporal regions were activated for lexical decision, suggesting semantic involvement. Further, the temporal pole was sensitive to semantic priming, suggesting a ‘first pass’ at semantics, or initial concept identification might occur in this region.

1.7.B.2 Semantic and Episodic interaction

As discussed earlier, semantic memory is not a process in isolation. It is heavily interdependent on other language and memory processes. The existing literature suggests that certain regions are important for both semantic and episodic memory, while patients show dissociations between the two memory types. Chapter 6 therefore directly examined
the independence and interaction between these two forms of long-term memory, and further examined an alternative dichotomy; that of self-relevant and non-self relevant memory.

The primary findings from this study were firstly the degree of commonality in the memory retrieval network, and secondly the functional division between adjacent brain regions. For example, the lateral anterior temporal lobe and parahippocampal gyrus were activated for memory retrieval regardless of type, whereas the temporal pole showed modulation of activation by self-relevance, and the hippocampus was activated most strongly for self-relevant context-specific memories. The findings are discussed with respect to their consistency with current models of long-term memory.

1.7.C Study of the disruption of semantic processing in patients

The second section of this thesis relates the findings in normals to patients with a selective semantic deficit. The use of patients in neuroimaging is fraught with difficulty. Many patients become excessively anxious, and are unable to tolerate the procedure; individual patients will use different strategies in order to perform a task, limiting the usefulness of examining individual subjects. The most important limitation to bear in mind however, is the ability to perform a task involving the cognitive component of interest. In neuropsychological terms, a patient is of interest when they demonstrate a selective deficit. In neuroimaging terms, that patient is not of interest unless they can perform a task that will tap a network of regions including those involved in the selective deficit. An example would be a patient with a category specific deficit in naming, but who can read the names of the same concepts normally. Imaging such a patient while reading would yield interesting information on naming, because both reading and naming activate overlapping regions in normal subjects due to common cognitive processes.

With the constraint that performance of a task is relatively normal (to exclude the possibility that abnormal activation reflects abnormal performance), the types of patients that are of interest are:

(i) Those who can perform a task despite damage to parts of the system involved in normals. This may be due to peri-damage activity, reorganisation at a cognitive or neural level, or as a result of the damaged region being unnecessary for task performance.
(ii) Those with selective preservation of a particular function. In such a case, the patient would perform the preserved function, and one would examine which systems continue to function normally.

(iii) Activation led patient selection in order to examine the effects of lesions on other intact regions.

The type of patient appropriate for scanning is therefore rather limited. The ideal situation would be to investigate a group of similar patients with a focal deficit in a complex network such as the semantic system, and intact functioning otherwise. Examining the group circumvents (to a degree) the issue of individual strategy use, and increases the generalisability of results. The group of semantic dementia patients studied here fit such a description. More prosaic difficulties exist with imaging patients, such as difficulty with normalisation, the importance of lowering the grey matter threshold so as not to exclude atrophied regions in the patients, and so on. These are discussed in Chapter 2 (General Methods, sections 2.4.C and 2.4.D).

In summary, the study of patients can provide information on the abnormal functional anatomy in patients, and on normal functional anatomy. While there are important caveats, such as the ability of a patient to perform a task, appropriate experimental design and patient selection can allow the examination of abnormal regional responses and, when used in conjunction with neuropsychology, enable the identification of regional function within the normal cognitive network.

1.7.C.1 Structural analysis in semantic dementia

Chapter 7 involves the use of voxel-based morphometry (Wright et al, 1995) to establish the significant structural deficits in patients with semantic dementia relative to a group of age-matched normals. The degree of neuronal atrophy is then correlated with the cognitive deficit. Semantic deficit is found to correlate with anterior-inferior temporal lobe atrophy, but not with ventromedial frontal lobe atrophy, confirming the importance of the anterior temporal lobe in semantic processing.

1.7.C.2 Functional analysis in semantic dementia

Chapter 8 develops this theme, examining the performance of these patients on a task known to activate the semantic system extensively during PET scanning. A major finding
here is that while much of the network is activated by both normal subjects and patients, a region distant to the damage is not activated in any of the patients, despite the region being structurally intact, at least macroscopically. A possible mechanism for this, and the proposed association of this result with the severe anomia found in these patients are discussed. Secondly, the anterior temporal lobe shows enhanced activation in the patients, despite significant atrophy in this region and an associated decrease in regional cerebral blood flow. Possible reasons for this finding are posited. Finally, both normal controls and semantic dementia patients activated the frontal lobe.

1.7.C.3 Investigation of the necessity of the frontal lobe in semantic processing
Chapter 9 investigates the necessity of frontal lobe activity in semantic tasks further by examining a patient with frontal lobe damage on the same task. It is demonstrated that the semantic task can be performed without activating the frontal region observed in the semantic dementia patients and the control subjects. These findings support the hypothesis that this region is involved in executive processing rather than semantic processing per se.

1.7.D General Discussion
The general discussion considers the above findings as a whole and attempts to integrate them in terms of critical or ‘convergence’ regions within the distributed semantic network, and in terms of how patient data can inform normal studies and vice versa. Limitations and future research directions are suggested.
Chapter 2
General Methodology

2.1 INTRODUCTION
This chapter provides an overview and background for the methodology involved in the subsequent experimental chapters. Common to all studies is the use of statistical parametric mapping (SPM); common to most is the use of volunteer subjects. Recruitment and population are first described followed by a section on the general methodology of positron emission tomography and the analysis used on the images obtained. Methodology specific to each chapter is described therein.

2.2 SUBJECTS
2.2.A Normal Volunteers
Volunteers were recruited for each study via either personal contacts or advertisement within the university. All volunteers had to satisfy certain criteria for inclusion in the studies. All were fit, healthy, on no medication and free from any history of neurological or psychiatric illness. All had English as their first language, and were strongly right-handed on the Edinburgh Handedness Inventory. Each gave informed, written consent prior to participation. Travel costs only were paid as reimbursement.

2.2.B Patients
Patients were recruited either from local hospitals or from the group undergoing study with Prof. John Hodges and Dr. Karalyn Patterson at the Applied Psychology Unit, Medical Research Council, Cambridge. All semantic dementia patients (Chapters 7 and 8) underwent clinical examination and a battery of psychometric tests to establish diagnosis, fitting the criteria for semantic dementia proposed by Hodges et al (1992). Further details are given in chapter 7 (section 7.2) of their demographics and performance on psychological testing. Patient SW (chapter 9) was recruited from Charing Cross Hospital, and had been extensively investigated prior to involvement in this study, having had a large middle cerebral artery infarction 5 years earlier. He completed a further battery of psychological tests just prior to scanning, to ensure his performance was adequate for the task.
2.3 ETHICS APPROVAL

All imaging studies were approved by the Administration of Radioactive Substances Advisory Committee (Department of Health) and the research ethics committee at the National Hospital for Neurology and Neurosurgery.

2.4 POSITRON EMISSION TOMOGRAPHY METHODOLOGY

2.4.A Rationale

Positron emission tomography (PET) was used in all of the studies (with the exception of Chapter 7) to investigate brain-behaviour relationships in both normals (Chapters 3, 4, 5, 6) and patients (Chapters 8 and 9). The technique takes advantage of the unique characteristics of positron-emitting radioisotopes. When positrons are emitted and collide with electrons, both are annihilated, creating two high-energy photons that travel at 180° in opposite directions. If both photons are sensed by detectors, then a line of origin for the annihilation can be established, allowing mapping of the distribution of annihilations by computer. In these studies, [\textsuperscript{15}O] water was used to measure cerebral blood flow. \textsuperscript{15}O is a radioactive atom with a half-life of 2 minutes. It is injected intravenously in the form of H\textsubscript{2}\textsuperscript{15}O; the oxygen radionuclide enters the bloodstream; the radioactivity that enters the brain is therefore proportional to cerebral blood flow. As it decays, it emits positrons, measured by detectors arranged around the head.

Each study involved the administration of <5 mSv effective dose equivalent of radioactivity per subject. For each scan, subjects received a 20s intravenous bolus of 8-10mCi of H\textsubscript{2}\textsuperscript{15}O at a concentration of 55 Mbq/ml and a flow rate of 10 ml/min through a forearm cannula. After a delay of approximately 40 seconds tracer reaches the cerebral circulation and the head counts peak about 10 seconds later (depending on individual circulation time). It is important to note that after a bolus injection, the radioactivity detected in the brain occurs as a linear function of regional cerebral blood flow (rCBF) (Collins, 1991; Frackowiak, 1989). When tissues of the brain are activated or are involved in increased neuronal function, a local increase in blood flow (rCBF) is demonstrable within seconds. Increased rCBF is thus a reliable indicator of increased neuronal activity in response to increased local demands from a given stimulus (Fox and Raichle, 1986). Measurement of rCBF therefore provides a tool with which to assess sites
of increased or decreased cerebral activity that occurs with cognitive activation. As blood flow changes correlate with the activity of energy dependent sodium pump mechanisms (Mata et al, 1980), blood flow changes are localised largely to synaptic junctions. Alterations in rCBF can therefore be interpreted to reflect local synaptic activity.

A low radioactivity dose is achieved with each bolus injection, so a sequence of scans may be carried out in each subject without exceeding radiation safety limits. Repeat measurements of rCBF in the same subject provide a powerful tool for comparing blood flow during differing cognitive activation tasks or with rest. During the studies described in this thesis, each subject underwent 12 PET estimations of brain activity over approximately 2 hours. The interval between successive $H_2^{15}O$ administrations was 8-10min (the interval was constant for each study, but varied between studies due to improvement in acquisition technique in the latter studies).

### 2.4.B Data Acquisition

Measurements of regional cerebral blood flow (rCBF) were obtained using a Siemens/CPS ECAT Exact HR+ (962) scanner with a total field of view in the z axis of 15 cm. Data acquisition was performed in the 3D mode, with the lead septa between detector rings removed. Data were acquired in one 90s scan frame (Silbersweig et al., 1993), beginning when the rising phase of the head curve reached four times the background counts. Behavioural tasks in each study were commenced 15s before the arrival of bolus in the brain and were continued during the 30s uptake phase and for 15s during the washout phase. Correction for attenuation was made by performing a transmission scan with an exposed $^{68}Ge$/$^{68}Ga$ external source at the beginning of the study.

Images were reconstructed by filtered back projection (Hanning filter, cut-off frequency 0.5Hz), giving a transaxial resolution of 6.5mm full width at half maximum (FWHM). The reconstructed images contained 128 x 128 pixels, each 2.05 x 2.05 x 2.00mm in size. The distribution of rCBF in the brain was indexed by the accumulated counts over the scanning period, which reliably reflects blood flow in the physiological range (Fox and Mintun, 1989; Mazziotta et al., 1985).
2.4. C Data Processing

Once a time-series for each subject had been acquired, the data were analysed with statistical parametric mapping (using SPM96/97 software from the Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab (Mathworks Inc, Sherborn, Mass, USA). Statistical parametric maps (SPM) combine the general linear model and theory of random Gaussian fields to make statistical inferences about regional effects (Friston et al, 1995a).

Voxel-based analyses require the data to be in the same anatomical space. The initial step was to remove movement-related variance components for each subject by estimating movement relative to the first scan and realigning the scans post hoc using these estimates. Data must also derive from homologous parts of the brain. Therefore, following realignment, all images were transformed into a standard space (Talairach and Tournoux, 1988), using a series of spatial transformations to move and 'warp' each scan until they conform to a reference template image that matches the standard space (Friston et al 1995b). For all bar the first study, these transformations were computed on the basis of co-registered high resolution anatomical MRI scans for each individual. In the first study, the transformations were computed on the basis of coregistration to a standard MRI template. As a final preprocessing step, images were smoothed with a Gaussian filter of 16mm. This had the effect of increasing signal to noise. It also ensured that haemodynamic changes from subject to subject were assessed on a spatial scale at which homologies in functional anatomy are typically expressed.

Of note, in patients the normalisation process can be difficult. Standard normalisation copes well with relatively mild atrophic deficits, such as those in the semantic dementia patients described in Chapters 7 and 8. However, in patients with extensive structural deficits, such as SW (chapter 9), the normalisation of the remaining viable tissue can be inaccurate. To circumvent this problem, PET and MRI data for SW were normalised using a nonlinear warping technique. This successfully prevented the remaining brain areas of interest being warped to 'fill' the deficit caused by the infarct.

2.4.D Statistical Analysis

Statistical parametric mapping (SPM) refers to the construction of spatially extended statistical processes to test hypotheses about regionally specific effects. SPMs are image
processes with voxel values that are, under the null hypothesis, distributed according to a Gaussian distribution. The physiological response in each condition is estimated using the general linear model and standard least squares, resulting in a parameter estimate (Friston et al 1995a). To test hypotheses about regionally specific condition effects, these parameter estimates are compared using linear compounds or contrasts. Each voxel is analysed using a univariate t-test; the resulting statistical parameters are assembled into an image – the SPM. Unlikely excursions of the SPM are interpreted as regionally specific effects, attributable to a cognitive process that has been manipulated experimentally. The significance of each contrast is assessed with a statistic whose distribution has Student's t distribution under the null hypothesis. The resulting set of voxel values for each contrast constitutes an SPM of the t statistic (SPMt). The SPMt values are transformed to the unit normal distribution (SPMZ). Statistical inferences are then made about local changes in the SPM(Z) above a specified threshold.

In this series of experiments, if an a priori hypothesis specified which regions would be activated for a given cognitive process, the threshold used was p<0.001 (uncorrected for the number of comparisons). If no a priori hypothesis was specified in terms of regional activation, a threshold of p<0.05 (corrected for the number of comparisons) was used. Specific hypotheses are listed in the individual experimental chapters.

In order to remove the potential confounding effects of global cerebral blood flow, a subject-specific ANCOVA was used as a covariate of no interest in each experiment. Any additional covariates of no interest, such as order effects, that were factored in will be discussed in the appropriate chapters.

A second special case in patient studies occurs at the analysis stage. This concerns the grey matter threshold used when excluding voxels for analysis. In normals, this is usually set at 80% (i.e. all voxels with less than 80% normal blood flow are excluded) in order to exclude regions of white matter and extracranial space from the analysis. However, in regions of atrophy or in peri-infarct areas, blood flow may be reduced, but the region may still be active. Therefore a threshold of 50% was used for both groups of patients in this thesis. Altering the grey matter threshold does not alter uncorrected p values, but because there are more voxels included in an analysis, inference becomes more conservative when the correction for number of comparisons is applied (chapters 8 and 9).
2.5 CATEGORIES OF EXPERIMENTAL DESIGN

Several forms of analysis were performed in the experimental chapters, which will now be described. Use of these allows testing for a variety of different effects.

2.5. A Eigenimage analysis

This is a method for segregating patterns of correlated activity and depicting the amount these patterns contribute to the variance-covariances observed in the imaging data. In other words it is a descriptive measure of functional connectivity, and characterises the activations in terms of distributed brain systems (Friston, 1994). Functional connectivity is defined as the temporal correlations between remote neurophysiological events. The imaging data from each scan is decomposed into a series of orthogonal patterns that show (in a top-down fashion) the greatest amounts of functional connectivity. Any voxel in which activity showed variance at $p<0.05$ (uncorrected) was entered into a principal component analysis, forming a series of orthogonal vectors (eigenimages). These represent the distributed systems that best account for the observed variance-covariance structure exhibited by the neurophysiological data. The post hoc functional attribution of these eigenimages is usually based on their condition-dependent profiles. It is important to realise that this is a descriptive analysis only. Such procedures make no comment on the significance of the resulting spatial modes. However, they are an extremely effective way of characterising the data with minimal bias introduced, and allow an initial investigation of the successful differentiation of conditions (for example, see chapter 3, section 3.3.A).

2.5. A Subtractive Analysis

This method of analysis initially underpinned all PET experiments, for example Petersen’s pioneering study of single word processing (1988), and is still widely used today. All the experimental chapters presented here rely on the subtraction technique to some extent. Essentially, the regional cerebral blood flow (rCBF) in one task is subtracted from the rCBF in another, producing a pattern of relative increase in rCBF for a particular contrast of conditions. This method assumes that the difference between two tasks can be formulated as a separable cognitive component and that the regionally specific differences in brain activity identify the corresponding functionally specialised area (see Figure 2.1). This is a powerful approach, but depends on the assumption that
cognitive states differ in components that can be purely inserted or removed with no interaction between them, both at the level of a function and its neural implementation. It is therefore limited, unless used with other forms of analysis.

2.5.C Conjunction analysis
This is an extension of the above technique, in that it combines a series of subtractions (Price and Friston, 1997a). Several hypotheses are tested asking whether all the activations in a series of task pairs are jointly significant. This is particularly useful when investigating the activations for a particular task that were common to all subjects. This method is also useful when it is desired to identify regionally specific activations due to a particular cognitive component. A series of task pairs are identified which share a common difference, and the region which activates in all the corresponding subtractions can be uniquely associated with the component in question (see Figure 2.1). This method was used in Chapters 8 and 9, where we wished to identify only the regions of activation that were common to all of the patients and normals (Chapter 8, section 8.3) or all of the normals in conjunction with patient SW (Chapter 9, section 9.3).

2.5.D Factorial Analysis
Here two or more factors are combined in the same experiment. The effect of one factor on the effect of the other is assessed by the interaction term. Two factors interact when the level of one factor affects the effect of the other factor (see Figure 2.1). This method has proved particularly useful when examining closely related functions, for example phonological retrieval and object recognition (Price et al, 1996). This form of analysis was used in Chapter 6 (section 6.3) to assess the effect of self-relevance on context-specificity; Chapter 8 (section 8.3) to assess the interaction between subject group and task effect (that is which areas were more active for semantic versus visual task in the normals than in the patients and vice versa), and again in chapter 9 (section 9.3) for the same reason in the patient with frontal lobe damage.

2.5.E Parametric Analysis
Parametric approaches test for systematic, monotonic relationships between neurophysiology and cognitive parameters. These systematic relationships are not constrained to be linear or additive and may show very nonlinear behaviour, reflecting complex interactions at a physiological or cognitive level. In this way, the cognitive
process is not tested as a categorical invariant, but as a dimension that can be expressed to a greater or lesser extent.

To look explicitly at linear and nonlinear functions, first and second order polynomials are used as covariates of interest, and the resulting SPM(F) map displays all areas showing significant variance correlating with these covariates either singly or in combination (Buechel et al, 1996). This technique was used in the analysis of Chapter 5 (section 5.2; 5.3) to examine the variation in activity caused by varying the amount of priming in a lexical decision task. The advantage of such a technique is that the type of variation (linear or nonlinear) assessed is not experimenter-biased, and obviates the need for a control condition, with its attendant disadvantages.

**Figure 2.1:** Diagrammatic representation of three types of analysis.

1. **Subtractive analysis**

   - Active
   - Control
   - Active − control → rCBF changes for cognitive component B

2. **Conjunction analysis**

   - Task Pair 1
   - Task Pair 2
   - Task Pair 1 → BC; Task Pair 2 → DE
   - Conjunction of the two → rCBF changes for cognitive component B

3. **Factorial analysis**

   - Object recognition
   - + TASK A TASK B
   - - TASK C TASK D

   - Phonological retrieval
   - Interaction ie (A-C) − (B-D) = effect that phonological retrieval has on object recognition.
2.5. F Covariate Analysis

In addition to the use of covariates for parametric analysis, it is possible to specify various covariates in the design matrix. These may be of interest, e.g. variation in activity with variation in performance, or correlation of age with activation. Often the converse is used, i.e. a variable is specified as a covariate of no interest in order to remove it as a confound (for example, order effects). In most study designs, this is not crucial due to task counterbalancing, but is important in some studies where the effects being looked for are subtle, and one wishes to ensure that order, or some other variable, is not a confound.

Examples of the use of covariates in this thesis include the following: In Chapter 3, there was a large degree of individual variability in the number of responses produced across subjects, so this was removed as a confound by specifying the number of responses as a subject specific covariate of no interest (section 3.3). In Chapter 5, the possible effect of order was counterbalanced for in the experimental design as much as possible, but as complete counterbalancing was not possible due to the number of conditions and subjects, order was used as a confounding covariate (section 5.3). In Chapter 8, I ensured that the differences reported were not just due to variability in performance (section 8.3) by performing a covariate analysis with performance as a covariate of interest. In all studies, global cerebral blood flow in each scan is used as a covariate of no interest, as a subject specific ANCOVA, in order to minimise erroneous findings due to individual variability in blood flow.

2.5. G Subject specific Analysis

Most PET studies involve group analysis, pooling over the individual responses to show a group effect. However, on occasion it is important to look at the individual responses. This is particularly the case in patient studies, when one wishes to know how each patient conforms or deviates from the normal pattern. In a group patient study (Chapter 8), the normals are analysed as a group, and the patients as individuals. This enables identification of the regions each patient activates or fails to activate relative to normals. In a single patient study (Chapter 9), the normals are analysed as individuals as well as the patient, and any activation specific to the patient was reported only when the patient differed from each of the normal controls.
2.6 DISPLAY OF RESULTS / TABULATION

All tabulated PET results refer to Talairach and Tournox coordinates (1988) for the voxels with the peak Z score within a particular activated region. In addition, the precise location of these local maxima have been verified by examining the averaged MRI of the subjects participating in the experiment (possible in all experiments except Chapter 3), and by using the Mai atlas (Mai et al, 1998) as well as the Talairach and Tournoxi atlas (1988). The corresponding Brodmann areas (BA) are given where possible. These can only be approximate, as the exact distribution of cytoarchitectonic zones in any individual is not known.

2.7 MRI STRUCTURAL ANALYSIS

In chapters 7 and 9, voxel based morphometry is used to describe the structural differences in grey matter between patients and normals in order to examine more precisely the significant alterations in macroscopic structure associated with disease. This technique was first described by Wright and colleagues (1995). It applies methods derived from functional imaging to convert structural MRI data into spatially normalised images of grey matter density, and to make inferences about the differences between normals and patients in a regionally specific and quantitative fashion. This method has several advantages over manual quantitative techniques in that it is non-operator dependent, can be utilised in vivo, is non-invasive, can be used for serial measurement, allows statistical comparison of atrophy with normal subjects, and permits description of changes at a gyral level.

For each subject (14 age-matched normals, 6 semantic dementia patients in chapter 7; one patient post-infarction in chapter 8), a T1 weighted high-resolution MRI scan was obtained, using a 2.0 Tesla vision system (Siemens GMBH, Erlangen, Germany) with 3D gradient echo sequence. The image dimensions were 256x256x256 voxels. The voxel size was 1x1x2 mm. Images were re-sampled to give a voxel size of 1.5x1.5x1.5mm. Resultant images obtained were normalised into standard Talairach and Tournoxi space in SPM98 using standard methods (Friston 1995a, 1995b; see section 2.6). They were then segmented into grey matter, white matter, CSF and scalp; the grey matter images were smoothed with a Gaussian filter of 12 mm (FWHM) to ensure that individual gyral variation in anatomy did not cause false positive results. After smoothing, grey matter
density for each patient was compared to the mean grey matter density for the control group at each voxel using statistical parametric mapping (SPM97) as previously described by Wright et al (1995).

2.8 behavioural statistical analysis
Reaction time data was collected for the studies described in Chapters 4, 5, 8 and 9. In each case, analysis was performed using the statistical package Statview (Abacus, ISI Institute, San Francisco, CA). Interactions between group/subject and cognitive task were analysed using ANOVA, and if a significant interaction was found, this was further analysed with post-hoc Schaeffer analysis. Statistical methods specific to chapters are described in more detail where relevant.

2.9 methodological issues in pet scanning
There are a number of limitations of this technique that must be borne in mind if the results are not to be misinterpreted (Sergent, 1994).

2.9.1 small blood flow changes
The changes in rCBF associated with activation of higher order cognitive functions are only approximately 2-5% change in blood flow compared with a 25% change in blood flow to primary motor and sensory cortex in response to functional activation (Fox and Mintun, 1989). This necessitates attempts to increase the signal-to-noise ratio by averaging rCBF maps across individuals for each of the series of stimulation tasks associated with a given behaviour. The maps are then subjected to formal statistical comparisons of activation tasks. The maps generated are “statistical parametric maps” (SPM technique; Frith et al, 1991).

2.9.2 numbers of subjects
A general issue in PET scanning is the small number of subjects that are used to investigate the experimental hypothesis. While this is important, the critical factor is the number of degrees of freedom. This is decided by the number of scans per condition, but weights the variance to within subject rather than between subject. However, ideally, the
use of large numbers of subjects would increase signal to noise and gives results that can be generalised.

2.9. C Limited spatial and temporal resolution
PET measures blood flow on a scale of about 6mm and 30 seconds. Due to the relatively long half-life of the tracers used, PET can only measure responses summed over fairly long periods of time, so can only be used to measure differences between brain states. In cognitive processing terms, where reading occurs over a time span of under 100msec, one therefore needs to administer a series of stimuli every few seconds, with repetition of the same cognitive processes multiple times during the course of one minute. The resultant blood flow changes therefore represent the integration and accumulation of multiple stages of processing of multiple stimuli.

Localisation is limited by the degree of smoothness of data – we have used a standard 16mm filter in order to minimise the potential confound of individual gyral variation. However, this obviously will limit localisation accuracy for a particular maximum to within approximately 10mm. For all of the studies described here, bar the first, subjects underwent a structural MRI in addition to the PET study. This was used to coregister individual anatomy to the PET data, as described below, allowing increased confidence in terms of localisation of regional activation.
Chapter 3

Dissociation between left temporal and frontal lobe function in word retrieval. Initial findings on functional correlates of category specificity

3.1 INTRODUCTION

The study of semantic memory in functional neuroimaging has been plagued by the difficulty in segregating semantic from phonological processing (see Price et al, 1997). However, neuropsychological data have shown that such processes are often dissociated in patients. This study attempted to dissociate these processes using a word retrieval task.

A benchmark test in neuropsychological testing is the capacity to retrieve words in response to verbal prompts, i.e. verbal fluency. A patient is asked to think of and articulate as many words as possible beginning with a certain letter (e.g. 'F') in initial letter fluency, or as many words as possible belonging to a particular category (e.g. 'land animals') in category fluency. This test is commonly used to examine frontal executive function (McCarthy and Warrington, 1990), and in this capacity it is considered sensitive to lesions of the left dorsolateral prefrontal cortex (Milner, 1964).

However, more detailed analyses of cued word retrieval have distinguished between initial letter and category fluency. The former seems to be more sensitive to pathology that affects either the frontal lobes or their subcortical connections, such as Huntington’s disease or Parkinson’s disease. In contrast, category fluency is relatively more impaired when the pathology involves predominantly posterior association cortex, for example in Alzheimer’s disease (DAT) (Martin and Fedio, 1983; Rosser and Hodges, 1994). Category fluency is also known to be one of the most sensitive measures of semantic breakdown, often impaired early in the course of DAT or semantic dementia (Hodges and Patterson, 1995; Hodges et al, 1992). Importantly, a double dissociation in performance on initial letter and category fluency has also been shown in normal subjects when concurrently performing additional interference tasks, thought to involve frontal functions (motor sequencing) and temporoparietal functions (object decision) respectively (Martin et al., 1994 – see Figure 3.1). It has therefore been argued that letter fluency depends more on frontal lobe function, whereas category fluency depends more on temporal lobe function, and that this is due to the differing resource demands of the two tasks (Moscovitch 1992).
At a more cognitive level, it is apparent that a number of psychological processes are common to both initial letter and category fluency: attention to the task; the formulation and initiation of search strategies; retrieval of the phonological forms of appropriate words with subsequent processing through to articulation; storage in working memory of both the cue and the exemplars produced (the latter to avoid perseveration of responses). Additional processes will be differentially involved in the two forms of fluency. Retrieving words in response to category labels depends critically upon the activation of semantic memory. In contrast, initial letter fluency can be performed at a phonological level since there is no requirement to consciously retrieve the meanings of the words selected on the basis of their initial sound.

Several neuroimaging studies have investigated the regions involved in word retrieval (e.g. Petersen et al., 1988; Wise et al., 1991; Warburton et al., 1996). Taken together, they suggest that the distributed system for retrieving words comprises the left inferolateral temporal lobe, the left posterior inferior parietal lobe, extensive regions of
the left premotor (lateral and medial) and prefrontal (dorsolateral) cortex and part of the supracallosal anterior cingulate gyrus. As discussed in chapter 1 (section 1.4.A), these studies have differed in the functional interpretation placed upon these activations, with some believing the frontal cortex is critical to semantic processing, while others prefer the temporal lobe as candidate for semantic processing. The study reported here directly contrasted activations associated with initial letter and category fluency. As many of the cognitive processes involved in the two tasks are similar, we did not expect to observe the entire neural system for word retrieval. It was predicted that phonologically based word retrieval during initial letter fluency would produce greater left dorsolateral frontal activation, whereas searches through semantic representations during category fluency would produce relatively greater left temporal and/or parietal activations.

A related point concerning internal organisation of the semantic system was also explored in this experiment. As previously discussed (chapter 1, section 1.5.B), neuropsychological studies have also shown a double dissociation for impaired knowledge about natural kinds and manmade objects. In view of the proposal that different kinds of conceptual knowledge may be differentially weighted with regard to sensory/motor domains (Warrington and McCarthy, 1987; Farah et al., 1991), word retrieval for categories was divided into natural kinds and manipulable man-made objects.

The aim of this experiment was to dissociate the regions critically involved in phonological and semantic processing by using the same task, but weighted differentially according to the instruction set. Intrinsically generated word retrieval to prompts was chosen as a task, as it is widely used in neuropsychological testing, and has been shown to produce robust activations (e.g. Warburton et al, 1996).

3.2 METHODS
3.2.A Subjects
Six volunteers took part in the study (5 males and 1 female, aged between 28 and 55 years). All conformed to the consent and handedness requirements outlined in Chapter 2 (section 2.2.A). PET scanning was performed under the standard conditions (Chapter 2, section 2.4). In addition, video was used to record the subjects’ responses to each cue for the duration of the scan.


3.2.B Experimental Design

Prior to scanning, all subjects underwent a practice session to familiarise them with the tasks used in the experiment. During scanning, cues were read out by the investigator at a rate of one per 20s. The subject was asked to articulate as many appropriate exemplars as possible in response to each stimulus until they heard the next stimulus, or the scan was complete. Throughout the periods when blood flow measurements were taking place the subject’s eyes were closed and the lights dimmed.

There were three types of cue: initial letters; category names of natural kinds; category names of manipulable man-made objects. Four scans were obtained for each type of cue, with the conditions counterbalanced across subjects to avoid time and order effects. No cue was repeated during the course of a subject’s study. Typical stimuli are shown below in Table 3.1.

Table 3.1: Examples of stimuli used for the fluency experiment

<table>
<thead>
<tr>
<th>Type of stimulus</th>
<th>Cue 1 (0 sec)</th>
<th>Cue 2 (20 sec)</th>
<th>Cue 3 (30 sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Man made objects</td>
<td>footwear</td>
<td>tools</td>
<td>toys</td>
</tr>
<tr>
<td></td>
<td>weapons</td>
<td>kitchen utensils</td>
<td>electrical equipment</td>
</tr>
<tr>
<td>Natural kinds</td>
<td>insects</td>
<td>vegetables</td>
<td>zoo animals</td>
</tr>
<tr>
<td></td>
<td>flowers</td>
<td>land animals</td>
<td>sea creatures</td>
</tr>
<tr>
<td>Initial letters</td>
<td>A</td>
<td>S</td>
<td>F</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>B</td>
<td>E</td>
</tr>
</tbody>
</table>

Behavioural piloting was carried out to ensure that these categories produced approximately the same number of exemplars per 20-second period. This was important as the increased dependence on frontal regions in letter fluency has previously been argued to be due to the higher demands placed on search and retrieval in retrieving words that are part of a ‘novel’ category (Martin et al, 1994). We wished to minimise this difference in the present experiment by equating the tasks for difficulty of retrieval as much as possible.
3.2. C Data Analysis

3.2. C. 1 Behavioural Data

Subjects' responses were recorded and checked for appropriateness. Statistical analysis (ANOVA) was performed to investigate whether there was any systematic effect of task type on the number of responses produced.

3.2. C. 2 PET analysis

Standard methods were used, involving a subject specific ANCOVA to remove the confound of global CBF variability (Chapter 2, section 2.5.F). In this analysis, a further covariate of no interest was used as a confound; that of number of responses produced per condition. An initial eigenimage analysis identified task-related variance in rCBF. A simple categorical or subtraction analysis was then performed (Chapter 2, section 2.5.A). All scans pertaining to category fluency were contrasted to those for letter fluency, and vice versa. Secondly, using just the scans where subjects were performing category fluency, those scans where cues were natural kinds were compared to those were cues were artefacts and vice versa.

Significance for left lateral regions implicated in word retrieval in previous studies (Petersen et al., 1988; Wise et al., 1991; Warburton et al., 1996) (posterior, inferior parietal lobe, inferolateral and anterior temporal lobe, premotor and dorsal prefrontal cortex, and primary sensorimotor cortex) was set at uncorrected P<0.001 (Z score >3.1). Homologous regions in the right hemisphere achieving this level of significance are reported as trends. In all other regions significance was set at a voxel-based (peak rCBF) threshold of P<0.05, corrected for the number of comparisons.

3.3 RESULTS

3.3. A Responses

The mean number of responses across the three tasks did not differ significantly: for initial letters the mean number of responses was 27.0 (range 17-38), for natural kinds 28.0 (range 18-38), and for inanimate objects 29.1 (range 19-47). The wide range within each condition reflects the considerable variation in the total number of responses produced by each subject. The number of responses made by each subject was therefore specifically factored out by making this a covariate of no interest in the analysis.
3.3.B Activation data

3.3.B.1 Eigenimages

Figure 3.2: The positive and negative correlation images are shown for the first two eigenvectors, in the form of SPM projections. The first 4 observations correspond to initial letter fluency, the next four (5 - 8) correspond to category fluency for natural kinds, and 9 - 12 to category fluency for inanimate objects.

An initial, descriptive (eigenimage) analysis was performed to characterise the activations in terms of distributed brain systems (Friston, 1994) (see Chapter 2, section 2.5.A). The principal eigenvector, accounting for 44 per cent of the variance, showed positive loading in the scans corresponding to letter fluency, and negative loading in those scans corresponding to category fluency. This correlated with changes in activity in the frontal lobes, and the left temporal lobe, respectively. The second eigenvector, accounting for 19 per cent of the variance, showed positive loading in the scans corresponding to category...
corresponding to category fluency for natural kinds, and negative loading in those corresponding to fluency for inanimate objects.

These results show that approximately 63 per cent of the variance was due to task effect; that there are striking differences in regional activation between category and letter fluency; and that further significant differences arise from the type of conceptual category.

3.3.B.2 Category versus letter fluency

Contrasting initial letter fluency with category fluency revealed a left frontal activation in area BA 44/6 and a smaller primary sensorimotor activation (Figure 3.3A; Table 3.2). The reverse contrast showed activations in the left temporal lobe - specifically the inferolateral and anteromedial cortex (Figure 3.3B).

Table 3.2: Brain regions showing significant activation in the categorical contrast of category and letter fluency. The table displays the approximate Brodmann area (BA); the regional maxima in x, y and z co-ordinates corresponding to Talairach and Tourneaux; the z-score as a measure of significance.

