Imaging the semantic system

The organisation of semantic memory

Uta Noppeney
Ph. D. Thesis

Wellcome Department of Imaging Neuroscience,
Institute of Neurology,

University College London

1

ProQuest Number: 10014334

All rights reserved

INFORMATION TO ALL USERS
The quality of this reproduction is dependent upon the quality of the copy submitted.

In the unlikely event that the author did not send a complete manuscript
and there are missing pages, these will be noted. Also, if material had to be removed,
a note will indicate the deletion.

ProQuest 10014334

Published by ProQuest LLC(2016). Copyright of the Dissertation is held by the Author.

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

Meiner Familie

Acknowledgements

Abstract

This PhD thesis investigates how conceptual knowledge is represented and processed in the human brain using functional imaging methods (PET, fMRI). In particular, the feature-based model of semantic organisation is evaluated, which postulates a specialization of brain regions for processing different types of semantic featrues.

For this, subjects were presented with semantic stimuli while the following factors were manipulated (i) stimulus modality (e.g. pictures vs. words), (ii) semantic content (e.g. action vs. visual features), (iii) task (e.g. explicit vs. implicit) and (iv) visual experience. This thesis focuses on action/tools and abstract/verbally-learnt knowledge:

Tool stimuli and action features elicited increased responses in a left lateralized visuo-motor action system encompassing ventral pre-motor, AIP (anterior intraparietal) and LPMT (left posterior middle temporal) areas. Critically, these responses were observed irrespective of stimulus modality but only during explicit semantic tasks. In contrast, ventral occipito-temporal regions exhibited category-selective responses to animals and tools. These effects were found irrespective of task but only when the stimuli were pictures. Collectively, these studies demonstrate that semantic responses are context-sensitive and lie in the interaction of semantic content with either (i) stimulus-bound factors such as modality or (ii) task. In terms of neural mechanisms, effective connectivity analyses demonstrate that they emerge from distinct interaction patterns among brain regions. Next, early blindness was used as a lesion model to investigate whether perturbation of early visual experience that alters the sensory-motor system also modifies the semantic system. Surprisingly, the action-selective LPMT response was retained in early blind subjects suggesting a considerable degree of innate and epigenetic specification of the semantic system.

Finally, abstract semantic concepts were investigated. Previous behavioural research has highlighted the importance of sentences for specifying the meaning of abstract concepts. In line with this, abstract concepts activated the same left fronto-temporal system as sentence processing.

In summary, this thesis contributes to our understanding of the neural systems engaged in representing and processing action and verbally-learnt knowledge.

Table of Contents

1 General Introduction

This thesis investigates how conceptual knowledge is represented and processed in the human brain using functional imaging methods (PET, fMRI). In particular, it tests the feature-based model of semantic organisation, which postulates a specialization of brain regions for processing different types of semantic representations such as action, sensory or abstract knowledge.

This introductory chapter discusses the contributions of functional imaging to our understanding of how conceptual knowledge is represented in the human brain. The first section outlines the feature-based account of semantic organisation. The second section describes the potential and pitfalls of functional imaging as a means to investigate the organisational principles of semantic memory. The third section provides a brief overview of functional imaging studies investigating semantic organisation, in particular those focussing on action, visual and abstract semantics. In the fourth section, this background information serves to motivate the questions and studies presented in this thesis.

1.1 The feature-based model of semantic memory

Since the seminal work of Warrington and Shallice (1984), double dissociations of semantic deficits have been established along the dimensions of:

- Abstract vs.concrete semantics (Goodglass et al., 1969;Coltheart, 1980;Breedin et al., 1994;Carbonnet et al., 1997;Cipolotti and Warrington, 1995;Marshall et al., 1996;Sirigu et al., 1991;Warrington, 1975)

- within the concrete domain, animate-inanimate (for review: Gainotti et al., 1995;Warrington and Shallice, 1984;Capitani et al., 2003; Gainotti and Silveri, 1996b;Farah et al., 1996;Gainotti and Silveri, 1996b;Hillis and Caramazza, 1991;Sacchett and Humphreys, 1992;Warrington and McCarthy, 1987)

These double dissociations persist even when attempts are made to control general processing differences due to confounding variables such as familiarity, visual complexity or word frequency (Farah et al., 1996;Sartori et al., 1993). They appear, therefore, to reflect some sort of semantic organisation at the neuronal level.

Among the many cognitive models that have been offered to explain these category-specific deficits, the feature-based account has received particular attention (see Figure 1.1). Within this framework (Allport, 1985;Gainotti and Silveri, 1996a;Martin et al., 2000;Shallice, 1988; Warrington and Shallice, 1984;Barsalou et al., 2003), conceptual knowledge is thought to be represented in a large distributed network, indexing a range of semantic features (e.g. visual, auditory, action, functional). Although category-specificity is not the underlying organisational principle, an apparent category-structure emerges because concepts rely differentially on, for example, sensory, action and verbally-learnt knowledge. Hence, the feature-based account explains category-specific semantic deficits for (i) concrete and abstract semantics and (ii) living and non-living items by their associations with different types of semantic knowledge:
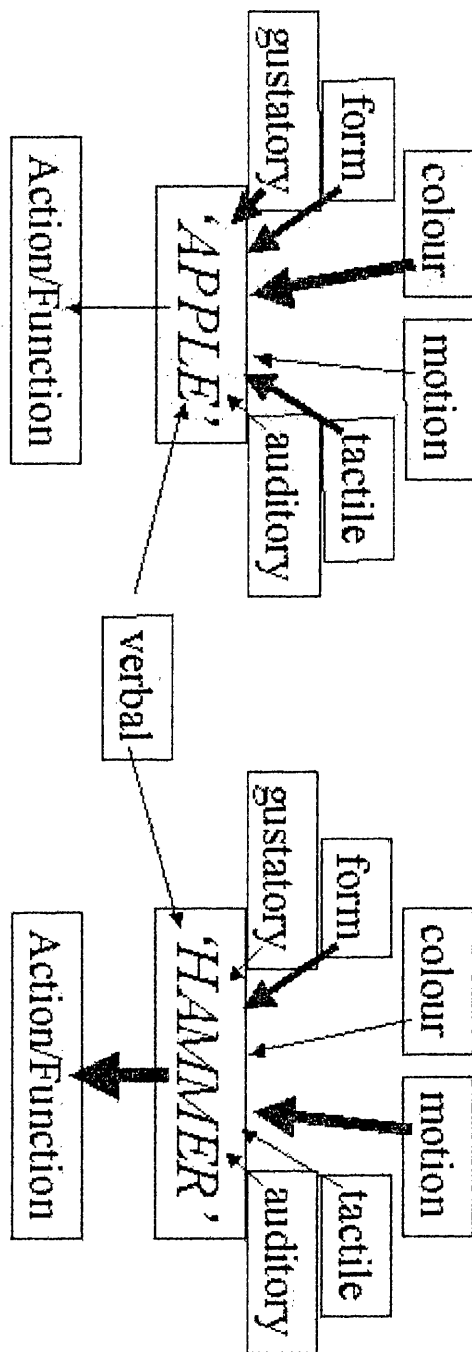
Figure 1.1 The feature based model of semantic memory. Illustration of the animate non-animate distinction.
Arrow width indicates the contribution of a semantic feature to a particular semantic concept.

- *Abstract and concrete concepts:* While the meaning of concrete concepts is primarily defined by perceptual features and their relation to physical everyday objects, the meaning of abstract concepts is thought to be verbally-mediated and to emerge from use in sentence contexts. Thus, the feature-based approach links concrete concepts with perceptual features and abstract concepts with verbally-learnt information (Breedin et al., 1994;Saffran, 2000).

- *Living and non-living items:* While sensory features are important for distinguishing between living items, action semantics plays a critical role in the representation of inanimate items, especially tools (Warrington and Shallice, 1984;Shallice, 1988). As a consequence, loss of sensory or action knowledge differentially disrupts the semantic representation of animate or inanimate objects respectively.

Sensory-action theory and the brain architecture

More recently, it has been proposed that the distinction between sensory (e.g. visual, auditory) and action (e.g. hand action, body motion) features is implemented in the human brain in terms of input and output channels (Martin et al., 2000;Martin and Chao, 2001). While sensory features are supposed to be subserved by brain regions close to or even overlapping with areas involved in modality-specific perception (e.g. visual association areas), action semantics is hypothesized to be related to motor output regions as well as to brain areas involved in motion / action perception. Thus, the neural substrates underlying semantic features are related to or even identical with the regions that were engaged when the particular type of semantic knowledge was acquired during original sensory-motor experience. For instance, there might be "semantic regions" that are selective for a particular type of semantic feature because of their afferent or efferent

connections to sensory-motor regions. Alternatively, "sensory-motor regions" themselves can sustain semantic representations or processes. The function of a "sensory-motor region" would then depend on the particular task-context, which influences the strengths of the connections to other brain areas. For instance, visual association areas might be involved in perception when being activated via forward (bottom up) connections from early visual areas but in semantic processes when being activated via backward (top down) connections from semantic retrieval regions (Barsalou et al., 2003;Price et al., 2003;Damasio, 1989;Noppeney et al., 2004b;Mechelli et al., 2003).

Other models of semantic organisation

Although the feature-based framework remains the dominant model for semantic organisation, it is not without criticism. For example, Caramazza and Shelton (1998b) have argued that category-specific deficits do not correlate with the degree of impairment in sensory and motor knowledge. Instead, they suggest that conceptual knowledge is represented in segregated brain areas that have developed specialised neural mechanisms for processing objects from different semantic categories (e.g. living items or artefacts) due to evolutionary pressures. Other models such as the conceptual structure account (Tyler and Moss, 2001;Tyler et al., 2000) assume a unitary distributed conceptual system that is structured according to the correlations amongst semantic features (i.e. the degree to which semantic features co-occur in the environment). Selective semantic deficits are explained by differences in the structure of concepts across categories. While living items are characterized by many features that are shared across categories, artefacts are defined by fewer and often more distinctive features.

1.2   Potential and pitfalls of functional imaging of semantic organsiation

Functional imaging experiments investigating the organisation of the semantic system have evolved along two lines of reasoning: The first approach compares brain activation elicited by stimuli from different object (e.g. animals, tools) or feature (e.g. colour, sound, tastes) categories while keeping the task constant. The second approach holds the stimuli constant, but changes the task instruction to focus the subject's attention selectively on different object features. For instance, subjects are required to make a semantic decision on the colour (e.g. Is it yellow?) or action (Do you peel it?) associated with fruits. These specific task instructions thus differentially weight access to perceptual or action features.

Although these two approaches are founded on rational grounds, a clear interpretation of their activation results is impeded by several confounding factors and unresolved problems:

Potential confounds of stimulus manipulations

Since the first approach compares brain activation evoked by stimuli from different categories, non-semantic as well as semantic properties of the stimuli might contribute to differences in brain response (Humphreys and Forde, 2001). Most notably, pictures of animate and non-animate objects differ in visual complexity and similarity. Therefore, increased brain responses to picture naming of the animate category, for example, does not necessarily reflect a category-specific semantic organisation, but might instead arise at the levels of early visual processing, structural encoding or object identification. Similar problems arise when using words as stimuli, as they place varying demands on phonological or orthographic processing. These examples demonstrate the importance of equating stimuli on their characteristic dimensions such as word frequency, familiarity,

word length, structural complexity and visual or auditory features. However, a perfect

stimulus match will often not be achieved. Some confounds can be removed by looking

for effects that are common to different stimulus (i.e. picture or word) or input (heard or

seen words) modalities using a conjunction analysis (Price and Friston, 1997). As

activation that is observed irrespective of stimulus/input modality is less likely to be

affected by pre-semantic processing differences, a conjunction can dissociate activations

due to semantic factors from those reflecting irrelevant non-semantic processing.

Potential confounds of task manipulations

Manipulating the task on the same stimuli avoids the problems of stimulus matching by

comparing the brain responses to equivalent stimuli. In this case, the semantic task is

designed to explicitly focus the subject's attention on different types of semantic features

and thus differentially weight their processing. Consequently, this approach is

particularly susceptible to the effects of implicit processing. Implicit processing refers to

the fact that many linguistic attributes are automatically processed by the human brain

irrespective of the explicit task demands (e.g. the Stroop effect, MacLeod, 1991). In

imaging studies, task irrelevant activation is illustrated by widespread activation in left-

lateralized language areas for words compared to consonant letter strings during a

feature detection task (Price et al., 1996), which does not explicitly require the

processing of words at a linguistic level. What does this imply for studies of the structure

of the semantic system? Despite task-induced attentional shifts to specific semantic

properties of an object, the entire semantic system might be activated in a highly

connected way and differential activation across types of semantic representations may

thus be reduced or missed.

Potential confounds of task and stimulus manipulations

In addition, both stimulus and task changes are also confounded by (1) general executive and (2) specific strategic processes:

- *'Executive' processes* include (effortful) retrieval, selection and evaluation of semantic information, working memory and response selection (Noppeney and Price, 2002a;Gabrieli et al., 1998;Thompson-Schill et al., 1997;Thompson-Schill et al., 1999b;Roskies et al., 2001;Fiez, 1997;Noppeney et al., 2004a). Even subtle task differences that might not be sensitively reflected in reaction times can place differential demands on these various executive processes and cause profound differences in activation pattern. For instance, Perani et al. (1999a) report increased activation in a system comprising the left dorso- and infero-lateral prefrontal cortex, the superior and middle temporal and the left occipital gyri for verbs relative to nouns, while no region was found more active for the reverse contrast. The activation pattern for verbs can easily be interpreted in terms of increased executive demands for verbs (in the context of longer reaction times) and therefore not be taken as evidence for an underlying segregation of verb/action and noun processing.

- Confounds from *specific strategies* are illustrated in the study reported by Phillips et al. (2002b), which used the question 'Is it bigger than a kiwi' for retrieval of visual knowledge and 'Do you peel it' for retrieval of action semantics. Only the visual question requires subjects to keep two objects in mind and make a size comparison, which might thus contribute to the activation differences.

These examples highlight the importance of a thorough task analysis to equate the cognitive processes involved across tasks when accessing different types of semantics. As it will often be difficult to discard task-induced confounds fully, experimental designs are required that modulate the task variable by either changing the task

instructions (e.g. 'Is it bigger than a kiwi?' vs. 'Is it round?' for accessing visual knowledge) or introducing several different tasks (e.g. semantic decision vs. picture naming or semantic generation) that do not share the same confound. Neglecting sensitivity issues, only brain regions that show consistently greater activation for one type of semantics relative to all others can be uniquely associated with a specific type of semantic representation.

In conclusion, in order to distinguish differential activation patterns that reflect the underlying semantic organisation from spurious activation differences due to confounds from non-semantic stimulus properties or general/specific strategic processes, one needs to identify brain areas that respond specifically to one type of semantic representation irrespective of (i) stimulus or input modality and (ii) instruction or task type. This requires either the integration of data from many studies or multi-factorial designs that independently manipulate the factors of (i) semantic type, (ii) stimulus or input modality and (iii) task instruction or task type.

1.3 Functional imaging studies of semantic organsiation

1.3.1 Overview

Over the last decade, a large corpus of functional imaging studies has investigated the feature-based model of semantic organisation and tested for anatomical segregation underlying different types of semantic features. These studies have primarily manipulated one or several of the following factors:

- *Semantic content of the stimuli:* The stimuli referred to different features (e.g. colour vs. hand action words) (Noppeney et al., 2002;Contreras, 2002; Hauk et al., 2004) or belonging to object categories that were strongly linked to particular semantic

features (e.g. tools that are associated with action features, for review see Price and Friston, 2002a;Joseph, 2001). This is of course the main factor required for identifying brain responses that are selective for a particular semantic content.

- *Stimulus modality:* The stimuli were presented as written words, spoken words or pictures that were either static or moving. This manipulation allows one to distinguish between selective responses primarily reflecting perceptual/structural or truly semantic processing.

- *Task:* Comparing implicit (shallow) and explicit (deep) semantic encoding tasks might provide insight into the role of cognitive set (or attentional effects) on semantic-selective activations. In addition, several studies have manipulated the task instructions of explicit semantic tasks to direct the subject's attention to particular semantic aspects while holding the stimuli constant (e.g. semantic decisions on tool stimuli with the task instructions: "Do you twist the object?" vs. "Is the object bigger than a kiwi", Martin et al., 1995;Phillips et al., 2002b;Kellenbach et al., 2002;Kellenbach et al., 2001;Damasio et al., 2001)

- *Additional factors:* Introducing additional factors such as experience or priming (Chao et al., 2002) permitted a further dissociation of brain regions based on their characteristic response patterns.

To test whether the feature-based account of semantic memory identifies the fundamental principles underlying semantic organisation, a wide range of different semantic types has been investigated such as action, visual (Noppeney and Price, 2002b;Kellenbach et al., 2001;Phillips et al., 2002b;Thompson-Schill et al., 1999a;Wiggs et al., 1999;Chao and Martin, 1999), auditory (Noppeney and Price, 2002b;Noppeney et al., 2002;Kellenbach et al., 2001), taste (Noppeney and Price, 2003),

functional-associative (Thompson-Schill and Gabrieli, 1999;Vandenberghe et al., 1996), abstract/verbally-learnt (Kiehl et al., 1999;Noppeney and Price, 2003;Noppeney and Price, 2004), spatial (Carpenter et al., 1999;Just et al., 2004;Damasio et al., 2001) and location knowledge (Cappa et al., 1998;Mummery et al., 1998). The following will primarily focus on action/tool, visual and abstract semantics, which will provide the framework for the studies reported in this thesis.

1.3.2 Action semantics

Introduction

This section characterizes the neural systems sustaining action semantics. First it examines their relationship to the visuo-motor system. Second, it discusses whether the neural systems for manipulation semantics can be further dissociated from those for whole body motion and functional knowledge. Third, it investigates the effect of visual experience, task context and input modality on action-and tool-selective responses. These task- and stimulus manipulations allow one to dissociate the functional role of the cortical regions engaged in action processing.

Action semantics and the visuo-motor system

The feature-based account (Martin et al., 2000) proposes that the neural substrates underlying action representations are anatomically and functionally related to brain regions taking part in a visuomotor action system encompassing the left ventral premotor cortex, the anterior intraparietal (AIP) and left posterior middle temporal gyrus (LPMT).

The AIP and ventral pre-motor circuitry is thought to play a crucial role in retrieving the appropriate action for a particular object and in the required visuomotor transformations. In the macaque, neurons in areas F5 and AIP have been identified that selectively

respond to action execution, observation and presentation of graspable objects (Rizzolatti and Luppino, 2001;Rizzolatti and Arbib, 1998;Kohler et al., 2002;Rizzolatti and Craighero, 2004;Rizzolatti and Luppino, 2001). Similarly, in humans, pre-motor cortex and the supramarginal gyrus/AIP have been implicated in action observation, simulation, imitation and execution (Grezes and Decety, 2001;Rizzolatti et al., 2002;Buccino et al., 2004b;Buccino et al., 2004a;Grezes et al., 1999;Grezes and Decety, 2002;Rushworth et al., 2003;Rushworth et al., 2001).