<table>
<thead>
<tr>
<th>Initial letter vs. category fluency</th>
<th>(BA44/6)</th>
<th>48</th>
<th>0</th>
<th>28</th>
<th>4.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precentral sulcus</td>
<td></td>
<td>-36</td>
<td>-4</td>
<td>24</td>
<td>3.6</td>
</tr>
<tr>
<td>&quot;</td>
<td></td>
<td>-58</td>
<td>-14</td>
<td>24</td>
<td>3.7</td>
</tr>
<tr>
<td>Primary sensorimotor cortex</td>
<td>(BA 6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-44</td>
<td>-6</td>
<td>-20</td>
<td>3.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category vs. initial letter fluency</th>
<th>(BA 20)</th>
<th>-44</th>
<th>-6</th>
<th>-20</th>
<th>3.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left temporal pole/inferior temporal gyrus</td>
<td></td>
<td>-32</td>
<td>-30</td>
<td>-16</td>
<td>3.2</td>
</tr>
<tr>
<td>Left parahippocampal gyrus</td>
<td></td>
<td>-20</td>
<td>-16</td>
<td>-16</td>
<td>3.2</td>
</tr>
</tbody>
</table>
illustrate the spatial extent of these activations, the threshold was set at $Z > 2.8$ ($p < 0.002$) in both contrasts.

3.3.B.3 Types of category fluency
Contrasting category fluency for natural kinds with that for manmade objects showed bilateral activation in the anteromedial temporal lobes, with additional activation in the right inferior parietal lobe (Figure 3.4A). The reverse contrast (i.e. fluency for objects versus that for natural kinds) showed activation in the left posterior temporal cortex (Figure 3.4B) and to a lesser extent in the premotor cortex (not shown in figure, see Table 3.3). The location and peak $Z$ scores for these contrasts are given in Table 3.3.

Figure 3.4: Regions of significantly increased blood flow (rCBF) in the contrast of A) inanimate objects with natural kinds; B) natural kinds with inanimate objects. $L = \text{left}; R = \text{right}$. 

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It is interesting to note that examination of the relative blood flow plots for the three conditions revealed a greater similarity in the inanimate category fluency condition and the letter fluency condition than in the animate category fluency condition, as is suggested by the vector pattern for the three conditions in Figure 3.1.

Table 3.3: Brain regions showing significant activation in the categorical contrast of category fluency for natural kinds and inanimate objects.

<table>
<thead>
<tr>
<th>Natural kinds vs. inanimate objects</th>
<th>Right inferior parietal lobule (BA 39)</th>
<th>44  -64  40</th>
<th>3.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left hippocampal gyrus</td>
<td>-16  -10  -16</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Right hippocampal gyrus</td>
<td>22   4   -12</td>
<td>3.0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inanimate objects vs. natural kinds</th>
<th>Left premotor cortex (BA 44/6)</th>
<th>-42  2   32</th>
<th>2.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left temporo-occipital junction</td>
<td>(BA 37)</td>
<td>-34  -58    8</td>
<td>4.3</td>
</tr>
<tr>
<td>Left posterior temporal lobe</td>
<td>(BA 21/37)</td>
<td>-42  -62    0</td>
<td>4.0</td>
</tr>
</tbody>
</table>

3.4 DISCUSSION

Word retrieval has been shown to activate a distributed system that is strongly left lateralised (Warburton et al, 1996), involving the inferolateral temporal lobe, temporoparietal junction, dorsolateral prefrontal/premotor regions, anterior cingulate
3.4 DISCUSSION

Word retrieval has been shown to activate a distributed system that is strongly left lateralised (Warburton et al., 1996), involving the inferolateral temporal lobe, temporoparietal junction, dorsolateral prefrontal/premotor regions, anterior cingulate gyrus and supramarginal gyrus (SMA). The results of this study demonstrate that the double dissociation between initial letter and category fluency observed in both patients and normal controls correlates with differences in regional activations within this network when normal subjects perform these tasks.

Initial letter contrasted with category fluency (for both natural kinds and manipulable, man-made objects) was associated with greater left premotor (BA 44/6) and sensorimotor activation. Some of the subjects reported use of the following strategy in performing this task: taking the initial letter cue (e.g. ‘p’), combining it with another consonant or a vowel (e.g. ‘pr’ or ‘pa’) and then internally “sounding out” this combination to facilitate word retrieval (e.g. précis, preamble, prerequisite, partner, panther, paternal). It is noteworthy that the left dorsal frontal activation seen for this task is 4mm from that found in two studies by Zatorre and colleagues (co-ordinates -48-3 24) when they contrasted an active phonological task (subjects listened to consonant-vowel-consonant syllable pairs and responded when they ended in the same consonant) with passive listening (subjects listened to the same syllables and responded to alternate stimulus pairs) (Zatorre et al., 1996). This finding lends further support to the hypothesis that this area is involved in a phonological component of inner speech (Demonet et al., 1992), or prearticulatory phonological processing. As the number of words retrieved for each scan by each subject was co-varied out, the activations are unlikely to be attributable to differences in the rate of articulating responses in initial letter and category fluency.

Category fluency appears to be a sensitive indicator of semantic impairment (Hodges and Patterson, 1995). Relative to initial letter fluency, the activations observed in category fluency were weighted towards the left temporal lobe. In semantic dementia, a neurodegenerative condition characterised by a progressive decline in semantic knowledge with relative preservation of phonological and syntactic abilities (see chapter 1, section 1.3.A), the main site of pathology is typically the left anterior and inferolateral temporal lobe (Hodges et al., 1992). Moreover, Alexander and colleagues have argued that stroke patients with the syndrome of transcortical sensory aphasia, in whom semantic
knowledge is impaired, have cortical or white matter lesions that isolated the left inferolateral temporal lobe (BA 37) and the left occipito-parietal junction (BA 19/39) (Alexander et al., 1989). The results from the present study are compatible with these lesion data. The absence of activation in left posterior perisylvian regions (Wernicke’s area) is not surprising, as the two types of fluency task did not differ in the number of cues heard or in the number of exemplars spoken.

The absence of differential activation in one further region should be noted. Previous studies of verbal fluency have shown activation in the left dorsolateral prefrontal cortex, thought to be due to intrinsic generation of responses (Frith et al, 1991). This region has become the topic of considerable debate in terms of its putative function, with some authors arguing for a role in semantic processing per se (e.g. Petersen et al, 1988; Gabrieli et al, 1997), while others have produced evidence that this region may be involved in selection or search (Thompson-Schill et al, 1997; Fiez, 1997). The role of this region is discussed further in Chapter 10 (section 10.4.B.1). However, before leaving the topic, it is worth mentioning that the lack of significant differential activation seen in this study for semantic conditions suggests that the selection/search hypothesis might be correct. Furthermore, it supports recent work on patients with lateral frontal lesions showing impairment on both category and letter fluency, suggesting that this is due to a lack of efficient organisation and development of retrieval strategies (Baldo and Shimamura, 1998). However, it is important to bear in mind that a negative finding should be interpreted with caution.

There were further differences of activation observed in the two category fluency tasks. Retrieving exemplars of man-made objects elicited a strong activation in the left posterior temporal cortex (BA 21/37). It has long been known that lesions here are associated with impairments of word retrieval (Newcombe, 1969). The activation spread dorsally, into territory supplied by the middle cerebral artery. The rare reports of category-specific deficits for manmade objects have applied to patients with lesions in the left temporoparietal region, and include stroke patients with infarction in the territory of the posterior branch of the middle cerebral artery (Hillis and Caramazza, 1991).

The premotor cortex also showed greater activation for inanimate category fluency. Several other studies have shown that activation in the left posterior middle temporal
gyrus and premotor cortex is greater for naming tools than for naming animals (e.g. Martin et al., 1995; Grabowski et al., 1997). It has been argued that this is possibly due to the importance of verbs in describing the unique attributes of inanimate objects (Martin et al., 1995). Supporting this account, damage to the premotor region has been shown to cause greater impairment for retrieval of verbs than for nouns (Damasio and Tranel, 1993). At the moment, however, this hypothesis remains speculative.

Retrieving names of natural kinds activated the anterior medial temporal lobes bilaterally. In a review of relevant lesion data, Gainotti and colleagues reported that most subjects with a category-specific deficit for natural kinds had lesions secondary to herpes simplex viral encephalitis (HSVE) (Gainotti et al., 1995). This disease typically produces anterior and ventral temporal lobe lesions, usually bilateral. From such data, it has been argued that ventral temporal regions are critical in the processing of semantic representations which are differentiated on the basis of visual information, as opposed to other attributes, i.e. in 'the perceptual components of semantic representations (Breedin et al., 1994). Work on the macaque monkey, lesioning the perirhinal cortex, has also suggested that this area may be important in the association and integration of various visual features inherent in particular objects (Gaffan D., 1994; Buckley and Gaffan, 1998). If the correct discrimination of natural kinds is critically dependent on visual features, then activation of this region should be expected whenever a task requires/involves semantic specification of natural-kind objects, as in our category fluency task. This point and related issues concerning category specificity are discussed further in Chapter 10, section 10.5.A.

Connectionist models of category specificity have explored the hypothesis that the semantic representation of an object consists of that object’s features (both sensory and functional), and that the similarity structure of such features across different objects leads to a natural clustering of objects within categories. This may occur without any necessarily explicit representation of categories per se (Small et al., 1995). The regional differences in the activations for manmade objects and natural kinds observed in this study might reflect the different weightings of their features within the distributed semantic field. This hypothesis is explored further in the next chapter.
3.5 SUMMARY

In summary, the results from this experiment show that the strategy used to retrieve words, and the type of word retrieved, matter. They have confirmed the critical role of the left inferolateral temporal lobe in semantically based retrieval (Hodges et al., 1998) and the role of area BA 44/6 in prearticulatory phonological processing (Zatorre et al., 1996). Finally, the results have suggested that category specificity can be shown functionally within the semantic system (using words), and may be secondary to the relative weighting of sensory and functional attributes for individual categories. The next experiment was designed to explore the issue of category specificity further, using a paradigm where issues such as frequency, concept accessed, and type of knowledge retrieved were controlled as much as possible, and both category and type of knowledge differences were examined in the same paradigm.
Chapter 4

Further investigation of category specificity in normals using a semantic feature-association task to determine how category of concept and/or type of knowledge are neurally represented.

4.1 INTRODUCTION

The previous study dissociated two forms of word retrieval which rely differentially on semantic and phonological processes. Frontal lobe regions showed greater activation for phonologically based fluency, while the inferolateral temporal lobe was activated more for semantically based fluency. Within the task engaging semantic processing, differences were observed for retrieval of object names from different semantic categories (living things and artefacts). The aim of this study was to explore further whether these category specific differences were due to the category per se, or due to differing demands on the visual and functional properties of these concepts. The neural underpinning of category specificity is a debate that has been conducted for many years in the neuropsychological literature (see Chapter 1, section 1.5.B). A welcome recent addition has been the use of functional imaging studies to address the issues of category specificity. The results of those performed to date are described in detail in Chapter 1 and in Appendices 2 and 3; in essence, they have shown the following:

Firstly, some degree of consistency has emerged with respect to brain regions showing enhanced activation for artefacts (especially tools) relative to living things. Experiments employing either picture naming or verbal fluency for semantic categories have produced greater activation for artefacts in left posterior temporal or temporo-parietal areas (Damasio et al., 1996; Martin et al., 1996; Mummery et al., 1996; Cappa et al., 1998) and also in a left inferior frontal region (BA 44/6) (Grabowski et al., 1997; Martin et al., 1996; Cappa et al., 1998; Perani et al., 1995). The opposite comparison has tended to yield somewhat weaker and less consistent results. The previous chapter described enhanced bilateral anterior medial temporal activation when subjects generated names of living things (see Chapter 3) and Damasio et al (1996) observed ventral temporal activation for naming animals, more anterior to that for tools. Both Martin et al. (1996) and Perani et al. (1996), however, reported more left medial occipital activation associated with viewing pictures of animals.
The findings for type of knowledge have also varied. Vandenberghe et al. (1996) observed no selective activation for either perceptual or associative similarity judgements about triads of pictures or words. On the other hand Martin et al. (1995), using word retrieval, found enhanced activation in the ventral temporal lobe for retrieval of associated colour (the perceptual condition), while retrieval of associated action (the functional condition) revealed increased activity in the left posterior middle temporal region.

Finally, in the only other study examining both category and type of knowledge in the same experiment, Cappa et al (1998), using an association task and word stimuli, found greater differential activation for type of knowledge than for category type, and bilateral activation for animals, but left-lateralised activation for tools.

This study was designed to assess the relative effects of object domain (animate/natural kind or inanimate/artefact) and attribute type (visual or associative). Written-word object names were used to minimise clues to visual/structural features of the object concepts. In each block of the PET experiment, subjects viewed a triangle of three words and chose one of the two lower words based on similarity to the upper target word on a specified dimension. The first experimental manipulation varied task, where the experimental task was a semantic similarity judgement and the control task was a judgement about word length in syllables. The second manipulation varied object domain, where the triads in each block consisted entirely of words denoting either living things or artefacts. The final manipulation varied type of knowledge attribute: in half of the semantic conditions, subjects chose the response word on the basis of a perceptual attribute (object colour); in the remaining half, the basis for the similarity judgement was an associative attribute (typical object location). Colour was chosen as a perceptual attribute common to both living things and artefacts, which has been used with success in previous experiments (Martin et al., 1996), affording an opportunity to test for consistency across study designs. The location task required subjects to retrieve information about where an object was likely to be found, that is to say, its typical spatial location within the environment. This was chosen as an associative attribute that applies equally well to living things as artefacts, unlike the typical action associated with an object which shows fundamental differences for the two domains - living things often have intrinsic action, whereas artefacts normally have extrinsic action placed upon them.
Our predictions, and their genesis, were as follows: (i) In keeping with prior functional imaging studies, we expected that semantic judgements (relative to phonological judgements about syllable number) would activate a distributed system, mainly in the left hemisphere, involving the inferolateral temporal lobe, the posterior inferior parietal lobe, and possibly the inferior frontal gyrus (e.g. Price et al., 1996, 1997; Vandenberghe et al., 1996). (ii) With regard to the two manipulations within the semantic conditions, we predicted more marked activation differences between attribute types than between object domains: processing of what an object looks like, or where it is to be typically found, seems a more likely basis for neuroanatomical specialisation than the conceptual distinction between living things and artefacts (Gainotti et al., 1995). (iii) Regarding specific cortical regions, our prediction was based primarily on the differentiation between “what” and “where” post-striate visual processing (Ungerleider and Mishkin, 1982). That is, we expected heightened ventral temporal activation in response to perceptual colour judgements and enhanced dorsal temporo-parietal activation for location judgements.

4.2 METHODS

4.2.A Subjects

Ten male subjects (age range 25 - 31 years) took part in the study, conforming to the inclusion criteria specified in Chapter 2 (section 2.2.A). PET scanning was performed according to the standard procedure outlined in Chapter 2 (section 2.4).

4.2.B Psychological Tasks

Stimuli for each scan consisted of a series of word triads (See Figure 4.1). These series were matched across all scans for frequency and number of syllables; no triad was seen more than once during a scanning session. In half of the scans the triads consisted entirely of words denoting living things, and in the other half the words described artefacts. Subjects had to perform one of three tasks: the two experimental tasks involved semantic judgements, either a colour similarity decision or a location similarity decision. For the colour judgement, the subject decided which of two alternative response words represented an object closer in colour to the target word (e.g. FLAMINGO: salmon, cherry). For the location judgement, subjects decided which of the two response words was typically found in the same location as the target object (e.g. PAPER: rake, ruler).
Subjects responded to each triad by pressing a response key in the right or left hand depending on whether they considered the left or right response word to be the best choice. The control task emphasised phonological rather than semantic processing: subjects decided which of two response words had the same number of syllables as the target word. This task was used as a control as it produces robust differences between semantic and phonological processing (Price et al, 1997), and should control for activation due to visual, orthographic and phonological processing of the words in the experimental tasks. Examples of stimulus triads are given below.

Figure 4.1: Examples of stimuli for the three conditions for living things. The stimuli were presented in a standard manner for all conditions and both object domains.

Semantic task 1: perceptual

flamingo
salmon
cherry

Semantic task 2: associative

mole
termite
toad

Control task: syllables

tangerine
alligator
butterfly

Reaction times and errors were recorded for each judgement. Prior to scanning, subjects practised until they understood and were able to perform the task.
Table 4.1: Examples of stimuli used for each condition

### Colour judgement

<table>
<thead>
<tr>
<th>Animate</th>
<th>Inanimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLAMINGO: salmon, cherry</td>
<td>ARMOUR: tinfoil, vaseline</td>
</tr>
<tr>
<td>LIME: grass, lemon</td>
<td>BUS: fire-engine, lifeboat</td>
</tr>
<tr>
<td>FROG: lettuce, onion</td>
<td>TRUMPET: crown, key</td>
</tr>
</tbody>
</table>

### Location judgement

<table>
<thead>
<tr>
<th>Animate</th>
<th>Inanimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>APPLE:</td>
<td>PAPER: ruler, rake</td>
</tr>
<tr>
<td>MOLE:</td>
<td>COMB: lipstick, candle</td>
</tr>
<tr>
<td>TADPOLE:</td>
<td>SAUCEPAN: ladle, toothbrush</td>
</tr>
</tbody>
</table>

### Syllable judgement

<table>
<thead>
<tr>
<th>Animate</th>
<th>Inanimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>TANGERINE:</td>
<td>CHAIR: spade, canoe</td>
</tr>
<tr>
<td>HORSE: snake,</td>
<td>PAINTBRUSH: blackboard, typewriter</td>
</tr>
<tr>
<td>LETTUCE: spinach, conifer</td>
<td>CANNON: guitar, bikini</td>
</tr>
</tbody>
</table>

4.2.2 Data analysis

The data were analysed using the standard SPM analysis as outlined in Chapter 2 (section 2.4). An initial eigenimage analysis was performed (Chapter 2, section 2.5.A).

This experiment employed a factorial design (Chapter 2, section 2.5.D) to investigate the effect that category and type of knowledge retrieved had on each other. In the main analysis, the data was examined for three types of main effect: (i) regions common to all semantic tasks versus syllable judgement, and vice versa. (ii) regions showing differential activity for associative (location) judgements and perceptual (colour) judgements; (iii) areas differentially activated for living things and artefact stimulus triads. Examination of the data was constrained to those regions activated by the semantic task relative to the control syllable task for comparisons of objects domain and comparison of type of knowledge, to ensure that the regions showing differential activation for either task or domain were involved in semantic processing over and above control processes. Significance threshold for regions implicated in semantic tasks in previous studies (Mummery et al, 1996; Petersen et al, 1988; Vandenberghe et al, 1996; Warburton et al, 1996) (posterior, inferior parietal lobe; inferolateral and anterior temporal lobe; inferior frontal gyrus; premotor frontal cortex) was set at an uncorrected...
p<0.001 (Z score greater than 3.1). For all other brain regions, we report regions surviving the same threshold, but interpret only those areas that satisfy a corrected threshold of p<0.05.

4.3 RESULTS

4.3.A Behavioural data

ANOVA post-hoc testing was performed to examine the data for significant differences in reaction times and error rates between the conditions (Table 4.2). The syllable task produced significantly longer RTs than the semantic tasks, (Scheffe test p<0.0001), though this was not mirrored in the error rates.

Table 4.2: Mean error rates and reaction times of subjects for each condition

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>Mean</th>
<th>S error</th>
<th>Mean No Errors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Living things (Location)</td>
<td>2449.3</td>
<td>43.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Artefacts (Location)</td>
<td>2125.2</td>
<td>39.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Living things (Colour)</td>
<td>2423.3</td>
<td>41.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Artefacts (Colour)</td>
<td>2498.7</td>
<td>35.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Living things (Syllable)</td>
<td>2637.2</td>
<td>37.5</td>
<td>1.2</td>
</tr>
<tr>
<td>Artefacts (Syllable)</td>
<td>2656.5</td>
<td>38.3</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Within the semantic conditions, the location task for artefacts yielded significantly shorter reaction times than any of the remaining semantic tasks (p<0.0001). No other RT differences were significant. The error rates were too low to justify significance testing between the conditions.

4.3.B PET results

4.3.B.1 Eigenimage results

An initial descriptive (eigenimage) analysis was performed to characterise the activations in terms of distributed brain systems (Friston, 1994). The principal eigenvector, accounting for 49% of the experimental variance, showed positive loading in the scans corresponding to semantic tasks, and negative loading in the scans corresponding to the syllable task. This vector correlated with changes in the left posterior temporo-parietal junction (BA 39), and bilateral supramarginal gyri (BA 40), respectively. No other
eigenvector accounted for more than 9% of the variance. This result was not simply due to the difference between tasks in "difficulty": a further analysis factoring out reaction times by using them as a covariate of no interest produced the same pattern. These results therefore confirm a dissociation in terms of cerebral processing between the semantic and phonological tasks.

4.3.B.2 Semantic vs Syllable

Table 4.3: Main effects of semantic – syllable task

<table>
<thead>
<tr>
<th>Area of activation</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Z score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semantic – Syllable (activations in predicted areas and/or reaching corrected level of significance)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left T-O-P junction (BA 39)</td>
<td>-46</td>
<td>-72</td>
<td>28</td>
<td>6.8</td>
</tr>
<tr>
<td>Left mTG (BA 21)</td>
<td>-56</td>
<td>-24</td>
<td>-6</td>
<td>5.1</td>
</tr>
<tr>
<td>Left PHG</td>
<td>-30</td>
<td>-30</td>
<td>-16</td>
<td>4.4</td>
</tr>
<tr>
<td>Left iTG (BA 20)</td>
<td>-44</td>
<td>-22</td>
<td>-16</td>
<td>3.9</td>
</tr>
<tr>
<td>Left medial sup frontal gyrus</td>
<td>-6</td>
<td>58</td>
<td>26</td>
<td>7.2</td>
</tr>
<tr>
<td>Left orbitofrontal gyrus (BA 10)</td>
<td>-14</td>
<td>54</td>
<td>-4</td>
<td>4.5</td>
</tr>
<tr>
<td>Left inferior frontal gyrus (BA 47)</td>
<td>-32</td>
<td>18</td>
<td>-16</td>
<td>3.7</td>
</tr>
<tr>
<td>Semantic – Syllable (activations not in predicted areas and reaching uncorrected level of significance)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Temporal Pole (med) (BA 38)</td>
<td>28</td>
<td>10</td>
<td>-22</td>
<td>3.4</td>
</tr>
<tr>
<td>Posterior cingulate</td>
<td>-6</td>
<td>-56</td>
<td>12</td>
<td>3.7</td>
</tr>
<tr>
<td>Caudate</td>
<td>-6</td>
<td>12</td>
<td>12</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Examining the data for regions activated in the semantic more than in the syllable tasks revealed mainly left lateralised activation spreading throughout the left lateral temporal lobe, from the temporo-occipito-parietal junction (BA 39/19), through the posterior middle temporal gyrus, and anteriorly to the inferolateral and inferomedial temporal lobe (see Table 4.3 and Figure 4.2). Weaker activations were seen in the right temporal pole and right inferomedial temporal lobe.
Figure 4.2: Regions of significantly increased regional cerebral blood flow (rCBF) common to all semantic tasks versus the syllable (control) task. Top row shows glass brain depiction of activations with plot of rCBF from coordinate -6, 58, 26 (z-score = 7.2). The bottom row shows activations superimposed on the averaged MRI of the subjects. (L = location judgement; C = colour judgement; S = syllable judgement; -It = for living things; -ar = for artefacts. Posterior = P, anterior = A, left = L, right = R).

Analysis of individual subject activations showed that in all but one participant, both anterior temporal lobes were activated; though in the posterior regions, only the left hemisphere was activated. Less significant activation of the left inferior frontal gyrus (BA 47) was present, and the left medial prefrontal cortex was also more active in the semantic tasks relative to control.
4.3.B.3 Syllable vs. Semantic

**Fig 4.3:** Regions of significantly increased regional cerebral blood flow (rCBF) for the syllable (control) task compared to all semantic tasks, depicted on a 3D rendering of the standard MRI brain.

The syllable judgement task, which was designed to emphasise phonological processes, showed significant activation relative to the two semantic tasks in bilateral supramarginal gyri (BA 40), bilateral premotor regions, left posterior fusiform gyrus (BA 19), right inferior temporal gyrus (BA 37/19), and cerebellum.

**Table 4.4:** Regions of significant activation in main effect of syllable – semantic task

<table>
<thead>
<tr>
<th>Region</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>z score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(activations reaching corrected level of significance)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left supramarginal gyrus (BA 40)</td>
<td>-56</td>
<td>-34</td>
<td>34</td>
<td>6.3</td>
</tr>
<tr>
<td>Left premotor/precentral gyrus (BA 4/6)</td>
<td>-52</td>
<td>-8</td>
<td>38</td>
<td>6.0</td>
</tr>
<tr>
<td>Right supramarginal gyrus (BA 40)</td>
<td>52</td>
<td>-40</td>
<td>46</td>
<td>7.4</td>
</tr>
<tr>
<td>Right posterior iTG/FG (BA 37)</td>
<td>56</td>
<td>-50</td>
<td>-22</td>
<td>5.1</td>
</tr>
<tr>
<td><strong>(activations reaching uncorrected level of significance)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right middle frontal gyrus</td>
<td>38</td>
<td>34</td>
<td>20</td>
<td>4.2</td>
</tr>
<tr>
<td>Right premotor/precentral gyrus (BA 4/6)</td>
<td>26</td>
<td>0</td>
<td>54</td>
<td>4.1</td>
</tr>
<tr>
<td>Right thalamus</td>
<td>10</td>
<td>-10</td>
<td>12</td>
<td>3.6</td>
</tr>
<tr>
<td>Precuneus</td>
<td>2</td>
<td>-46</td>
<td>66</td>
<td>3.6</td>
</tr>
<tr>
<td>Left cerebellum</td>
<td>-28</td>
<td>-58</td>
<td>-30</td>
<td>3.9</td>
</tr>
</tbody>
</table>
4.3.B.4 Attribute Type

Table 4.5: Effects of attribute type

<table>
<thead>
<tr>
<th>Area of activation</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>z score</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>z score</th>
</tr>
</thead>
<tbody>
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<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Main effect</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location - Colour common to both domains</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left sOG (BA 19)</td>
<td>-32</td>
<td>-78</td>
<td>32</td>
<td>4.4</td>
<td>-32</td>
<td>-72</td>
<td>38</td>
<td>4.6</td>
</tr>
<tr>
<td>Left T-O-P junction (BA 39)</td>
<td>-50</td>
<td>-68</td>
<td>20</td>
<td>4.2</td>
<td>-44</td>
<td>-72</td>
<td>26</td>
<td>7.6</td>
</tr>
<tr>
<td>Left occipitoparietal sulcus</td>
<td>-16</td>
<td>-56</td>
<td>14</td>
<td>3.8</td>
<td>-12</td>
<td>-58</td>
<td>18</td>
<td>6.1</td>
</tr>
<tr>
<td>Posterior cingulate gyrus</td>
<td>-4</td>
<td>-58</td>
<td>26</td>
<td>4.1</td>
<td>-2</td>
<td>-58</td>
<td>20</td>
<td>4.7</td>
</tr>
<tr>
<td>Medial parietal lobe</td>
<td>-12</td>
<td>-60</td>
<td>20</td>
<td>3.8</td>
<td>-8</td>
<td>-60</td>
<td>20</td>
<td>3.8</td>
</tr>
<tr>
<td>Colour - Location common to both domains</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anteromedial temporal lobe</td>
<td>-10</td>
<td>-4</td>
<td>-24</td>
<td>3.4</td>
<td>-14</td>
<td>-6</td>
<td>-24</td>
<td>4.0</td>
</tr>
<tr>
<td>Caudate</td>
<td>6</td>
<td>8</td>
<td>23.4</td>
<td></td>
<td>2</td>
<td>8</td>
<td>6</td>
<td>4.0</td>
</tr>
</tbody>
</table>

| Location - Colour common to both domains                |     |     |     |         |     |     |     |         |
|                                                        |     |     |     |         |     |     |     |         |
| Colour - Location common to both domains                |     |     |     |         |     |     |     |         |
|                                                        |     |     |     |         |     |     |     |         |

Figure 4.4: Regions of significant rCBF increase for (A) location judgements versus colour judgements and for (B) colour judgements versus location judgements. As in figure 4.1, this is divided into glass brains, plot of significant rCBF (A coordinates -50, -68, 20 (z=4.2); B coordinates -10, -4, -24 (z = 3.4) and activations superimposed on the averaged MRI.

(A) Location - Colour

(B) Colour - Location
Within the semantic system, differences were observed depending upon attribute type (see Table 4.5 and Fig 4.4). Fitting reasonably well with our predictions, semantic judgements based on similarity of object location differentially activated the left temporo-occipito-parietal (T-O-P) junction (BA 39/19), posterior cingulate and medial parietal lobe, whereas colour judgements activated the anteromedial left temporal lobe and caudate nucleus.

4.3.B.5 Object Domain

Comparison of object domains (Table 4.6 and Fig 4.5) revealed enhanced activation associated with artefacts common to both tasks in the left posterior middle temporal gyrus (BA 37/21), and left parahippocampal gyrus. There were no regions that were significantly more active for artefacts than living things specific to location or colour judgements.

No areas were significantly activated for living things over and above artefacts common to both tasks. There was enhanced activation in the left middle frontal gyrus (BA 9) and the right T-O-P junction (BA 39) for location judgements about living things relative to all other conditions. There were no regions that were significantly more active for colour judgements about living things.

Table 4.6: Effects of object domain

<table>
<thead>
<tr>
<th>Arterfacts – Living Things common to both attributes</th>
<th>Main effect</th>
<th>artefacts – syllable</th>
<th>living things – syllable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left post mTG (BA 37/21)</td>
<td>-54, -54, 0</td>
<td>3.7</td>
<td>-54, -50, -2</td>
</tr>
<tr>
<td>Left PHG</td>
<td>-30, -28, -16</td>
<td>3.2</td>
<td>-30, -26, -14</td>
</tr>
</tbody>
</table>

Living Things – Artefacts common to both attributes

nil significant

Living Things – Artefacts for location only

<table>
<thead>
<tr>
<th>Living Things – Artefacts for location only</th>
<th>Left mFG (BA 9)</th>
<th>Right T-O-P junction (BA 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-30 24 26</td>
<td>48 -66 26</td>
</tr>
<tr>
<td></td>
<td>3.6</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td>-30, 20, 32</td>
<td>48, -64, 22</td>
</tr>
<tr>
<td></td>
<td>2.1</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>-32, 20, 28</td>
<td>5.1</td>
</tr>
</tbody>
</table>
**Figure 4.5:** Regions of significant rCBF for the contrast of words denoting artefacts versus those denoting living things. Top row from left to right shows sagittal and transverse sections through glass brains, and plot of significant rCBF from coordinate –54, -54, 0 (z = 3.7). Bottom row shows activations superimposed on corresponding sagittal and transverse sections of the averaged MRI.

**4.4 DISCUSSION**

We predicted several specific findings in this study; results germane to these predictions are presented in two main sections: (i) those areas common to both semantic tasks for both object types and (ii) areas showing differential activation for firstly attribute type, and secondly object domain. The control and behavioural results are then briefly discussed.

**4.4.A Common semantic activations**

We have shown activation of a left-lateralised, distributed network, extending from the left T-O-P junction (BA 39), through the inferolateral temporal lobe, to the inferior frontal gyrus (BA 47). The areas activated by the semantic tasks are largely consistent with previous imaging studies, supporting the hypothesis that these regions form a common network for the retrieval of semantic knowledge, regardless of stimulus modality (pictures versus words: Vandenberghe et al., 1996) and task (word generation: Martin et al., 1996; Warburton et al., 1996; Wise et al., 1991; semantic decision: Price et al., 1997; Vandenberghe et al., 1996).
4.4.A.1 Temporal activations

Some of the results from the present study are consistent with lesion data. In semantic dementia, a neurodegenerative condition characterized by a progressive, selective, decline in semantic knowledge (see Chapter 1, section 1.3.A), the principal locus of pathology typically involves the left anterior and inferolateral temporal lobe (Hodges and Patterson, 1997; Hodges et al., 1992). Consistent with the more posterior activations, Alexander et al (1989) argued that stroke patients with transcortical sensory aphasia, in whom semantic knowledge is impaired, have lesions isolating the left inferolateral temporal lobe and the left T-O-P junction (BA 39).

Our findings are also in accord with some previous experimental data both from functional imaging and from other methodologies such as Event Related Potentials (ERPs). The activation of anterior temporal regions is supported by ERP studies such as that by Nobre et al. (1994), in which anteromedial temporal lobe regions close to entorhinal cortex were found to be sensitive to semantic manipulations. The left anterior temporal lobe (BA 20/38) is also more active when subjects perform category fluency relative to initial letter fluency (Chapter 3; Mummery et al., 1996), but the more posterior left T-O-P regions (BA 39) that were particularly activate for location judgements in the current study showed no differential activation in any of the conditions in the fluency tasks. The activation seen in the left TOP junction (for semantic association but not for fluency) may be related to the association of knowledge about attributes of an object with the name seen on the screen. It is also possible (though unlikely) that the posterior activation is due to the specific association of semantic knowledge with visual input. We discuss this region further in section 4.4.B.

4.4.A.2 Frontal activations

The role of the frontal lobes in semantic processing is more controversial, as mentioned in Chapter 1 (section 1.4.A; 1.4.C). The left inferior frontal region (BA 47) observed in some previous semantic tasks (Petersen et al., 1988; Vandenbergh et al., 1996) was also activated in this study, though the z-score was smaller than for the temporal regions. The first experiment did not produce activation of the left inferior frontal region in the semantic task, perhaps because this area supports a process common to both category and letter fluency, as speculated upon in Chapter 1. The left medial prefrontal region (BA...
10/11) also showed activation in the semantic relative to the control task. The reason for this activation is uncertain, though BA 11 has been seen before in semantic similarity judgements (Vandenberghe et al., 1996). These frontal regions are less likely to be involved in the representation of semantic knowledge per se, in that there are no cases we are aware of where lesions of this medial frontal region, or indeed of the inferior frontal region, cause deficits in semantic knowledge. The possible role of such frontal regions is discussed in Chapter 10, section 10.3.B.

4.4.B Dissociations within the semantic system

4.4.B.1 Attribute Type

Neuropsychological data suggest that different cortical regions may be differentially involved in certain types of knowledge (Chapter 1, section 1.5.B). Our results provide some support for this notion, though the substantial consistency of activation patterns across semantic conditions suggests that implicit processing of all aspects of semantic knowledge may occur regardless of explicit task. Nevertheless, location judgements showed enhanced activation in the left posterior T-O-P region (BA 39 and BA 19) relative to colour judgements, in addition to activating the posterior cingulate and medial parietal lobe. The posterior parietal region was superior to that seen in the study by Martin et al. (1995) who compared imagining the action of an inanimate object with imagining its colour. In the present study, the associative task involved a spatial co-location judgement rather than a motion judgement, and the spatial component might be expected to activate a more dorsal region in the posterior inferior parietal cortex (Ungerleider and Mishkin, 1982), as indeed the results demonstrate (see Appendix 3).