Consistent with the feature-based account, activation in the left pre-motor cortex has indeed been observed in studies comparing generation of semantically related action words relative to naming of an object (Warburton et al., 1996;Grafton et al., 1997;Grezes and Decety, 2002). While these studies are confounded by internal verbalization and thus phonological retrieval, the seminal study by Martin et al. also revealed increased left premotor activation for generating an action associated with an object relative to its colour (Martin et al., 1995). Intriguingly, a recent study has even shown selective activation along the (pre)-motor cortex in a somatotopic fashion for action words referring to face, arm or leg actions (e.g. lick, pick, kick) in a passive reading task (Hauk et al., 2004).

In addition to AIP and ventral pre-motor areas, the left posterior middle temporal region (LPMT) has consistently been associated with action semantics. As LPMT is just anterior to motion area MT/V5, its role in action semantics might be engendered by its functional relation to action/motion perception mediated by afferents from area MT/V5. Consistent with this conjecture, LPMT is activated for observing grasping movements relative to static objects (Perani et al., 2001;Rizzolatti et al., 1996), hands (Grezes et al., 1998; Grezes et al., 1999) or random motion (Bonda et al., 1996;Beauchamp et al., 2002;Grezes et al., 2001). While these activation differences might be due to specific

motion characteristics of the stimuli at the perceptual level, LPMT activation was also increased for static pictures or sentences with implied motion/action relative to similar stimuli that did not imply motion (Kourtzi and Kanwisher, 2000;Ruby and Decety, 2001;Senior et al., 2000). Most importantly, in semantic decision or generation tasks, LPMT is activated for retrieval of action (e.g. "Do you twist this object?") relative to retrieval of visual semantics (e.g. "Is the object bigger than a kiwi?"), when the stimuli are written words or pictures referring to real world objects (Martin et al., 1995;Phillips et al., 2002b). Similarly, LPMT activation is increased for semantic tasks on heard or seen words referring to action (e.g. "twist") relative to visual (e.g. "red"), auditory (e.g. "pop"), motion (e.g. "run") or abstract (e.g. "idea") semantic features (Noppeney et al., 2002; see Chapter 4). These effects were observed when the semantic task was held constant across conditions (i.e. semantic similarity judgement on triads of words) as well as when the task instructions changed to direct the subject's attention to the specific semantic content of the stimulus (e.g. "Does the hand action involve a tool?"). Taken together, these studies demonstrate that LPMT is more engaged in action semantics relative to a range of other semantic types regardless of whether action semantics is invoked by the task instruction or by the stimulus. Moreover, action-selectivity in LPMT is observed irrespective of whether the stimuli are (i) written words or pictures and (ii) heard or seen. Thus, the activations cannot be attributed to low level stimulus characteristics. Instead, these results characterize LPMT as a multimodal semantic region associated with action.

The distinction between hand manipulations and whole body movements

"Actions" can be classified as hand manipulations or whole body movements. A distinction between these two categories can be drawn at the perceptual and at the semantic level. At the perceptual level, hand manipulation movements are characterized by simple motion trajectories. For instance, the movement for using a saw is primarily a simple translation movement. By contrast, whole body movements are described by complex motion trajectories. Thus, humans can independently move different body parts that are connected by articulated joints. At the semantic level, hand manipulations are more strongly associated with tools and utensils, while whole body movements are primarily linked with humans and animals. Based on these distinctions, the question arises whether LPMT responds more to hand manipulations than to whole body movements. At the perceptual level, this question has recently been addressed (Beauchamp et al., 2002) by comparing the activations during observation of (i) natural simple tool movements (e.g. sawing), (ii) artificial simple tool movements (e.g. a rotating saw), (iii) natural complex human movements (e.g. running) and (iv) artificial simple human movements (e.g. a rotating human). All types of tool and human movements activated area LPMT relative to moving gratings. Consistent with studies of category-specific effects, activation in LPMT was higher for moving tools than moving humans. Similarly, semantic decisions on words referring to whole body movements and hand manipulations increased LPMT activation relative to judgements on words referring to visual features (Contreras, 2002) or a non-semantic baseline. Consistent with the category-specific effect for tools, LPMT activation was higher for tool manipulations than for animal whole body movements. A direct comparison of hand manipulations and whole body movements (after accounting for the category effect of tools) revealed only small non-significant activation increases for hand manipulations relative to whole body

movements at the perceptual and semantic level (Beauchamp et al., 2002;Noppeney et al., 2002, see Chapter 4). In summary, studies of action observation and semantic retrieval provide converging evidence that LPMT activation is commonly increased for hand manipulation as well as whole body movements. So far there is weak evidence that hand manipulations relative to whole body movements further enhances LPMT activation.

The distinction between manipulation and functional knowledge: knowing "how" and knowing "what for"

Tools or objects can be characterized by the motion features of an associated hand action (i.e. knowing "how" = manipulation knowledge) and by their function (i.e. knowing "what for" or the context of usage = functional knowledge). Although a particular type of manipulation can sometimes be associated with a specific function (e.g. a saw and a knife are associated with similar actions and have similar functions), the mapping between manipulation and functional properties is many to many. For instance, a piano and a record player subserve similar functions but are manipulated differently, while a piano and a typewriter fulfil different functions but are manipulated similarly. Recently, neuropsychological studies (Buxbaum et al., 2000;Sirigu et al., 1991) have reported patients who could match items on the basis of their function but not on the basis of how they are manipulated and vice versa. This double dissociation suggests that the neural substrates of function and manipulation knowledge may be anatomically segregated and one might hypothesize that ventral premotor, AIP or LPMT respond to manipulation more than functional knowledge. Consistent with this notion, previous studies (Cappa et al., 1998;Mummery et al., 1998;Thompson-Schill et al., 1999a) have not reported activation in any of these regions for retrieval of functional relative to visual semantics.

A recent study (Kellenbach et al., 2002) directly compared retrieval of (i) an action associated with a manipulable object (e.g. 'Does using a saw involve a twisting or a turning movement?'), (ii) a function of a manipulable object (e.g. 'Is a saw used to put a substance on another object?') and (iii) a function of a non- manipulable object (e.g. a traffic light). This experimental design revealed distinct activations patterns in different cortical regions: In LPMT and ventral premotor cortex, activation was significantly increased for manipulable relative to non-manipulable objects and non-significantly enhanced when comparing retrieval of action with functional knowledge for manipulable objects (see Gerlach et al., 2002b) for converging results in the ventral pre-motor cortex). In contrast, in AIP, activation was increased for (i) manipulable objects relative to non-manipulable objects and (ii) action decisions relative to function decisions. Thus, while AIP showed an effect of stimulus (manipulable vs. non-manipulable objects) and task (action vs. function retrieval), LPMT and the ventral pre-motor cortex showed only an effect of stimulus.

These results suggest that activation in the visuomotor system is primarily driven by manipulation knowledge. Furthermore, in LPMT and the ventral pre-motor cortex, this manipulation-selective response is automatically/implicitly invoked by manipulable objects irrespective of the specific task instructions. In contrast, in AIP it is modulated by the particular task demands.

The influence of sensory experience on action-selective LPMT response

The 'sensori-motor theory' hypothesizes that semantic information is represented in a distributed neuronal network encoding semantic features (e.g. visual, auditory, action), which are anatomically linked to the sensory (or motor) areas that are active when the

features (e.g. motion, colour) are experienced (Allport, 1985;Martin et al., 2000;Warrington and McCarthy, 1987). Thus, the functional anatomy of semantic memory is predicated on the organisation of sensory systems. From this perspective, one might expect that sensory deprivation that leads to the restructuring of sensory systems will also modify the neural systems underlying semantic representations. In particular, one might hypothesize that visual deprivation, which enforces action experience via somatosensory-motor associations rather than visual motion perception, reduces the action-selective response in LPMT. Contrary to this conjecture, in both blind and sighted subjects, LPMT activation increased for semantic decisions on heard words referring to actions relative to words referring to visual, auditory or motion features (see Chapter 5; Noppeney et al., 2003). This surprising resilience of LPMT action-selectivity to visual deprivation suggests two potential mechanisms: the action-selective role of LPMT (i) develops due to innately-specified neurobiological mechanisms and not just experiential factors or (ii) it depends on its efferent connections to motor areas.

The effects of task-context on action-selective LPMT responses

The results reported so far have emphasized that LPMT responds selectively to action retrieval during focussed semantic tasks. One might therefore be tempted to label LPMT as an "action semantic area". However, this assertion might suggest that LPMT has a single function and that action selectivity occurs irrespective of the task-context. In contrast, a recent study (Noppeney et al., 2002) demonstrated that although LPMT is more active for action relative to visual, auditory or motion features during focussed semantic decision tasks, it responds equally to all semantic features, when subjects silently repeat/read and think about the meaning of the words. The LPMT response to auditory and visual features during repetition is incompatible with an action-selective

role for LPMT irrespective of the task-context. Instead, this activation pattern suggests that LPMT action-selectivity may be better understood as an interaction between semantic type and task, which might be interpreted in two ways: From one perspective, LPMT performs the same process in both task-contexts, and this is either enhanced for action or suppressed for non-action words during the semantic decision task. Alternatively, LPMT may perform different functions during repetition and semantic decision. For instance, during repetition LPMT might be involved in phonological processing, while during semantic decisions on action words it might subserve task-induced strategies such as action imagery, which are not required for retrieval of the other types of semantics. Irrespective of the precise function(s) the implication is that LPMT action-selectivity depends on the task-context (see Chapter 4).