The associative location task is complex, perhaps engaging a number of different strategies as well as intrinsic semantic properties, but we can base some hypotheses about the possible contribution of the regions activated on lesion data from both humans and monkeys. Lesioning the parieto-occipital region in the macaque monkey has been shown to disrupt the ability to locate a foodwell with reference to a landmark, indicating an impairment on spatial discrimination tasks (Mishkin et al. 1982). In humans, this region has been associated with the syndrome of neglect (albeit mainly with lesions to the right hemisphere), often attributed to a deficit in directed spatial attention; however, it has been shown that such lesions can also cause deficits in representational memory (Bisiach and Luzzatti, 1978), and it has been postulated that the disorder of neglect
involves a disrupted mental representation of space (Hussein, 1996). The inferior posterior parietal lobe therefore appears to be critical not only for the integration of sensory information for spatial judgements about objects within the current visual field, but also for spatial judgements involving representational space. Activation of the medial parietal lobe in this task, an area thought to be important in “mind’s eye imagery” (Fletcher et al., 1995a) is consistent with the hypothesis that the location judgements require internal imagery. Indeed, several subjects reported that there was a greater degree of visualisation of objects in this task than in the colour judgements.

We also saw areas more active for colour than for location judgements. The colour task produced stronger activation in regions of the left anteromedial temporal lobe and the caudate nucleus, the latter being an area observed in a recent study of colour naming (Price et al., 1996). The left anteromedial temporal activation corresponds closely to that found in category fluency when subjects generated the names of living things versus artefacts (Mummery et al., 1996; maxima 4 mm distant). Thus the same region has been found for attribute type and category type but in two different experiments. As described in the previous chapter, the left anteromedial temporal cortex may be important in the association and integration of different visual features characteristic of individual objects (Gaffan, 1994).

4.4.B.2 Object domain
Activation differences found for one or other object domain were smaller than those related to differing types of knowledge. In fact, when the data were examined for regions that activated more for words denoting living things than for names of artefacts, no significant differences were seen across tasks (see section 4.4.B.1 for discussion of enhanced activation for location judgements). This failure to find any regions specifically associated with processing of living things regardless of task is discussed further in Chapter 10 (section 10.6.A).

Location judgements about living things relative to artefacts activated the right TOP (BA 39) and left frontal lobe (BA 9). Right BA 39 was also associated with living things in the fluency experiment (Chapter 3). Finally, Cappa et al (1998) showed activation of this area for living things. The consistency found leads one to speculate a role for this region in knowledge about living things, though the precise form that role takes remains
uncertain. The left prefrontal region (BA9) has been seen in several studies involving semantic retrieval (e.g. Frith et al., 1991; Martin et al., 1995; Martin et al., 1996).

It must be remembered that in this study, the difference between attribute types (color vs. location) was an explicit focus of judgements for subjects, while the difference between object domains (natural vs. manmade) was never drawn to the subjects’ attention, thus remaining implicit. The advantage of designing the experiment in this manner is that any differences seen for category should be genuine, however, we cannot yet claim a full understanding of the conditions under which concepts from the domain of living things do produce regional activation. It is possible that the ventral temporal areas are critical for natural kind identification, but are equally capable of being engaged by any object if a subject is explicitly focussed on a task requiring access to perceptual knowledge.

Despite a lack of significant differential activation for natural kind relative to artefact concepts across tasks in this experiment, the reverse comparison revealed activation in the left posterior middle temporal gyrus (BA 21/37) for words denoting artefacts. The rare reports of category-specific deficits for artefacts have been described in patients with extensive left middle cerebral artery strokes which are likely to have included this region (Gainotti et al., 1995; Hillis and Caramazza, 1991; Warrington and McCarthy, 1987). This region is close to, and overlaps with, that found by Martin et al. (1995, 1996) when subjects either imagined actions of inanimate objects, or named tools (distance between respective activation maxima = 8mm). The exact function of this region within the semantic system remains an open question. What can be concluded, however, is (a) that this region is activated more for artefacts than living things (represented both as words and pictures), (b) responds specifically to semantic tasks (see blood flow plot Fig 3), and (c) is activated more by imagining an action than by imagining a colour (Martin et al., 1996). These findings suggest that this area is indeed critical for artefacts, especially as it is one of the few regions that has been reliably observed in studies from separate research centres using differing semantic tasks but for a consistent class of concepts. It remains a plausible hypothesis that this specialisation results from the relative importance of functional/associative knowledge for artefacts as opposed to living things. This point is discussed further in Chapter 10, section 10.6.A.2.
The left parahippocampal gyrus also showed greater activation for artefacts than for living things. This area has previously been activated in a semantic comparison task, more for words than for pictures (Vandenberghe et al., 1996), more for category than for letter fluency (Mummery et al., 1996), and more for naming of animals than tools (although activated to some degree for both object categories, Damasio et al. (1996)). No clear conclusion about this region can yet be drawn from functional imaging studies of the semantic system, though there is increasing consensus that it must play some semantic role.

4.4.C Control activations

The syllable judgement task was designed to control for basic visual, orthographic, phonological and working memory processes common to both the semantic and syllable tasks. The regions activated by the syllable judgements more than by the semantic attribute judgements are consistent with previous findings for syllable judgements on words (Price et al., 1997), letter fluency contrasted with category fluency (Chapter 1; Mummery et al., 1996), and phonological monitoring studies, which showed activation of (i) the left premotor gyrus, attributed to prearticulatory phonological encoding (Demonet et al., 1992; Mummery et al., 1996; Zatorre et al., 1996), and (ii) supramarginal gyrus, attributed to phonological short term memory (Paulesu et al., 1993). In the basal temporal lobes, bilateral posterior fusiform/inferior temporal gyrus activations were also seen, consistent with a role in the processing of words presented visually (Nobre et al., 1994).

4.4.D Behavioural results

Subjects found the syllable judgement task more demanding than the semantic tasks, and this difference was reflected in the mean reaction times (RTs), though not the error rates for the two tasks. This RT difference suggests that any activation by semantic as opposed to syllable judgements is unlikely to be confounded by difficulty. Within the semantic tasks, RTs for location judgements on artefacts were significantly shorter than those for all other semantic decisions. Previous RT-based studies of feature judgements by normal subjects have produced similar results (Laws et al., 1995), which the authors attributed to the critical status of this kind of associative knowledge for artefacts. In keeping with our data, Laws et al. (1995) also found no significant RT difference between associative and perceptual judgements about living things. This pattern suggests a greater differential
in the weighting between perceptual and associative knowledge for artefacts than for living things.

4.5 SUMMARY

In summary, the results of this study show that, when normal adults make semantic similarity judgements on written words, a network of cortical areas is activated, remarkably consistent with those found in other studies using both spoken words (Binder et al., 1997a), and pictures of objects (Vandenberghe et al., 1996). Within this common distributed system, there were regions that were differentially involved when the system was weighted for a certain type of task. Judgements about object location (relative to colour) were associated with enhanced activation of the left T-O-P region, while the reverse contrast (colour vs. location) produced stronger activation in the left antero-medial temporal lobe and caudate nucleus. Consistent activation of the left posterior middle temporal gyrus for words denoting artefacts for both perceptual and associative tasks also confirms the importance of this region for inanimate objects. On the other hand, the lack of any differential activation for words denoting living things relative to artefacts may suggest that, when the task demands and stimulus attributes are carefully controlled, there are no areas specific to the semantic processing of words denoting living things. These results suggest that the more prominent neural distinction relates to type of semantic attribute rather than object domain.

An important limitation of the two studies described so far, is the fact that in both the semantic knowledge accessed has to be retrieved voluntarily. The next study makes use of a well validated psychological paradigm that accesses semantic memory implicitly.
Chapter 5

Examination of the neural correlates of semantic priming—an implicit semantic memory task modulates activation in the anterior temporal lobe

5.1 INTRODUCTION

The first two experiments in this thesis explored activation seen for word retrieval and semantic association. One obvious question concerns how much of this activation is due to explicit retrieval from the semantic system, and how much is due to semantic processing per se. In other words, if a patient is unable to perform a test requiring voluntary retrieval of information, it is uncertain whether this deficit is due to a deficit in retrieval processes or due to damage to the store of information itself. Activation during an ‘on-line’ or ‘implicit’ semantic task was therefore examined in normal subjects. Such a task has been used in the study of disordered semantic processing in patients. Regions common to explicit and implicit semantic tasks should be involved in semantic processing per se, rather than in access to the semantic store.

Semantic priming refers to the facilitating effect seen on the response to a word (target) when preceded by a semantically related word (prime), compared to an unrelated word (e.g. Meyer and Schvaneveldt, 1971; Moss et al, 1995). The shortened latency and improved accuracy is thought to reflect automatic, implicit access to semantic information, in contrast to many standard semantic tests that rely on voluntary, explicit access and retrieval of semantic information. The facility that priming offers to examine implicit processing has led to the widespread use of priming paradigms in the study of disordered semantic processing in patients. For example, patients with ‘semantic access’ deficits, but not patients with a ‘degraded store’ of semantic knowledge, can explicitly retrieve the meaning of a word when preceded by presentation of a semantically related word (Warrington and Shallice, 1979; Shallice, 1988; Cipolotti and Warrington, 1995). In contrast, ‘degraded store’ patients such as those with progressive aphasia (Tyler et al, 1997) or Alzheimer’s disease (Chertkow et al, 1989) show intact implicit semantic priming, as indicated by speeded lexical decision latency when a related word is presented prior to the target word. This effect can be present to an abnormally high degree, so called hyperpriming (Chertkow et al, 1989; see also Moss and Tyler, 1995). Priming paradigms therefore provide a means to distinguish different types of semantic deficit.
Theoretical accounts of semantic priming have been of two broad types: automatic (e.g. Collins and Loftus, 1975; McClelland and Rumelhart, 1985) and strategic/attentional (Posner and Snyder, 1975; McKoon and Ratcliff, 1992). Neither type of account can individually explain all the complex behavioural phenomena associated with semantic priming, leading to hybrid proposals comprising elements of several accounts (e.g. Posner and Snyder, 1975; Neely, 1977; 1991). It is now generally accepted that there are both automatic and attentional processes involved that can be differentially weighted according to experimental variables. For example, behavioural studies have shown that automatic effects predominate when the interval between prime and target is less than 400ms (short stimulus onset asynchrony (SOA); (Neely, 1977)), and that at longer SOAs strategic processes take over (de Groot, 1984; Den Heyer et al, 1983). Other evidence suggests that selective attentional mechanisms can influence semantic priming to some extent at both short (240ms) and long (840ms) SOAs (Henik et al, 1994). In addition, the proportion of related prime-target pairs can have an effect, with strategic processes becoming more involved when the proportion of related prime-target pairs is high (Neely, 1991). It appears that while the relative contribution of automatic and strategic processes varies, a hybrid mechanism underpins semantic priming.

The physiological corollary of priming will differ both quantitatively and qualitatively depending upon the relative contribution of automatic and strategic processes. Automatic processes should cause changes in activity in semantic regions. Connectionist models predict decreased activation for a related target compared to an unrelated target, either because less activation is necessary to reach the threshold (due to partial activation of representations by the preceding prime) or because the activation threshold is reached more rapidly (as pathways are more easily utilisable) (Collins and Loftus, 1975; Plaut and Shallice, 1993). Finally the neurophysiological phenomenon of repetition suppression, which may well be related to the processes involved in perceptual identity priming (Wiggs and Martin, 1998), has been found to have a correlate in reduced cell firing in studies of macaque inferior temporal cortex (e.g. Miller et al, 1991). It is plausible that semantic priming could have a similar neurophysiology based on overlapping semantic features in the primed and target words.

Any of these hypothesised mechanisms should lead to less activation in a semantic region for a scan involving related word pairs than for a scan involving no related word pairs. A
purely 'automatic account' of priming therefore predicts a decrease in activation in lexico-semantic regions with increasing proportions of related targets, i.e. an inverse correlation. Strategic theories, on the other hand, suggest activation changes both in regions specialised for semantic processing and in regions involved in attentional modulation of such processing. In contrast to automatic priming, such attentional modulation of semantic activation could reasonably be expected to produce summed increases in activity with increases in the proportion of related targets. Increasing attention also increases the degree of priming behaviourally; it is therefore possible that in semantic regions, no overall change in activity would be seen when attentional and automatic processes exert an equal influence. Finally, if a hybrid of automatic and strategic processing underpins semantic priming, with automatic processes dominating in low proportions of related prime-targets, and strategic processes dominating in high proportions, then a complex pattern of variation in activation is possible. In short, there are three possible outcomes of increasing the proportion of related targets: automatic processing predicts decreases in activation, attention predicts increases (or no overall change in activity), and a combination of the two predicts a complex relationship.

To my knowledge, there have been no functional neuroimaging studies published investigating short-term semantic priming. Neuroimaging studies of priming thus far have focussed exclusively on long-lasting repetition priming, both conceptual identity and perceptual identity (for a current review see Schacter and Buckner, 1998). While repetition/identity priming and semantic priming (as defined here) differ behaviourally (e.g. in the duration of effect and attentional mechanisms involved (Farah, 1989)), they also share common features: both are forms of implicit memory and may be intact in patients with deficits in explicit/declarative memory; both show facilitation of the identification of primed stimuli, and inhibition of the identification of nonprimed stimuli. Findings from previous studies of repetition priming may therefore have some bearing on the current study.

Several of the studies on repetition/identity priming have investigated changes in neural activity associated with repeating items during the same task and during different tasks. The responses are mainly anatomically and task specific, with extra-striate occipital regions showing reduced activation when recall from visually presented stimuli is primed (using word-stem completion: e.g. Buckner et al, 1995; Squire et al, 1992), and prefrontal
regions showing reduced activation when an item is repeated during a semantic retrieval task (e.g. Demb et al, 1995). The essential findings have therefore been a decrease in regional cerebral blood flow in regions specific to the task performed, implying facilitation of perceptual processing in perceptual identity priming, and facilitation related to semantic processing in conceptual identity priming. Of note, differential activation of other regions has been found in repetition priming studies. For example, Schacter et al (1996), using a stem-completion task, replicated the findings in extrastriate cortex, but in addition found significant decreases in the right premotor cortex and right parietal cortex, areas thought to be involved in attentional mechanisms (Mesulam, 1990).

Given the huge body of neuropsychological literature examining “automatic” and “controlled” mechanisms in semantic priming in normals and patients, it seemed timely to attempt an initial definition of these mechanisms in terms of brain regions involved. I investigated the neural correlates of semantic priming using lexical decision, a task recognised as sensitive to priming, and one which has been investigated before with functional imaging, where it has activated left inferior frontal and anterior temporal regions (Price et al, 1994; Rumsey et al, 1997). Cognitive components such as orthographic processing and response selection were controlled by contrasting activity during lexical decision and a letter decision task on consonant letter strings. To maximise semantic analysis in the lexical decision task, category co-ordinate stimuli were used with pure semantic relationships rather than associated/semantic relationships (see Moss and Tyler, 1995), and the nonword stimuli were made as word-like as possible in order to strongly engage semantic processing. I expected that the categorical comparison of lexical decision versus letter decision would reveal lexico-semantic regions involved in lexical decisions on visually presented words. For this contrast left lateralised activations were predicted, involving the inferior frontal and anterior/inferior temporal lobes (Vandenberghe et al, 1996).

5.2 METHODS

5.2.A Subjects/Scanning
Nine healthy males (age range 27-31 years) took part, who satisfied the inclusion criteria discussed in Chapter 2 (section 2.2.A). The standard PET scanning technique was used as previously described (Chapter 2, section 2.4).
5.2.B Tasks

Figure 5.1: Diagrammatic representation of the lexical decision task

Stimuli consisted of letter strings presented visually in the centre of a screen (Figure 5.1). Each target was highlighted by pairs of lines at the side of the stimulus. A single-word lexical decision presentation was used, simplifying the subject’s task, and allowing a short prime-target interval, emphasising automatic semantic processing (de Groot, 1984; Posner and Snyder, 1975). The initial stimulus (prime) was shown for 200ms, followed by a blank screen for 50ms, then the target was presented for 400ms. The SOA of 250 ms was chosen as it is well within the 400 ms suggested cut-off point (Neely, 1977) and has been used by several investigators before as an automatic-biased SOA (e.g. Tyler et al, 1997). Stimulus pairs were presented every 2500 ms with 18 pairs of stimuli shown per scan.

Subjects were told they would see pairs of letter strings presented serially, and were instructed to respond only to the second stimulus seen of each pair (target). In response to the target stimulus, subjects had to perform one of two tasks: (a) In two scans, the primes and targets were consonant letter strings and the task was letter decision ("is there a ‘b’ present?"). (b) In ten scans, the primes were words, the targets were either words (concrete nouns) or nonwords and the task was lexical decision ("is it a real word?").
For the lexical decision task, the concrete words used for word pairs were category coordinate stimuli (within category e.g. horse-dog), because priming effects have been shown to be robust with these stimuli. Twelve stimulus pairs were word-word pairs, and 6 were word-nonword pairs. Nonwords were made up from words by altering one letter, making the lexico-semantic decision more pertinent. To ensure semantic processing occurred rather than low-level lexical processing, I used pure semantic relationships (e.g. pig-horse) as opposed to associated/semantic relationships (e.g. dog-cat) (Moss and Tyler, 1995). The word series were matched across all scans for frequency and length, and all categories were mixed equally across scans. No prime-target pair was repeated, to avoid the possible confound of ‘episodic’ or repetition priming.

To look for possible nonlinear (complex) priming effects, a correlational design was used within the active task: the proportion of related word pairs varied from 0 to 100% (i.e. in the ratios 0:12, 3:9, 6:6, 9:3, and 12:0) across the lexical decision scans. Reaction times and error rates were recorded throughout. Subjects practised prior to scanning until they could perform the tasks. Scan order was pseudo-counterbalanced within and across subjects.

5.2.C Analysis
The data were analysed with statistical parametric mapping (SPM97 - Wellcome Department of Cognitive Neurology, London, UK). The reconstructed images were realigned, normalised and smoothed (16mm) as described in chapter 2 (section 2.6). The generated statistical images had a full width half maximum (FWHM) resolution of 9.5 x 9.7 x 9.9mm. Main effects of condition were assessed using ANCOVA and linear contrasts as described earlier (Chapter 2, section 2.7). Two types of analysis were performed: (i) categorical comparisons of lexical decision with letter decision. (ii) nonlinear correlational analysis (using lexical decision data only) looking for regions showing variation in activity with varying proportions of related targets (see section 2.8.E). First and second order polynomials were derived from the proportions of related targets used and entered as covariates of interest. The resulting SPM(F) map displayed all areas showing significant variance correlating with these covariates either singly or in combination (Buechel et al, 1996). For both analyses, confounding order effects were removed by using scan order as a covariate of no interest (section 2.8.F).
Results are reported in terms of (i) areas showing effects of task; (ii) areas showing effects of priming. Significance was set at uncorrected $p<0.001$ for regions previously implicated in semantic tasks (e.g. Vandenberghe et al, 1996); (temporo-occipital-parietal junction, inferolateral and anterior temporal lobe, inferior frontal gyrus). For all other brain regions, only areas satisfying a corrected threshold ($p<0.05$) are interpreted. In the nonlinear analysis I report regions at a threshold of $p<0.001$ (uncorrected) when they showed increased activity in the categorical contrast of lexical decision relative to letter decision. For all other brain areas, I report regions only if they survive a corrected threshold ($p<0.05$).

5.3 RESULTS
5.3.A Behavioural data

Table 5.1: Behavioural effect of task and proportion of related targets on individual stimulus reaction times

<table>
<thead>
<tr>
<th>% related word pairs</th>
<th>All stimuli</th>
<th>Nonword targets</th>
<th>Word targets</th>
<th>Related prime-target</th>
<th>Unrelated prime-target</th>
<th>Priming effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (ms) (se)</td>
<td>Mean (ms) (se)</td>
<td>Mean (ms) (se)</td>
<td>Mean (ms) (se)</td>
<td>Mean (ms) (se)</td>
<td>Mean (ms) (se)</td>
</tr>
<tr>
<td><strong>LEXICAL DECISION</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>733.3 (14.3)</td>
<td>800.26 (24.5)</td>
<td>700.5 (17.2)</td>
<td>---</td>
<td>700.5 (17.2)</td>
<td>---</td>
</tr>
<tr>
<td>25%</td>
<td>677.0 (10.7)</td>
<td>783.2 (19.9)</td>
<td>623.1 (10.8)</td>
<td>598.2 (16.7)</td>
<td>631.8 (13.3)</td>
<td>33.6</td>
</tr>
<tr>
<td>50%</td>
<td>687.9 (11.5)</td>
<td>791.2 (21.5)</td>
<td>640.1 (12.4)</td>
<td>609.6 (15.6)</td>
<td>671.1 (18.8)</td>
<td>61.5</td>
</tr>
<tr>
<td>75%</td>
<td>659.7 (11.8)</td>
<td>750.1 (22.5)</td>
<td>614.5 (12.5)</td>
<td>592.5 (12.8)</td>
<td>679.8 (30.4)</td>
<td>87.3</td>
</tr>
<tr>
<td>100%</td>
<td>646.9 (9.9)</td>
<td>720.0 (16.3)</td>
<td>611.3 (11.6)</td>
<td>611.3 (11.6)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Mean over scans</td>
<td>680.5 (5.3)</td>
<td>768.4 (9.5)</td>
<td>637.5 (5.9)</td>
<td>604.1 (7.0)</td>
<td>672.1 (9.4)</td>
<td>68.0</td>
</tr>
</tbody>
</table>

| **LETTER DECISION**   |             |                 |              |                      |                        |               |
| All stimuli           |             |                 |              |                      |                        |               |
| No ‘b’ present        | 732.0 (12.5)| 835.3 (25.0)   | 681.7 (12.5)  |                      |                        |               |
| ‘b’ present           |             |                 |              |                      |                        |               |

Table 5.1 shows mean error rates and reaction times (RTs) for each task. The letter decision (control) task produced significantly longer RTs than those for the semantic tasks ($p<0.005$),
though there was no difference in the error rates. No significant differences in errors were seen between any of the conditions.

Within the lexical decision (active) conditions, there was a significant difference between RTs for words and nonwords, both related and unrelated word targets showing significantly shorter RTs than nonword targets. A priming effect was seen for all proportions of related targets, with a significant mean decrease in reaction time of 68 ms for related relative to unrelated word targets (p<0.0001) as measured by subtracting the RTs for related word-pairs from unrelated RTs in each condition. RTs for related targets were remarkably consistent, suggesting automatic priming was occurring. However, for unrelated targets and nonword targets there was an effect of the proportion of related targets per condition on RTs, indicating the influence of strategic processes (see discussion). RTs to non-words decreased significantly (p<0.05) with increasing proportion of related targets, using a non-parametric trend test (Pages' L trend test). RTs for unrelated targets showed i) a 69 ms decrease between the conditions containing no related primes and 25% related primes, and ii) a 48 ms increase between the conditions containing 25% and 75% related primes (which resulted in a corresponding increase in the size of the priming effect as the proportion of related word-pairs was increased, though this did not reach significance) – see Table 5.1.

5.3.B PET results
5.3.B.1 Task effects – categorical analysis
Contrasting lexical decision with letter decision revealed that relative increases in activity for lexical decision were mainly left lateralised, involving the predicted temporal regions (inferior temporal gyrus (BA 20), anterior temporal lobe (BA 38), posterior middle temporal gyrus (BA 21) and left inferior frontal/insular region (see Table 5.2; Figure 5.2). Midline activation was seen in the orbitofrontal gyrus (BA 11) extending into the anterior cingulate cortex.
Figure 5.2: Regions of significant cerebral blood flow (rCBF) change in lexical decision – letter decision. Top images display glass brain sections showing significant activity, with a plot of the adjusted response in the anterior temporal lobe (coordinates -40, -28, -18) for all tasks; bottom images show slices through local maxima (Table 5.2) on standard MRI brain sections, at the given z coordinate.

Table 5.2: Regions of significant activation for lexical decision versus letter decision

<table>
<thead>
<tr>
<th>Area</th>
<th>BA</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>z score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left inferior temporal gyrus</td>
<td>(20)</td>
<td>-40</td>
<td>-28</td>
<td>-18</td>
<td>4.8</td>
</tr>
<tr>
<td>Left ant superior temporal gyrus</td>
<td>(22/38)</td>
<td>-50</td>
<td>10</td>
<td>-2</td>
<td>4.8</td>
</tr>
<tr>
<td>“</td>
<td>(22/38)</td>
<td>-46</td>
<td>8</td>
<td>-20</td>
<td>3.7</td>
</tr>
<tr>
<td>“</td>
<td>(21/22)</td>
<td>-52</td>
<td>-2</td>
<td>-8</td>
<td>4.1</td>
</tr>
<tr>
<td>Left post middle temporal gyrus</td>
<td>(21)</td>
<td>-66</td>
<td>30</td>
<td>4</td>
<td>4.0</td>
</tr>
<tr>
<td>Left inferior temporal/parahippocampal gyrus</td>
<td>(20)</td>
<td>-36</td>
<td>8</td>
<td>-20</td>
<td>3.8</td>
</tr>
<tr>
<td>Left temporal operculum</td>
<td>(21/22)</td>
<td>-50</td>
<td>-2</td>
<td>-2</td>
<td>3.4</td>
</tr>
<tr>
<td>Left precentral gyrus</td>
<td>(6/44)</td>
<td>-58</td>
<td>6</td>
<td>8</td>
<td>4.8</td>
</tr>
<tr>
<td>Left inferior frontal gyrus</td>
<td>(47)</td>
<td>-50</td>
<td>20</td>
<td>-6</td>
<td>4.7</td>
</tr>
<tr>
<td>Right inferior frontal gyrus</td>
<td>(47)</td>
<td>36</td>
<td>20</td>
<td>-22</td>
<td>4.4</td>
</tr>
<tr>
<td>Orbitofrontal gyrus/ant cingulate cortex</td>
<td>(11)</td>
<td>0</td>
<td>54</td>
<td>-14</td>
<td>4.4</td>
</tr>
</tbody>
</table>
The reverse contrast (letter decision – lexical decision) revealed increased activity for letter decision in the left supramarginal gyrus (BA 40), bilateral superior parietal lobes (BA 7), right occipito-temporal junction (BA 19/39) and right superior frontal gyrus (BA 8) (see Table 5.3 and Figure 5.3).

Table 5.3: Regions of significant activation for letter decision versus lexical decision

<table>
<thead>
<tr>
<th>Area</th>
<th>BA</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>z score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left supramarginal gyrus</td>
<td>(40)</td>
<td>-40</td>
<td>-46</td>
<td>40</td>
<td>4.7</td>
</tr>
<tr>
<td>Left superior parietal lobe</td>
<td>(7)</td>
<td>-14</td>
<td>-68</td>
<td>54</td>
<td>4.4</td>
</tr>
<tr>
<td>Right superior parietal lobe</td>
<td>(7)</td>
<td>18</td>
<td>-66</td>
<td>56</td>
<td>4.7</td>
</tr>
<tr>
<td>Right occipito-temporal junction</td>
<td>(19/39)</td>
<td>34</td>
<td>-70</td>
<td>26</td>
<td>5.2</td>
</tr>
<tr>
<td>Right superior frontal gyrus</td>
<td>(8)</td>
<td>30</td>
<td>6</td>
<td>48</td>
<td>4.4</td>
</tr>
</tbody>
</table>

Figure 5.3: Regions of significant cerebral blood flow (rCBF) change in the categorical contrast of letter decision – lexical decision. The top panel shows activation on a rendered image of the standard brain MRI. The middle and bottom panels show the activations on transverse slices at z co-ordinates as described above each section.
5.3.B.2 Priming effects

Nonlinear correlational analysis revealed significant variations in response to differing proportions of related targets in two regions (Fig 5.4) that were also identified in the main effect of lexical decision relative to letter decision (see 5.3.B.1): the left anterior temporal lobe (BA 38) and anterior cingulate cortex. As can be seen from the plots depicted in Figure 5.4, the response in the left anterior temporal lobe (BA 38) consisted of a decrease in activation with increasing proportions of related targets, except for the highest proportion of priming where activation increased. The anterior cingulate cortex showed a nonlinear decrease in activity with increasing proportion of related targets (Figure 5.4). This decrease was only pronounced when the proportion of related targets was high. Two other regions that were not differentially active for lexical decision (in the categorical contrast) showed significant variation in response that survived a corrected threshold: the right superior parietal lobe (BA 7) and right premotor region (BA 6). These two regions showed a nonlinear decrease in activity with increasing proportion of related targets that differed in shape to that seen for the anterior cingulate, and to an extent mirrored the shape of the plot for the anterior temporal lobe. Table 5.4 lists the coordinates and peak z scores for the regions showing significant variance in the SPM(F) map.

Table 5.4: Significant cortical regions showing nonlinear changes in activity with increasing proportion of related targets

<table>
<thead>
<tr>
<th>Area</th>
<th>BA</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>z score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regions also showing enhanced activity for lexical decision</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior temporal lobe</td>
<td>38</td>
<td>-40</td>
<td>4</td>
<td>-28</td>
<td>4.1</td>
</tr>
<tr>
<td>Anterior cingulate cortex</td>
<td></td>
<td>2</td>
<td>28</td>
<td>8</td>
<td>3.5</td>
</tr>
<tr>
<td>Regions surviving corrected threshold</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right superior parietal lobe</td>
<td>7</td>
<td>42</td>
<td>-38</td>
<td>62</td>
<td>4.8</td>
</tr>
<tr>
<td>Right premotor cortex</td>
<td>6</td>
<td>64</td>
<td>-6</td>
<td>42</td>
<td>4.6</td>
</tr>
</tbody>
</table>
Figure 5.4: Regions of significant rCBF change in the nonlinear analysis of the lexical decision data displayed on a 3D rendering of a standard brain MRI. Regions showing enhanced activity for lexical decision and nonlinear decrease in activity with increasing relatedness proportion are circled in blue. Regions surviving a corrected threshold and showing a nonlinear decrease in activity are circled in green.

5.4 DISCUSSION

5.4.A Behavioural effects

Behavioural data confirmed a significant priming effect, i.e. responses during lexical decision were facilitated when the target was preceded by a related prime. A short prime-target interval was used to emphasise automatic processing. Consistent with this the speed of related prime responses remained constant (per stimulus) as the proportion of related primes changed (Faureau and Segalowitz, 1983).

However, the behavioural data also suggested the additional contribution of strategic processes. First, as previously shown by Neely (1991), there was a significant decrease in the nonword RTs as the proportion of related prime-targets increased, even though the number of nonwords remained constant. This effect is consistent with the criterion for producing a “No” response being under strategic control (Seidenberg and McClelland,
1989). Second, there was an increase in RTs to unrelated word targets when the proportion of primes increased from 25% to 75%. This increase in the RTs to unrelated targets (while the RTs to related targets stayed constant) resulted in a nonsignificant increase in the size of the priming effect (see Table 5.1). Overall, the behavioural data indicate both automatic and strategic effects seen in this experimental design, even with the short SOA. Consistent with previous behavioural findings, the strategic effect becomes increasingly important with higher proportions of related word pairs.

5.4. B PET Data
My primary aim was to discover whether there is a physiological correlate of the behavioural phenomenon of priming. The experimental design allowed me (i) to ensure lexical decision was activating regions involved in semantic processing, and (ii) to examine the data for nonlinear variations in activity with changes in the proportion of related targets. The task effect (categorical analysis) is discussed prior to the effect of priming (nonlinear analysis).

5.4. B.1 Lexical Decision
The left inferior temporal gyrus, anterior temporal lobe, posterior middle temporal gyrus, temporal operculum, inferior frontal/insular region, and orbitofrontal cortex showed activation with lexical decision, consistent with previous studies using this task (Price et al, 1994; Rumsey et al, 1997), semantic categorisation tasks (Vandenberghe et al, 1996; Price et al, 1997), and word retrieval tasks (e.g. Mummery et al, 1996). Patient data (Hodges et al 1992; Hodges and Patterson, 1997; Kapur et al, 1994) have also shown that anterior temporal regions are involved in semantic processing. In contrast, frontal lobe lesions do not generally result in semantic deficit. Hagoort (1997) has demonstrated that frontal lobe lesions cause impaired strategic priming but intact automatic priming. These observations from patients plus recent imaging findings (Thompson-Schill et al, 1997) have led to the view that the inferior frontal lobe plays an executive role during semantic tasks (Fiez, 1997). It is noteworthy that, in this study, the inferior frontal region activated for lexical decision does not show sensitivity to semantic priming. It is possible that this is due to the nature of the role of frontal cortex in lexical decision when block design is used. If it is important in setting up a mode of operation for performance of a task, then no differential activity would be expected within the lexical decision conditions. The orbitofrontal cortex has been previously activated by semantic decisions (Vandenberghe
et al, 1996; Price et al, 1997), and there are patient studies (Bechara et al, 1998) that indicate a role for this region in decision making.

I conclude that lexical decision in this context requires semantic processing when the distractors are very word-like and does not, as some have argued (Shelton and Martin, 1992), rely solely on pre-semantic processes.

5.4.B.2 Letter decision

The reverse contrast (letter decision – lexical decision) revealed activation in bilateral superior parietal lobes (BA 7), right superior frontal gyrus (BA 8), right temporo-occipital junction and left supramarginal gyrus (BA 40). This pattern of relative deactivations for lexical decision has been shown previously in language tasks (e.g. Shulman et al, 1997; Rumsey et al, 1997). Notably, the left supramarginal gyrus was activated more for syllable decision – semantic decision (Chapter 4), and though non-significant, showed greater activation for letter fluency – category fluency (Chapter 3). This region is thought to be important in sublexical processing (Price, 1997).

5.4.B.3 Prime - Target Relationship

As discussed in the introduction, certain patterns of response were predicted dependent on the processes involved in semantic priming. Purely automatic processing should lead to decreases with increasing priming; purely attentional processing should lead to increases or no change; a hybrid of automatic and attentional mechanisms suggests a complex pattern of activation response.

I looked for linear and nonlinear changes in activity as the proportion of related targets increased. The areas that are sensitive to priming fall into two categories: one left lateralised region (anterior temporal lobe; BA 38) normally associated with semantic processing, and three regions associated with attention. The involvement of “attentional” regions confirms that strategic post-lexical semantic matching occurs in addition to automatic processing when performing this task. The areas associated with attention and semantic processing are discussed separately below.
5.4.B.3.1 “Semantic” regions

In most regions that were more active for the lexical decision task (relative to the letter decisions task), e.g. the inferior temporal cortex (BA 20), there was no effect of semantic priming seen. However, one temporal region (the anterior temporal lobe) showed variation in activity with increasing proportion of related prime-target pairs. Support for a role for the anterior temporal lobe in semantic priming comes from studies using diverse methodologies. For instance, cortex in this region is thought to be the neural generator of the N400 (Nobre et al, 1994), an electrophysiological signal that is attenuated by semantic priming (Kutas and Hillyard, 1984). Lesion data have shown that left temporal lobectomy patients have impaired individual item recollection while retaining intact information about semantic attributes (Seidenberg et al, 1993). These findings taken together imply that the anterior temporal lobe (BA 38) is important in the identification of a concept denoted by a word, acting in concert with other semantically associated regions that are insensitive to semantic priming (such as the inferior and middle temporal gyrus (BA 20/21)).