Selectivity for action semantics and for the category of tools

The feature-based theory predicates category-specific effects on anatomical segregation for different types of semantics. In particular, it links the category-specific effects of tools to effects specific to action semantics. In support of this hypothesis, many studies have consistently reported tool-selective activation in one or several regions of the visuo-motor action system: the left premotor cortex (Mecklinger et al., 2002;Chao and Martin, 2000;Grabowski et al., 1998;Grafton et al., 1997;Martin et al., 1996;Devlin et al., 2002;Gerlach et al., 2002a;Gerlach et al., 2000), the left posterior middle temporal (Chao et al., 1999;Damasio et al., 1996;Mummery et al., 1998;Perani et al., 1999b;Devlin et al., 2002;Cappa et al., 1998; Chao and Martin, 2000;Chao et al., 2002;Devlin et al., 2002;Martin et al., 1996;Moore and Price, 1999;Mummery et al., 1996;Phillips et al., 2002a) and AIP (Chao and Martin, 2000;Devlin et al., 2002;Chao et al., 2002;Cappa et al., 1998). These studies suggest that semantic category (e.g. tools

versus animals) and semantic type (e.g. action versus visual) might modulate the neural response in overlapping regions and thus action-selectivity can account for category-specific effects of tools.

Indeed, a recent study that independently manipulated stimulus-category (i.e. tools vs. fruits; Phillips et al., 2002b) and task / type of semantics (i.e. action vs. visual) in a 2X2 factorial design revealed that the tool and the action-selective effects influence LPMT in an additive fashion: Tools relative to fruits activated LPMT irrespective of whether action or visual semantics is retrieved. Conversely, retrieval of action relative to visual knowledge activated LPMT regardless of whether tools or fruits are presented (see Figure 1.2, top and bottom left). Thus, even when the stimuli were fruits, LPMT was more active when subjects made a semantic decision on an appropriate action (i.e. 'Can you peel it by hand') than on its real life size (i.e. 'Is it bigger than a lemon'). This pattern of results was replicated in a follow-up study (Contreras, 2002), where subjects made semantic judgements on visual or action features that referred to animals or tools. Again, tools relative to animals and action relative to visual features increased LPMT activation in an additive fashion (see Figure 1.2, bottom).

Similarly, increased AIP activation was reported for (i) manipulable objects relative to non-manipulable objects and (ii) action decisions relative to function decisions (see above, Kellenbach et al., 2002). However, as this study was not designed factorially, it cannot clarify whether the effects of stimulus (manipulable objects) and retrieved action knowledge influence AIP response in an additive fashion.

In conclusion, consistent with the feature-based account, tools that are more strongly linked to action semantics than animals, fruits or non-manipulable objects automatically activate regions that also respond during action retrieval. Moreover, both action semantics and tools increase LPMT (and possibly AIP?) responses independently.
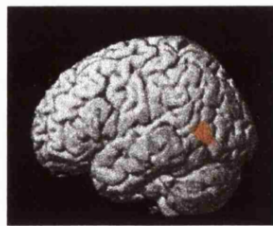
Figure 1.2 Additive effects of tool category and action retrieval in LPMT

Top: Activation for action > visual semantics (p<0.05 corr.) masked with action semantics > baseline (p<0.001 uncorr.) is rendered on an averaged normalised brain.

a) Data from Phillips et al. (2002 b). Subjects were presented pictures or written words that referred to tools or fruits. In the activation conditions, they made a decision on action (e.g. Do you peel it by hand?) or visual semantics (e.g. Is it bigger than a kiwi?). In the baseline condition, they made a decision on the screen size of the stimulus. Parameter estimates for semantic conditions averaged over pictures and words relative to baseline are shown at the peak co-ordinate of action > visual semantics (x=-56 y=-60 z=0). T = Tools, F = Fruits; Black = Action, White = Visual.

b) Data from Contreras (2002). In the activation conditions, subjects were presented with two written words referring to an object's properties (eg. WEIGH and MEASURE) followed by three potential written object names (eg. SCALES, MIRROR, BED). The properties were visual, action or functional attributes and the objects were household items or animals. Subjects decided which of the three objects was described by the two properties. Parameter estimates for each semantic condition relative to baseline are shown at the peak co-ordinate of action > visual semantics (x = -62 y = -58 z = 2). T = Tools, A = Animals; Black = Action, White = Visual.

Dorso-ventral dissociation of tool-selective activations

In addition to activations in the visuomotor action system, tool-selective responses have also been found within the ventral occipito-temporal cortex: Within the fusiform, activations have been found medially for tools and laterally for animals. Three recent studies have dissociated the functional roles of the dorsal visuo-motor system and the ventral occipito-temporal cortex in tool processing based on their distinct response patterns using additional manipulations:

The first study (Chao et al., 2002) manipulated semantic category (animals vs. tools) and visual experience (primed vs. unprimed) and demonstrated a priming induced response reduction non-selectively for tools and animals in the medial fusiform, but selectively for tools in LPMT. This unselective priming effect in the occipito-temporal area suggests that the "fusiform tool region" shows only a preferential response to tools but in fact responds to both categories similarly.

The second study (Beauchamp et al., 2003) manipulated (i) semantic type (i.e. human motion vs. tool motion) and (ii) stimulus display (real objects vs point light display) in a factorial design and showed a tool motion selective response in LPMT irrespective of stimulus display but in the medial fusiform primarily for real objects. Again, this suggests that LPMT is responsive to tools irrespective of stimulus modality, whereas the medial fusiform is driven by pictures of objects.

The third study (Noppeney et al., 2004b) manipulated the (i) semantic category (tool vs. animals), (ii) task (explicit vs. implicit semantic one-back-task) and (iii) stimulus modality (pictures, spoken or written words) factorially. While category-selective activations in ventral occipito-temporal cortex depended on the stimulus modality, they were modulated by task-context in the tool-selective regions within the visuo-motor system (see Chapter 6).

Collectively, the regionally distinct activation patterns in the dorsal visuomotor system and the ventral occipito-temporal cortex suggest that these two category-selective systems may support different cognitive operations: The tool-selectivity in occipito-temporal regions is strongly influenced by stimulus-bound factors such as modality (pictures vs. words), display (real objects vs point lights) or perceptual priming. These regions might therefore be engaged in structural processing of tools. In contrast, similar to the task-dependent action-selectivity in LPMT, tool-selective responses in regions of the visuo-motor system were modulated by the task-context and only observed for explicit semantic tasks. These regions might therefore play a role in strategic semantic processing.

In conclusion, tool-selectivity lies in the interaction of semantic content with either (i) stimulus-bound factors such as modality (=ventral occipito-temporal system) or (ii) task (=dorsal visuomotor system).

Summary

Consistent with the feature-based account, action observation, semantic processing of action features and tools increase activation in a visuomotor system encompassing the ventral premotor cortex, AIP and LPMT. Of those regions, LPMT has been most consistently associated with action semantics. Increased LPMT activation has been reported for tasks accessing action relative to visual, sound and abstract semantics irrespective of whether the stimuli were (i) words or pictures and (ii) seen or heard. This action-selective LPMT response was also observed in early blind subjects, who experienced actions primarily via sensory-motor associations. Moreover, LPMT also responds selectively to tools that are more strongly linked with action/manipulation semantics than to other semantic categories such as animals or fruits. Importantly,

however, while action and tool-selectivity in the visuomotor system is observed irrespective of stimulus modality, it is strongly modulated by task-context. It is only observed for explicit semantic tasks suggesting a role in strategic semantic processing.

1.3.3 Visual semantics

The feature-based account of semantic memory hypothesizes an association between animals and visual semantics. The primary candidate area for visual semantics is a left anterior fusiform region which is anterior and lateral to the fusiform area involved in colour perception (Lueck et al., 1989). So far, only few functional imaging studies of (i) retrieval of colour semantics and (ii) visual imagery have provided evidence for this hypothesis. The initial evidence was provided by a study that compared generation of colour to generation of action words and reported increased activation in the bilateral fusiform when the stimuli were pictures and in the right fusiform when the stimuli were written words (Martin et al., 1995). Further studies by the same group have also reported left fusiform/inferior temporal activation for colour generation relative to object naming (Chao and Martin, 1999;Wiggs et al., 1999). However, as this comparison involved a task-change (i.e. semantic generation vs. picture naming) and picture naming did not control for many cognitive processes involved in colour generation (eg. suppression of verbalizing the object's name, semantic search, working memory), activation was also enhanced in a widespread fronto-parietal system rather than specifically in the fusiform area. Therefore, the fusiform/inferior temporal activation increase might be due to task-related processing differences rather than reflecting colour retrieval per se. Studies of visual imagery have also provided evidence for a role of the fusiform gyrus in visual semantics. Left anterior fusiform activation has been revealed when (i) comparing

imagery of concrete words with listening to abstract words (D'Esposito et al., 1997), (ii) sentence verification tasks on visual relative to non-visual attributes (Thompson-Schill et al., 1999a) and (iii) correlating the effect of word imageability during listening, reading and semantic decision (Wise et al., 2000). By contrast, the right fusiform has been associated with colour imagery (Howard et al., 1998). Critically, the degree of lateralization and the exact locations of left anterior fusiform responses to visual semantics show considerable variation.