In descriptive terms, the response in the left anterior temporal lobe (BA 38) consisted of a decrease in activation with increasing proportions of related targets, except for the highest proportion of priming where activation increased (see Fig 5.4). A similar U-shaped function over a range of values has been observed previously in at least one functional imaging study, where it was explained by two different effects maximal at the two ends of the continuum (Fletcher et al, 1996). The nature of the nonlinear response in this experiment together with the behavioural data also raises the possibility that it is derived here from two processes acting concurrently. Automatic priming leads to decreases in semantic activation but this effect is attenuated and ultimately reversed as strategic mechanisms become involved with higher proportion of related targets. One speculative explanation for this is that semantic priming effects include a direct automatic effect, with an indirect influence of strategic processing principally affecting the non-word responses. Although the behavioural data support this hypothesis, the nature of the experiment precludes separation of the neural response to individual stimuli. The most critical finding, however, is that at least two different patterns exist in the regions held to be involved in semantic processing.

5.4.B.3.2 “Attentional” Regions

The anterior cingulate cortex showed increased activity during lexical decision (relative to letter decision), and a nonlinear decrease in activity with increasing proportion of related
targets (Fig 5.4). This decrease was only pronounced at high priming densities, that is at the priming densities where the reduction in non-word response RTs occurred. This pattern fits with a change in the way the task was carried out - from greater to lesser supervisory control in the terminology of Norman and Shallice (1986). This perspective relates to a variety of characterisations of anterior cingulate cortex function (e.g. Paus et al, 1999; Carter et al, 1998) which suggest that the more active the anterior cingulate is, the less routine the task is. In other words, when the proportion of related words is low, there is little strategic expectation and the task is not routine. In such a situation, activity in the anterior cingulate would be high. Conversely, when the proportion of related words is high, expectation is high and the task is routine, leading to less activity in the anterior cingulate cortex.

Two further regions showed no differential activity in the categorical analysis, but survived correction for multiple comparisons in the nonlinear analysis. The right superior parietal lobe (BA 7) and the right premotor region (BA 6) revealed equivalent activity for lexical and letter decision when no priming was occurring. However, these regions were sensitive to priming, showing a nonlinear decrease in activity with increasing proportion of related targets. These regions are thought to be involved in visuo-spatial attention, and along with the anterior cingulate have been previously associated with attentional mechanisms in previous anatomical (Mesulam, 1990) and imaging studies (Nobre et al, 1997). My experimental design has allowed me to differentiate between these regions in the type of response seen, albeit at a descriptive level. A more precise definition of the functional roles these regions play in semantic priming will require further research. However, the sensitivity of attentional regions to varying degrees of priming suggests the importance of attention in priming, even at short SOAs.

5.4.B.3.3 Semantic priming versus repetition priming
Finally, these findings suggest certain similarities between semantic and repetition priming. Previous repetition priming studies have also shown decreases in activation in task-specific regions and decreases in right superior parietal lobe and right premotor regions, very close to the regions we describe (Schacter et al, 1996). While there are substantial differences between these two forms of implicit memory, my result suggests that attentional brain areas may be involved in both semantic and repetition/identity priming, while there are unique responses to semantic priming in the left anterior temporal lobe, possibly due to automatic processing.
5.5 SUMMARY

In summary, I have shown a nonlinear physiological response to priming correlating with a significant behavioural effect, and differential sensitivity within semantic regions to semantic priming. The behavioural data and PET findings together support a dual-process theory of semantic priming with coexistent automatic and attentional mechanisms. Finally, taken together with previous neuroimaging results on repetition priming, the data suggest that attentional mechanisms underlying semantic priming may be common to different types of priming, while the automatic component is task-specific. Importantly, I have shown activation for implicit tasks in two of the regions known to be involved in explicit semantic tasks: the anterior temporal lobe (BA 38) and inferior temporal lobe (BA 20). This suggests that these regions are processing semantic information rather than performing explicit or implicit retrieval of information, confirming the importance of the regions activated in both Chapters 3 and 4 in the inferolateral temporal lobe in semantic processing.
Chapter 6
An investigation into the neural correlates of long term memory: how unique is the semantic memory network?

6.1 INTRODUCTION
When studying patients with semantic dementia, it becomes apparent that their cognitive deficit cannot be explained simply in terms of loss of semantic knowledge. The behavioural phenomenology described implies that the proposed dichotomy between semantic memory and episodic memory is not straightforward. In particular, information given by a patient in response to a question requiring a semantic response is often autobiographical in nature, related to the personal experience of the subject (see Chapter 1, section 1.6). This observation suggests that the strategy used by patients with semantic dementia to retrieve semantic knowledge has altered in order to compensate for their impoverished semantic representations. In other words, the cognitive architecture underlying the retrieval of semantic memory has altered, at least in emphasis, from that seen normally.

There has recently been considerable debate surrounding this phenomenon, with some (Snowden et al, 1996) suggesting that autobiographical memory helps maintain the remaining semantic memory these patients have. Others concur that these patients do show preserved autobiographical memory, but disagree that this interacts directly with semantic memory (Graham and Hodges, 1997). This chapter aimed to perform an initial exploration of the neural substrates of differing types of remote memory, to investigate the functional-anatomical relationship between them and whether they do indeed interact. A secondary aim was to use naturalistic stimuli and examine the commonalities and differences in activation between such stimuli and more controlled lab stimuli (e.g. word lists), such as those used in the earlier experimental chapters.

As discussed in the general introduction (section 1.6), memory has traditionally been dichotomised into impersonal facts (semantic), and events with a specific temporal context (episodic) (Tulving, 1972). The relationship between these memory subtypes is the topic of continued debate, with some proposing a unitary hypothesis, believing that declarative memory subsumes both memory for personal events and memory for general facts (Squire and Knowlton, 1995). Others view episodic memory as a special extension
of semantic memory, and believe that retrieval of stored information can be asymmetrically affected by medial temporal lobe damage as dissociations between episodic and semantic memory can occur (Tulving and Markowitsch, 1998). Recent findings have implied differential reliance of semantic and episodic memory on the medial temporal lobe structures. Children with bilateral damage to the hippocampal region from early life (Vargha-Khadem et al, 1997) were amnesic for context specific ‘episodic’ memories, but had acquired near average levels of semantic information. The proposal was made that context-free semantic memories could be supported by parahippocampal structures, while the hippocampus was necessary to process context-rich episodic memories. The importance of the hippocampal region in episodic memory (Scoville and Milner, 1957) is unchallenged, however the involvement of multiple cortical regions is a recent notion (Tulving and Markowitsch, 1997). While semantic memory also relies on a distributed network, it is more impaired than episodic memory in patients with lateral temporal cortex damage where the hippocampus is relatively spared (Hodges et al, 1992; Snowden et al, 1996). A recent review of patient deficits has suggested that within the temporal lobe, medial lesions and lateral lesions are associated with differing deficits, the medial lesions causing more severe deficit in autobiographical memory (Nadel and Moscovitch, 1997).

Memory deficits reported in patients are typically characterised in terms of autobiographical personal episodic memory deficits, or impersonal non-context specific memory deficits. However, neuropsychological evidence suggests that a dissociation may exist between personally-relevant and nonpersonally-relevant memory independent of temporal context (De Renzi et al, 1987; Hodges and McCarthy, 1995). As the factors of personal relevance and temporal context are typically confounded, the precise influence of either factor on how memories are stored or retrieved and whether this has specific instantiation at a neural level is as yet unclear (Nadel and Moscovitch, 1997).

Imaging studies to date have examined the neural correlates of memory using specific tasks such as word-pair association (Shallice et al, 1994), or stem cued recall (Buckner et al, 1996); tasks very much removed from everyday use of memory. There has been no functional neuroimaging study investigating personal relevance and temporal context separately. Given the acknowledged importance of studying “real-life memory” (Eichenbaum, 1997), and the possible dissociation between personal and impersonal
memories, it is critical that the functional neuro-anatomy of more naturalistic forms of memory retrieval are examined. Here I examine ‘real-life’ memory retrieval, seeking to address the debate about whether proposed memory subtypes are anatomically distinct. Crucially, I also unconfound the factors of personal relevance and temporal context.

6.2 METHODS

6.2.A Subjects/Data Acquisition

Eight healthy right-handed male subjects (age range 28-41 years) participated in the study, after satisfying the standard inclusion criteria (section 2.2.A). PET scanning was performed in the standard manner as described in Chapter 2 (sections 2.4, 2.5).

6.2.B Tasks

6.2.B.1 Prescanning questionnaire

Several weeks prior to scanning, subjects completed a questionnaire to ascertain details of personal memories and knowledge of public events. Subjects were naive to the purpose of the questions. Statements were constructed from this information and tailored to individual subject’s memories for each of the active conditions. These comprised memories differing along two factors: (i) those with a specific locus in time (T+) or not (T-); (ii) those that were relevant to a subject personally (P+) or not (P-). This manipulation yielded four memory subtypes: autobiographical events (T+P+), public events (T+P-), autobiographical facts (T-P+) and general knowledge (T-P-).

6.2.B.2 Scanning tasks

During scanning, subjects listened via headphones with their eyes closed to spoken statements. The statements were derived from the questionnaire responses and subjects had to indicate whether each was true or false, making a key press response. The statements for each temporally-specific scan were matched for recency, reflecting a range of time points spanning the past twenty years (1977-1997). As well as being matched across scans for the temporal gradient in long-term memories, stimulus statements were also matched in terms of ease of recall using a graded response measure, controlling for relative salience. All four memory types contained semantic knowledge; in this factorial design the critical variables were whether the stimuli were personally relevant to the
individual (P+/−), and whether the stimuli were associated with an identifiable locus in time (T+/−). In the control conditions, subjects heard sets of function words (including prepositions, conjunctions) used in the active scans, but no memory information. Control condition P+ was matched to the personally-relevant memory conditions by containing personal pronouns ("you"/"your"); control condition P− contained no personal pronouns. Subjects decided whether the last word in each control set of function words contained one syllable or more.

A statement was presented every 8 sec, presentation of the statement typically lasting 3-4 sec. Eight statements were presented per scan, with eight sets of function words per scan for control tasks. In all memory scans, two of the eight statements were false, their position within the scan was counterbalanced across scans. Stimuli were matched across scans for number of syllables. Tasks were counterbalanced in terms of scan position across subjects. Subjects were debriefed after scanning and did not suggest any task was more difficult than another. Stimulus examples: (T+P+) “You were Mike’s best man at his wedding”; (T+P−) “Zola Budd tripped with Mary Decker”; (T−P+) “Ray is the youngest of your brothers”; (T−P−) “Presenter Chris Evans has red hair”; (control P+) “While yet your therefore still about this”; (control P−) “Ago rather he yet if because”. Every subject had twelve PET scans, with two performances of each of the six tasks.

6.2. C Data Analysis
The data were analysed with statistical parametric mapping (SPM97 - Wellcome Department of Cognitive Neurology, London, UK). The reconstructed images were realigned, normalised and smoothed (16mm) as described in chapter 2 (section 2.4). The generated statistical images had a full width half maximum (FWHM) resolution of 9.5 x 9.7 x 9.9mm. Main effects of condition were assessed using ANCOVA and contrasts as described earlier (Chapter 2, section 2.4). The contrasts of interest were as follows: (i) main effect of memory vs. control; (ii) main effect of personal relevance; (iii) main effect of temporal specificity; (iv) interaction between personal relevance and temporal specificity (masked with memory versus control). Significance levels were set at P<0.05 (corrected for multiple comparisons).
6.3 RESULTS

6.3.A Main effect of memory versus control

For the comparison of memory with control tasks, the control P- condition was used as baseline as it contained only prepositions/function words and not the added component of personal pronouns as in the control P+ task. The appropriate use of this condition as baseline is confirmed by findings of difference in activation when the two tasks were compared, as later described.

Figure 6.1: A transverse view of the statistical parametric map (SPM) showing activated areas in the comparison of all memory tasks versus control task P-.. Surrounding the SPM are these activations displayed on a 3-D rendered standard MRI.
I first examined which brain regions were involved in memory retrieval, irrespective of memory type (see Figure 6.1). Comparing all memory tasks to the control (P-) task revealed an extensive, predominantly left-lateralised network consisting of the following regions: medial prefrontal cortex (BA 10), the anterolateral middle temporal gyrus (BA 21), temporal pole (BA 38), hippocampus, parahippocampal gyrus (BA 28), posterior cingulate cortex (BA 31) and the temporoparietal junction (BA 39). The right temporoparietal junction was also activated. One further region was activated that did not reach corrected significance - the anteromedial thalamus bilaterally. Comparison of each memory task individually with the control (P-) task revealed activation of the identical network of regions.

Table 6.1: Maxima of peak activations in main effect of memory retrieval

<table>
<thead>
<tr>
<th>Area</th>
<th>Brodmann area</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>z-score</th>
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<tbody>
<tr>
<td>Medial prefrontal cortex</td>
<td>(BA 10)</td>
<td>-4</td>
<td>64</td>
<td>20</td>
<td>6.6</td>
</tr>
<tr>
<td>Left anterior mTG</td>
<td>(BA 21)</td>
<td>-60</td>
<td>-4</td>
<td>-18</td>
<td>7.5</td>
</tr>
<tr>
<td>Left temporal pole</td>
<td>(BA 38)</td>
<td>-48</td>
<td>12</td>
<td>-28</td>
<td>7.2</td>
</tr>
<tr>
<td>Left hippocampus</td>
<td></td>
<td>-22</td>
<td>-12</td>
<td>-14</td>
<td>4.9</td>
</tr>
<tr>
<td>Left parahippocampal gyrus</td>
<td>(BA 28)</td>
<td>-20</td>
<td>-18</td>
<td>-20</td>
<td>5.1</td>
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<tr>
<td>Posterior cingulate cortex</td>
<td>(BA 31)</td>
<td>-4</td>
<td>-56</td>
<td>24</td>
<td>6.9</td>
</tr>
<tr>
<td>Left temporoparietal junction</td>
<td>(BA 39)</td>
<td>-48</td>
<td>-64</td>
<td>24</td>
<td>7.2</td>
</tr>
<tr>
<td>Right temporoparietal junction</td>
<td>(BA 39)</td>
<td>52</td>
<td>-66</td>
<td>26</td>
<td>5.4</td>
</tr>
<tr>
<td>Thalamus</td>
<td></td>
<td>0</td>
<td>-4</td>
<td>8</td>
<td>3.8</td>
</tr>
</tbody>
</table>

6.3.B Differential activity for memory subtypes

Strikingly, however, differential activation was apparent for different memory types within parts of this retrieval network when regional cerebral blood flow (rCBF) plots were examined (Figure 6.2). Direct comparison of personal memories with non-personal memories \{[[T+P+]+(T-P+)] - [(T+P-)+(T-P-)]\} confirmed increased activation of medial frontal, temporopolar, and temporoparietal junction for personally relevant memories. Comparison of temporally-specific memories with non-temporally-specific memories, \{[[T+P+]+(T+P-)] - [(T-P)+ (T-P-)]\}, did not show any significant difference in activation.
Figure 6.2: The plot of the rCBF across tasks for each of the maxima of peak activations for the memory versus control P- comparison. Three clear patterns of activity were apparent, represented by examples A, B and C. For each plot, the activity for each memory condition is expressed as percentage change in activity from the control tasks.

A: The left anterolateral temporal cortex, the left parahippocampal gyrus (shown here) and the posterior cingulate cortex showed no difference in activity between memory tasks, numbered in blue on the SPM in Figure 6.1.

B: Enhanced activity for personally relevant memories irrespective of temporal context was apparent in the temporoparietal junction activations (left shown here), numbered in green on the SPM in Figure 1.

C: Enhanced activity for personally relevant time-specific memories was apparent in the medial frontal cortex, left temporal pole (shown here) and left hippocampal activations, numbered in red on the SPM transverse section in Figure 1.
The medial frontal cortex, the hippocampus and the temporal pole all showed enhanced activity for memories that were personally relevant and had a specific locus in time (T+P+). Such effects cannot be attributed to personal episodic memories merely being more demanding on the memory retrieval system as a whole, compared to the other memory tasks, as the temporoparietal junction activations also showed a differential response to personal memories, but did not discriminate on the basis of locus in time (equal for T+P+ and T-P+). Further, the anterolateral temporal cortex, the parahippocampal gyrus and the posterior cingulate cortex were activated similarly for all memory types, and did not respond selectively on the basis of person or time.

**Figure 6.3:** Interaction between personal relevance, temporal-specificity and task type (memory or control) revealed increased activity in the left hippocampus for the memory tasks but particularly when time-specific memories were personally-relevant. Coordinates: -28, -16, -16, z=3.6 (P< 0.001 uncorrected).

Having used a factorial experimental design, I could delineate regions showing an interaction between personal relevance, locus in time and task type (memory or control). This revealed increased activity in the left hippocampus for memory tasks, particularly when time-specific memories were personally-relevant (Figure 6.3). Interestingly, even across task types the left hippocampus showed enhanced activity for personal relevance, being more responsive to control P+. Direct comparison of the two control tasks [control (P+) - control (P-)] confirmed increased activation in the left hippocampus for the control
sets containing personal pronouns (P+). In summary, the medial frontal cortex and temporal pole are particularly responsive to personally relevant time-specific memories. The left hippocampus responds to all memory types, but it too is relatively more responsive to personal relevance, both in the context of time-specific memories and within basic sets of function words.

6.4 DISCUSSION

While previous functional neuroimaging studies have examined memory retrieval (e.g. Squire et al, 1992; Shallice et al, 1994), and documented involvement of some of the brain regions noted here, none has examined real-life memory retrieval unconfounding the personal relevance and temporal-specificity of memories. This study confirms that memory retrieval of any type utilises a common neural network. The network of limbic, paralimbic and cortical regions activated for all memory tasks corresponds remarkably well to proposed anatomical models of explicit memory processing which have emphasised the distributed nature of structures involved in memory (Mesulam, 1990; Markowitsch, 1995), and confirms the importance of regions outside the medial temporal lobe (Tulving and Markowitsch, 1997).

Critically, however, a subset of regions within this network act in concert responding preferentially to personal episodic memories, while other regions are active for information retrieval in general. This study has shown that even brain areas that are in close proximity behave differently, the lateral temporal and polar cortex show different responses, as do the parahippocampal gyrus and the hippocampus, with the former in each case involved in the retrieval of information per se, and the latter more active for personally relevant specific episodes.

The dissociability of personal and non-personally relevant memories was until recently little studied, but neuropsychological evidence is accumulating, and indicates that the distinction between the two types of memory is valid. Reciprocal connections between the temporal pole, orbitofrontal areas and the hippocampal formation are well documented (Van Hoesen, 1997). Anatomical and neuropsychological data have shown the importance of the temporal pole in personally relevant memory (Kapur et al, 1992; Markowitsch et al, 1993), and it has been speculated that this region encodes the spatiotemporal uniqueness of specific events, and integrates information from
hippocampal structures with information from posterior association regions (Damasio, 1989). The medial frontal region has also been implicated in personal memory; for example, Hodges and Gurd (1994) report a deficit in personally relevant memory in a patient with frontal lobe Pick's disease. Tasks requiring consignment of "agency" or a "theory of mind" to others have activated the same area (Frith, 1996). In the present study, this region may be involved in the verification of memory in reference to oneself, consonant with its proposed role in the memory supervisory system (Shallice, 1988). The activation of the temporoparietal junction is ubiquitous in memory retrieval studies, both imaging (Cabeza et al, 1997) and electrophysiological (Wilding and Rugg, 1996), but its precise role remains unspecified. Its identified preference here for personal memories irrespective of temporal context has not been explored previously but clearly requires further investigation.

Functional neuroimaging of normal subjects reveals those brain areas that are involved in certain cognitive processes, in contrast to patient data which show the brain regions that are critical to a function. Activation of the hippocampus was observed for all memory types. This finding of the hippocampus involved in memory retrieval per se seems compatible with the declarative theory of memory and amnesia (Squire and Knowlton, 1995). However, the additional modulation of hippocampal activity by personal time-specific memories in particular, suggests that it is this aspect of memory retrieval that critically depends on the hippocampus and is impaired with hippocampal pathology. Thus, certainly for memory retrieval, these data support the 'episodic' view of memory (Tulving and Markowitsch, 1998). Further evidence for this comes from the concordance of these results with the functional profiles of the children with bilateral hippocampal damage (Vargha-Khadem et al, 1997). As previously noted, the conclusion from that study was that extra-hippocampal cortex was able to support context-free semantic memories, but that context-rich episodic memories required additional processing provided by the hippocampus. The present study shows contrasting responses in the parahippocampal cortex (and indeed lateral temporal and posterior cingulate cortices) which is responsive to information retrieval in general, and in the hippocampus which is more responsive to personally experienced specific episodes.

In addition to the parahippocampal gyrus, the anterolateral middle temporal gyrus, posterior cingulate cortex and dorsomedial thalamus were activated for memory retrieval,
regardless of type. Deficits in retrieval of general semantic knowledge have been emphasised in patients with anterolateral temporal damage e.g. semantic dementia (Hodges et al, 1992; Snowden et al, 1996). While such patients are known to have deficits in their store of knowledge, the residual knowledge they show is often personally relevant (Snowden et al, 1995). The posterior cingulate cortex is involved in memory, and has been activated by both episodic (Fletcher et al, 1995b) and semantic (Mummery et al, 1998) memory tasks. The thalamus has also been activated by memory retrieval (Fletcher et al, 1995b), and infarction of this region causes memory retrieval deficits, thought to be due to disconnection of frontal retrieval regions and posterior storage components of the memory system (Hodges and McCarthy, 1993). Finally, it is interesting to note that the dorsolateral prefrontal cortex, activated in previous imaging memory retrieval studies (Fletcher et al, 1995b; Nyberg et al, 1996; Fletcher et al, 1998), was not apparent in any of the comparisons in the present study. This region is reported to play a role in monitoring processes necessary for optimal recall (Fletcher et al, 1998). Given that such demands were present in all of the memory tasks, and that monitoring was also required in the control tasks, it is likely that any processes dependent on this region were similarly active across all tasks.

The pattern of activations observed in this study were predominantly left-lateralised. While this may be due to the auditory-verbal nature of the task, previous imaging studies have shown a common network for semantic processing of both words and pictures in the left hemisphere (Vandenberghe et al, 1996), and few hemispheric differences in recall of visual or verbal stimuli (Buckner et al, 1996). A previous PET study examining episodic memory retrieval found largely right-sided activations associated with the memory for personal emotional events (Fink et al. 1996). However, in that study, recency of memories was not controlled for, and although subjects listened to auditory stimuli, the main task was to “imagine” what happened to the people in the memories featured. Patient data has not successfully resolved the issue of laterality with most cases of retrograde amnesia having bilateral damage limiting any conclusions drawn. Thus, it seems that laterality is not a simple issue of left for verbal and right for visual memory processing, and that both modalities can involve the left hemisphere.

Finally, the finding of differential responsiveness in the lateral anterior middle temporal gyrus and the more medial temporal pole suggests a speculative explanation for the
reliance on personally relevant semantic information in patients with semantic dementia. Atrophy in patients with semantic dementia is greatest in the anterior temporal regions, and appears to spread from lateral to medial regions. Limbic areas are largely spared. It appears that the lateral cortical areas and polar region while strongly interconnected, belong to differing (though overlapping) networks – the medial system involving the medial frontal lobe and temporal pole, the lateral involving the anterior middle temporal gyrus and posterior association cortex. (It should be noted here that the posterior association cortex appears to play an integrative role in terms of the two networks). It is possible that the patients are relying on the medial network more heavily than normal subjects in order to access semantic knowledge via personally relevant information. This hypothesis is explored in the second section of this thesis where the prediction is that patients with semantic dementia will activate medial areas more strongly than normals for a semantic task, and have structural damage on the lateral surfaces.

6.5 SUMMARY
This experiment identified a distributed network of cortical and medial temporal brain regions common to the retrieval of long-term real-world memories. Many of these regions bear a remarkable similarity to those activated for semantic retrieval or association, as seen in Chapters 3, 4 and 5. Within this memory retrieval network, the left hippocampus is differentially responsive to personally relevant memories with specific temporal contexts, as are the left temporal pole and medial frontal cortex. The temporoparietal junction activations also show a differential response to personal memories but do not discriminate on the basis of locus in time. In contrast, the left parahippocampal gyrus is involved in information retrieval generally, as are the anterolateral temporal and posterior cingulate cortices.

The differential responses observed clarify the patterns of deficit reported in patients with damage to disparate areas within this memory network. These findings support the view that apparently distinct subsystems in memory are in fact supported by associations between subsets of regions within a common memory retrieval network. Secondly, they show correspondence using real-world and lab-orientated stimuli. Finally, they reveal the degree of commonality within the long-term memory network, but also that certain regions are critical for context-specific memory such as the hippocampus.
Chapter 7

Investigation of the structural deficit in patients with semantic dementia using voxel-based morphometry – correlation of temporal lobe atrophy with semantic deficit

7.1 INTRODUCTION

The previous chapters have explored the functional neuroanatomy of semantic processing in normals. The next stage was to apply these findings to a group of patients with deficits in semantic processing. The remaining chapters of this thesis explore the structural and functional deficits seen in patients, and relate the findings to those in normals. This chapter describes the neuropsychological profile of the group of patients used, and reports the results of a structural analysis performed to delineate the areas of significant grey matter loss in the patients, as compared to a group of age-matched normals. The cognitive and structural deficit are compared both descriptively and formally, in order to confirm a relationship between the severity of cognitive deficit and degree of temporal lobe atrophy.

It is now well recognised that different forms of degenerative brain disease are associated with distinct patterns of neuropsychological deficit which correlate with the distribution of pathology (Mesulam, 1982; Neary et al, 1986). While syndromes associated with focal cortical atrophy were initially reported in the literature more than a century ago (Pick, 1892), interest was rekindled after Mesulam’s 1982 report of six patients with progressive aphasia and left perisylvian atrophy. Over the decade or so following this influential paper it became apparent that there are two major sub-types of (primary) progressive aphasia, non-fluent and fluent, which differ both in terms of the typical distribution of cortical atrophy and the pattern of language impairment (Snowden et al, 1996; Hodges and Patterson, 1996; Mesulam and Weintraub, 1992).

7.1.4 Neuropsychological profile in semantic dementia

This study is concerned with deficits found (both structural and cognitive) in fluent progressive aphasia, or semantic dementia - a term coined to convey the nature of the underlying cognitive deficit which results in a loss of the conceptual database (semantic memory) underlying language usage (Snowden et al., 1989; Hodges et al., 1992; Warrington, 1975) (see also section 1.3.A).
Patients with semantic dementia present with a progressive loss of expressive and receptive vocabulary, and typically complain of difficulty in 'remembering' the names of people, places and things. Patients also perform very poorly on non-verbally based tests of semantic knowledge. The language impairment appears strikingly restricted to lexico-semantic components; syntactic and phonological processes are largely uncompromised until late in the course of the disease (Breedin et al., 1994; Hodges et al, 1994). Importantly, test results show a high degree of consistency between sessions, suggesting a deficit in the semantic store, rather than access to the semantic system (Shallice, 1988). Relevant to the debate concerning category specific deficits, these patients on the whole do not show deficits for one category over another, although occasional individuals have shown animate specific deficits (Snowden et al, 1996; Cardebat et al, 1996). Naming is severely affected, and appears to be secondary to the semantic deficits (Patterson et al, 1994) – patients produce semantic errors, and there is a close association between word comprehension and naming, i.e. if a name is not understood, then that name will not be produced in naming. Importantly, reading is relatively spared (requiring retrieval of phonology), in contrast to the early deficit in naming (requiring semantics).

In contrast to Alzheimer's disease, patients with semantic dementia have relatively intact autobiographical memory (at least for recent events: Graham and Hodges, 1997; Hodges and Graham, 1998). Memory for non-personal events, such as news events, is impaired (Snowden et al, 1996). They also achieve average or even superior scores on tests of visuospatial skills, frontal executive functions and non-verbal problem solving, which do not require comprehension of specific semantic concepts.

Clinically, these patients therefore show impaired comprehension and naming in the presence of fluent speech and preserved repetition and reading. Object and face recognition is also impaired in the presence of well preserved non-semantic perceptual skills. Speech is empty of content, with word-finding difficulties and occasional semantic errors, but is fluent, syntactically well structured, with normal phonology. A striking feature of this syndrome is the ability of patients to perform complex activities and remain independent until late in the course of the disease, being able to find their way, keep track of appointments and remember
day-to-day events. They often continue complex skills such as driving, shopping, and cooking. At a later stage, however, patients may exhibit behavioural changes such as increased rigidity and stereotypic behaviour with a preference for routine; obsessional behaviour can become a feature with many developing a preoccupation with time, housekeeping or particular foods (Edwards-Lee et al, 1997; Hodges et al, 1998; Snowden et al., 1996).

7.1.B Structural Deficit in Semantic Dementia
Semantic dementia is generally regarded as a variant of frontotemporal dementia in which the brunt of pathology falls upon the temporal lobes (Hodges et al, 1998; Snowden et al., 1996; Neary, 1997). Several structural imaging studies have now described focal temporal lobe atrophy visible on MRI, typically bilateral, though sometimes markedly asymmetrical. In some cases, abnormalities have apparently been confined to the left temporal lobe (Patterson et al., 1994a; Hodges and Patterson, 1996; Hodges et al, 1998; Tyrell et al., 1990). The regions of most prominent atrophy are thought to be in anterolateral temporal cortex, especially the temporal pole, inferior and middle temporal gyri (Hodges and Patterson, 1996; Snowden et al., 1996). This syndrome is therefore of considerable theoretical interest since it produces a cognitive deficit restricted to a specific domain, and appears to be associated with restricted neuroanatomical abnormalities on structural imaging.

7.1.C Structural deficit assessment
The methodology available for determining the precise distribution of the disease process has until recently been limited to pathological examination of brains post-mortem. The few investigations which have related pathological findings to cognitive deficits have yielded largely supporting evidence that the anterior temporal lobe is the region most severely affected by disease (Snowden et al, 1996; Schwartz et al, 1998; Graff-Radford et al, 1990). In a somewhat discrepant case studied by Harasty and colleagues (1996), bilateral posterior temporal (BA 37) and parietal regions were the most significantly affected. Others (Graff-Radford et al, 1990) have specifically noted sparing of posterior temporal relative to anterior temporal regions. Of note, no investigation has reported significant hippocampal atrophy in patients with semantic dementia, in line with the relative sparing of episodic memory on cognitive testing.
While results from such post-mortem studies are undoubtedly informative, many patients exhibit more generalised cognitive deficits and extensive pathology by the time of death. The importance of more accurate quantitative techniques to define the neuroanatomical progression of degenerative disease has been highlighted by recent work on dementia of Alzheimer's type (DAT). Most investigations using MRI or CT to quantify atrophy have involved manual measurements of specific structures thought to be most affected in DAT (De Carli et al, 1990; Jobst et al, 1992; Jack et al, 1998). These may ignore changes occurring in other regions of the brain, and are observer dependent. Recently semi-automated procedures using co-registration of serial MRIs have drawn attention to the presence of widespread atrophy, as well as hippocampal atrophy, in patients with DAT (Fox et al, 1996).

To date, there have been very few attempts to examine regional atrophy in vivo in patients with any form of frontotemporal dementia (FTD). Anderson et al. (1997) used manual volumetry on MRI and SPECT to compare the temporal lobe volumes of normal controls with three groups of patients classified as having temporal lobe atrophy, frontal lobe degeneration or DAT. Examining the progression of disease, they found asymmetrical temporal lobe atrophy (left more than right) in the temporal-lobe group, whereas in DAT patients atrophy was symmetrical. Unfortunately, the methodology allowed the investigators only to discuss the temporal lobe as a whole, rather than specific structure regions within it. Moreover, no attempt was made to correlate changes in specific cognitive domains with imaging. Frisoni et al. (1996) also compared a (combined) group of patients with FTD to a group with DAT and controls; they reported common hippocampal involvement for the two degenerative diseases, but relative sparing of the medial temporal lobe in FTD, measured as thickness of the narrowest part of the structure. These researchers specifically excluded patients with progressive aphasia, and once again used manual measurement of structures of interest.

In order to examine more precisely the significant alterations in macroscopic structure associated with semantic dementia at a relatively focal cognitive stage, I have used voxel-based morphometry, a technique first described by Wright and colleagues (1995). This technique applies methods derived from functional imaging to convert structural MRI data into spatially normalised images of grey matter density, and to make inferences about the
differences between normals and patients in a regionally specific and quantitative fashion. There are a number of advantages to this approach. Relative to manual quantitative techniques, it is completely automatic and therefore non-operator dependent. Relative to post-mortem procedures, voxel based morphometry can be utilised \textit{in vivo} - to enable description at an early stage, to monitor disease progression and, most importantly, to explore the neural correlates of specific components of cognition.

7.2 PATIENTS AND METHODS

7.2.A Patients and Control subjects

Six patients participated in this study who fulfilled currently accepted criteria for the diagnosis of semantic dementia (Hodges et al., 1992; Hodges et al, 1994; Hodges and Patterson, 1996), with anomia and loss of meaning for words and objects. The mean age at investigation was 60.5, range 58 - 65 (5 female, 1 male). Results of neuropsychological evaluation are shown in Table 1.

Though the range of severity was broad, the six patients showed a consistent pattern of deficit in semantic knowledge as evidenced by subnormal scores on the Hodges and Patterson (1995) semantic battery and Pyramids and Palm Trees Test (Howard and Patterson, 1992). As with other reported cases of semantic dementia, these six showed sparing of non-semantic linguistic functions such as syntax and phonology, and of non-semantic, non-linguistic cognitive abilities such as visuo-perceptual and spatial skills, and non-verbal problem solving. Importantly, episodic memory was also relatively spared although the two most advanced cases showed some impairment on tests of episodic recall. It should be noted that the patient at the mildest stage of semantic dementia (DM) performed within the normal range on some tests of semantic knowledge, although he showed clear cut impairment on more stringent tasks (such as synonym judgement and generation of verbal definitions) and has also progressed significantly since the completion of this study (see Hodges and Graham, 1998). The heterogeneity in severity of semantic deficit provided us with a range of performance to correlate with the degree of regional cortical atrophy.
Table 7.1: Neuropsychological test results on the six patients involved in the study.