Other studies have not observed activation specific to visual semantics either in the fusiform area or elsewhere in the brain. For instance, left anterior fusiform activation was equal for retrieval of colour and verbally-learnt knowledge (Noppeney and Price, 2003) see Chapter 7. Likewise, studies investigating visual semantics using real life size judgements did not observe any significant activation difference (Phillips et al., 2002b;Vandenberghe et al., 1996) anywhere in the brain. To add to this inconsistency, several studies have associated retrieval of visual semantics with regions outside of the fusiform area. Thus, associating words on the basis of colour relative to location increased activation in the left anterior temporal gyrus (Mummery et al., 1998), while retrieval of colour / size relative to sound features enhanced activation in the right inferior temporal gyrus (Kellenbach et al., 2001). Furthermore, semantic decisions on luminance/form (e.g. blue, light) and auditory features (e.g. pop, noisy) relative to abstract concepts (e.g. value, truth) increased activation in a left anterior temporal pole region but only during semantic decisions and not during auditory repetition (Noppeney and Price, 2002b). These effects have not been replicated in subsequent studies even when identical stimuli and focussed semantic decisions were used. Thus, they are likely due to the confounding influences from (i) task-type, (ii) specific instruction and (iii) possibly subject-specific strategies on the activation evoked by different types of

semantic features. Taken collectively, these results suggest that the anterior temporal pole activation does not reflect visual semantic retrieval but rather task-induced strategies that might vary across subjects.

Summary

Studies of visual semantics have primarily produced inconsistent results. While studies of visual imagery and some studies using semantic retrieval tasks have implicated the left/right anterior fusiform gyrus in visual semantics, others have reported null-results (Noppeney and Price, 2003;Phillips et al., 2002b;Vandenberghe et al., 1996;Phillips et al., 2002b;Vandenberghe et al., 1996) or activation specific to visual semantics elsewhere in the brain (Kellenbach et al., 2001;Mummery et al., 1998;Noppeney and Price, 2002b;Mummery et al., 1998;Noppeney and Price, 2002b). One way to explain these divergent results is to appreciate the effects of implicit and task-induced semantic processing. For instance, as semantic knowledge about objects is strongly based on visual experience (at least in sighted subjects), one might hypothesize that brain areas related to visual semantics are implicitly activated even when the stimuli or task direct the subject's attention to other types of semantics. As a consequence, differential activation between visual and non-visual semantic conditions might be reduced and thus missed in the analysis. Implicit processing might therefore explain the series of null-results. Conversely, the inconsistent positive activation results might reflect strategic processes that depend on the task-type, the specific task-instructions and subject-specific strategies. Thus, further studies are required to ascertain whether visual semantic knowledge is segregated from other types of semantics, as predicted by the sensory-motor theory.

1.3.4 Abstract or verbally-learnt semantics

The feature-based account links abstract concepts with verbally-learnt or propositional-based information (Breedin et al., 1994;Saffran et al., 1998). One might hypothesize that processing abstract concepts engages the neural systems sustaining sentence processing. However, in contrast to the action and perception systems, the neural systems for processing propositional-based information remain to be defined. Hence, the feature-based account does not provide strong predictions as to the regions engaged in representing and processing of abstract concepts.

Only a few studies have been designed to delineate the neural substrates underlying abstract semantics by contrasting abstract and concrete words during lexical decision (Kiehl et al., 1999), reading (Beauregard et al., 1997;Wise et al., 2000), imagery (D'Esposito et al., 1997), semantic decision (Wise et al., 2000) or pleasantness judgements (Grossman et al., 2002). These studies have provided only inconsistent results: Lexical decisions on abstract relative to concrete words activated the right anterior temporal pole (Kiehl et al., 1999), while listening to abstract words relative to mental imagery of concrete words activated the right superior frontal gyrus and precuneus (D'Esposito et al., 1997). A multi-study analysis encompassing reading, listening and synonym judgements on heard words (Wise et al., 2000) associated abstract concepts with the left superior temporal gyrus. Similarly, pleasantness judgements on abstract concepts relative to implements and animals (Grossman et al., 2002) increased left postero-lateral middle temporal activation. However, several of these functional imaging results are confounded by differences in task performance as indicated by increased reaction times for abstract concepts (Grossman et al., 2002) and therefore difficult to interpret (Wise et al., 2000). Nevertheless, a recent study that manipulated semantic type (abstract vs. concrete) and task difficulty factorially (Noppeney and Price,

2004) during a semantic decision task demonstrated increased activations for abstract relative to concrete words in a left frontotemporal system that is usually involved in semantic processing especially at the sentence level. These differential activations were observed irrespective of task difficulty. Therefore, they could not be attributed to task difficulty confounds, but might reflect a particular retrieval mechanism or strategy for abstract concepts: As the meaning of abstract concepts is largely specified by their usage in language rather than by their relations to the physical world, subjects might generate an appropriate semantic context that fully explores and specifies the meaning of abstract concepts (see Chapter 8).

While the studies of abstract semantics discussed so far manipulated the stimuli i.e. compared abstract to concrete words, a further study investigated verbally-mediated knowledge by manipulating the task instructions on the same stimuli. Comparing retrieval of verbally-learnt facts to perceptual semantic features about food items (Noppeney and Price, 2003) revealed increased activation in bilateral and medial parietal regions that are usually found for memory retrieval functions.

In summary, the few studies comparing abstract/verbally-learnt and concrete/sensory-experienced concepts have yielded inconsistent results. These different activation patterns across studies are more consistent with an interpretation in terms of retrieval mechanisms or strategies than in terms of different neural representations.

1.4   Overview of thesis

This thesis uses functional imaging to characterize the organisation of the semantic system. Based on the feature-based model of semantic memory, it investigates whether different cortical regions respond selectively to particular types of semantic knowledge.

In particular, the first three studies focus on action and tool semantics, while the remaining two studies aim to delineate the neuronal systems underlying processing of abstract concepts or verbally-learnt knowledge.

The first study, reported in Chapter 4, investigates whether LPMT action-selectivity is modulated by input modality or task context. For this, words referring to action (e.g. "twist") features were compared to visual (e.g. "red"), auditory (e.g. "pop"), motion (e.g. "run") or abstract (e.g. "idea") semantic features (Noppeney et al., 2002) whilst manipulating the task (semantic decision, repetition, reading) and the stimulus modality (written, spoken words).

The second study, presented in Chapter 5, investigated whether visual deprivation modifies the neural systems underlying retrieval of action semantics that is in part acquired via visual experience. Using early onset blindness as a lesion model, LPMT action-selective responses were compared in sighted and early blind subjects. The hypothesis was that visual deprivation, which enforces action experience via somatosensory-motor associations rather than visual motion perception, reduces the action-selective response in LPMT i.e. action-selectivity of LPMT depends on visual experience.

The third study, reported in Chapter 6, addresses questions related to Chapter 4 but focuses on tool- rather than action-selectivity. Thus, Chapter 6 investigates whether tool-selective responses are modulated by stimulus modality and/or task context. For this, a multi-factorial design was used to manipulate semantic category (tools vs. animals), stimulus modality (pictures vs. words) and task (implicit vs. explicit semantic one back task). This design allowed category-selective regions to be segregated into two classes: In one class, category-selectivity was modality-dependent and primarily observed for

pictures. In the other class, it was task-dependent and observed when subjects were engaged in explicit semantic tasks. In a second step, we then used Dynamic Causal Modelling (DCM; Friston et al., 2003) to investigate the neural mechanisms that mediate these context-sensitive, category-selective responses.

Chapter 7 and 8 turn to the dissociation between abstract/verbally-learnt and sensory-experienced knowledge. Two experimental designs are used to characterize the neural systems that sustain processing of abstract concepts and verbally-learnt information: In Chapter 7, retrieval of verbally-learnt fact (i.e. the origin of food items with retrieval of their colour and taste) is compared with the retrieval of colour and taste while holding the stimuli constant. In contrast, Chapter 8 manipulates the stimulus dimension and compares abstract concepts to words referring to action, visual and auditory features during a semantic association task. As abstract concepts are usually more difficult to process than concrete concepts, each trial is also classified as easy or difficult post-hoc based on the subject's reaction time. This allows us to test for activations selective for abstract concepts unconfounded by differences in task difficulty.

2 Methods: Data acquisition in functional imaging

2.1 Introduction

To investigate human brain function, non-invasive functional imaging methods are needed that can provide insight into the time-course and the neuro-anatomical localization of brain activations. The various approaches that have been used can be grossly classified as either (i) electro-magnetic or (ii) haemo-dynamic metabolic methods. One important distinction between these two complementary classes lies in their different spatial or temporal resolutions. Electro-magnetic methods can directly measure electric potentials or magnetic field strength that are generated by neuronal depolarisation. They can thus define the underlying cortical neuronal events in real-time (10-100 msec). However, as they can infer electric/magnetic sources within the brain only indirectly from measurements on the scalp (the so-called inverse problem), they provide relatively poor spatial resolution. In contrast, haemo-dynamic metabolic methods such as PET or fMRI are based on increases in blood flow accompanying neuronal activation (Gjedde, 2001). They can therefore provide a high spatial resolution, but their temporal resolution is limited by the much slower haemodynamic changes that are associated with neuronal depolarisation.

The studies reported in this thesis employed either PET or fMRI. In the following, the basic principles of PET and fMRI will be described.

2.2   Positron Emission Tomography

2.2.1   Overview

Positron emission tomography (Cherry and Phelps, 1995) utilizes a variety of radioactively labelled biological probes (e.g. $H_2^{15}O$, ^{18}F-FDG, ^{18}F-Dopa) to provide insight into physiological (e.g. blood flow), metabolic (e.g. glucose metabolism) or neurotransmitter processes (e.g. dopamine receptors). This thesis reports only functional PET studies that measured regional cerebral blood flow (rCBF) using $H_2^{15}O$ in order to make inferences about neuronal activations. As the tracer has a relatively short half-life of 2.07 minutes, the isotope is produced in a cyclotron close to the PET scanner. It is introduced into the human body by intravenous injection. The distribution of these molecules in brain tissue can then be measured by making regional measurements of PET counts in the brain.