<table>
<thead>
<tr>
<th></th>
<th>DM</th>
<th>MJ</th>
<th>JH</th>
<th>GC</th>
<th>MS</th>
<th>DG</th>
<th>Controls (n=24)</th>
</tr>
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<td><strong>Memory</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Mean (SD)</strong></td>
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<tr>
<td>Digit Span Forwards</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>6.0 (1.0)</td>
</tr>
<tr>
<td>WRMT Word (25)</td>
<td>19</td>
<td>-</td>
<td>16</td>
<td>22</td>
<td>18</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Faces (25)</td>
<td>23</td>
<td>-</td>
<td>19</td>
<td>20</td>
<td>18</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Rey recall (36)</td>
<td>26</td>
<td>17</td>
<td>14.5</td>
<td>25</td>
<td>5</td>
<td>3.5</td>
<td>15.2 (6.4)</td>
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<tr>
<td>Picture Recognition Test (64)</td>
<td>64</td>
<td>59</td>
<td>62</td>
<td>64</td>
<td>52</td>
<td>50</td>
<td>62.9 (2.4)</td>
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<td></td>
<td></td>
<td></td>
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</tr>
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<td>Category Fluency (5 categories)</td>
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<td>6</td>
<td>11</td>
<td>52</td>
<td>7</td>
<td>39</td>
<td>113.7 (19.8)</td>
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<td>Naming (48)</td>
<td>42</td>
<td>6</td>
<td>6</td>
<td>27</td>
<td>4</td>
<td>10</td>
<td>43.6 (2.3)</td>
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<td>Word-Picture matching (48)</td>
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<td>33</td>
<td>26</td>
<td>37</td>
<td>26</td>
<td>23</td>
<td>47.4 (1.1)</td>
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<td>Pyramid and Palm Trees Words (52)</td>
<td>46</td>
<td>39</td>
<td>35</td>
<td>36</td>
<td>39</td>
<td>34</td>
<td>51.2 (1.4)</td>
</tr>
<tr>
<td>Pictures (52)</td>
<td>43</td>
<td>37</td>
<td>33</td>
<td>44</td>
<td>36</td>
<td>22</td>
<td>51.0 (1.2)</td>
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<td><strong>Syntactic Ability</strong></td>
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<tr>
<td>TROG (80)</td>
<td>75</td>
<td>NT</td>
<td>67</td>
<td>70</td>
<td>70</td>
<td>62</td>
<td>78.8 (1.8)</td>
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<tr>
<td><strong>Visuo-Spatial</strong></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>VOSP: Cubes (10)</td>
<td>9</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>-</td>
<td>10</td>
<td>9.0 (1.0)</td>
</tr>
<tr>
<td>VOSP: Position Discrimination (20)</td>
<td>20</td>
<td>20</td>
<td>18</td>
<td>20</td>
<td>18</td>
<td>19</td>
<td>19.3 (0.8)</td>
</tr>
<tr>
<td>Rey Copy (36)</td>
<td>34</td>
<td>31</td>
<td>32</td>
<td>35</td>
<td>21.5</td>
<td>25.5</td>
<td>34.0 (3.0)</td>
</tr>
</tbody>
</table>

The control group comprised 14 subjects age-matched to the patients (mean age 62; range 60-65; 9 female, 5 male) who satisfied the inclusion criteria described in chapter 2 (section 2.2.A).

7.3 MORPHOMETRIC ANALYSIS

7.3.A Significant density loss in individual patients

For each subject, a T1 weighted high-resolution MRI scan was obtained, using a 2.0 Tesla vision system (Siemens GMBH, Erlangen, Germany) with 3D gradient echo sequence. The images were processed as described in Chapter 2 (section 2.7), using SPM 97 to delineate the regions of significant atrophy in each patient, relative to the control group. A conjunction analysis (Price and Friston, 1997a; section 2.5.C) was subsequently performed to determine the common maxima for those regions showing consistent density loss for all patients.
Regions reported survived a significance threshold of p<0.05 (corrected for multiple comparisons).

7.3.4.1 Results of individual analysis

Figure 7.1 displays areas of significant grey matter atrophy in each patient, relative to the group of age-matched normals. The figures are thresholded at p<0.001 (uncorrected) to show the extent of damage. Table 7.2 shows the Talairach coordinates and significance level of the deficits common to all patients, thresholded at p < 0.05, corrected.

Table 7.2: Regions of significant grey matter density difference in a conjunction analysis for all patients, thresholded at p<0.05, corrected

<table>
<thead>
<tr>
<th>Region</th>
<th>Hemisphere</th>
<th>Brodmann area</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>z score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal Pole</td>
<td>(L)</td>
<td>BA 38</td>
<td>-54 9</td>
<td>-38</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>“</td>
<td>(R)</td>
<td>BA 38</td>
<td>-32 16</td>
<td>-28</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>“</td>
<td></td>
<td></td>
<td>42 21</td>
<td>-32</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>“</td>
<td></td>
<td></td>
<td>21 12</td>
<td>-30</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>Amygdaloid complex</td>
<td>(L)</td>
<td></td>
<td>-22 5</td>
<td>-27</td>
<td>5.8</td>
<td></td>
</tr>
<tr>
<td>“</td>
<td>(R)</td>
<td></td>
<td>24 5</td>
<td>-28</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>Middle Temporal gyrus</td>
<td>(L)</td>
<td>BA 21</td>
<td>-66 6</td>
<td>-15</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>“</td>
<td></td>
<td></td>
<td>-66 36</td>
<td>-6</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td>“</td>
<td></td>
<td></td>
<td>-58 57 8</td>
<td></td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>Inferior Temporal gyrus</td>
<td>(L)</td>
<td>BA 20</td>
<td>-58 12</td>
<td>-30</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>“</td>
<td></td>
<td></td>
<td>-40 33</td>
<td>-22</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>Anterior FG at junction with perirhinal cortex</td>
<td>(L)</td>
<td></td>
<td>-27 3</td>
<td>-42</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>“</td>
<td>(R)</td>
<td></td>
<td>-34 9</td>
<td>-40</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>“</td>
<td></td>
<td></td>
<td>38 6</td>
<td>-38</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Insula</td>
<td>(L)</td>
<td></td>
<td>-42 3</td>
<td>2</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td>VMF Cortex</td>
<td></td>
<td>BA 11</td>
<td>-2 21</td>
<td>-18</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-4 14</td>
<td>0</td>
<td>4.9</td>
<td></td>
</tr>
</tbody>
</table>

All patients showed significant atrophy of the left temporal pole (BA 38). In one case (DM), the temporal pole abnormality was confined to the left side; in the other five patients it also affected the homologous area in the right temporal lobe. Lateral regions of the left temporal lobe were atrophied in five of the six patients (left middle temporal gyrus (BA 21), left inferior temporal gyrus (BA 20)). There was no involvement of the posterior third of the
superior temporal gyrus, or of the temporo-parietal junction, even when the data were
examined at a lower threshold ($p<0.01$).

Figure 7.1: Rendering of standard MRI displaying areas of significant neural loss in each
patient relative to the group of 14 age-matched normals. The figures are thresholded at
$p<0.001$ (uncorrected) to show the extent of damage.
From the prominent neuronal loss at the pole, atrophy extended medially to involve the amygdaloid complex bilaterally, and posteriorly to the junction of the fusiform gyrus with anterior perirhinal cortex, around the collateral sulcus (see Figure 7.2). There was no significant atrophy of the hippocampus, the entorhinal cortex, or perirhinal cortex proper.

**Figure 7.2:** Coronal sections depicting the significant atrophy in temporal lobe, with sparing of the hippocampus.

![Coronal sections](image)

In addition to the changes in the temporal lobe, the ventromedial frontal cortex (BA 11/32) was significantly affected in all patients. Finally, no evidence of consistent lateral prefrontal cortical atrophy was found, the only exception being the case GCB.

The different laterality patterns in these patients are also noteworthy. While four of the patients showed a marked preponderance of atrophy in the left hemisphere, GCB showed bilateral distribution (but still more marked on the left); DG's pattern in fact revealed more extensive atrophy in the right than the left temporal lobe. The heterogeneity in degree of lateralisation may prove important in terms of precise cognitive deficit; we return to this point in the Discussion.

The individual patient analyses allowed us to correlate cognitive function with extent of atrophy at a descriptive level. In Figure 7.1 the patients are ordered in terms of severity from top to bottom. This revealed a relatively coherent pattern with increasing extent of affected temporal and ventromedial frontal structures largely corresponding to increasing severity of the cognitive deficit. It can also be seen that the left temporal lobe atrophy extends further posteriorly as the semantic deficit increases, except for DG, who has more extensive atrophy on the right.
7.3.B Correlation of severity of semantic deficit with degree of neuronal loss

Correlational analysis was performed to test the hypothesis that specific anterior temporal lobe atrophy, rather than merely the overall degree of atrophy, is critically related to the semantic deficit. The relative grey matter density values were derived for each patient in the two regions showing significant atrophy in all 6 patients, i.e. the ventromedial frontal cortex (VMFC) and the left anterior temporal lobe (ATL). Severity of semantic deficit for each patient was measured by performance on the word-picture matching component of the semantic battery (Hodges et al., 1992). This task correlates well with other tests of semantic processing, but also has the advantage that it does not require spoken word production, a component of semantic language processing that may be disproportionately impaired in progressive fluent aphasia (Hodges and Patterson, 1997). Performance on word-picture matching was correlated with the relative grey matter density value for each maximum in each of the two neuroanatomical regions using a non-parametric correlational analysis (Spearman’s rho).

7.3.B.1 Results

Figure 7.3: Histogram depicting the relative density values for each patient in the ventromedial frontal cortex and left anterior temporal lobe in order of word-picture ranking.
As predicted, the degree of atrophy in the left anterior temporal lobe correlated significantly with semantic performance (Spearman rho = 0.783, p<0.05 one tailed), but the degree of atrophy in the ventromedial frontal region did not (Spearman rho = -0.029, n.s.). Results are shown in graphic form in Figure 7.3.

7.4 DISCUSSION
We have used a novel method to quantify, for the first time, the distribution of cortical atrophy in a group of six patients with semantic dementia, in vivo, and to relate these neuroanatomical results to the patients' degree of semantic degradation. Our findings have both clinical and theoretical relevance.

The precise and automated technique of voxel-based morphometry, as applied to patients with the temporal variant of FTD, has revealed consistent atrophy in circumscribed regions of the anterior temporal lobe and the ventromedial frontal cortex, with sparing of both the most medial temporal structures and of lateral frontal cortex. The anatomical proximity of the two affected areas, which are functionally disparate, suggests the manner of spread of this disease. Anatomical and reciprocal connections between temporal association cortex, medial temporal regions, amygdala and ventromedial frontal cortex are well known (Jones and Powell, 1970; Aggleton and Brown, in press; Van Hoesen, 1997); spread of disease along such neural connections is plausible. In the present study, the degree of correspondence across subjects in terms of significantly atrophied regions is striking, and implies a common pathological process. The temporal and medial frontal findings will be discussed separately.

7.4.A Temporal atrophy
7.4.A.1 Polar and lateral regions
The most significant and consistent temporal regions affected were the temporal poles (BA 38; left more than right), and left inferior and middle temporal gyri (BA 20 and BA 21). This finding corroborates several reports of atrophy of the anterior and inferior regions of the temporal lobe at post-mortem (Snowden et al, 1996), and on visual inspection of MRI scans (Hodges and Patterson, 1996; Schwartz et al, 1998; Graff-Radford, 1990), but in an observer-
independent fashion and allowing much more precise definition of atrophied regions (within the limits of the spatial resolution).

While the six subjects showed substantial consistency in the regions affected, they varied in terms of severity of semantic deficit. It is apparent from Figure 7.1 that as the degree of semantic deficit increases, the disease process advances posteriorly along the middle and inferior temporal gyri. It is noteworthy that the posterior superior temporal gyri (including Wernicke's area) and the most posterior part of the inferior temporal gyri were not significantly affected. Sparing of Wernicke's area is consistent with the relative preservation of phonological processing in these patients.

These results are in keeping with several functional imaging studies which have demonstrated decreased metabolism in the temporal lobes of patients with semantic dementia (Breedin et al, 1994; Patterson et al, 1994a; Graham et al, 1997). It should be emphasised, however, that changes in functional measures do not necessarily indicate pathology in that region. This point is illustrated by the findings in the next chapter, examining the functional disruption of the semantic network in four patients with semantic dementia (four of the six cases presented here). The present study, with the same (slightly larger) patient group, establishes a significant correlation between semantic processing (word-picture matching) and the degree of atrophy of the left anterior temporal lobe, confirming the central role of this region in semantic processing. It should be noted, however, that since other temporal lobe regions were not included in the present correlational analysis we cannot exclude a functional deficit in other regions.

7.4.A.2 Medial temporal regions

None of the six patients had significant atrophy of the hippocampal region, which underlines the substantial neuroanatomical (and resulting behavioural) differences between semantic dementia and DAT. While temporal polar atrophy extended medially to the amygdaloid complex (see Table 7.2), the hippocampus and entorhinal cortex were spared. The perirhinal cortex was affected at the junction with the fusiform gyrus rostrally but the more caudal portion was probably normal. In a number of patients with semantic dementia, a striking dissociation has been established between performance on semantic vs. episodic memory
tasks with especially marked preservation of memory for recent episodes (Hodges and Graham, 1998; Graham and Hodges, 1997). This behavioural finding correlates well with the dissociation between lateral temporal lobe damage and medial temporal lobe sparing. The finding of relative sparing of perirhinal and entorhinal cortex is relevant to recent demonstrations of preserved recognition memory in semantic dementia (Graham et al, 1997) since there is growing evidence that these structures can support recognition memory performance (Vargha-Khadem et al, 1997; Aggleton et al, 1997). A note of caution is, however, required concerning interpretation of the distribution of atrophy in the medial temporal structures. The exact location of the perirhinal and entorhinal cortex in man remains somewhat controversial. While cytoarchitectonically discrete areas corresponding to these areas in non-human primates can be identified histologically in man (Van Hoesen, 1997; Amaral and Insanti, 1990), the exact surface landmarks which delineate their boundaries are less clearly defined and may be variable. Moreover the voxel-by-voxel method employed here may not offer the resolution to settle these issues. Of importance, however, is the documented preservation of the hippocampus.

7.4.B Frontal atrophy
The medial frontal atrophy documented here justifies the use of the term fronto-temporal dementia to encompass the syndrome of semantic dementia. It also draws attention to the connectivity of the VMFC and the temporal pole. In a study of patients with temporal variant of FTD (Edwards-Lee et al, 1997), the only region consistently affected in addition to the anterior temporal lobe was the ventromedial frontal cortex, matching these results.

Patients with semantic dementia develop behavioural deficits as the disease progresses. The march of the disease from the temporal pole posteriorly along the temporal lobe and anteriorly to the ventromedial frontal cortex correlates well with the syndrome’s natural history. Edwards-Lee et al (1997) reported significant behavioural deficits in patients with temporal variant FTD, and suggested either that the temporal lobes are important mediators for social behaviour, or that the ventromedial frontal cortex and anterior temporal structures work reciprocally to control behaviour. In general, evidence appears to support the latter account. Firstly, medial temporal lobe lesions affecting the limbic system including the
amygdala have long been associated with behavioural deficits (Butter et al, 1970). Consistent with other patient studies (Snowden et al, 1996) we have shown significant atrophy of the amygdala in this group of patients. Secondly, there is overwhelming evidence that the VMFC is involved in processing motivational and emotional stimuli and that damage to this region produces disturbances of emotional and social behaviour in animals (Butter et al, 1970; Myers et al, 1973). The human ventromedial frontal cortex has also previously been implicated in decision making (Bechara et al, 1998), risk assessment (Rogers et al, 1998) and in the pathophysiology of obsessive compulsive disorder (Zald and Kim, 1996; Ames et al, 1994). This latter association is interesting in view of the common observation that patients with semantic dementia become increasingly rigid in aspects of daily life such as time-keeping and domestic routine (Snowden et al, 1996; Hodges et al, 1998).

The data presented here, together with converging evidence from animal and other human studies, suggest that behavioural abnormalities arise from disruption to a network of limbic regions, including the ventromedial frontal cortex, amygdala and connections to anterior temporal lobe structures. Whether temporal neocortex itself plays a role in these social/emotional behavioural processes cannot be determined from our data. It seems most likely that the medial temporo-limbic system and lateral temporal cortical system dissociate in terms of function, with the former crucially involved in behavioural aspects, and the latter critical to semantic processing. This not only correlates well with the behavioural changes in such patients, but also partially upholds the view proposed in chapter 6 (section 6.5) that the patients may be using the more medial temporal regions to compensate, at least in early stages of the disease. The ventromedial frontal cortex is unlikely to be directly involved in the representation of semantic knowledge: no correlation was seen here between performance on word-picture matching and frontal lobe atrophy, and there are no cases I am aware of where lesions of this medial frontal region disrupt semantic processing.

7.5. **SUMMARY**

Voxel based morphometry has been used to delineate the significant cortical areas of atrophy in six patients with semantic dementia, both individually and as a group. I identified well-circumscribed regions of atrophy in individual subjects, namely bilateral temporal poles (left more than right), left inferior temporal gyrus, left middle temporal gyrus, left amygdaloid
complex and ventromedial frontal cortex. The degree of semantic deterioration across the six cases correlated significantly with the severity of left anterior temporal damage. My findings are consistent with previous functional imaging studies emphasising the critical role of the anterior temporal lobe in semantic processing, and extend our knowledge of the disease process in semantic dementia. The finding of ventromedial frontal atrophy fits well with the behavioural deficits (stereotyped, obsessional features) shown by these patients. Objective structural analysis of MRI scans adds a further dimension to the investigation of patients with degenerative disease. Having delineated the structural deficit accurately, the functional deficit can now be assessed using PET, and related to these findings. Chapter 8 examines the activation for a semantic task in the same group of patients with semantic dementia compared to a sub-group of the normals used in the structural analysis.
8.1 INTRODUCTION

The previous chapter described the macroscopic structural changes in a group of semantic dementia patients. The objective in the study described in this chapter was to examine how this focal structural change affects the distributed system activated when performing a semantic task. It is well known that the location and extent of structural abnormality may be a misleading guide to the brain systems specifically responsible for a cognitive impairment: structurally undamaged areas may fail to operate normally if they receive inadequate activation from regions to which they are anatomically connected.

As discussed in Chapter 1 (section 1.4.C), experiments with normal subjects have documented a reasonably consistent network of brain regions active during semantic processing (Demonet et al, 1992; Mummery et al, 1996; Pugh et al, 1996; Price et al, 1997; Vandenberghe et al, 1996; Wise et al, 1991). This network involves predominately left-sided areas, including the left anterior temporal region that is atrophied in semantic dementia.

By comparing activation patterns for patients with semantic dementia to those of normal subjects in a semantic activation study, we can ask at least two important questions:

(i) Do the behavioural deficits in semantic dementia result directly, and solely, from malfunction of atrophied anterior temporal regions, or are they also attributable to under-activation of relatively intact, but disconnected brain structures? The evidence most germane to this question, from functional imaging studies, is currently extremely meagre. Cardebat et al (1996: SPECT) and Patterson et al (1994a: resting PET) both reported significant hypometabolism in the left inferolateral temporal lobe, which is scarcely surprising. To our knowledge, there have as yet been no activation studies performed on patients with semantic dementia.
(ii) Might there be areas of significant activation in patients that are not observed when normal subjects perform the same task? A positive answer here would suggest that such areas might be recruited in partial compensation for damage to the normal semantic network. For example, if homologous right-hemisphere regions (which do not seem, from existing PET evidence, to be essential for semantic tasks) can contribute to semantic processing when left-sided structures are compromised, we might expect increased activation for patients in these regions, and decreased activation relative to normals in the left hemisphere. Alternatively, if the patients' residual semantic abilities are based on partial functioning of the standard network, then activation for both patients and normals should be seen primarily in the left hemisphere.

I used positron emission tomography (PET) to examine changes caused by focal disease to the operation of the network of regions activated by a semantic task. Subjects diagnosed as patients with semantic dementia on the basis of a battery of semantic tests designed by Hodges and colleagues (Hodges et al, 1992; Hodges and Patterson, 1995) were scanned while performing both a semantic task and a non-semantic control task using similar stimulus materials. The differences in regional activation patterns for the two tasks in the patients were compared to those in six age- and education-matched normal control subjects. The semantic task, a modified version of the Pyramids and Palm Trees test (PPT: Howard and Patterson, 1992), was selected for two reasons. First, results of a previous PET study by Vandenbergh et al (1996) employing this same task allowed prediction of the loci of activation in normal participants. These included inferior frontal regions, anterior and posterior temporal regions, and temporo-occipito-parietal (T-O-P) junctions, all mainly left lateralised. Secondly, all of the patients had been tested on the standard PPT test and were able to cope with its requirements. Analyses first established regions of consistent activation in the six control subjects. I then examined areas where the normals and patients showed activation in common, and areas where there were consistent differences in activation between the two groups, thus allowing assessment of regions with normal and abnormal function.
8.2 METHODS

8.2.A Patient details

Six patients were selected for the study, as described in the previous chapter (section 7.2.A). To be suitable for the study, each patient had to be able to perform the Pyramids and Palm Trees test (Howard and Patterson, 1992) on which the semantic PET task was modelled. The PPT is an assessment of semantic associative knowledge which can be administered with either pictures of the concepts or their names (either spoken or written); the PET version used here is described in greater detail below, under “Psychological Tasks” (section 8.2.E). Given the semantic deficit which is the hallmark of semantic dementia, it is not surprising that - with the exception of one patient (DM, who is at an early/mild stage of progression) - all of the patients scored below normal limits when they were tested on the published version of the PPT, with pictures or written words or both. Nonetheless, in standard hospital or home testing, each of the six patients was able to follow the instructions of the task and to cope with its requirements, as indicated by an above-chance score. Under these usual test conditions, there is no time pressure; but for the PET version, in order to standardise experimental conditions across subjects, it was necessary to impose a time deadline for each trial. Either because of this additional time pressure, or because the general atmosphere of being tested in a PET scanner is more anxiety-provoking than the usual over-the-desk condition, two of the six patients did not manage to score above chance on the associative task performed during scanning. These two subjects were therefore removed from analysis, and will not be considered further here. Of the remaining four patients, three were female, one male; age range 58-60 years (mean 58.75 years). In the previous chapter, Table 6.1 provides a summary of their performance on a range of neuropsychological tests. The patients who were able to perform the associative task were DM, GCB, MJ, MS.

8.2.B Control group

The control group consisted of six normal, right-handed volunteers, age and education matched to the patient group. All control subjects (3 males, 3 females; age range 52-64, mean 57) satisfied inclusion criteria described in Chapter 2 (section 2.2.A).
8.2.C Data acquisition

Each subject underwent 12 PET scans in the standard manner, as described in chapter 2 (section 2.4). Practise of the task and familiarisation of the patients with the scanner was paramount in this study to minimise further impairment of performance by anxiety. All patients were therefore extensively practised on the task (with different stimuli) until they were able to perform reliably within the time limit specified.

8.2.D Psychological Tasks

Each subject was scanned three times in each of four conditions composed of two modalities (words or pictures) crossed with two tasks (semantic and visual judgement). Each trial consisted of a triad of words or pictures arranged in triangular format (as in the PPT test and the PET version designed by Vandenberghe et al, 1996; pictures from Snodgrass and Vanderwart, 1980), with the reference stimulus at the top of the triangle and the two response choices side-by-side. (see figure 8.2).

Figure 8.2: Illustration of tasks performed by subjects during scanning. The 4 conditions are depicted as a 2x2 factorial design i.e. semantic judgements on (i) objects (ii) words; visual judgments on (i) objects (ii) words.
In the semantic task, on each trial, subjects pressed a left or right key-press button to indicate the response choice that was more closely semantically associated with the reference item; for example COW: horse, bear; SWITCH: light bulb, candle; COAT: glove, sock; CUCUMBER: tomato, corn (note that in these examples, the correct response is the one on the left; in the test, the correct response occurred in left/right position on half of the trials in random order). The visual control task consisted of a matching to sample task for physical size on the screen. Each trial contained the identical concept (word or picture) in all positions of the triangle; the correct response choice was the one closest in size to the reference stimulus. The correct response differed by 15% in size from the reference item, and the distractor was a further 15% different in size. Once again, subjects pressed a left or right key-press button to indicate their choices.

Each subject saw a particular concept triad only once, in either word- or picture-modality, and mode of presentation was counterbalanced across subjects such that each triad occurred equally often in the two modalities. Each run consisted of 12 within-condition trials, with a new triadic stimulus presented every 6 seconds. Note that this is a slower task pace than the 4.5 s inter-stimulus interval used in Vandenberghe et al (1996). Presentation of tasks was also counterbalanced. Subjects were practised on each of the conditions prior to scanning.

8.2.E Data analysis

The data were analysed with statistical parametric mapping as described in Chapter 2, section 2.7). The search volume went from z = -48 mm to z = +60mm, with a final image resolution (full width half maximum) x = 10.7 mm, y = 11.0 mm, z = 11.4 mm. The SPMt values were transformed to the unit normal distribution (SPMZ) and thresholded at p = 0.001 uncorrected for multiple comparisons.

Analysis was performed using a multistudy design, allowing assessment of the contribution of all individual subjects to the group effects. This approach distinguishes areas of consistent activation across subjects from areas yielding significant intersubject variability (see section 2.5.G). To identify group effects, I summed over the effects from the six normal subjects or the four patients. To identify differences between normal and
patient effects, I report and interpret only those areas where each patient showed a significant difference from the normal group, i.e. the activation difference was consistent within each group (either patients or normals). This was achieved using a conjunction analysis on the four interaction terms (see section 2.5.C). By using conjunction analysis, effects that were not consistent across patients were removed. This was critical, as patient variability is great and interpretation of differences in each patient would be difficult.

Areas were first identified in the normals that were significantly more active (i) for the semantic task than the visual task; (ii) for semantic activation for words than for pictures, and vice versa (i.e. the interaction between stimulus type and task). Areas were then identified that were consistently activated across the two groups (normals and patients) for the above contrasts. Finally, areas that were significantly more active in normals than in all patients, or vice versa, were identified from the series of task by subject group interactions.

Usually, with normal subjects, the grey matter threshold with PET images is set at 80% of whole brain activity (see section 2.4.D). However, as these patients had significant focal atrophy, the grey matter threshold was lowered to 50% to test for activation within and around atrophied regions.

It was expected that normal control subjects would show activity in a network of regions similar to that previously reported for this task (Vandenberghe et al, 1996): the left inferior frontal gyrus (iFG) (BA 45, 11, 47); left inferolateral temporal region, involving areas BA 21, 20, 21/37; left temporo-parietal junction (TP, BA 19/39); left superior occipital gyrus (sOG) (BA 19); left hippocampus (BA 34) and right cerebellum. These and homologous regions in the right hemisphere were used as regions of interest, interpreting activity significant at an uncorrected level of p<0.001 (Z>3.09). For areas outside these regions, I discuss areas surviving a corrected threshold of p<0.05 (Z>4.3), though tables include all areas significant at p<0.001 (uncorrected).
8.3 RESULTS

8.3.A Neuropsychological profile
In the previous chapter, the general and semantic deficits were described. Here the relevant semantic deficits for the four patients analysed are briefly summarised. (Table 8.1). The most consistent and significant neuropsychological deficit shown by the patients with semantic dementia was in naming. It has been shown previously that the anomia in semantic dementia can be explained on the basis of progressive dissolution of the lexico-semantic system (Patterson et al, 1994).

Table 8.1: Summary of the patients' psychological profile prior to scanning for semantic tasks. PPT = Pyramids and Palm Trees; GNT = Graded Naming Test; Tests marked with the symbol are from the Hodges & Patterson semantic battery.

<table>
<thead>
<tr>
<th>SEMANTIC TESTS</th>
<th>DM</th>
<th>MJ</th>
<th>JH</th>
<th>GCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPT Words</td>
<td>49</td>
<td>39</td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td>PPT Pictures</td>
<td>51</td>
<td>37</td>
<td>33</td>
<td>44</td>
</tr>
<tr>
<td>*Naming</td>
<td>40</td>
<td>6</td>
<td>6</td>
<td>27</td>
</tr>
<tr>
<td>GNT</td>
<td>12</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>*Word-picture matching</td>
<td>48</td>
<td>33</td>
<td>26</td>
<td>37</td>
</tr>
<tr>
<td>*Fluency - category living (4 categs)</td>
<td>41</td>
<td>5</td>
<td>5</td>
<td>35</td>
</tr>
<tr>
<td>*Fluency - manmade (4 categs)</td>
<td>37</td>
<td>1</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>- letter (FAS)</td>
<td>61</td>
<td>15</td>
<td>12</td>
<td>28</td>
</tr>
</tbody>
</table>

The patients were also deficient on semantic tasks such as PPT and word-picture matching, though the group was heterogeneous in terms of the degree of loss of semantic knowledge. For example, DM, who is at a relatively early stage of semantic dementia, appears normal on these relatively easy semantic tasks but is below normal limits on more stringent semantic assessments (Hodges and Graham, 1998). This variability between individual patients underlines the importance of constraining interpretation of patient activations to those that were common to all individuals in the group. In contrast to the significant deficit on tests of naming and semantic knowledge, the patients were, as predicted, relatively well preserved on tests of cognitive function outside the semantic domain.
8.3. B Behavioural profile during scanning

For the semantic task conducted during the PET study, the patients were reliably less accurate than the controls in performance for both modalities (words p=0.006; pictures p=0.03), although each of the four patients achieved a score above the chance level of 50% (see Table 8.2).

**TABLE 8.2:** Mean reaction times (RT), standard error (S Err) and accuracy (as mean % correct for each condition) for controls and patients during the scanning tasks. Vis words = visual judgements on words; Vis pict = visual judgements on pictures; Sem words = semantic judgements on words; Sem pict = semantic judgements on pictures.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th></th>
<th></th>
<th>Patients</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean RT</td>
<td>S Err</td>
<td>Accuracy (mean %)</td>
<td>Mean RT</td>
<td>S Err</td>
<td>Accuracy (mean %)</td>
</tr>
<tr>
<td>Vis words</td>
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<td>93.5</td>
<td>2563</td>
<td>(94)</td>
<td>95.8</td>
</tr>
<tr>
<td>Vis pict</td>
<td>2446</td>
<td>(79)</td>
<td>91.2</td>
<td>2345</td>
<td>(65)</td>
<td>97.2</td>
</tr>
<tr>
<td>Sem words</td>
<td>3376</td>
<td>(109)</td>
<td>90.2</td>
<td>3621</td>
<td>(159)</td>
<td>71.8</td>
</tr>
<tr>
<td>Sem pict</td>
<td>3691</td>
<td>(109)</td>
<td>85.2</td>
<td>3224</td>
<td>(113)</td>
<td>68.8</td>
</tr>
</tbody>
</table>

The two subject groups responded with remarkably similar RTs, with the one exception that patients were faster than controls in semantic judgements on pictures (p=0.004). There may have been a hint of speed/accuracy trade-off between the two modalities in the semantic condition for patients, although their (slight) accuracy advantage for words > pictures did not approach statistical significance.

Within the semantic task, the two groups showed differing RT patterns across modality: the controls made faster semantic decisions for words than pictures (p=0.04), whereas the patients were quicker to respond to pictures than words (p=0.04). When RTs for individual subjects were analysed, each normal showed a consistent tendency to be faster with words, but none of the effects were significant. The individual patients' response times were heterogeneous: one was significantly faster on semantic decisions for pictures than for words; three showed no significant differences (one of which showed a reverse
trend, i.e. words faster than pictures). There were no consistent effects of modality on accuracy in either direction in either group.

The visual control task was easier than the semantic task, as reflected in both significantly faster reaction times (RTs) (p<0.0001 for both groups) and higher accuracy on the size judgements than on the associative semantic judgements (control group p=0.05; patient group p<0.0001). The visual tasks showed no significant differences in reaction time or accuracy either within group or between the two groups.

8.3. C PET Results
8.3. C.1 Normal activations
As noted above, it was expected that semantic judgements would activate a network of regions for the normal group similar to that seen with previous use of this task in normals (Vandenberghe et al, 1996), despite somewhat different stimulus parameters. This expectation was fulfilled (see Appendices 4 and 5 for tabulated results for the two groups). Regions activated in the main effect of semantic tasks versus visual size discrimination tasks (for both words and pictures) included the left iFG (both BA 47 and 45), left posterior inferior temporal gyrus (iTG) (BA 37/19), bilateral TP junction (BA 19/39), left sOG (BA 19) and anterior cingulate cortex. The left middle temporal gyrus (mTG) (BA 21/37) was more active for words than pictures in the semantic condition, in common with previous findings (Vandenberghe et al, 1996). In this study, further areas produced significantly higher activation with semantic judgements for words than for pictures: the left iTG (BA 20), left temporal pole (BA 38), and left iFG (BA 47), which were previously reported as common to both modalities (although with higher z-scores for words than for pictures). Comparison of the size discrimination task in the two modalities suggests that this differential activation for the two semantic conditions may have resulted in part from activation of the semantic network by the control (size discrimination) task for pictures. Pictures may have provoked automatic semantic processing even when subjects were only asked to judge their relative size. This could in part be a consequence of the longer exposure duration (6s) used. No areas were found to be significantly more active for semantic judgements for pictures than for words.
(BA 47), left iTG (BA 20), left temporal pole and posterior cingulate were more active for semantic judgements on pictures relative to words in the patient group, whereas the same region was the site of a modality effect in the opposite direction in the normal group (words > pictures). While this differential activation was relatively consistent for all normals, the patient group showed considerable variability in activation of the temporal regions. For example, two patients activated the iTG (BA 20) more for semantic judgements on words, but the other two relatively more for semantic judgements on pictures. This interaction between modality and group on the PET data was also observed on the behavioural measure of response times. Since this study is concerned with common differences between patients and normals, I do not place much emphasis on the interaction between subject group and stimulus modality.

**Figure 8.3:** Regions of significant regional cerebral blood flow (rCBF) change common both to patients and normals for the main effect of semantic judgements minus visual judgements.

8.3.C.2 Reduced for patients relative to normals

The left posterior iTG (BA 37/19) and right TP junction (BA 39) were significantly less active in all patients than in normal subjects regardless of stimulus modality (Fig 8.4). Neither of these regions was the site of significant structural damage (chapter 7, Fig 7.2).
Because the patients were reliably less accurate than normal subjects on the semantic processing task, it is important to try to assess the possible relevance of this difference in performance to the activation abnormalities observed for the patients. Two additional analyses were therefore performed. First, a correlational analysis examined variation of PET activation with performance on the semantic task, and found NO significant correlation between success of semantic judgements and level of activity in the left posterior iTG (BA 37/19) and right TP junction (BA 39).

A second analysis used only the scans where performance was matched for the two groups. The accuracy range for control subjects on the semantic judgement task (across the 36 separate scans: 6 subjects x 6 semantic scans each) was 56-100 per cent (mean 84.8). All patient scans (5 of 24) on the same task that fell outside this range were therefore discounted, giving an accuracy range of 60-100 per cent (mean 78.6) for the patients. Analysis using these scans showed the same pattern of activation differences between normal participants and patients as the initial analysis, notably in the anterior and posterior temporal lobe. These results demonstrate that significant reduction in regional activation for the patients relative to normals did not result simply from the patients' less competent performance on the semantic task.
8.3.C.3 Enhanced for patients relative to normals

The semantic dementia patients in turn activated certain areas consistently more than normal subjects during semantic tasks. Specifically, the left premotor region (BA 44/6), left anterior STG, and right anterior temporal lobe all showed enhanced activity for both words and pictures in patients relative to normals (Fig 8.5). Differential activation for the two groups is tabulated in Appendix 5.