2.2.2   The basic principles of PET

The positron emitting isotopes are generated in a cyclotron by bombarding stable target nuclei with rapidly accelerated protons. Because of their excessive positive charge, the emerging isotopic nuclei are unstable and will decay by emitting a positron and a neutrino (see Figure 2.1). The positron will travel a short distance, lose energy by colliding with atomic electrons and finally annihilate with an electron by producing two 511-keV gamma rays (i.e. photons) that are emitted with an angular separation of 180°. Due to their high energy, most of these photons will not be attenuated by the brain tissue or the skull and can thus be detected by the array of scintillation detectors around the

head, which constitute the recording apparatus of the PET scanner. The detectors are connected with fast timing circuits to identify two "coincident" events on opposite sides of the head. Detection of two coincident gamma photons defines a line, which intersects the position of the aninhilation event. By combining lines of responses from many different angles, data can be reconstructed using mathematical algorithms and correction techniques to obtain a count density that reflects the concentration of the positron emission probe in the tissue.
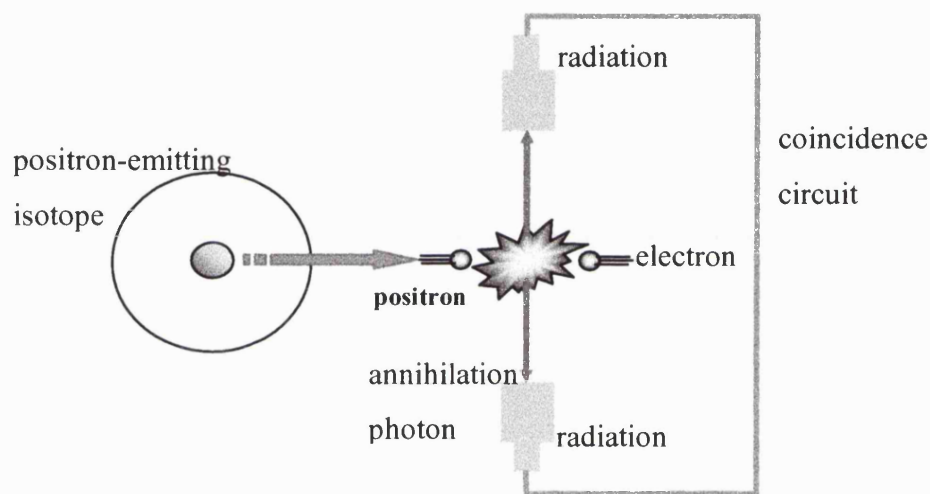
Figure 2.1 Schematic of positron emission and coincidence detection.
Adapted from Reiman et al. (2000)

2.2.3   Sensitivity, temporal and spatial resolution

Sensitivity and temporal resolution

The sensitivity of PET (i.e. number of events registered per unit of dose injected) is primarily determined by the efficiency of the detectors and the scan length. To allow for optimal sampling of radiotracer decay and maximise sensitivity, counts will be acquired during extended scanning periods (depending on the kinetics of the tracer e.g. $H_2^{15}O$: 60s). The signal in the resulting PET images is proportional to the time-integrated activation. Therefore, a PET study requires the behavioural conditions to be blocked and can provide only low temporal resolution.

Spatial resolution

Irrespective of any technical developments (e.g. detectors), the spatial resolution of PET is ultimately limited by two physical factors. First, the 180° emission of gamma photons is not exact, as positron and electron are not entirely at rest when they annihilate. Second, the positron will travel a short distance before annihilation. This is particularly relevant for $H_2^{15}O$ – PET, because the positron that is emitted from $H_2^{15}O$ isotope possesses a relatively high energy and will travel for a longer distance. Both, the first angulation errors and the second positron range effects cause a degradation of spatial resolution. As these two effects are not additive, this yields an overall spatial resolution limit of just over 2mm for PET.

2.3   The physics of MRI

2.3.1   Spin and net magnetization

A fundamental property of nucleons (i.e. protons and neutrons) is that they have an angular momentum. Individual unpaired protons and neutrons each possess a spin of ½. The number of protons and neutrons determines the net angular momentum of an atomic nucleus. For instance, the hydrogen nucleus ^1H possesses a spin of ½. As the nucleus is positively charged, the spinning motion results in a magnetic field (see Figure 2.2). Thus, when placed in an external magnetic field B_0, nuclei behave as little dipoles and gradually align with the field (= parallel) or against it (=antiparallel). The states in which the nuclear spins are aligned parallel or antiparallel differ in a specific amount of energy ΔE. The Larmor equation states that this energy ΔE is proportional to the strength of the applied magnetic field B_0 and to the size of the magnetic moment of the nucleus that is defined by the magnetogyric ratio γ (with h = Planck's constant):

$$\Delta E = h\nu = h\gamma B_0 / 2\pi \quad \text{(with h = Planck's constant, } \nu \text{ = frequency)}$$

As parallel alignment is a lower energy state, slightly more spins will align parallel than anti-parallel to the field, resulting in a net magnetization from the ensemble. At equilibrium, the net magnetization vector lies along the direction of the applied magnetic field B_0 and is called the equilibrium magnetization M_0. In this configuration, the Z component of magnetization M_Z, also referred to as longitudinal magnetization, equals M_0 and there is no transverse (M_X or M_Y) magnetization (Matthews, 2001;Jezzard and Clare, 2001).

2.3.2   Spin excitation and free induction decay

At equilibrium, the spins precess about the steady magnetic field B_0 at the Larmor frequency with a mean magnetization vector directed along the static magnetic field. As there is no time dependent change in net magnetization, no signal is detected in a conducting coil that is placed around the sample. However, if an additional radio frequency field B_1 that oscillates at the Larmor frequency (i.e. "in resonance") is applied orthogonal to the main static magnetic field B_0, the spins are perturbed and excited to the high energy state. This transfer of energy to the nuclear spins creates a coherence along the direction in the x,y plane and nutates (=deviates) the net magnetization away from the equilibrium z-axis. The degree to which the RF pulse pushes the net magnetisation into the transverse (x, y) plane depends on the amplitude and the duration of the additional B_1-field. The angle to which the magnetization vector is rotated is termed the flip angle. The smaller the flip angle, the smaller the transverse magnetisation will be. A 90-degree RF pulse produces a 90° rotation of the net magnetisation, i.e. a 90° flip angle (see Figure 2.3).

After the radio frequency B_1- field is switched off, the magnetisation vector continues to precess about B_0 at the Larmor frequency and induces a voltage in a receiver coil positioned in the xy plane. It can thus be measured as an oscillating signal. As the nuclear spins in different parts of the sample gradually lose their phase coherence and become realigned with B_0, the oscillating signal decays away under an exponential envelope. This signal decay is called "free induction decay" (FID).
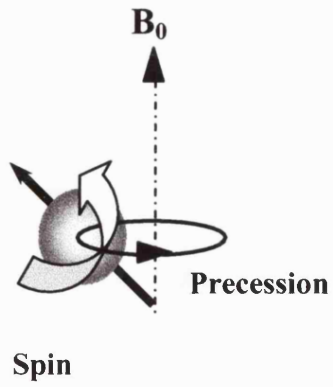
Figure 2.2 Spin and precession of a single proton.
The proton possesses the quantum quality spin. In an external magnetic field, the proton precesses around the longitudinal magnetisation vector (B_0).
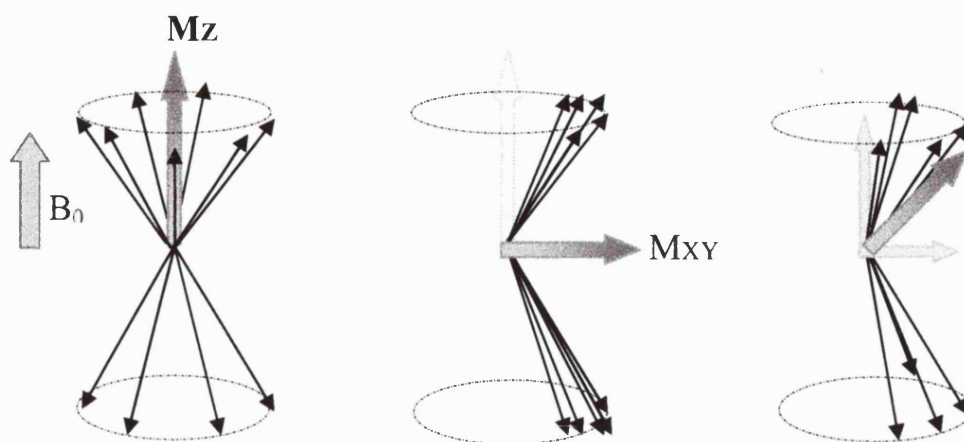
Figure 2.3 The effect of RF pulses on a group of atoms.

2.3.3   Nuclear magnetic relaxation and contrast

After excitation, the spin system will ultimately return to its low energy equilibrium state by emission of the radiofrequency energy that is detected in MRI. The efficiency with which this spin relaxation occurs depends on the interactions of the spins with their surrounding environment. The time constants that describe these relaxation processes are thus tissue-specific. Therefore, not only differences in proton density but also in relaxation rates allow us to generate contrasts between different tissue types (e.g. gray matter, white matter, cerebrospinal fluid in structural MRI or blood oxygen level dependent contrast in functional MRI).

There are three relaxation times that are of primary interest in MRI, namely T1, T2, T2*:

T1 relaxation

The spin-lattice or T1-relaxation characterizes the recovery of the longitudinal component of the net magnetisation following the RF pulse. The recovery of longitudinal magnetisation is an exponential process that is described by the equation:

$$M_z = M_0 \left(1 - e^{-t/T1}\right) \quad \text{(for 90° flip angle)}$$

T1–relaxation involves the release of the absorbed energy to the molecular environment or lattice (hence the term: spin-lattice relaxation). The efficiency of this energy dissipation depends on the strength of the randomly fluctuating magnetic field at the Larmor frequency. This explains why the tissue type or the composition of the environment affects the T1-time-constant. If the local molecular motion has a component at the Larmor frequency, then the equilibrium will be reached rapidly. Conversely, if there is only a very small component of random tumbling at the Larmor frequency, the T1 relaxation will be slow. For example, the free water molecules in cerebrospinal fluid

resonate at a much higher frequency then the Larmor frequency. In contrast, the rotation frequency of medium-sized molecules such as lipids is similar to the Larmor frequency of protons. Hence, lipid-rich tissues have shorter T1 relaxation times.

In tissues with short relative to long T1 relaxation times, there will be a larger longitudinal component of the recovered magnetisation and therefore a stronger transverse component after the subsequent RF pulse. This effect will be enhanced for short TRs that maximise the difference in amounts of relaxation (i.e. recovered longitudinal magnetization) between tissues with different T1 relaxation times. In these T1-weighted images with short TR, tissues with long T1 (e.g. CSF) will therefore have a low signal and appear dark, whereas tissues with short T1 (e.g. lipid) will have a higher signal and appear bright.

T2 relaxation

The spin-spin or T2-relaxation characterizes the decay of the net magnetization in the transverse xy plane back to zero. The T2-relaxation is an exponential process that is described by the equation:

$M_{XY} = M_0 e^{-t/T2}$ (for 90° flip angle)

Spin-spin relaxation is caused by proton-proton interactions that are very small but sufficient to affect the overall homogeneity of the magnetic field to which the spins are exposed. These local field inhomogeneities modulate the precessional frequencies of the individual protons resulting in a loss of coherence in the phases of their resonance emissions (also known as dephasing or phase dispersion). As spin-spin relaxation results from interactions of each proton with the field generated by adjacent protons, it is inherent to the tissue. It is most efficient in tissues where the major constituents are

macromolecules with slow molecular motion rates causing slow fluctuations in the magnetic field. For instance, the T2-relaxation time is shorter for lipid-rich tissues than for water. Similarly, the transverse component of the magnetisation decays faster in lipid-rich than in water-rich tissues. As the disparity in amount of dephasing increases with time, differences in T2-relaxation rates or contrast between tissues can be maximised by increasing the echo time (i.e. the interval before the signal is sampled). Images where the signal intensity has been sampled at a long TE are termed T2 weighted and are characterized by high signal intensities for tissues with long T2 (e.g. CSF) and low signal intensities for tissues with short T2 (e.g. lipid), i.e. the reverse of T1 weighted images.

T2* relaxation

Dephasing can also be caused by external magnetic field inhomogeneities. As each spin is exposed to a slightly different magnetic field strength, external magnetic field inhomogeneities make protons in different locations precess at different frequencies. This loss of transverse magnetisation due to inhomogeneous fields is often much shorter than the natural T2 signal decay and is characterized by another exponential time constant, T2'. The value of this time constant is determined by the technical implementation of the magnetic field and any field inhomogeneity caused by the properties of the object itself. T2* relaxation reflects the combination of T2 and T2' signal decays:

$1/T2* = 1/T2 + 1/T2'$

T2* relaxation and magnetic susceptibility: The BOLD-contrast

BOLD-fMRI sequences image the signal contrast that arises from changes in T2* due to magnetic susceptibility. Magnetic susceptibility is an index of the extent to which an applied magnetic field B_0 is distorted as it interacts with molecules in the sample material. Based on their magnetic susceptibility effects, two classes of molecules can be distinguished: Diamagnetic molecules have paired electron spins that interact with B_0 to create a small induced magnetisation anti-parallel to the applied magnetic field. They cause a local reduction in the field strength and thus have a negative susceptibility effect. For paramagnetic molecules with unpaired electron spins, the resultant electron magnetisation aligns parallel to B_0 causing a local increase in the field strength (i.e. they have a positive susceptibility effect). These local field inhomogeneities make the protons in the tissue precess at different frequencies resulting in greater dephasing and decreased MRI signal.

Haemoglobin is the primary carrier of oxygen in the blood. Oxygen binds to iron, a constituent of the haem component of haemoglobin. While iron is paramagnetic in deoxygenated haemoglobin, it becomes diamagnetic in the oxygenated form. Thus, blood susceptibility is negatively correlated with blood oxygenation. As neural activation primarily causes increased blood flow and decreased concentrations of deoxyhemoglobin, it will be associated with increased MRI signal. Therefore, hemoglobin can be used as an endogenous contrast agent indexing neuronal activation.

In summary, the ability of changes in blood oxygenation to modulate magnetic susceptibility –hence T2*-relaxation rates and MRI signal- is the basis for blood oxygen level dependent (BOLD) contrast, which is the most commonly used contrast mechanism in fMRI.

2.3.4   Spatial encoding in MRI

The signal that is detected by the RF receiver coil encodes frequency, phase and amplitude of the precessing magnetisation in the sample. In a completely uniform external magnetic field B_0, all the protons will resonate at the same frequency regardless of their spatial location. Spatial specificity is introduced by superimposing small magnetic field gradients on the larger homogeneous static magnetic field of the imaging magnet. A spatially variant, inhomogeneous magnetic field causes the signal frequency and phase to vary systematically with position. Thus, the basic principle of spatial encoding in MRI is to "transform" spatial information into frequency and phase information in the measured signal by applying small magnetic field gradients. A two - dimensional Fourier transform is then used to determine the spin density and additional weighting due to local values of certain MR parameters (like T1, T2, T2*) as a function of spatial location (see below).

Three dimensional images are obtained by combining orthogonal gradients in three stages before or while the signal is acquired:

Slice selection

The first stage in this process is the selection of a slice from which the signal is collected. This is achieved by applying a slice selective excitation pulse in the presence of a linear field gradient perpendicular to the plane of interest. Such a pulse perturbs only those spins whose Larmor frequency is within the bandwidth of the RF pulse, whilst leaving the spins outside the selected plane unperturbed. The thickness of the slice and thus the spatial resolution (in this direction) in the final MR image is determined by both the amplitude of the gradient and the bandwidth of the RF pulse. Higher spatial resolution can be achieved by strong gradients and a small bandwidth.

Frequency encoding

Once a selected slice of spins has been excited, it is necessary to encode the spatial location of these spins within the imaging plane. The spatial position along one axis of the plane is encoded into the frequency content of the MR signal by applying a frequency-encoding gradient during signal acquisition (hence also referred to as read-out gradient). This gradient causes protons to precess at different frequencies as a function of their spatial location.

Phase encoding

The remaining stage in this process is the application of the phase-encoding gradient, which encodes spatial position along the remaining in-plane axis in the phase of the MRI signal. The phase-encoding gradient is applied briefly between the RF pulse and the read-out of the MR signal. Whilst the gradient is turned on, the protons along the gradient axis precess at different frequencies and thus begin to dephase. The amount of dephasing, the phase difference between spins in different positions, is determined by the gradient-time product. It –and thus also the spatial resolution- increases with the strength of the gradient and the time it is applied. These location-specific phase shifts persist, after the phase-encoding gradient is switched off and the protons revert to the Larmor frequency imposed by the main magnetic field B_0.

In summary, the imaging procedure starts with a slice-selective excitation by the transient application of a slice-selection gradient during the RF pulse. This is followed by a brief phase-encoding gradient before image acquisition that causes persistent phase

differences along the y in-plane axis. Frequency encoding is achieved by applying the frequency-encoding gradient in the x in-plane axis during image acquisition.

The final spin density image (which may include additional MR parameter weighting) is obtained by submitting the measured signal to a 2-dimensional Fourier transform that expresses the signal intensity as a function of frequency.

K-space

The gradient-time product determines the position-dependent phase shifts and thus the spatial resolution of the image. Therefore, it is useful to represent the measured signal in k-space, with k_x and k_y being defined as the gradient-time products along the two axes:

$$k_x = \gamma \cdot \int_0^T G_x(t)\, dt$$

$$k_y = \gamma \cdot \int_0^T G_y(t)\, dt$$

where RF pulse occurs at t=0 and respective data point is acquired at t=T.

Then, each point along the axis K_X represents the frequencies imposed by the frequency-encoding gradient, whereas each point along the axis K_Y is equivalent to each phase-encoding step. As the spatial frequencies increase with the gradient-time product, signal acquired near the origin of k space contain low spatial frequency information, while that acquired towards the k space periphery represents high spatial frequencies. Furthermore, the central portion of k-space represents protons that have experienced least dephasing and thus shows maximal signal amplitude.

In summary, k-space representation provides information about the spatial frequency content and the intensity of the signal collected during the course of an imaging

sequence. A particular pulse sequence manipulates the magnitude and duration of the magnetic field gradients such that it navigates through k-space and samples all locations in the $k_x k_y$-Matrix.