Figure 8.5 Regions of significantly enhanced activation in patients relative to normals

8.4 DISCUSSION

This study has shown differences between a normal group and patients with a focal semantic deficit in the network of areas activated by a semantic task. The control group showed activations consistent with those reported by Vandenberghe et al (1996), thus successfully replicating — for an older group of participants and with different presentation parameters — some previous findings on the network of brain regions critically involved in this kind of semantic processing. A considerable part of this same network was activated by semantic judgements in the patient group as well, specifically the iFG (BA 44,45,47), left mTG (BA 21/37), left TP junction (BA 19/39), left sOG (BA 19), anterior cingulate cortex and right cerebellum. Taken in conjunction with the behavioural data, this finding suggests that, despite the significant (and expected) difference in performance accuracy between patients and normals, the two groups were performing the tasks in a largely similar manner. Of considerable importance, however, there were also significant differences in regional activation between the two subject
behavioural data, this finding suggests that, despite the significant (and expected) difference in performance accuracy between patients and normals, the two groups were performing the tasks in a largely similar manner. Of considerable importance, however, there were also significant differences in regional activation between the two subject groups in the contrast between semantic and visual control tasks, and these differences will now be discussed with reference to the appropriate lesion data and previous functional imaging findings. Changes in the temporal/parietal lobes and frontal lobes will be dealt with separately.

8.4.A Temporal/Parietal lobes

8.4.A.1 Posterior regions - no lesion, functional deficit
Discrete areas activated in the controls - the left posterior iTG (37/19) and right TP junction (19/39) - were consistently absent in all patients across both modalities of stimulus input. The left posterior iTG, first referred to by Nielson as a language formulation area (1946), and since then as the basal temporal language area (Burnstine et al, 1990) has direct connections to Wernicke’s area (DiVirgilio and Clarke, 1997). It has been shown that lesions in this region may cause specific naming deficits (Luders, 1991); more recently, damage in the posterior inferior portion of BA 37 has been linked to anoma without major associated semantic deficit, and a role proposed for this region in “allowing the semantic system access to stored lexical information” (Foundas et al, 1998).

Supporting evidence for this hypothesis comes from previous functional imaging studies, which have shown activation in left BA 37 using several different language tasks, including naming (of objects and words - Bookheimer et al, 1995; of letter/colours/objects - Price and Friston, 1997a) and semantic word generation to auditory cues (Wise et al, 1991; Warburton et al, 1996). These studies suggest a role for the left basal posterior temporal area (BA 37/19) in retrieval of the name of a concept (Price and Friston, 1997a), independent of modality of the stimulus prompting retrieval. This putative role is consistent with the finding that the posterior iTG is consistently not activated in these four anomic patients. The fact that the patients had a variable degree of semantic associative deficit is not incompatible with the above conclusion. As previously
noted, other regions are activated commonly by semantic tasks, crucially including the anterior temporal lobe. I am not claiming that the lack of activation of the posterior inferior part of BA 37 is responsible for the patients' core semantic deficit, merely that this physiological deficit is consistent with the patients' most severe and consistent behavioural abnormality, i.e. anomia.

The patients showed no consistent posterior temporal atrophy on MRI, and the morphometric analysis performed revealed no differences in the posterior iTG (BA 37/19) compared to the six age matched normals either. Recent work has shown in at least one case of progressive fluent aphasia/semantic dementia (Harasty et al, 1996) that there can be pathological (post-mortem) evidence of disease in BA 37; the present study, however, provided no structural counterpart in these cases. Although the possibility cannot be excluded that the lack of activation is due to pathological involvement at the microscopic level, a more plausible explanation seems to be that this region is structurally intact but failing to function normally because of reduced input from the anterior temporal lobe. This hypothesis predicts relatively normal activation of BA 37/19 in tasks that do not require the anterior temporal lobe. Further imaging studies are therefore required to adjudicate between alternative explanations of this striking result.

The posterior middle temporal gyrus was activated in both patients and controls. This area is contiguous with the basal temporal lobe though lies more anterior and dorsal, including part of BA 37 and extending into BA 21. The posterior mTG is known to be activated by semantic tasks (e.g. Martin et al, 1995; Mummery et al, 1996; Vandenberghe et al, 1996), and is commonly affected in patients with aphasia plus a semantic deficit (Cappa et al, 1981; Chertkow et al, 1997). Both lesion and functional imaging data are accumulating to suggest that the region designated BA 37 is functionally “divided”, though its differing roles are intimately connected. Both parts seem involved in word retrieval, but the middle temporal gyrus may be more concerned with some aspect of semantic knowledge, whereas the more infero-posterior temporal region may be more critical in the interface between semantics and phonology.
The other posterior temporal/parietal region to show decreased activation in patients relative to controls was the right TP junction. This was activated significantly more for both modalities in normals relative to patients, whereas the left TP junction activated consistently in both groups. Lesion studies suggest that damage to the left TP junction also causes comprehension deficits (Dejerine, 1892; Hart and Gordon, 1990), and this left area has been activated in previous studies of semantic processing (e.g. Vandenberghe et al, 1996; Wise et al, 1991; Martin et al, 1995). The preservation of activation of the left TP junction suggests that it may be involved in maintaining the patients’ residual ability to perform the semantic task; the decrease in the right TP junction could reflect a number of task-related differences between the two groups, including performance and degree of attention. For example, it has been shown that activity in this region induced by reading words is modulated by stimulus duration (Price and Friston, 1997b).

8.4.A.2 Anterior regions - structural deficit, continued activation

Previous imaging and lesion data concur that the anterior temporal lobes are involved in semantic processing (e.g. Damasio et al, 1996; Vandenberghe et al, 1996; Hodges et al, 1992). Structural analysis in these patients revealed significant anterior temporal lobe atrophy in all cases (left more than right) consistent with previous findings (Hodges, 1994). Activation of the atrophic left temporal pole was significantly decreased in patients compared to controls (though for word stimuli only). However, some parts of the anterior temporal lobes were activated in the patients, despite focal atrophy. In particular, both the left anterior sTG and right anterior temporal lobe (BA 38) actually showed enhanced activity in patients compared to controls for both task modalities. It must be emphasised that these effects are due to relative increases in blood flow in the semantic task as compared to the visual task: regional cerebral blood flow in the anterior temporal lobes (regions of significant structural change) was unsurprisingly lower in patients than in normals. However, examining the relative difference in blood flow between the semantic and control tasks, this relative change was greater for patients than normals. Patients therefore showed peri-damage activation close to significant structural changes. In addition, the right-sided activation suggests that the patients may be relying more than normals on these homologous right hemisphere structures for semantic processing.
Nevertheless, the patients’ significant semantic deficit clearly demonstrates that right temporal structures are not sufficient for adequate semantic performance.

8.4.A.3 Summary of temporal lobe findings
Most of the currently available evidence suggests that while some posterior cerebral regions are involved in semantic processing per se, the posterior iTG is more critically involved in accessing and retrieving phonological output from semantics (Foundas et al, 1998; Raymer et al, 1997). Extrapolating from these results to our data, it is feasible that in normals the posterior inferior temporal region (BA 37/19) is involved in retrieving the name of a concept and in semantic dementia this function is significantly compromised due to disrupted interaction between anterior and posterior temporal structures. Although no explicit naming is required in the PPT semantic task, implicit activation of regions involved in naming may occur for many semantic tasks (e.g. Price et al, 1997).

8.4.B Frontal regions
A large swathe of activity in the left frontal lobe was found in both groups for both modalities in the semantic task, extending from the iFG (BA47) through BA 44/45 to premotor and motor cortex. Although the role of the inferior frontal gyrus (BA 44/45/47) in semantic processing is under considerable debate, I suggest (along with Fiez, 1997, and Thompson-Schill et al, 1997) that these frontal areas are more likely to be involved in the strategic control or selection of semantic material than with semantic processing proper. The two main reasons for this, in my view, are the complementary facts (i) that there is no evidence for comprehension deficits in patients with damage restricted to frontal regions, and (ii) that patients with substantial semantic impairment, like MJ and JH from the present study (see Table 8.1) often have no damage to frontal structures (see chapter 7, Figure 7.2).

Within the large left frontal region activated for the semantic task in both control and patient groups (Figure 8.3), several sub-regions were in fact significantly more active for patient than normals (Figure 8.5). If, as suggested above, these frontal structures are important for strategic control or selection in semantic judgement tasks, then it is
possible that the patients' semantic impairment enhances the requirement for frontal involvement.

8.5 SUMMARY

In summary, this study has shown activation of a network of regions for a semantic associative task in a group of patients with a focal cognitive deficit affecting naming and semantic knowledge. A number of regions in the network were activated alike for normal controls and patients (explaining why the patients are able to perform the task to some degree); but consistent differences between subject groups were also found. The behavioural deficits in patients with semantic dementia apparently result both from malfunction of atrophied anterior temporal regions and underactivation of additional temporal regions, specifically left BA 37/19. The lack of activation of the posterior inferior temporal lobe is consistent with the observation that such patients all have anomia. I conclude that changes in activity in regions distant to the patients' structural damage support the argument that their prominent anomia is due to disrupted temporal lobe connections. While further research is required to establish a definitive account of this result, it provides a powerful argument for the importance of functional imaging studies in neuropsychology.

One major question that arises from these findings, however, is the role of the frontal lobe in such a task. The large swathe of activation that was seen for both groups showed increased activation in the patients relative to the controls. It was hypothesised that this was due to either increased effort of retrieval in the patients, or due to altered strategy for retrieval of semantic information. However, this point could not be addressed in the present study. The next chapter therefore describes the results from a study of a patient with extensive frontal lobe damage, performing the identical task in an attempt to investigate whether these frontal regions are indeed necessary for performance of the semantic task.
Chapter 9

Investigation of performance of a semantic task in a patient with extensive left prefrontal cortex damage; structural and functional findings.

9.1 INTRODUCTION

In the previous study of the disordered semantic system in patients, both normals and patients showed enhanced activation of an extensive left frontal region during the semantic task. In fact, this activation was significantly greater in the patients than in the normal subjects. The explanation proffered was that the region was involved in an executive function, perhaps selection or search through semantics, and that the patients, making a more effortful search in order to perform the task, activated the region more strongly. An alternative hypothesis is possible however: this region could be involved in semantic processing per se, and the patients could be activating that region more strongly due to lack of activation in other regions, such as the posterior inferior temporal lobe. In order to resolve this issue, it is necessary to show that the semantic task can be performed without activation in the frontal lobe. This chapter presents the results on the same task of a patient with a large left frontal and perisylvian lesion due to cerebral infarction.

The ongoing debate concerning the precise role of the frontal lobe in semantic processing is discussed in detail in chapter 10 (section 10.4.B). In brief, recent findings have cast doubt on the initial conclusions of authors such as Petersen et al (1988), who suggested that the left prefrontal cortex is critical to semantic processing. While many studies have activated this region in semantic processing tasks (with notable exceptions), neuropsychological studies have failed to demonstrate the necessity of the left iFG for semantic retrieval. It has been hypothesised that this frontal region is involved in high level selection processing (e.g. Thompson-Schill et al, 1997; Fiez et al, 1997), consistent with earlier proposals of a role in intrinsic selection of a response (e.g. Frith et al, 1991).

The primary hypothesis explored in this study was that the role of the frontal lobe is executive in nature and that performance of a semantic task is still possible with damage to this region, i.e. that the frontal region activated in many semantic tasks is not necessary for semantic processing. Second, the aim was to investigate the reorganisation of the semantic network after damage. Chapter 8 suggested that peri-damage activity may occur in the temporal lobes following atrophy, and that at high levels of cognitive function such
as semantic processing, there is limited functional reorganisation involving the right hemisphere. The study described in this chapter enabled us to examine the possibility of functional reorganisation in the frontal lobes, and peri-infarct activity within both the frontal and temporal lobes. Patient SW was studied, who was able to associate words and pictures on the basis of semantic relationships despite extensive damage to the left frontal, inferior parietal and superior temporal cortices. The same task was used as in the previous chapter in order to compare the performance of patient SW and the semantic dementia patients.

9.2. NEUROPSYCHOLOGICAL PROFILE

SW (DOB 5/1/37) suffered an extensive left middle cerebral artery infarct on 16th May 1993. He was assessed behaviourally in terms of comprehension and phonological skill in April 94; August 95; July 97. He has no residual speech output, but is able to comprehend task requirements and make decisions to respond appropriately. Single word recognition and comprehension were assessed with lexical decision, the Pyramids and Palm Trees test (Howard and Patterson, 1992), and synonym judgements from the PALPA battery (Kay et al, 1992). At the time of PET scanning, SW was aged 50.5 years. Results of serial test sessions are presented in Table 9.1.

9.2.A Semantic tasks

SW was able to perform lexical decision quickly and easily within the normal range for both high and low imageable words. He also performed within the normal range of accuracy on Pyramids and Palm Trees. On synonym judgements, he performed well above chance for both high and low imageability words but fell just below the normal cut-off. A similar pattern of deficits was seen on both written and auditory sentence comprehension tasks from PALPA.

9.2.B Phonological and orthographic tasks

Results indicated impairment on phonological decisions from visually presented words. These tasks require the retrieval of phonology prior to the judgement. SW’s ability to make rhyme judgements when given the phonology (i.e. in the auditory modality) indicated an impairment in phonological retrieval. SW was also impaired on writing words to dictation or from visually presented pictures.
Table 9.1: Details of language assessment at time of imaging study

<table>
<thead>
<tr>
<th></th>
<th>SW</th>
<th>Chance</th>
<th>Normal cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SEMANTICS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual Word to Pictures (P and PT)</td>
<td>49/52</td>
<td>26/52</td>
<td>48/52</td>
</tr>
<tr>
<td>Visual Word Pairs (synonym judgements) High Im</td>
<td>35/38</td>
<td>19/38</td>
<td>36/38</td>
</tr>
<tr>
<td>Visual Word Pairs (synonym judgements) Low Im</td>
<td>29/38</td>
<td>19/38</td>
<td>33/38</td>
</tr>
<tr>
<td>Lexical Decision on Visual Words and Pseudowords</td>
<td>155/160</td>
<td>80/160</td>
<td>158/160</td>
</tr>
<tr>
<td>Visual Sentence to Picture matching</td>
<td>46/60</td>
<td>20/60</td>
<td>55/60</td>
</tr>
<tr>
<td>Auditory Sentence to Picture matching</td>
<td>41/60</td>
<td>20/60</td>
<td>55/60</td>
</tr>
<tr>
<td><strong>PHONOLOGY FROM AUDITORY WORDS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spoken Word to Picture matching</td>
<td>35/40</td>
<td>8/40</td>
<td>39/40</td>
</tr>
<tr>
<td>Auditory Word Rhyme judgements</td>
<td>28/30</td>
<td>15/30</td>
<td>29/30</td>
</tr>
<tr>
<td><strong>PHONOLOGY FROM VISUAL WORDS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual Word rhyme judgements</td>
<td>17/30</td>
<td>15/30</td>
<td></td>
</tr>
<tr>
<td>Homophone judgements</td>
<td>52/100</td>
<td>50/100</td>
<td></td>
</tr>
<tr>
<td><strong>ORTHOGRAPHIC OUTPUT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthographic output to Dictation</td>
<td>4/10</td>
<td></td>
<td>10/10</td>
</tr>
<tr>
<td>Orthographic output to Pictures</td>
<td>5/10</td>
<td></td>
<td>10/10</td>
</tr>
<tr>
<td>Copying Words</td>
<td>10/10</td>
<td></td>
<td>15/15</td>
</tr>
</tbody>
</table>

9.3 MORPHOMETRIC ANALYSIS

SW underwent a structural MRI scan, obtained with a 2T magnetom VISION scanner. As described before, the extent of the lesion was investigated by contrasting the grey/white matter density with that of the 6 control subjects used in the functional study. The technique used (voxel-based morphometry) was implemented as previously described (chapter 2, section 2.5.C; Wright et al, 1995).

9.3.4 Results

Figure 9.1 shows the extent of the cerebral infarct in the left hemisphere. It can be seen that SW has a large left lateralised lesion, involving an extensive part of the left frontal lobe including the inferior frontal gyrus and premotor regions. This extends back to involve the superior temporal gyrus, supramarginal gyrus and parietal lobe. These findings are entirely consistent with a left middle cerebral artery territory lesion, and show clearly the distribution of blood supply from that artery. In addition to delineating
the extent of the infarct, the technique also revealed reduced grey matter in the right cerebellum, consistent with the occurrence of crossed cerebellar atrophy (diaschisis) (Dow and Moruzzi, 1958).

**Figure 9.1:** Section A shows the regions of reduced grey matter relative to normal controls on a rendered image of the brain. A typical distribution corresponding to a left middle cerebral artery infarct can be seen with crossed cerebellar atrophy (diaschisis). Section B illustrates the lesion on transverse MRI slices normalised to the MNI template.

9.4 FUNCTIONAL IMAGING STUDY

The aim of the functional neuro-imaging experiment was to identify regional activation associated with semantic processing.
9.4. A Tasks
The identical Pyramids and Palm Trees semantic association task was used as in Chapter 8 (section 8.2.D). The control subjects were the same group as used in Chapter 7 (section 7.2.A).

9.4.B Data Analysis
Data acquisition was performed in the standard manner with three scans per condition, 12 in total. The data were analysed using SPM97 software and the procedures discussed in Chapter 2 (section 2.4). Analysis aided to identify the regions where SW showed i) normal activation; ii) reduced activation relative to normals and iii) increased activation relative to normals. This was achieved using a multi-study design with replications. Subject specific analysis (section 2.5.G) was used in order to distinguish areas that were activated by every subject from those where there was intersubject variability, in particular where SW's activation pattern differed from that of each control subject. As in the previous chapter (see methods, section 2.4.D), the grey matter threshold was lowered, in this case to 20%, in order to test for peri-infarct activation around SW's lesioned region.

Areas activated by every subject were identified using conjunction analysis (Section 2.5.C) to sum over the simple main effects of task (word semantic – word visual and picture semantic – picture visual) for each subject. An uncorrected threshold of p<0.001 was used for the main effect over subjects and for the interactions between controls and SW but the threshold was reduced to p<0.05 for detecting the contribution of individual subjects in areas identified by the main effects and interactions.

Areas where there was activation for all the normal controls but not for SW were identified where there was i) a significant interaction between task and subject group (i.e. greater activation for normal controls than SW p<0.001; ii) a significant simple main effect for each control subject - p<0.05; and iii) no activated voxels for SW.

Areas where there was activation for SW but not the normal controls were identified where there was i) a significant interaction between task and subject group (i.e. greater activation for SW than controls; ii) a significant main effect for SW and iii) no equivalent activation in any of the control subjects.
Of note, in this chapter the results of the word semantic task are focussed upon. This evoked reliable prefrontal activation in each of the normal controls. The results of the picture semantic task are not discussed as activation of the left inferior frontal gyrus for picture semantics only reached significance in half the normal subjects. As this chapter focuses on the frontal activation, it is important to use a paradigm that reliably activate the region of interest.

9.4.B Results

9.4.B.1 Behavioural

Behavioural data from the scanning task indicated an accuracy for normals of 87.5% (range 78.1-93.7). SW performed within the normal range, significantly above chance ($X^2 = 4.2$, $p<0.01$, 2 tailed) and less than one standard deviation below the mean. Together with his performance on P PT outside the scanner, this suggests that he was fully engaged in the semantic task. The range of normal response for the actual size task was 83% - 100% (mean 91%). SW fell just below this range (81%), but his performance did not differ significantly from the normals.

Mean normal response on the semantic task was 3.38 seconds; on the visual task it was 2.45 seconds. SW was slower on the semantic task (5.13 sec) and the visual task (3.57 sec). A two way ANOVA confirmed that he was significantly slower than normal ($F (1,427)= 39.2$, $p<0.0001$). There was also a significant main effect of task ($F (1,427)= 29.3$, $p<0.0001$) as responses to the semantic task were slower than those for the visual task. However the interaction between task and subject group was not significant ($F (1,427)= 1.9$, $p=0.16$.

SWs responses could be slower for a number of reasons: i) damage to regions involved in semantic tasks, e.g. the left inferior frontal lobe. However, he was also slower with visual decisions. ii) differences in motor control relative to normals, either generally or due to an inability to use his dominant hand because of a right hemiplegia secondary to the infarct; iii) reduced vision in one visual field due to ophthalmological problems, iv) damage to the frontal region causing deficits in response selection for both tasks. It is not possible to distinguish between these possibilities in the present experiment, but it can be concluded that SW could perform the task, albeit slower than normal subjects.
9.4.B.2 PET Results

9.4.B.2.1 Conjunction of normal and patient activations

Despite the extent of the lesion, the patient activated several areas in common with the normal controls, including inferolateral temporal regions (BA 21, 22, 28, 37); the temporoparietal junction (BA 39); the parieto-occipital junction (BA 19/39), and the medial parietal lobe (BA 19) (see Table 9.2). As can be seen from Figure 9.2, some of the temporal and parietal activation observed in SW lies close to damaged regions, consistent with peri-infarct function.

**Figure 9.2: Areas activated during semantic decision a) normal system; b) SW activating in common with normals; c) areas SW fails to activate.**

9.4.B.2.2 Areas activated by normals but not SW

Each normal subject activated the left inferior frontal gyrus (BA 47) and right cerebellum (as well as the regions activated by both normal subjects and SW) during the semantic task relative to the visual task. SW failed to activate any voxels in those areas (p<0.05 and below). These differences were confirmed by highly significant subject by task interactions in these regions. It can therefore be concluded that the failure to activate these regions is a direct result of his neurological deficit.
Table 9.2: Regions of significant activation for a) normals and SW; b) normals but not SW.

<table>
<thead>
<tr>
<th>Region activated</th>
<th>BA</th>
<th>Main effect</th>
<th>Control gp</th>
<th>SW</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normals and SW in common</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior superior temporal</td>
<td>22</td>
<td>-60 2 -8</td>
<td>4.1</td>
<td>-60 2 -8 2.4</td>
</tr>
<tr>
<td>Left anterior middle temporal</td>
<td>21</td>
<td>-68 -28 -2</td>
<td>3.7</td>
<td>-68 -28 -2 3.2</td>
</tr>
<tr>
<td>Left anterior medial temporal</td>
<td>28</td>
<td>-14 -6 -24</td>
<td>3.9</td>
<td>-14 -6 -26 3.6</td>
</tr>
<tr>
<td>Left inferior temporal</td>
<td>37</td>
<td>-60 -48 -10</td>
<td>3.5</td>
<td>-70 -42 -14 2.7</td>
</tr>
<tr>
<td>Left posterior middle temporal</td>
<td>39</td>
<td>-66 -72 22</td>
<td>4.0</td>
<td>-66 -70 16 4.1</td>
</tr>
<tr>
<td>/angular gyrus</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Left angular gyrus</td>
<td>19</td>
<td>-52 -78 40</td>
<td>3.6</td>
<td>-54 -76 44 2.6</td>
</tr>
<tr>
<td>Left cuneus/precuneus</td>
<td>19</td>
<td>-24 -90 38</td>
<td>3.8</td>
<td>-18 -82 38 2.7</td>
</tr>
<tr>
<td><strong>All normals but not SW</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left inferior frontal</td>
<td>45/47</td>
<td>-48 28 -6</td>
<td>5.7</td>
<td>-48 28 0 5.5  NS</td>
</tr>
<tr>
<td></td>
<td>47</td>
<td>-48 36 -12</td>
<td>4.4</td>
<td>-50 34 -6 3.9  NS</td>
</tr>
<tr>
<td></td>
<td>47</td>
<td>-40 36 -22</td>
<td>4.2</td>
<td>-40 36 -20 4.1  NS</td>
</tr>
<tr>
<td>Right cerebellum</td>
<td>20</td>
<td>-64 -32</td>
<td>4.4</td>
<td>16 -64 -30 4.5  NS</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>-60 -36</td>
<td>4.5</td>
<td>34 -64 -44 4.1  NS</td>
</tr>
<tr>
<td>Left cerebellum</td>
<td></td>
<td>-58 -60 -46</td>
<td>4.0</td>
<td>-60 -58 -42 3.8  NS</td>
</tr>
</tbody>
</table>

9.4.B.2.3 Other areas activated by SW

SW also showed activation in the right ant middle temporal cortex (56, -10, -16; 3.4), medial superior frontal cortex (BA 10) (0, 70, 22; 3.6) and left inferior parietal cortex (BA40; -52, -34, 50; 3.2) at p< 0.001. However, these regions were also activated in between one and four of the normal subjects, so we cannot be certain that they reflect compensatory changes following neurological damage.

9.4.C Summary of results

In summary, the results show that SW performs the semantic task within normal limits, and activates only the temporal regions seen in normals. In addition, no evidence of functional reorganisation was seen, and no evidence of peri-infarct activation in left inferior frontal cortex, though there was peri-infarct activation in the temporal lobe.

9.5 DISCUSSION

This study combined neuropsychological data, structural and functional analysis to examine the brain regions sufficient for performance of a semantic task. It has been shown that a patient with extensive frontal lobe damage is still able to perform a semantic
task, and that while doing so, he activates regions of the left temporal lobe previously associated with semantic processing.

The structural data revealed that areas known to be crucial for language production have been severely damaged, that is Broca's area, the superior temporal lobe and the left supramarginal gyrus. SW is unable to articulate any speech sounds, write single words, or access phonology from seen words. This complete deficit in retrieval of phonology and speech generation suggests that premorbidly SW's ability to produce language depended on at least a subset of the brain regions damaged by his stroke.

In contrast, SW still has preserved comprehension of both low and high imageable words, and is able to maintain and control access to semantic information in order to make high level decisions, albeit at a slower rate than in normal subjects. Fiez (1997) has suggested that the brain region responsible for control of semantic information during the execution of semantic tasks is the left inferior frontal cortex (BA 47). Examination of the MRI scan showed some preservation of this region. It was therefore possible that SW managed to perform semantic tasks by activating peri-infarct tissue in the left inferior frontal lobe. Functional imaging was performed to address this question.

SW showed activation in common with normal controls in several inferolateral temporal and temporoparietal regions. Some of this activity was very close to damaged tissue, indicating peri-infarct activity. As discussed in Chapter 8, these inferolateral temporal and parietal regions have been implicated as critical for semantic processing, and have been activated consistently in this thesis for several semantic tasks. The precise roles of these regions are discussed in Chapter 10 (section 10.4.A).

In contrast to the semantic dementia patients investigated in chapter 8, SW has no damage to the left anterior and inferior temporal cortices. There is therefore a double dissociation in function and lesion sites for SW and semantically impaired aphasics, verifying the importance of extrasylvian temporal regions for semantics. We have also shown that activity in extrasylvian temporal tissue is sufficient to perform semantic tasks.

The second important finding concerns the left inferior frontal cortex (BA 47). This region has been activated significantly by semantic tasks (Vandenberghe et al, 96).
However, the findings presented have shown that inferior frontal cortex is not necessary for the types of semantic decision that SW is able to perform. This suggests that the activation seen in normal subjects is incidental to the semantic component of task, or simply increases the efficiency with which the task is performed.

SW’s responses were slower than normal, but this effect was not specific for semantic tasks. Accuracy on the semantic task was within the normal range. The behavioural data therefore suggests that although BA 47 normally becomes more active during semantic than visual decisions, it does not play a crucial role in performance accuracy. It is possible that normal function in BA 47 contributes to the efficiency of the semantic decisions or that activity in this region represents preparation for effortful semantic tasks. This may relate to the increased activation seen in frontal cortex in the semantic dementia patients, though this is only an interesting observation. SW’s increased response latencies across tasks suggest that such a ‘preparation’ or ‘selection’ role for the inferior frontal gyrus may also generalise to non-semantic processes.

In addition to the findings in the frontal lobe, SW failed to activate the right cerebellar cortex. This functional deficit mirrored the structural deficit discussed earlier. The reduced grey matter in the right cerebellar cortex is presumed to result from atrophy following crossed cerebellar diaschisis (Dow and Moruzzi 1958; Lenzi et al 1982; Feeney and Baron, 1986). The reduced activation may be due to reduced input from the nonfunctioning frontal regions, or alternatively directly due to atrophy of the cerebellum.

**9.6 SUMMARY**

In summary, results from this study show that activity in the left inferolateral temporal and left temporoparietal regions is sufficient to make semantic similarity judgements. The inferior frontal activity, seen in both normal subjects and patients with semantic dementia (Chapter 8), appears to be unnecessary for performance of the semantic task presented. In addition, the results suggest that, at least when insult is sudden (e.g. infarction), complex cognitive processes such as semantic processing rely on peri-infarct activation, rather than compensatory use of the right hemisphere.
Chapter 10

General Discussion: Evidence for common distributed system for semantic processing, and the critical role of the anterior temporal lobe. Theoretical and neural implications

10.1 INTRODUCTION

This thesis has presented a series of studies showing that a functional imaging approach can be used, in combination with neuropsychological and behavioural measures, to advance our understanding of the distributed semantic system in normals and patients. The use of disparate tasks to investigate semantic processing has allowed convergence upon critical semantic areas in the temporal and temporo-parietal regions. The use of both structural and functional imaging has allowed investigation of the neural correlates of dissolution of the semantic network in patients. The combination of neuropsychology and neuroimaging is a relatively unexplored avenue for imaging studies. It enables inferences to be made on both the mechanism of cognitive disruption in patients and the function of specific regions activated for semantic tasks in normal subjects.

As discussed in the Introduction (section 1.7.A), research on semantic memory has focused on two broad issues: i) theoretical psychological questions, involving the relationship of semantic processing to other language and memory functions, and the internal organisation of the semantic system; ii) more neurologically based issues, such as the neural basis of semantic memory and how this might be disrupted by disease. The data presented here make it apparent that these questions are closely interlinked; neurological hypotheses inform theoretical ones and vice versa. Therefore I will not attempt to examine these questions individually, but will combine them in order to discuss the implications of this data. The chapter begins with a brief summary of the key findings presented. The implications of the results presented in this thesis will then be considered and used to assess some of the neuropsychological hypotheses described in chapter 1.

10.2 SUMMARY OF RESULTS

10.2.A Summary of Chapter 3

Differences in regional cerebral activity during word retrieval in response to different prompts were investigated. The contrast of semantically-based category fluency versus phonologically-based initial letter fluency resulted in selective activation of left
inferolateral temporal regions. The reverse contrast yielded activation in left frontal regions. A further comparison between types of category fluency demonstrated a more anterior left temporal response for natural kinds and more posterior left temporal activation for manipulable manmade objects. These results support behavioural data suggesting that category fluency is relatively more dependent on temporal-lobe regions, and initial letter fluency on frontal structures. Secondly, they confirm that categorical word retrieval is not a uniformly distributed function within the brain, compatible with the category-specific deficits observed after some focal lesions. Finally, the data suggest that objects in various conceptual domains place differential demands on a complex network of semantic knowledge.

10.2.B Summary of Chapter 4
This study revealed that, when normal subjects made semantic similarity judgements on written words, a network of cortical areas was activated that was remarkably consistent with those found for other types of semantic tasks. Within this common distributed cortical system, certain regions were differentially involved when the system was weighted for a certain type of task. Judgements about object location (relative to object colour) were associated with enhanced activation of the left temporo-occipito-parietal region, while the reverse contrast (object colour versus object location) produced stronger activation in the left antero-medial temporal lobe and caudate nucleus. Consistent activation of the left posterior middle temporal gyrus for words denoting artefacts for both perceptual and associative tasks confirmed the importance of this region for inanimate objects. On the other hand, the lack of any differential activation for words denoting living things relative to artefacts suggested that, when the task demands and stimulus attributes are carefully controlled, there are no areas specific to the semantic processing of words denoting living things. These results suggested that the more prominent neural distinction relates to type of semantic attribute rather than object domain.

10.2.C Summary of Chapter 5
This study investigated the brain regions activated during lexical decision, and described the semantic regions that are sensitive to manipulation of semantic priming. First, we demonstrated that lexical decision (relative to letter decision) activated regions previously observed for semantic tasks, i.e. the left anterior and inferior temporal gyrus, and left
inferior frontal gyrus. Behavioural analysis confirmed a significant priming effect. It also suggested the contribution of both automatic and strategic processes in semantic priming. During lexical decision, changes in the proportion of related prime-target word pairs produced activity changes in (i) the left anterior temporal lobe (BA 38): a region involved in lexico-semantic processing; (ii) the anterior cingulate cortex, right premotor region (BA 6) and right superior parietal lobe (BA 7): regions involved in attentional processing. The differential sensitivity to priming in the anterior and inferior temporal lobe suggests differing semantic roles for these two regions. Secondly, the data supported the involvement of both automatic and strategic processing in semantic priming.

10.2.D Summary of Chapter 6
Real world stimuli were used to compare the network of regions activated for non-context specific (semantic) memory retrieval and context-specific (episodic) memory retrieval. In addition, following the observed bias towards self-relevant memory retrieval in semantic dementia patients, an alternative memory dichotomy was investigated: that of self and non-self relevant memory. A common network for memory retrieval was activated involving largely left lateralised regions, many of which were common to the previous studies of semantic processing. Specifically, the temporal pole, anterior middle temporal gyrus, temporoparietal junction, parahippocampal gyrus, hippocampus, posterior cingulate and medial frontal lobe were activated for all memory tasks versus control. Within this set of regions, a subset were more responsive for self-relevant memory i.e. the hippocampus, medial frontal cortex, temporal pole and temporoparietal junction; critically, the hippocampus was most strongly activated for context-specific, self-relevant memory retrieval. These findings supported the view that apparently distinct subsystems in memory are in fact supported by associations between subsets of regions within a common memory retrieval network, and provided a means of unifying patient data (suggesting dissociations between memory types) with anatomical accounts (supporting a unitary distributed network).

10.2.E Summary of Chapter 7
The cortical anatomy of six patients with semantic dementia (relative to a group of age-matched normals) was investigated using a structural analysis technique, namely voxel-based morphometry. Circumscribed regions of significant neuronal loss were seen, the left temporal pole (BA 38) was the most significantly affected region. Consistent cortical
atrophy also involved the right temporal pole (BA 38), the left infero-lateral temporal lobe (BA 20/21) and ventro-medial frontal cortex (BA 11/32). The medial temporal lobe structures showed little significant atrophy; in particular the hippocampal formation was spared. The degree of neuronal loss in the left anterior temporal lobe (BA 38) was found to correlate significantly with performance on word-picture matching, whereas there was no significant correlation between performance on the same task and degree of neuronal loss in the ventro-medial frontal cortex (BA 11). These results confirm the view that the anterior temporal lobe is critically involved in semantic processing, and dissociate the function of this atrophied region from that of the ventro-medial frontal cortex.

10.2. F Summary of Chapter 8
This study examined the functional consequences of focal damage to the anterolateral temporal cortex in a group of patients with semantic dementia. We measured activation associated with a semantic decision task relative to a visual decision task in four of the patients described in Chapter 7 compared to activation seen for six age-matched normal controls. Normals activated a network of regions consistent with previous studies of the semantic system. The patients activated some areas consistently with the normals, including some regions of significant atrophy. However, they also showed substantially reduced activity particularly in the left posterior inferior temporal gyrus (iTG) (Brodmann Area 37/19), and increased activity despite reduced general cerebral blood flow in the anterior temporal lobes, plus increased activity in some frontal regions. The results suggested that functional changes can occur distant to the site of structural damage in these patients, and support a role for the posterior inferior temporal lobe in the interface between semantics and phonology.

10.2.G Summary of Chapter 9
To further examine the role of the frontal lobe in semantic processing a patient with severe expressive aphasia (secondary to extensive infarction of the left fronto-parietal region) was tested on the identical semantic association paradigm to that used in Chapter 8. Behavioural data showed that he was able to perform the semantic task as well as the semantic dementia patients. Activation of several temporal regions was seen in common with the control subjects. However, the patient SW failed to activate any prefrontal cortex. The findings suggest that the temporal lobe regions are sufficient to perform
semantic similarity judgements, and that the frontal regions are not necessary for task performance.

A summary of the activations found in these studies is shown in Appendix 6. Also shown are the regions of significant atrophy in the patients studied in chapter 7.

10.3 THE DISTRIBUTED SEMANTIC SYSTEM

10.3.A Overview

This investigation of the neural basis of semantic processing is focused on the systems level, i.e. distributed neuroanatomical regions, each comprised of thousands of neurons. This type of investigation differs to that which has been carried out for many years in the study of patients with focal cortical lesions. Information gained from the lesion deficit model has led to models concerning the critical regions for a particular cognitive function. For example, the study of patients with aphasia (Broca, 1861; Wernicke, 1874; Geschwind, 1971) led to the first models of language; the study of patients such as HM and investigations following Scoville and Milner's initial work (1957) led to the emergence of the hippocampus as a critical structure in memory. However, as discussed in Chapter 1 (section 1.2.B.1), there are difficulties with ascribing function purely on the basis of lesion localisation.

The advent of connectionist modelling and neuroimaging has added power and subtlety to this established methodology. The structure of semantic memory is now commonly visualised as a distributed system, rather than critically reliant on one cortical region alone. This distributed system is visualised at two levels: the featural level (Collins and Loftus, 1975; McClelland and Rumelhart, 1985; Allport, 1985; Shallice, 1988) and the systems level (Damasio, 1989; Damasio and Damasio, 1994; Moscovitch, 1992; Squire and Knowlton, 1995; Mesulam, 1990). Allport (1985) proposed the following view of the semantic system, where specialisation within a region is conferred by its connections to other multiple regions:

"Instead of conceiving of the semantic system as a set of discrete subsystems it may be more useful to think of it as a giant distributed net in which regions tend to be more specialised for different types of process. For an object, these might include the representations of non-visible sensory features; knowledge related to relevant actions; knowledge related to what would be found near it; somewhat more abstract aspects, such as knowledge related to an object's function; and even more abstract operations, such as how it was manufactured... The
specialisation could arise because of the different pattern of connections — outside the semantic system itself — used by each particular process. On a distributed network approach such a developmental process can be viewed as one in which individual units (neurons) within the network come to be most influenced by input from particular input channels, and in turn, come to have most effect on particular output channels. An individual concept will come to be most strongly represented in the activity of those units that correspond to the pattern of input-output pathways most required in the concept's identification and use. The capacity to distinguish between members of a particular category would depend on whether there are sufficient neurons preserved in the relevant partially specialised region to allow the network to respond clearly differentially to the different items in the category.'

(Allport 1985)

In other words, information is stored in memory in the form in which it is experienced, and various types of information pertaining to a concept become linked via temporal co-occurrence. Therefore selective damage to the brain could isolate components, as seen in patients with focal lesions (see Chapter 7), but normally the sub-regions are tightly interconnected via reciprocal activation, leading to activation of a distributed network for a particular cognitive function (see Chapters 4, 5, 6, 8). It should be clear that, although this particular account was very much based on featural semantic level, it can be seen as directly relevant to the findings presented in this thesis at a systems level.

Systems models such as those proposed by Mesulam (1990; 1998) of language and memory and by Damasio (1989) of information processing draw both on such connectionist views and on more traditional neurological techniques. These models have emphasised the importance of multiple cortical regions in processes such as semantic processing, and have included critical 'bottleneck' regions where processes interface, for example, in Damasio's proposed model (1993), the anterior temporal lobe is one such critical 'convergence' region. In the terminology of Mesulam, the temporal pole and temporoparietal junction are seen as critical 'transmodal nodes', playing a vital role in binding widely distributed multimodal representations into coherent concepts (Mesulam, 1998). Both of these authors concur that such regions are not the 'storage centre' of representations, rather they act as a 'gateway' or 'indexer' for the integration of information from distributed brain regions, and as such are extremely vulnerable to lesion-induced deficits. When using imaging to examine cognitive systems, we are investigating regions of maximally consistent activity during a specific cognitive process. It is therefore perhaps unsurprising that the regions activated most consistently are those 'bottlenecks' mentioned above.
My first hypothesis, based on previous imaging studies and lesion data, was that a
distributed system of regions would be activated for semantic tasks. This was confirmed,
as can be seen from the tabulated results (see Appendix 6). A predominantly left-
lateralised network of brain regions was activated. The network that has been identified is
remarkably consistent with an increasing number of imaging studies and
neuropsychological data, supporting the hypothesis that these regions form a common
network for the retrieval of semantic knowledge, regardless of stimulus modality (pictures
versus words: Buckner et al., 1996; Vandenberghe et al., 1996) and task (word generation:
Martin et al., 1996; Warburton et al., 1996; Wise et al., 1991; semantic decision: Binder
et al., 1997; Price et al., 1997; Vandenberghe et al., 1996).

Importantly, this network was activated for context-specific and non-context specific
remote memory retrieval (see Chapter 6). The regions seen correspond remarkably well to
proposed models of memory retrieval, involving limbic, paralimbic and cortical regions
(e.g. Mesulam, 1990; Markowitsch, 1995). Much of the activated network responded to
information retrieval independent of type. Specifically, the left inferolateral temporal
region, anterior temporal and middle temporal gyrus, parahippocampal region and
temporoparietal junction were activated for semantic processing tasks relatively
consistently. The left inferior frontal region was also activated for many of the tasks used
in this thesis, but was shown to be unnecessary for performance of the semantic similarity
(P&P) task used (Chapters 8 and 9). These results also appear to be independent of age -
both young (Chapters 3, 4, 5, 6) and older subjects (Chapters 8 and 9) activated a
consistent network of regions.

Other regions were selectively activated, dependent on the type of task being used. This,
in conjunction with data from other experimental methodologies, gives us a degree of
insight into the roles these regions may play within semantic processing. The role of
specific regions will be discussed in detail in section 10.3.B.

10.3.B Lateralisation of the semantic network
The degree of left lateralisation seen in all of the studies described raises the question of
whether there is equivalent lateralisation of semantic knowledge within the brain.
Functional imaging studies of semantic processing in normal participants have
documented mainly left lateralised activation for semantic tasks when contrasted to
phonological or visual baseline tasks (Binder et al, 1997; Demonet et al, 1992; Vandenberghe et al, 1996; Mummery et al, 1996; Price et al, 1997). A largely common network for semantic processing of words and pictures has been demonstrated in the left hemisphere that includes the anterior temporal lobe, middle and inferior temporal gyrus, and posterior regions such as the tempo-parietal junction (BA 39) (Chapters 3, 5, 7, 8; Vandenberghe et al, 1996). It might be suggested that the predominant left-sided activation seen in the studies described in this thesis is due to the verbal nature of the tasks used. However, the semantic association task used in Chapter 7 and 8 also produced left-lateralised activation with pictures, consistent with the common network shown by Vandenberghe and colleagues for words and pictures (1996). Secondly, few hemispheric differences were seen in a separate study in recall of visual or verbal stimuli (Buckner et al, 1996). The consistent left lateralisation of the inferolateral temporal regions activated for semantic processing supports at least a degree of left lateralisation in the semantic system. However, two parts of the network showed a less consistent degree of lateralisation:

10.3.B.1 Temporal pole lateralisation

In normals, temporal pole activation was left-sided in the studies of a) verbal fluency (Chapter 3), b) lexical decision (Chapter 5) and c) sentence verification (Chapter 6), but was bilateral for semantic feature similarity judgements (Chapter 4). The findings in normals suggest that the right temporal pole may be involved in semantic processing, though they do not support the right being as consistently involved as the left. In comparison, the consistency of left temporal pole activation across semantic tasks strongly supports the critical role of this region in semantic processing.

In patients, the temporal poles were the most significantly atrophied regions, left more than right (Chapter 7). In all bar one patient there was more extensive atrophy in the left hemisphere. Only one patient of the six had unilateral temporal polar atrophy (DM), and as discussed (section 8.3.A), this patient's semantic deficit was extremely mild at the time of scanning. In addition, both left and right temporal poles were more strongly activated by all patients than normals for a semantic association task, despite decreased cerebral blood flow in these regions (Chapter 8). This result suggests that perhaps the patients were showing greater activation (relative to the control) due to an attempt to compensate
for impoverished semantic representations. It is also possible that they were relying more heavily on the right temporal pole than the control subjects for performance of the task.

Other studies have also supported the involvement of the right temporal lobe in some types of semantic processing. For example, right temporal activation has been seen for face processing relative to scrambled faces and for proper name processing relative to consonant strings (Gorno-Tempini et al, 1998). Reports also exist of patients with selective damage to the right temporal lobe and a selective deficit in proper name retrieval (Evans et al, 1995; Greene and Hodges, 1996).

Recent neuropsychological work has shown that, in semantic dementia patients, the clinical picture differs dependent on the degree of lateralisation in terms of atrophy (Lambon-Ralph et al, 1998). Patients with predominantly left-sided atrophy have a marked anomia, only developing significant semantic associative deficit late in the course of the disease. In contrast, patients with predominantly right-sided atrophy show anomia plus semantic associative deficit from presentation. The bilateral functional abnormality in the anterior temporal lobes found in our group of patients (Chapter 7), and the left sided functional deficit in the posterior inferior temporal lobes correlates with findings suggesting that the anomia correlates with left sided atrophy and comprehension deficits correlate with both left and right.

The work presented here cannot resolve the issue of whether the right anterior temporal lobe is involved in semantic processing. However, there are at least suggestions from our studies, when taken in conjunction with other work described, that bilateral polar atrophy may be necessary to produce substantial semantic impairment in terms of both comprehension and naming.

10.3.B.2 Temporoparietal junction lateralisation
In two studies (chapters 6 and 8), the temporoparietal junction (TPJ) was activated bilaterally for semantic task versus control. In category fluency (chapter 3), the right TPJ was activated more for animate than for inanimate and more for location judgements on animate than location judgements on inanimate (Chapter 4). Finally, the same region showed greater activation in chapter 5 for letter decision relative to lexical decision. Given this variability, it is difficult to draw any strong conclusions concerning the role of
the right TPJ in semantic processing. As discussed in chapter 8 (section 8.4.A.1),
activation in this region could reflect a number of task-related differences including
degree of attention. For example, it has been shown that activity in this region induced by
reading words is modulated by stimulus duration (Price and Friston, 1997b). However, it
is not possible to conclude that the right TPJ has no role in semantic processing.

10.3.C Relationship of semantic memory to episodic memory

The functional imaging data in this thesis has shown a network of regions involved in the
performance of several differing semantic tasks. The question then arises, 'How specific
are these regions to semantic memory?' As discussed in the Introduction (section 1.1),
semantic processing is not a process in isolation. Rather, it is an interface between
language and memory, critical to both.

In Chapter 6, I described an attempt to place semantic memory within a broader
framework, that of declarative or remote memory, and to examine how the network
sustaining semantic memory differs from that sustaining context specific (episodic)
memory. A distributed system was involved for retrieval of all memory types, both
semantic and episodic. Of note, this system overlapped considerably with the system
described using more traditional methods of activating semantic processing: anterior
lateral temporal neocortex, the temporal pole, the parahippocampal gyrus and the
temporoparietal junction, plus regions thought to be important in the retrieval of episodic
memory e.g. the hippocampus and posterior cingulate. Differential activation was seen in
some regions. The temporal pole, orbitofrontal region and hippocampus were more
responsive to episodic or context-specific memories, and the hippocampus showed
particular responsiveness to episodic, self-relevant memory.

The degree of commonality seen for the retrieval of context-specific memories
(traditionally thought of as episodic) and noncontext-specific memories (semantic)
supports unitary models of information retrieval, such as that proposed by Damasio and
Damasio (1994). However, the differential activation within this network in regions
consistent with patient data (for example, the activation of the hippocampus for self-
relevant, context-specific memories) strongly suggests that apparently distinct subsystems
in memory are in fact supported by differing associations between subsets of regions
within a common memory retrieval network. Such a finding is compatible with the well-
known patient dissociations (e.g. Scoville and Milner, 1957; Hodges et al, 1992). In some ways reminiscent of connectionist accounts (e.g. Allport, 1985; section 1.2.A and section 10.2.A), this finding unifies the anatomically based accounts (suggesting a unitary distributed model for memory retrieval) and experimental evidence from patients (suggesting modularity in the system) by providing evidence of differential involvement within a distributed system. Secondly, it suggests that the dichotomy between self-relevant and non-self-relevant information is greater than that between retrieval of context-specific memory and non-context-specific memory, factors that in previous studies have been confounded. While the findings described here are only preliminary, further work into the interrelationships between memory types is critical to the understanding of deficit types in patients.

10.3.D Semantic Access or Semantic Store? Converging evidence from Implicit and Explicit semantic tasks

An important limitation of many semantic tasks is the explicit nature of the task. For example, in Chapter 3, subjects had to voluntarily retrieve names of objects. While the semantic processing used in Chapters 4, 6, 8 and 9 did not require retrieval of a name, they still necessitated voluntary access to semantic information. The organisation of the semantic system was addressed in a different way in Chapter 5. This study examined activation for an implicit semantic task (the effect of semantic priming on lexical decision) in order to compare this with the explicit tasks used in previous chapters. In theory, if an implicit task and an explicit task are used to investigate the neural correlates of semantic processing, regions activated by both are strong candidates for semantic processing per se, as opposed to being responsible for access to the semantic system (see section 1.7.B.1). Lexical decision activated two regions (amongst others) previously seen for semantic tasks: the anterior temporal lobe (BA 38) and the inferior temporal lobe (BA 20). As discussed before, these are the most severely and consistently damaged regions in patients with semantic deficits. Importantly, this study showed an effect of semantic priming in the anterior temporal lobe when no voluntary effort was required to access the semantic system, confirming a critical role for this region (see sections 10.3.A.1 and 10.3.A.2).
10.3.E Parts of the distributed system necessary for semantic processing

Having established that the system for memory retrieval is distributed and common to differing memory subtypes, we must then determine the criticality of the regions within the network. As discussed in the introduction (Section 1.7.C), patient studies allow us to ask which brain regions activated in normal subjects are necessary for a task. The data from chapters 7, 8 and 9 (on patients) provide clues as to the parts of the semantic network that are necessary.

In classical neuropsychological terms, frontal lobe patients (e.g. SW: Chapter 9) and the semantic dementia patients (Chapter 8) together show a double dissociation in functional deficit and lesion sites. The frontal lobe patient (SW) has relatively intact semantic processing, but a severe production deficit. This is associated with an extensive left frontoparietal lesion which spared inferolateral temporal regions. In contrast, the semantic dementia patients have a focal deficit in semantic processing with relatively preserved production; damage to the inferolateral temporal lobes, and abnormal activation in the temporal poles but continued activation of the frontal lobes. This double dissociation verifies the importance of extrasylvian temporal regions for semantics, and implies that activity in extrasylvian temporal tissue is sufficient to perform semantic tasks. In addition, the lack of activation in the frontal lobe in SW confirmed that the frontal regions are not necessary for performance of the semantic task. Further studies of patients will be invaluable in further delineating the regions that participate but are not necessary for a particular task.

10.3.F Mechanisms of residual function

The use of neuroimaging in patient studies also allows us to formulate and test certain hypotheses in terms of residual function, having delineated the regions important for a certain function in normal subjects. First, it is possible that patients with damage continue to activate regions within the damaged part, suggesting that these regions can still compensate for lost function initially. This is supported by the peri-infarct activation seen in patient SW in the temporal lobes (Chapter 9), and by the continued (though abnormal) activation in the anterior temporal lobes in the semantic dementia patients (Chapter 8). Second, one can investigate the question of whether patients after damage compensate by using regions in homologous regions of the contralateral hemisphere. In this case, SW did not show activation of right sided regions when performing a semantic task, whereas the
semantic dementia patients activated the right anterior temporal lobe more than normal subjects.

Two factors must be considered here. The speed of insult to the brain may be important. In SW, an infarct was responsible for the damage sustained - a sudden insult to the brain, allowing few compensatory mechanisms to develop. In this patient, no contralateral activation was seen. This result is supported by a recent paper (Warburton et al., 1999) where patients post-infarct showed peri-infarct activation for verb generation. In contrast, the semantic dementia patients suffered gradual progressive atrophy. In these patients, contralateral activation of temporal poles was seen (notably, the rest of the activations were still left lateralised). This suggests that the patients with degenerative disease might have progressively relied on right temporal pole activity in addition to left temporal pole activity when the left alone was not sufficient, an opportunity that was not afforded to patient SW. These suggestions are tentative – given the paucity of experimental data on neuronal and cognitive reorganisation in patients, much more work is needed to delineate the precise mechanisms.

10.4 POSSIBLE ROLES OF REGIONS WITHIN THE SYSTEM

While the distributed system shown for semantic processing correlates well with anatomical models, we know from patient literature that function is not uniform amongst the regions described as involved in semantic processing. The studies performed as part of this thesis, when taken in conjunction with existing literature, suggest differing roles for these regions. The next section of the discussion combines our findings with those from other imaging studies, from lesion data and other methodologies, and suggests possible functions for the brain areas activated for semantic processing.

10.4.A Temporal regions

10.4.A.1 Temporal pole (BA 38) / anterior temporal lobe

In the studies of normal subjects, the anterior temporal lobe / temporal pole was activated

a) for self-generated retrieval of an object name (Chapter 3),
b) for lexical decision (Chapter 5, where a word has to be identified as real or not),
c) for semantic association when the different objects were close in meaning (Chapters 8 and 9), but not when the differentiation of attributes was critical, rather than the differentiation of object identity (Chapter 4),
d) for semantic and episodic memory retrieval relative to syllable judgement (Chapter 6). Notably in this study, a differential response was seen in the temporal polar region (BA 38) but not the anterior middle temporal gyrus (BA 21/38). In the former region only, activation was modulated by self-relevance,
e) finally, the anterior temporal lobe / temporal pole was unique within the defined semantic network, in that it was sensitive to semantic priming (Chapter 5).

In the patient studies,
a) the temporal pole was the most significantly atrophied region in the group of semantic dementia patients (Chapter 7). The degree of atrophy in this region correlated with severity of semantic deficit, as measured by word-picture matching,
b) in the functional study (Chapter 8), the patients did not have normal function in this region: cerebral blood flow across tasks was significantly less than that in the control subjects for all patients. However, they still showed activation of this region, in fact showed greater differential activation than the normals between semantic and visual tasks.

The finding in normals of activation during various semantic tasks supports the proposed importance of this area in semantic processing (Hodges et al, 1992; Snowden et al, 1996). The correlation of degree of atrophy with severity of semantic deficit confirms this hypothesis, and the enhanced relative activation in patients despite atrophy (and reduced cerebral blood flow) could be explained as due to attempted compensation for impoverished semantic representations. The question then is whether the data presented here allows any more precise definition of the role of this region to be proposed.

Other neuroimaging studies have shown activation of this region in semantic tasks (semantic judgement vs. phonological judgement (Price et al, 1997). Activation is greater in this region for familiar or unique faces than for non-familiar faces (Gorno-Tempini et al, 1998), suggesting that the ‘unique identity’ of a concept is in some way a part of its role. In addition, BA 38 is more active for sentences relative to unrelated words (Bottini et al 1994) and for stories relative to unrelated sentences (Fletcher et al, 1995). The role of this region in semantic processing is supported by evidence from other methodologies. For example, neurophysiological data have shown that this region, is the neural generator
of the N400 (Nobre et al, 1994), thought to be a neurophysiological correlate of semantic processing.

Although the above evidence strongly supports the involvement of the temporal pole in lexico-semantic processing, one needs to take into account certain findings that might be seen as contrary to this role. First, we will discuss the findings from epilepsy patients with anterior temporal regions excised. It has been argued that as patients after anterior temporal lobectomy have only a mild (if any) demonstrable semantic deficit, the temporal pole cannot be critical to semantic processing. There are two points to be made here. First, the operation is usually unilateral. As discussed in the section on lateralisation (section 10.2.B), the temporal poles can be bilaterally activated during semantic tasks. If both poles are necessary to semantic processing, this may explain why so much language is maintained when one side is removed. Secondly, testing on patients post-lobectomy may miss subtle deficits. It is only recently that such patients have undergone a battery of tests explicitly designed to tap semantic processing, as opposed to general language function. It is important to bear in mind the following proviso when considering evidence from epilepsy patients; cognitive processing in such patients may have undergone reorganisation, and one therefore needs to be cautious in interpretation of findings.

However, data exists on some temporal lobectomy patients that hints at the possible function of the temporal pole. Wilkins and Moskovitch (1978) found that left temporal lobectomy patients were impaired at making speeded semantic categorisation into living versus manmade categories for both words and pictures. Seidenberg et al (1993) presented data suggesting that lobectomy impairs retrieval of an individual item within a semantic field, retaining intact information about semantic attributes.

At first glance, some of the findings described above suggest that the temporal pole is important in extracting meaning regardless of the type of knowledge. However, the selective nature of the deficits shown by patients post-lobectomy suggests a more precise hypothesis, which takes into account the sensitivity of this region to priming, both in our study (Chapter 5) and in electrophysiological studies (e.g. Kutas and Hillyard, 1984).

We know from the monkey literature that lesions at or near the temporal pole can cause impairments in both recognition memory and concurrent discrimination learning. The
deficits produced have led authors such as Gaffan to suggest that this part of the anterior temporal cortex is important in monkeys in forming a coherent 'whole' from its separate features, in addition to a role in object memory (Buckley and Gaffan, 1998; Gaffan, 1994).

It has been suggested that 'when primates acquired language, the pre-existing object-recognition system [was] adapted to attribute meaning to nouns' (Vandenberghe et al, 1996). Extrapolating from the monkey literature, it is not too far-fetched to suggest that in humans the role of the temporal pole is one of conceptual integration to form an 'identity', whether it be concerning attributes (e.g. Chapter 6) or sentences/stories (Bottini et al, 1994; Fletcher et al, 1995c). The term 'identity' here is taken to mean the unique representation of a concept that consists of a multimodal featural representation, rather than person-specific identity. The sensitivity of the temporal pole to semantic priming tends to confirm such a hypothesis. If this is the critical zone for initial convergence of information in order to form a conceptual identity, the prior administration of information related to that identity should decrease the amount of activation required to access that identity according to theoreticians such as Plaut and Shallice (1983). This is exactly what is seen in this region.

The lack of activation of the temporal pole in chapter 4 when subjects make judgements based on features rather than identity is perhaps unsurprising. The task demands in this experiment maximised comparison of sensory or associative features for items that were not closely related (within animate or inanimate) other than in colour or location, i.e. emphasis was placed on the sensorial or associative attribute of the items. In the second semantic association experiment (Chapter 8, 9) the task demands maximised holistic comparison of closely related items, emphasising the degree of relatedness of each concept. This null finding indirectly supports the suggestion that the region is mainly involved when a synthesis of the analysed attributes into a unique configuration is required. Such a synthesis can be associated with the attribution of this region to a 'storehouse' for central representations of objects (Mishkin et al, 1982; Weiskrantz, 1990; Weiskrantz and Saunders, 1984). Direct links to the hippocampal formation, to auditory, visual and multimodal association areas, and to frontal executive regions (Van Hoesen, 1997) mean that the area is well placed for this integrative role.
I am not proposing that the temporal pole is the sole region critical to semantic processing, far from it. I hypothesise a role for the temporal pole in the integration of information to form an identity, a convergence region in the parlance of Damasio and colleagues (1989, 1994), or ‘transmodal node’ in Mesulam’s terminology (1998), which acts in concert with other temporal lobe regions involved in the storage of semantic representations, such as the inferior and middle temporal gyrus (BA 20/21). Once this function has occurred, the retrieval of the name associated with that identity could be performed, possibly due to activation of the posterior inferior temporal region (see section 10.3.A.4).

Finally, the difference in activation pattern in the temporal pole and anterior middle temporal gyrus is noteworthy. The temporal pole showed modulation of activity by the self-relevance of information being retrieved in contrast to the anterior middle temporal gyrus (Chapter 6). Anecdotal evidence suggests that, while patients with semantic dementia are impaired on retrieving semantic knowledge, any residual information they successfully retrieve is often self-relevant (Snowden et al, 1995). The finding of sensitivity to self-relevant information is consistent with patient data (e.g. Kapur et al, 1994; Markowitsch et al, 1993) showing the importance of this region in self-relevant memory. It has been speculated that this region encodes the unique spatiotemporal complexity of specific events, and integrates information from hippocampal structures with information from posterior association regions (Damasio, 1989). The question arises how does this region, which is atrophied, sustain self-relevant memory information in semantic dementia patients. If the regions showing increased responsiveness for self-relevant information are examined, it is clear that they make up a limbic-cortical network, involving predominantly medial structures, but including the temporal pole. It is possible that in patients with semantic dementia and atrophy affecting the temporal pole and lateral temporal regions, the connections to medial structures remain relatively intact, allowing access to semantic information via self-relevant connections. Of course, this is speculation only, and requires further investigation.

10.4.A.2 Anterolateral temporal lobe (BA 20/21)

The antero-lateral temporal lobe was activated for semantic similarity judgements (Chapter 4), for lexical decision (Chapter 5) and for semantic association (Chapters 9 and 8). The region showed no sensitivity to priming, and no differential activation for
differing types of information retrieval (context-specific and general; self-relevant or not) unlike the temporal pole (Chapter 6). In addition to temporal pole atrophy, all the semantic dementia patients showed atrophy of the inferolateral temporal lobe, though in one patient (DG) this was right sided. Despite this atrophy, the region was activated in all of the patients (see main effect of semantic – visual task, section 8.3.C.2).

The generality of this activation across semantic judgement tasks suggests a role in semantic processing. The lack of differential activation for category versus letter fluency may be because both the semantic task and the control task involved implicit access to semantics, the difference between tasks being in the type of retrieval used. The lack of activation for sentence verification is less easy to explain, but is presumably task-related. The lack of differential activation in the inferolateral temporal region for different object domains or types of semantic feature is consistent with the fact that patients with semantic dementia (and anterolateral temporal lobe damage) very rarely show a strong living-things deficit, except perhaps where the atrophy extends medially (Barbarotto et al., 1995).

It is known from previous studies that activation in the inferolateral temporal cortex is not modality-specific. In addition to the activation seen in these studies for paradigms involving words (and in Vandenberghe et al, 1996 for both words and pictures), it has been activated for object recognition in humans (Price et al, 1996; Haxby et al, 1991), and is known to be involved in object recognition in primates (Mishkin et al, 1982; Ungerleider and Mishkin, 1982). This region has also been activated in concert with temporoparietal regions (e.g. Demonet et al (1992) when subjects heard names of animals associated with an adjective and had to make a categorical decision about the size of the animal and the nature of the attribute). Finally, others have implicated the inferior temporal lobes in language using stimulation studies (Burnstine et al, 1990).

There is some data from monkey literature supporting firstly a role for the temporal pole in memory (George et al, 1989), and secondly a distinction between the role of the anterolateral temporal lobe and the temporal pole within memory processing (Buckley and Gaffan, 1998). Evidence in humans points to a role for this region in retrieval of semantic knowledge or information which is ‘non-unique’ i.e. not belonging solely to one
entity (Damasio, 1989). The lack of modulation of activation by category type, priming, and information type confirms this general ‘storehouse’ role.

10.4.3 Temporo-parietal junction

Although the precise location and lateralisation varied, activation was seen in or around the left temporo-parietal junction for all semantic tasks used in this thesis, with the exception of category relative to letter fluency (see Appendix 6). In both category and letter fluency, meaningful concepts were actively retrieved. The only difference was in the method of retrieval. It is possible that the temporoparietal junction was activated equally for both tasks as both involved accessing meaning. It is also noteworthy that nearby brain areas in the left hemisphere were activated more strongly for inanimate categories more than animate categories (posterior middle temporal gyrus), and for tasks tapping associative knowledge more than tasks tapping perceptual knowledge (see section 10.5.A for further discussion).

The activation of the temporoparietal junction is ubiquitous in memory retrieval studies (Cabeza et al, 1997). It is the most consistently activated part of the semantic network, and has been seen for many other semantic tasks (e.g. semantic association, Vandenbergh et al, 1996; verb generation, Wise et al, 1991; attribute retrieval, Martin et al, 1995). It has also been activated during sentence comprehension tasks (Bottini et al 1994), and related versus unrelated sentences (Fletcher et al, 1995). Finally, electrophysiological evidence supports involvement in both semantic processing and memory (Wilding and Rugg, 1996; Rugg et al, 1998; Connolly et al, 1995).

Turning to lesion data, the importance of the left temporoparietal junction for comprehending written and spoken language has been well established for more than a century (Dejerine, 1892; Geshwind, 1971; Hart and Gordon, 1990). Moreover, Alexander and colleagues have argued that stroke patients with the syndrome of transcortical sensory aphasia, in whom semantic knowledge is impaired, have cortical or white matter lesions that isolated the left occipito-parietal junction (BA 19/39) (Alexander et al., 1989). Notably, however, this region was not consistently atrophied in patients with semantic dementia using voxel based morphometry (Chapter 7).
How might one explain these findings? The activation seen in the left TOP junction may be related to the association of knowledge about attributes of an object rather than the synthesis of such attributes into an identity as proposed for the anterior temporal lobe. In semantic association tasks, the individual identity of a concept is less important; the individual attributes are critical. The posterior association areas are close to sensory association cortex, and may well be sites of accessing meaning from featural information; or associations from cortex experientially involved in such attributes. Certainly the proximity to regions that are activated more for associative attributes (chapter 4; Martin et al, 1995) and for inanimate categories (chapters 3 and 4, Martin et al, 1996) suggest an integrative associative role, extracting meaning from associations, regardless of context (Price, 1998).

This possible role fits reasonably well with the findings of no significant atrophy in the semantic dementia patients, who maintain the ability to successfully retrieve attributional knowledge concerning a concept for a considerable period of the disease, while they are markedly anomic and unable to retrieve the identity of the same concept. In fact, these patient often make semantic errors, suggesting that their impoverished semantic base is still able to integrate such associated features using the posterior association cortex, but finds difficulty in accessing the precise identity of the concept, which relies on more anterior parts of the network.

10.4.A.4 Posterior inferior temporal lobe (BA 37/19)
The left posterior inferior temporal gyrus was activated for semantic processing relative to baseline in both studies where the control task used was visual (Chapters 5 and 8), but not where the control task was phonological (Chapters 3, 4, 6). Previous activation has been shown in the posterior inferior temporal lobe (BA 37/19) for semantic tasks when compared with visual tasks (e.g. Vandenberghe et al, 1996) and by several different language tasks, including naming (of objects and words - Bookheimer et al, 1995; of letter-colours/objects - Price and Friston, 1997a); semantic word generation to auditory cues (Wise et al, 1991; Warburton et al, 1996); braille reading (Buchel et al, 1996).

It is known that electrical stimulation of this region can cause specific naming deficits (Luders, 1991); more recently, damage in the posterior inferior portion of BA 37 has been linked to anomia without major associated semantic deficit, and a role proposed for this
region in “allowing the semantic system access to stored lexical information” (Raymer et al, 1997; Foundas et al, 1998). These studies, along with the normal studies quoted, suggest a role for the left basal posterior temporal area (BA 37/19) in retrieval of the name of a concept, independent of modality of the stimulus prompting retrieval.

The findings in patients support such a role for this region. The semantic dementia patients showed no activation in the posterior inferior temporal lobe despite it being structurally intact, whereas all normals activated this region in the contrast of semantic decision versus visual decision. The lack of activation in patients is interpreted by postulating a failure of the posterior inferior temporal gyrus to function normally because of reduced input from the anterior temporal lobe. It is possible that the patients’ anomia is due to this failure to activate the posterior inferior temporal lobe.

I propose that this part of the network activated for semantic tasks is involved in the interface between semantics and phonology. Consistent with such a role, the region has direct connections to Wernicke’s area (DiVirgilio and Clarke, 1997). Second, the region responds to multimodal stimuli. The proposed hypothesis predicts relatively normal activation of BA 37/19 in tasks that do not require the anterior temporal lobe. Further imaging studies are therefore required to adjudicate between alternative explanations of this striking result.

It is noteworthy that the posterior middle temporal gyrus (BA 37/19) and inferior temporal gyrus (BA 21/37), often labelled as parts of the same region, behave differently. The posterior middle temporal gyrus was activated in both patients and controls, and was activated by some of the semantic tasks in this thesis (semantic association (Chapters 4 and 7); lexical decision (Chapter 5). It has also been activated during semantic tasks by other authors (e.g. Martin et al, 1995; Vandenberghe et al, 1996; Price et al, 1997). This area is commonly affected in patients with aphasia plus a semantic deficit (Cappa et al, 1981; Chertkow et al, 1997). It seems that both lesion and functional imaging data are accumulating to suggest that the region designated BA 37 is functionally “divided”, though its differing roles are intimately connected. Both parts are involved in word retrieval, but the middle temporal gyrus may be more concerned with some aspect of semantic knowledge, in a similar role to the more anterior inferior temporal gyrus (BA
20), whereas the more infero-posterior temporal region may be more critical for the interface between semantics and phonology.

10.4.A.5 Medial temporal lobe

One part of the semantic network that has been activated in other studies, but with little interpretation offered, is the more medial part of the temporal lobe: a region usually associated with episodic (context-specific) memory deficits. Both the parahippocampal and hippocampal regions were activated, though show a different functional profile, as discussed below.

10.4.A.5.1 Parahippocampal gyrus

In the studies described, the parahippocampal gyrus was activated for category fluency (Chapter 3), semantic feature judgements (Chapter 4), lexical decision (Chapter 5) and for sentence verification (Chapter 6). Notably, in the category fluency study no differential activation was seen for inanimate versus animate categories. The region was not activated for semantic association judgements (Chapter 8), but has been activated previously in the same semantic comparison task on young subjects (using a slightly different paradigm), more for words than for pictures (Vandenberghe et al., 1996). It has also been activated more for naming of animals than tools (although activated to some degree for both object categories (Damasio et al., 1996). The parahippocampal region has been shown to be sensitive to the imageability of words, showing a positive correlation of activity with increasing imageability when subjects listened to words (Wise et al, submitted). Highly imageable (concrete) words are no different in terms of phonological or orthographic make-up from those with low imageability (abstract), therefore any differences in terms of activation with changing imageability must reflect a difference in semantic processing.

Recent patient findings have highlighted the possibility of such areas as the parahippocampal gyrus playing a part in semantic processing (Vargha-Khadem et al, 1997). Vargha-Khadem showed that patients with selective deficits in day-to-day memory and lesions confined to the hippocampus since early life had still been able to acquire general knowledge to a virtually normal level. A model was proposed where representations formed in the cerebral cortex are bound together into semantic associations by the parahippocampal regions (i.e. this region may support recognition memory). The authors speculated that semantic knowledge can be acquired via the
parahippocampal regions, supporting its involvement in semantic processing. Both this region and the hippocampus are relatively spared in patients with semantic dementia (see chapter 7). In a number of patients with semantic dementia, a striking dissociation has been established between performance on semantic versus episodic memory tasks, with especially marked preservation of memory for recent episodes (Hodges and Graham, 1998; Graham and Hodges, 1997). This behavioural finding correlates well with the dissociation between lateral temporal lobe damage and medial temporal lobe sparing.

10.4.A.5.2 Hippocampal formation
The hippocampus or hippocampal gyrus was activated for memory retrieval in general, but more so for context specific autobiographical memory than for other memory types (Chapter 6). This is consistent with the vast neuropsychological literature on episodic memory implicating the hippocampus in episodic memory retrieval, but also supports the distributed nature of the memory network. In particular, it supports the view of authors such as Squire and Zola (1998), suggesting the common involvement of medial and lateral temporal regions in both ‘episodic’ and ‘semantic’ memory processing.

The involvement of the hippocampal region to an extent in all types of memory retrieval during the study described in Chapter 6 highlights the difference between functional studies and lesion studies – while these regions may be activated by normals when retrieving such information, the necessity of such regions to retrieval of that information is only discovered when a lesion has removed the function of that region. More research is needed to determine whether patients with damaged restricted to the hippocampus show deficits in semantic processing, as until recently, work has focussed almost exclusively on its function in episodic memory processing.

10.3.A.5.3 Summary of medial temporal lobe function
The work presented here has confirmed the differential involvement of the parahippocampus and hippocampal formation in semantic and autobiographical memory – the parahippocampal gyrus able to support noncontext specific memory; the hippocampus critical for the indexing of context specific memories (Vharga-Khadem, 1997). However, these differential roles must be placed in the context of common activation for memory processing within an extensive network of regions.
10.4.B Frontal regions

The role of the frontal cortex in semantic processing remains controversial. While the focal point of this thesis was the role of the anterior temporal lobe in semantic processing, some of the data presented allows a tentative differentiation of roles within the left frontal cortex. Examining the summary of activations in Appendix 6 shows that certain regions of the frontal lobe were differentially activated in the experiments presented.

10.4.B.1 Frontal lobe activation during semantic tasks

10.4.B.1.1 Anterior inferior frontal cortex (BA 47)

In control subjects, two frontal regions were more active in the semantic task than in the control task for three experiments. The left inferior frontal gyrus (iFG; BA 47) and orbitofrontal gyrus (BA 11) showed increased activation for semantic feature judgements (Chapter 4), lexical decision (Chapter 5) and semantic association judgements (Chapter 8). These regions did not show differential activity for verbal fluency (Chapter 3) or for memory retrieval (Chapter 6).

The semantic dementia patients produced greater activation than normals in the iFG, and had no consistent damage to this region. Conversely, SW, who had extensive damage to this region, showed no activation in the inferior frontal cortex (while he was still able to perform the semantic task).

The debate concerning the role of the frontal lobe in semantic processing has been pervasive in functional imaging literature on language since the pioneering work by Petersen et al (1988), showing activation of the left frontal lobe in a comparison of verb generation to reading aloud. In that contrast, activation was seen in left dorsolateral prefrontal cortex and anterior cingulate. It was concluded that the left prefrontal cortex was associated with semantic processing. Since then, the left inferior frontal gyrus has been activated by many studies examining the neural correlates of semantic processing, using a range of different tasks (Buckner et al, 1995; Demonet et al, 1992; Martin et al, 1995; Raichle et al, 1994; Kapur et al, 1994; Demb et al, 1995; Gabrieli et al, 1998). There are, however, a number of studies that have failed to show activation during semantic retrieval tasks. For example, naming pictures or verifying word associations does not consistently lead to left inferior frontal gyrus (IFG) activation (Martin et al, 1996; Wise et al, 1991). Continued debate surrounds the function of this region,
especially as neuropsychological studies have failed to demonstrate the necessity of left IFG for semantic retrieval; patients with frontal lobe damage do not show semantic impairment, and patients with semantic impairment do not generally have frontal lobe damage; typically such impairments are associated with temporal lobe pathology (Hodges et al, 1992; Hodges and Patterson, 1995; Saffran and Schwartz, 1994).

More recent studies have attempted to segregate the function of this frontal region from others in the semantic network, and have shown functional dissociation between this region and the posterior temporal areas, and also within the frontal region. For example, Thompson-Schill et al. (1997), using three different semantic tasks (word generation, semantic classification and semantic comparison), showed that activation in the inferior frontal lobe during an fMRI study was dependent on selection demands in all three tasks. In one task the degree of semantic processing was varied independently of selection demands in one of the tasks, and showed no left iFG activity. They concluded that activation of the region is due to the need to select some relevant feature of semantic knowledge from a set of competing alternatives, rather than semantic processing per se. Unfortunately, it was not possible to conclude from their data whether such a 'selection' role is specific to semantic processing. Gabrieli and colleagues (1998) contend that the region is involved in semantic specific working-memory. However, other data suggest that the role is not specific to semantic processing. For example, activation close to this region has been seen for episodic retrieval (Fletcher et al, 1998) and for verbal working memory (Paulesu et al, 1993). The degree of specificity of the inferior frontal cortex for semantic processing therefore remains uncertain.

In retrospect, the suggestion that the inferior frontal region is involved in high level selection processing is not new. Frith et al (1991) contrasted word generation (intrinsic generation) with lexical decision (extrinsic generation) and found left iFG activation. They argued that this activation was the result of intrinsic generation of a response. Shallice (1988) proposed that the prefrontal cortex is necessary for performance of novel tasks; Kimberg and Farah (1993) have suggested that the prefrontal cortex mediates selection of activation by the weighting of information active in working memory. Their model implies that demands on prefrontal cortex will be high in any task that requires selection among competing sources of information in working memory to guide a response, concurring with Thompson-Schill et al (1997) and Fiez (1997). Consistent with
this, neurophysiological studies have shown that damage to this region does not affect automatic semantic priming, but impairs strategic semantic priming (Hagoort et al, 1997).

While selection processes were not directly examined in this thesis, the results reported allow some tentative conclusions to be drawn concerning the role of the iFG. The activation of the iFG for several semantic tasks replicates previous findings. More importantly, the lack of differential activation for category versus letter fluency supports recent work on patients with lateral frontal lesions showing impairment on both category and letter fluency. The authors suggested that the impairment was due to a lack of efficient organisation and development of retrieval strategies (Baldo and Shimamura, 1998). The lack of differential activation in the sentence verification task is consistent with the hypothesis that the iFG plays a role in monitoring processes necessary for optimal recall (Fletcher et al, 1998).

It is also necessary to explain the increased activation of this region in patients with semantic dementia. While this is consistent with the suggestion that the role of inferior frontal cortex is executive and that it is used to control effortful retrieval or selection of semantic information from posterior temporal regions (Fiez, 1997), the increase in activation in the patients could alternatively be explained as increased activation in frontal semantic processing due to damage in other areas. The findings from patient SW allow exclusion of the latter hypothesis. SW was able to perform the semantic task as well as the SD patients, but showed no activation of the inferior frontal region. The double dissociation in these two patient types provides evidence that the frontal region is not necessary for performance of a semantic task, and that normal function in the temporal regions is sufficient for such a task. When the temporal lobes are not responding normally, there may be more competition between responses necessitating more executive selection control from the frontal lobes. It is possible that normal function in BA 47 contributes to the efficiency of the semantic decisions or represents preparation for effortful semantic tasks.

In conclusion, the studies presented support a possible role for this region in selection or search of an appropriate response, and that this function is not necessary for semantic processing to occur.
10.4.B.1.2 Medial frontal cortex (BA 11/10)

The ventro-medial frontal region was activated in tasks involving decision-making, i.e. semantic featural/associative similarity judgements (Chapter 4 and 8; also Vandenberghe et al., 1996; Price et al., 1997; Giorno-Tempini et al., 1998), and lexical decision (Chapter 5). This region also showed consistent atrophy in the semantic dementia patients, though the degree of atrophy in this region did not correlate with degree of semantic deficit (Chapter 7). There are patient studies that indicate a role for this region in decision making (Bechara et al., 1998); in terms of psychopathology, Zald and Kim (1996) has shown that abnormal function of the area is associated with obsessive compulsive behaviour. This is consistent with the fact that semantic dementia patients often develop obsessive compulsive problems and behavioural difficulties later in the course of their disease.

A more dorsal region (BA 10) was activated in semantic feature judgements (Chapter 4) and sentence verification (Chapter 6). Tasks requiring consignment of “agency” or a “theory of mind” to others have activated the same area (Frith, 1996). In the macaque, this region is known to receive visual input from the inferior temporal cortex and temporal pole, and projects efferents back to inferior temporal cortex and cingulate cortex. The region is involved in animals in the successful performance of an action appropriate to learning of reward related behaviour (Rolls, 1996). It has previously been implicated in personal memory; for example, Hodges and Gurd (1994) report a deficit in self-relevant memory in a patient with frontal lobe Pick’s disease. In humans, this region may be involved in some form of hypothesis testing, consonant with its proposed role in the memory supervisory system (Shallice, 1988).

10.4.B.1.3 Summary

Two regions of the frontal lobe showed increased activity in semantic tasks. Damage to these regions is not known to cause semantic deficits. The findings from these studies and other convergent evidence confirm a differential role for the medial frontal cortex and lateral inferior frontal cortex. The studies here were not designed to examine such roles in more detail. However, it seems that both of these areas are involved in executive function, and that the precise form this takes differs for the two regions. Importantly, the data suggests that, at least for the inferior frontal gyrus (BA 47), this role is not necessary for semantic processing to occur.
10.5 PROPOSED MODEL OF ROLES WITHIN THE SEMANTIC SYSTEM

The diagram below proposes tentative roles for the regions activated for semantic tasks in the experiments described, derived from the discussion above.

**Figure 10.1:** Diagram of the possible roles of the regions activated within the semantic network

10.6 THEORETICAL ISSUES – THE INTERNAL ORGANISATION OF SEMANTIC MEMORY

10.6.A Category Specificity

10.6.A.1 Overview

One of the major ongoing theoretical debates in the neuropsychological literature concerns the internal organisation of semantic memory, in particular how and why category specific deficits arise (see chapter 1, section 1.5.B). Investigation of patients has suggested several possible mechanisms underlying category specificity. Much of this work has concerned the double dissociation observed between animate and inanimate deficits, as discussed in the introduction (section 1.5.B). Authors such as Caramazza (1998) maintain that patient data supports a principled division between animate and
inanimate categories, i.e. differing neural substrates subtending the two types of object. Currently, the more widely held view is that experience governing the acquisition of information has influenced the regions critical to retrieval of information about a concept, for example sensory information is critical for the identification of animals, functional information is critical for tools (e.g. Warrington and McCarthy (1987). A similar account proposes that the semantic system is organised in terms of featural representation, with proponents such as Small et al (1995) and Devlin et al (1998) showing that category specific effects can be produced by lesioning a network model of the semantic system involving no explicit categories, but featural description alone. Neuroimaging has added to the debate, with several recent studies showing differential activation for performance of tasks on different categories of objects and words in normal subjects (Martin et al, 1995; 1996; Damasio et al, 1996; Mummery et al, 1996; Perani et al, 1995). Results of these studies are summarised in Appendices 4 and 5.

10.6.A.2 Categorical organisation or perceptual/functional division?

The initial investigation of category specificity in Chapter 3 produced results that would tend to support a principled categorical division, with animate concepts instantiated in the anteromedial temporal lobes, and inanimate concepts more left lateralised in the posterior middle temporal gyrus. These results appear to be supported by findings from other labs (see Introduction, section 1.5.D, and 10.5.A.1). Differential activation has been seen for categories whether using words (Mummery et al, 1996; Martin et al, 1996) or pictures (Martin et al, 1996; Damasio et al, 1996; Perani et al, 1995). However, Chapter 4 revealed that these activation differences are due at least in part to the type of knowledge that is critical to the identification of that concept. The failure to replicate the anteromedial differential activation for animate concepts found in Chapter 3, and to find any regions specifically associated with processing of living things regardless of task, is interesting in light of the rather dramatic deficits specific to living things reported in the neuropsychological literature (Gainotti et al., 1995; Hart and Gordon, 1992; Sartori et al, 1993; Silveri and Gainotti, 1988; Warrington and Shallice, 1984). Notably, these deficits are typically secondary to HSVE, a disease that produces anterior and ventral temporal lobe lesions, usually bilaterally.

One possible interpretation of the lack of differential activation we find for animate versus inanimate is that presemantic differences in the processing of natural kind
concepts may be in part responsible for category specific differences in patients (Humphreys et al, 1995). If the difference between the object domains were largely in visual processing, one might only expect to see differential activation for artefacts and living things when they are presented in picture form but not (as in the present study) in word form. This account does not however explain the dramatic deficits sometimes observed for living things in word tasks as well as in picture tasks (e.g. Warrington and Shallice, 1984), nor does it explain the differences seen in Chapter 3, using words.

An alternative explanation relates to the proposed ‘conceptualisation’ of visual integration regions in the evolution of the human brain (Vandenberghe et al, 1996; section 10.3.A.1). The region that showed differential activation for animate relative to inanimate in the fluency experiment, i.e. the left anteromedial temporal lobe, corresponds closely to the area activated more for the perceptual task than the associative task in Chapter 4. This region is close (but medial) to the temporal pole area activated for many of the studies (see section 10.3.A.1). Work on the macaque monkey, lesioning the perirhinal cortex, has suggested that this area may be important in the association and integration of different visual features characteristic of individual objects (Gaffan, 1994; Buckley and Gaffan, 1998). In humans, it has been proposed that ventral temporal regions are critical in the processing of semantic representations which are differentiated on the basis of visual information, as opposed to other attributes, i.e. in ‘the perceptual components of semantic representations (Breedin et al, 1994). Support for this hypothesis comes from patients with a category-specific disorder for natural kinds, who are selectively impaired in the ability to retrieve visual features defining different members of living categories (Sartori et al., 1993).

This anterior medial temporal region may be critically involved in the representation of items that are differentiated on the basis of fine-grained visual information: the task of deciding whether a salmon or a cherry is closer in colour to a flamingo requires precisely that differentiation (Chapter 4). This leads us to a possible explanation for why no differential activation is seen for animate concepts in Chapter 4. It is possible that the ventral temporal areas are critical for natural kind identification, but are equally capable of being engaged by any object if a subject is explicitly focussed on a task requiring access to perceptual knowledge. The activation for words in the studies described
suggests that this visual differentiation occurs at a semantic level rather than solely at a pre-semantic level.

Inanimate categories produced much more consistent differential activation. The left posterior middle temporal gyrus (BA 21/37) was activated in both Chapters 3 and 4 for inanimate more than for animate concepts, across modalities and tasks. This region is close to that found by others (Martin et al., 1996; Damasio et al., 1996) when subjects named tools. The rare reports of category-specific deficits for artefacts have been described in patients with extensive left middle cerebral artery strokes which are likely to have included this region (Gainotti et al., 1995; Hillis and Caramazza, 1991; Warrington and McCarthy, 1987). Further investigation is needed into the role of the posterior middle temporal gyrus, but it remains a plausible hypothesis that this apparent specialisation for inanimate objects results from the relative importance of functional/associative knowledge for artefacts as opposed to living things.

In addition to the posterior temporal region, a left frontal region has been found to be more active for tools than for animate objects in Chapter 3, and by Perani et al (1995) and Grabowski et al (1997). The left fronto-parietal areas overlap close to regions involved in sensorimotor functions, and it is possible that manipulability, and the attendant sensorimotor experiential component that these objects afford is heavily weighted in their semantic representations. It is known that damage to the premotor region can cause greater impairment for retrieval of verbs than for nouns (Damasio and Tranel, 1993; Danieli et al, 1994), and there is evidence of a relationship between verb impairments and deficits on artefacts (Breedin et al, 1998). These data suggest a link between verbs that encode actions and the representation of inanimate objects, though further work is needed to determine the precise relationship.

How might one distinguish between the role of the posterior temporal region and the premotor region? We know that the temporal region is close to V5, an area involved in the perception of visual motion. We also know that imagining actions activates a nearby region (Martin et al, 1995). Apraxic patients tend to have extensive lesions involving frontal and temporoparietal regions (De Renzi and Lucchelli, 1994). The knowledge of an action placed upon an object (its use) is closely related to praxis as well as to verbs. Such a function would be far less relevant to the function of an animate object, therefore the
hypothesis can be made that the posterior middle temporal gyrus is involved in the knowledge of action placed upon an object, whereas actions of both animate and inanimate objects are associated with activation in the premotor cortex. An experiment studying the activation of V5 and the posterior middle temporal gyrus in use of objects and the activation of premotor cortex for verbs describing actions of animals as well as tools has not been performed (to my knowledge), but could be a worthwhile addition to the current literature.

10.6. A. 3 Perceptual versus associative/functional knowledge

A direct test of the hypothesis that type of knowledge is more important in the production of category specificity than object domain was performed in chapter 4. This study found that differences seen for type of knowledge retrieved were larger than those seen for category (consistent with the findings from Cappa et al, 1998). In our study, the visual (colour) task activated the anteromedial temporal lobe, or the 'what' pathway, and the associative task (location) activated the left posterior temporo-occipito-parietal region, or the 'where' pathway. Cappa et al (1998) found, consistent with our results, that parietal activation was greater for associative/functional knowledge than for visual knowledge. Therefore these studies therefore, while not showing completely consistent results in terms of location, reveal differences between retrieval of perceptual and functional/associative knowledge that respect the division between the ventral and dorsal visual pathways.

10.6.A.4 Summary

In summary, the neuroimaging evidence suggests that the semantic attributes of concepts are represented close to the cortical regions that mediate the perception of the relevant attributes. When internally generating the names of objects, the strategy used is determined by the subject. It is possible that such a strategy might take advantage of the most critical attributes to define such objects, in the case of animate objects, visual/sensory features; in the case of inanimate objects, functional/associative features. This would lead to differential activation for these categories in regions important for accessing such features in a task such as fluency, or naming. However, when attention is directed towards a particular attribute (sensory or associative) such differences would be minimised unless certain features were unique to the class of object being investigated. Both animate and inanimate objects possess sensory attributes, leading to a lack of
differential activity for these two classes when such retrieval is explicitly controlled. However, inanimate objects possess particular, well-described functions. It appears that even when directed towards a particular type of knowledge, this category difference is strong enough to be seen as differential activity.

10.6.B Internal semantic organisation – the elements

This subject will only be touched on briefly, as we have performed only one experiment investigating the possible mechanisms underlying semantic activation, using semantic priming. In Chapter 5, semantic priming was manipulated within a lexical decision paradigm to discover the regions of semantic network sensitive to such manipulation.

One temporal lobe region showed sensitivity to semantic priming – the temporal pole. While this finding suggests certain functions for this region, the qualitative nature of the response in the temporal pole also suggests particular mechanisms underlying it. This is discussed in detail in Chapter 5. What is important to note at this point, is that the complex response seen in the anterior temporal lobe to semantic priming suggests that the mechanisms of spread within the semantic system is a hybrid of automatic and attentional processes. This finding is consistent with accounts such as Neely (1991), who proposed that the behavioural phenomenon of priming is caused by rapid, automatic responses such as spreading activation and slower attentional processes such as post-lexical matching, the relative contribution of the two depending upon the experimental paradigm.

We have therefore shown that a region critical to semantic processing (the anterior temporal lobe) is showing a physiological correlate of ‘spreading of activation’, and in addition, that this mechanism is attenuated and ultimately reversed as the attentional component increases. This point is important in two respects. First, it shows a neurophysiological correlate of the theoretical mechanism of spreading activation; second, it is pertinent to the oft-cited temporal limitation of positron emission tomography: i.e. its inability to look at temporally brief mechanisms, due to the blocked design of stimuli. The use of correlational designs with nonlinear analysis will allow much more sensitivity and flexibility in terms of the processes investigated.
10.7 LIMITATIONS

10.7.A The use of words
One of the prime reasons for using tasks involving words in this thesis was the concern that using objects will more readily activate object recognition pathways involving potential confounding factors such as visual complexity. The use of words bypasses this by accessing the semantic system via orthography and phonology without involving structural description. Of course, this involves its own complications. The route to the semantic system is more indirect and one is open to the accusation that any regions seen are bound to be left lateralised as the task is verbal. However, with a carefully designed paradigm, some of these issues can be avoided.

10.7.B The use of patients
While the study of patients is critical in examining the neuropsychology of disease, several criticisms have been levelled. These relate to the use of patients to investigate the disruption of processing in disease, and secondly to the use of patients to inform normal anatomy.

10.7.B.1 Investigation of the disruption of semantic processing
Firstly, and most importantly, one cannot study patients in the same way that is used in conventional neuropsychology. A selective deficit in cognitive processing allows one to discuss the necessary regions for a task, but such a deficit cannot be scanned; if a patient cannot perform a task, the function of brain regions activated during that task cannot be delineated. There are two approaches to this problem. Firstly, a task that the patients can perform is used, which activates regions of interest implicitly (e.g. semantic association). This highlights the importance of comparison to normals at all times. Secondly, selective preservation of a cognitive process may be used; for example, patient SW had preservation of semantic processing, while the rest of his language processing was severely impaired. These are two sides of the same coin; performance is the key variable. A difficulty arises here when discussing findings in the patients with semantic dementia. The key deficit in these patients is dissolution of semantics. Study of semantic processing is therefore open to the criticism described above. However, these patients show the most severe deficit in naming, thought to be secondary to semantic dissolution (Patterson et al, 1994). As seen in Chapter 7, they were still able to perform a semantic association task, though less well than normals. Performance on the association task did not correlate with
changes in activity in the areas of interest, therefore allowing the conclusion that the failure to activate the posterior inferior temporal gyrus was not due to performance, and was consistent with their naming deficit.

A second criticism relates to the limitation of imaging to show the contribution of regions to a task. Some of the activated regions could be superfluous to performance of a task. The use of neuropsychology in conjunction with patient imaging allows us to examine the regions that are necessary and those that are sufficient for a task. The use of patients with lesions in regions activated for a task, but no deficit in task performance allows further interpretation of the sufficiency of, for example the inferolateral temporal regions, for performance of a cognitive process (see Chapter 9).

A third criticism is the small number of patients used. It is important to use a group if at all possible in order to minimise the confound of individual strategy variations while performing the task. This approach was used in chapter 7. It is also important that the activations for patients are compared to those seen in normals. Even using such caveats, generalisation from patient findings should be cautious. For example, regions outside the brain areas activated for normals are difficult to interpret. At such an early stage in the imaging of patients, we have therefore limited ourselves to the ‘normal’ brain region set. With greater experience in the imaging of patients, it may be possible to relax this restriction.

The use of alternative cognitive strategies by a patient is an inevitable part of the disease process. It is not therefore possible to state whether the changes seen in the studies performed here are due to cognitive or neural change. However, the use of differing tasks in the future, including implicit tasks such as semantic priming, where automatic activation of the semantic system occurs, will assist the identification of neural changes.

10.8 FUTURE DIRECTIONS
It would be naïve to think that this work represents any more than an initial foray into the organisation of the semantic system. Many questions have been left unanswered; for example, the role of the posterior middle temporal gyrus in the semantic processing of inanimate objects; the reason for lack of differential activation for animate objects; the
importance of the right temporal pole in semantic processing; the precise role of the
temporal pole and of the temporoparietal junction; the degree of specificity the inferior
frontal gyrus shows for semantic selection; the questions continue. An important future
direction is to explore these results further using patients with differing lesions, and to
serially scan patients to investigate changes in function. This unfortunately requires the
recognition of such patients early in the course of their disease, something which has until
recently been unusual. However, with improved diagnosis of cognitive disorders, and
increased numbers of specialist clinics this should improve.

10.9 CONCLUSIONS
It can now be said with some confidence that imaging data has increased our knowledge
of the regions involved in certain cognitive functions, and together with connectionist
models and neurophysiology, has begun to challenge the predominant views of language
and memory processing held until 10 years ago. The data presented in this thesis has
confirmed the critical role of the left anterior temporal lobe in semantically based
retrieval. I have been able to place this region within the context of a mainly left-
lateralised retrieval system, common to both context-specific and non-context specific
memory retrieval. The use of patient studies has allowed us to define the sufficient
regions for semantic processing, and to form hypotheses about the specific roles of
regions such as the anterior and inferior temporal lobe.

I have also shown that the semantic system is not homogeneous in terms of function. The
investigation of category specificity suggested that the more prominent neural distinction
relates to type of semantic attribute rather than object domain, and that category
specificity may be secondary to the relative weighting of sensory and functional attributes
for individual categories. In terms of the relationship between semantic memory and
episodic memory, my findings support the view that specialisation in the memory
retrieval system results from associations between subsets of regions within a common
memory retrieval network, and clarify the patterns of deficit reported in patients with
damage to disparate areas within this memory network.

The structural and patient investigations, in addition to informing us about normal
function, have extended our knowledge of the disease process in semantic dementia. The
use of new techniques such as voxel-based morphometry will enable more refined investigation into the correlation of structure and function. The functional studies confirm that it is possible to perform activation tasks with patients, provided certain criteria (such as ability to perform the task) are adhered to. A critical finding in relation to this was that changes in activity can occur in regions distant to the structural damage. While further research is required to establish a definitive account of this result, it provides a powerful argument for the importance of functional imaging studies in neuropsychology.
References


Wernicke C. (1874) *Der aphasische Symptomenkomplex*. Breslau: Cohn, Weigert.


Appendix 1: Schematic representation of the various explanations of semantic category-specific deficits

CATEGORICAL

Taxonomic

Evolutionarily salient domains

Caramazza & Shelton (1998)

Warrington (1981)
Laiacone et al. (1997)

REDUCTIONIST

Artefactual

Emergent property

Neural separation

Modality-specific

Correlational structure

Warrington & Shallice (1984)
Silveri & Gainotti (1988)
Farah & McClelland (1991)
Gainotti & Silveri (1996)


Funnell & Sheridan (1992)
Stewart et al (1992)
Gaffan & Haywood (1993)

Caramazza et al (1990)

Gainotti & Silveri (1996)
Appendix 2: Tabulation of regions found in imaging studies investigating category specificity – animate vs inanimate

<table>
<thead>
<tr>
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<tbody>
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<td>Frontal</td>
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<td>Left medial inf frontal</td>
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<td>Right mFG (10)</td>
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<tr>
<td>Temporal</td>
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<tr>
<td>Left anterior temporal</td>
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<tr>
<td>Right post inf temporal</td>
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<td></td>
<td>I-A -42 -62 0</td>
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<tr>
<td>Right STG</td>
<td></td>
<td></td>
<td></td>
<td>I-A -34 -38 8</td>
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<tr>
<td>Left SMG</td>
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<td></td>
<td></td>
<td></td>
<td>I-A -54 -54 0</td>
<td>I-A -30 -28 -16</td>
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<tr>
<td>Occipital</td>
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<tr>
<td>Exstrastriate cortex</td>
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<td>A-T -32 -82 -20</td>
<td>A-T -2 -94 0</td>
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<td></td>
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<tr>
<td>Basal ganglia</td>
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<tr>
<td>Thalamus</td>
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<td>T-A 24 -22 0</td>
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</tr>
</tbody>
</table>
Appendix 3: *Tabulation of regions found in imaging studies investigating category specificity – perceptual vs associative*

<table>
<thead>
<tr>
<th>Region</th>
<th>Martin et al. '95 (PICT)</th>
<th>Martin et al. '95 (WORD)</th>
<th>Cappa et al. '98 (WORD)</th>
<th>Mummery et al. '98 (WORD)</th>
</tr>
</thead>
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<td><strong>Frontal</strong></td>
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</tr>
<tr>
<td>Left Broca’s area</td>
<td>-44 6 4 Act-Col</td>
<td>-42 18 4 Act-Col</td>
<td>-26 52 12 Vis-Ass</td>
<td></td>
</tr>
<tr>
<td>Left mFG (10)</td>
<td></td>
<td></td>
<td>-38 24 20 Vis-Ass</td>
<td></td>
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<tr>
<td>Left mFG (9)</td>
<td></td>
<td></td>
<td>-40 -2 32 Vis-Ass</td>
<td></td>
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<tr>
<td>Left precentral (6)</td>
<td></td>
<td></td>
<td>-18 26 36 Vis-Ass</td>
<td></td>
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<tr>
<td>Ant cingulate</td>
<td></td>
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<tr>
<td>OFC</td>
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<tr>
<td>Right mFG (10)</td>
<td></td>
<td></td>
<td>32 46 8 Vis-Ass</td>
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</tr>
<tr>
<td>Right precentral (6)</td>
<td></td>
<td></td>
<td>42 6 28 Vis-Ass</td>
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<tr>
<td><strong>Temporal</strong></td>
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<tr>
<td>Left mTG</td>
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<tr>
<td>Left TPJ</td>
<td>-50 -52 24 Act-Col</td>
<td>-54 -38 20 Act-Col</td>
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<tr>
<td>Left inferior temporal cortex</td>
<td>-42 -46 -12 Col-Act</td>
<td>50 -38 -12 Col-Act</td>
<td></td>
<td></td>
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<tr>
<td>Right inferior temporal cortex</td>
<td>42 -42 -20 Col-Act</td>
<td>28 -30 -16 Col-Act</td>
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<tr>
<td>Right PHG</td>
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<tr>
<td><strong>Parietal</strong></td>
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<tr>
<td>Left SMG</td>
<td></td>
<td></td>
<td>-44 -50 36 Vis-Ass</td>
<td>-12 -60 20 Loc-Col</td>
</tr>
<tr>
<td>Medial parietal lobe</td>
<td></td>
<td></td>
<td>0 -50 32 Ass-Vis</td>
<td></td>
</tr>
<tr>
<td>Right SMG</td>
<td></td>
<td></td>
<td>44 -44 40 Vis-Ass</td>
<td></td>
</tr>
<tr>
<td><strong>Occipital</strong></td>
<td></td>
<td></td>
<td>-32 -78 32 Loc-Col</td>
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<tr>
<td>Left sOG</td>
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<tr>
<td><strong>Basal Ganglia</strong></td>
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<tr>
<td>Putamen</td>
<td>-24 6 0 Vis-Ass</td>
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<td></td>
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<tr>
<td>Caudate</td>
<td></td>
<td></td>
<td>6 8 2 Col-Loc</td>
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</tbody>
</table>
Appendix 4: Regions of significant activation in the main effect of semantic minus visual tasks activated by both patients and normals: (a) regions activated for both words and pictures; (b) regions activated significantly more for words than pictures; (c) regions showing differential activation across modalities i.e. greater activation for patients (relative to controls) in the semantic task on pictures, and greater activation for controls (relative to patients) in the semantic task on words. \(N(W-V) = \text{semantic} - \text{visual for words in normals}\); \(N(P-V) = \text{semantic} - \text{visual for pictures in normals}\); \(P(W-V) = \text{semantic} - \text{visual for words in patients}\); \(P(P-V) = \text{semantic} - \text{visual for pictures in patients}\).

<table>
<thead>
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<th>Main Effects Simple Main Effects</th>
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<tbody>
<tr>
<td>a) For both modalities</td>
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<td>Both groups</td>
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<tr>
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<td>Left iFG</td>
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<tr>
<td>Left TP junction</td>
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<tr>
<td>Left sOG</td>
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<tr>
<td>Left ant cingulate</td>
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<tr>
<td>Right iFG</td>
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<tr>
<td>b) Greater activation for Words than Pictures</td>
</tr>
<tr>
<td>Left mTG</td>
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<tr>
<td>Right cerebellum</td>
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<tr>
<td>c) Differential activation for Words and Pictures</td>
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<tr>
<td>Interaction *</td>
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<tr>
<td>Left post cingulate</td>
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<tr>
<td>Left iFG</td>
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<tr>
<td>Left iTG</td>
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<tr>
<td>Left temporal pole</td>
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</table>

* Larger z score for interaction indicates activation for words and deactivation for pictures
Appendix 5: Regions of significant differential activation for the patient and control groups in the contrast of semantic - visual tasks. The group by task interaction is reported followed by the simple main effects for each contrast. (a) Regions with significantly reduced activation for patients relative to normals for both modalities; (b) Regions with significantly increased activation for patients relative to normals for both modalities.

<table>
<thead>
<tr>
<th>Region</th>
<th>Main Effects</th>
<th>Simple Main Effects</th>
</tr>
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<tbody>
<tr>
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<td>Normals &gt; Patients</td>
<td>Normals</td>
</tr>
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<td>Left iTG BA 37</td>
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<td>-54 -46 -10 4.9</td>
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<tr>
<td>Right TP junction BA 39/40</td>
<td>62 -60 24 4.0</td>
<td>62 -62 22 3.9</td>
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<table>
<thead>
<tr>
<th>Region</th>
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<th>Normals</th>
<th>Patients</th>
<th>N(W-V)</th>
<th>N(P-V)</th>
<th>P(W-V)</th>
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<td>--------</td>
<td>-68 -10 26 3.4</td>
<td>2.2</td>
<td>2.8</td>
<td>3.1</td>
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<tr>
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<td>--------</td>
<td>-66 -2 8 3.8</td>
<td>2.4</td>
<td>3.1</td>
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<td>--------</td>
<td>50 18 -32 3.7</td>
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### Appendix 6: Table summary of experimental results for control subjects and structural deficit in SD patients

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<thead>
<tr>
<th>Lateral temporal structures</th>
<th>Fluency (Ch 3)</th>
<th>Sem simil (Ch 4)</th>
<th>LexD (Ch 5)</th>
<th>Sass (Ch 8)</th>
<th>SNS (Ch 6)</th>
<th>Pt Struct (Ch 7)</th>
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<td>-46 8 -20</td>
<td>-28 14 -36</td>
<td>-48 12 -28</td>
<td>-54 9 -38</td>
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<td>Left TOP jin</td>
<td>39</td>
<td>-34 -58 8 (I-A)</td>
<td>-46 -72 28</td>
<td>-50 -68 20</td>
<td>-32 -76 46</td>
<td>-48 -64 24</td>
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<td>Left ant mTG</td>
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<td>-42 -62 0 (I-A)</td>
<td>-56 -24 -6</td>
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<td>-52 -2 -8</td>
<td>-60 -4 -18</td>
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<td>Left mTG</td>
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<td>-56 -24 -6</td>
<td>-54 -54 0 (I-A)</td>
<td>-52 -2 -8</td>
<td>-60 -4 -18</td>
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<td>-60 -4 -18</td>
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<td>Left PHG</td>
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<td>-32 -30 -16</td>
<td>-30 -30 -16 (I&gt;A)</td>
<td>-36 -8 -20</td>
<td>-20 -18 -20</td>
<td>-27 -3 -42</td>
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<tr>
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<td>-20 -16 -16</td>
<td>-16 -10 -16 (A-I)</td>
<td>-10 -4 -24 (C-L)</td>
<td>-22 -12 -14</td>
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<td>-4 64 20</td>
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<tr>
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<td>-50 20 -6</td>
<td>-42 28 -6</td>
<td>-44 20 24</td>
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<td>Left iPL (39)</td>
<td>45</td>
<td>-42 2 32 (I-A)</td>
<td>-48 0 28</td>
<td>-52 -8 38</td>
<td>-58 6 8</td>
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<td>Left premotor cortex</td>
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<td>-48 0 28</td>
<td>-52 -8 38</td>
<td>-58 6 8</td>
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<td>42 21 -32</td>
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<tr>
<td>Right HG</td>
<td>22 4 -12 (A-I)</td>
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<td>38 -6 -38</td>
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<tr>
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<td>34 -70 26</td>
<td>62 -62 22</td>
<td>52 -66 26</td>
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Activations are listed if seen in semantic tasks. If also seen in control tasks from the first three studies, they are listed in red. Findings from the structural study are listed in blue.