2.3.5   The EPI-pulse sequence

As echo-planar imaging sequence (EPI) (Jones et al., 2001;Cohen, 1998) measures all lines of k space after a single excitation, it greatly reduces imaging time and makes it an ideal sequence for dynamic MRI techniques such as fMRI. Generally, EPI-sequences are designed as follows: First, a single slice is excited by transmitting an RF pulse in the presence of a selecting gradient. Thereafter, brief negative pulses of the frequency- and phase-encoding gradients displace the signal to the lower left corner of k space. Then, rapidly switching the polarity of the readout gradient causes the signal trajectory to oscillate between minimum and maximum k_x value. Short pulses or "blips" of the phase-encoding gradient causes the trajectory to move up one line along the phase-encoding axis. Thus, the combination of the frequency- and phase-encoding gradients causes the k-space trajectory to follow a rasterlike path.
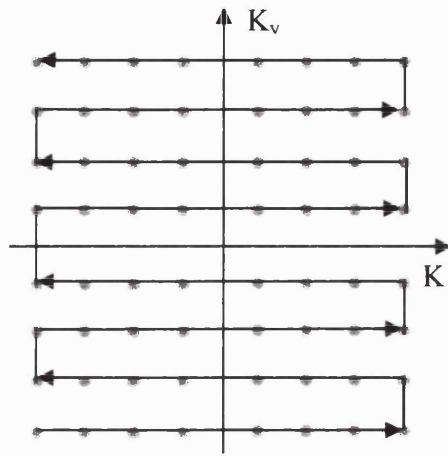
Figure 2.4 Trajectories through k-space for echo-planar imaging.

3 Methods: Statistical Analysis of functional imaging data

3.1 Introduction

To fully understand the functional organisation of the human brain, functional imaging results need to be considered from two distinct but complementary perspectives: functional specialization and integration. These two perspectives do not only lead to different neurobiological hypotheses but also require distinct methodological approaches for the characterization of functional neuroanatomy. The conventional general linear model analysis as implemented in SPM (Statistical Parametric Mapping) is generally used to identify functionally specialized brain responses. In contrast, the perspective afforded by functional integration requires methodological approaches that investigate the relationship amongst activity in one brain area versus others.

This chapter describes the series of steps that are involved in analysing functional neuroimaging data using SPM (Friston et al., 1995;Frackowiak et al., 2004).

The first section deals with spatial pre-processing: Realignment uses spatial transformations that remove or at least reduce the effects of subject movement during a scanning session. Normalisation spatially transforms the data into a standard anatomical space using linear and non-linear warps. Finally, the data are spatially smoothed.

The second section describes the mass-univariate approach that is used by SPM to test hypotheses about regionally specific effects. It describes (i) the general linear model that partitions the observed neurophysiological response into components of interest, confounds and error, (ii) parameter estimation and (iii) classical inference about the interesting effects in relation to the error variance. The theory of Gaussian Random Fields is introduced as a means to correct for multiple comparisons in the context of continuous, spatially extended statistical fields.

The third section introduces psychophysiological interactions (Friston et al., 1997) and dynamic causal modelling (Friston et al., 2003) as two approaches that characterize effective connectivity amongst brain areas. Effective connectivity has been defined as the influence that one neural system exerts over another.

The studies presented in this thesis have either been analysed using SPM99 or SPM2 (+and SPM2-pre-versions).
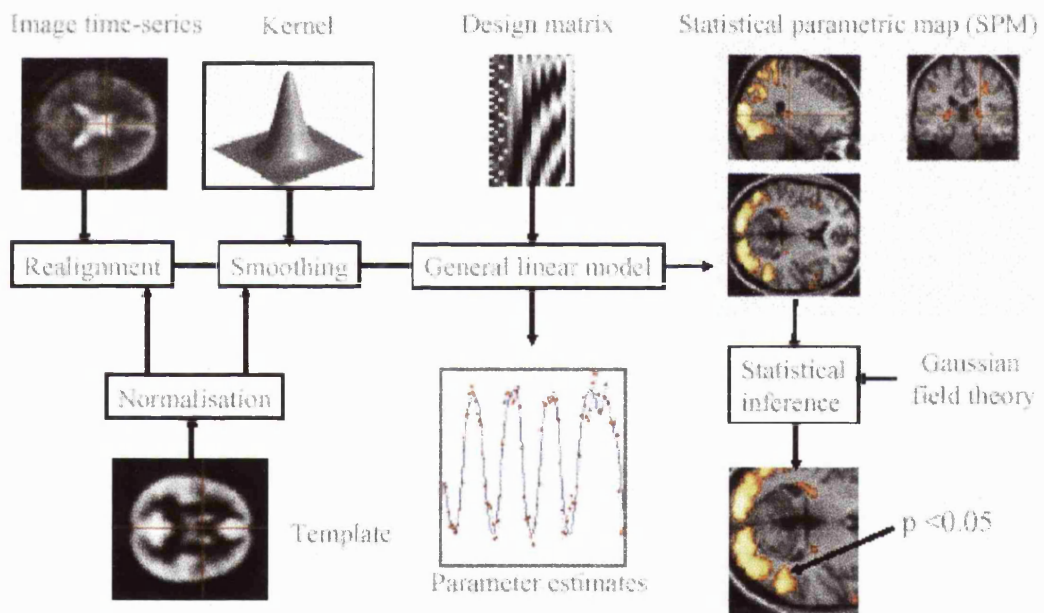
Figure 3.1 Schematic of data analysis in SPM
(from Frackowiak et al., 2004)

3.2   Spatial Pre-Processing

3.2.1   Realignment

Head motion during fMRI can give rise to artifactual changes in signal intensity and thus create a serious confound particularly in fMRI studies. Realignment removes variance from a time series, which would otherwise be attributable to error (hence decreased sensitivity) or to evoked effects i.e. if movement is correlated with the cognitive task.

Realignment involves (i) estimating the 6 parameters of an affine 'rigid body' transformation that minimises the [sum of squared] differences between each successive scan and the first and (ii) applying the transformation by resampling the data using sinc (SPM99) or B-spline (SPM2) interpolation.

3.2.2   Coregistration

Images from different modalities (e.g. structural and functional MRIs) are coregistered by optimising an information theoretic objective function i.e. maximising the mutual information across images (SPM2). Coregistration of structural and functional MRIs is - for instance- useful to anatomically localize activations.

3.2.3   Normalisation

After realignment, a mean image of the time series is used to estimate the warping parameters that map it onto a template (in fMRI this is a template EPI image) that already conforms to a standard anatomical space (in the case of SPM this is the space defined by MNI; Evans et al., 1992). The estimation involves (i) a 12-parameter affine transformation where the parameters constitute a spatial transformation matrix and (ii)

non-linear warping/deformation based on linear combinations of smooth discrete cosine basis functions.

Using an iterative Gauss-Newton scheme, the parameters are estimated in a Bayesian framework where one aims to find the deformation parameters that have the maximum posterior probability given the data.

3.2.4   Smoothing

After normalisation, the fMRI data are smoothed by applying a Gaussian kernel (point spread function), of known width, to each voxel. Smoothing the data is important to:

- Render the errors more normal in their distribution (central limit theorem) and thus ensure the validity of parametric statistical tests.

- Fulfil the lattice assumption of Gaussian Random Field Theory (see later).

- Express regional effects at a spatial scale where homologies in functional anatomy exist over subjects and thus justify averaging across subjects.

- Increase the signal to noise ratio. By the matched filter theorem, the optimum smoothing kernel corresponds to the size of the effect anticipated. According to optical imaging experiments, the spatial scale of the haemodynamic response is about 2-5 mm.

3.3 Conventional General Linear Model analysis

3.3.1 Modelling

The general linear model expresses the observed response variable Y in terms of a linear combination of explanatory variables X (collectively called design matrix) and errors that are assumed to be distributed identically and independently (sphericity assumption):

$$Y = X\beta + \varepsilon$$

The general linear model subsumes simpler variants such as the analysis of variance (ANOVA), the one- or two-sample T-tests. The so-called design matrix X, which contains the explanatory variables, determines the type of model. Each column of the design matrix (i.e. regressor) corresponds to some effect that is built in the experiment or may confound the results. For instance, in PET the regressors might be simple dummy variables indicating the type of condition, while in fMRI they might be condition-specific stimulus functions convolved with a haemodynamic response function (and possibly their temporal derivative and dispersion). In addition, confounds might be entered modelling motion artefacts or low frequency variations in signal due to aliased biorhythms.

3.3.2 Parameter Estimation

The relative contributions of each of these explanatory variables to the experimental variance are assessed using ordinary least squares (SPM99) or maximum likelihood (SPM2) estimation. The inferences about these contributions that are represented by the β estimates are made using T or F statistics. The validity of the ensuing statistics critically depends on the correctly estimated variability of the parameter estimates and

thus the underlying errorcovariance structure. While generally the errors are assumed to be spherical (see above), in neuroimaging studies, departures from sphericity might arise (i) due to serial autocorrelations in fMRI in single subject analyses or (ii) when entering multiple measurements per subject into a second level analysis over subjects (e.g. entering coefficients of multiple basis functions). In the cases of non-sphericity, SPM99 and SPM2 use different approaches to construct a valid statistics:

SPM99 uses an ordinary least square estimation scheme and compensates only for sphericity violations associated with serial correlations. Using the Satterthwaite approximation, it corrects the degrees of freedom based on the correlation structure that is imposed by additional temporal smoothing. This correction is mathematically identical to and provides the same effective degrees of freedom as the Greenhouse-Geisser correction used in other statistical packages.

In SPM2, the error covariance structure is estimated from the data by defining a basis set (i.e. variance components) for the normalised error covariance matrix and then using an iterative restricted maximum likelihood (ReML) algorithm to estimate the so-called hyperparameters controlling these bases. While this normalised error covariance matrix is estimated "pooled over voxels", it is pre-multiplied with a scalar variance estimate that is calculated separately for each voxel. The ensuing non-sphericity estimates are used in a filtering scheme to decorrelate the error terms. This "pre-whitening" renders the ordinary least squares parameter estimates maximum likelihood estimators, which are the most efficient of all unbiased estimators. In this case, the effective degrees of freedom revert to the maximum that would be attained in the absence of non-spherical errors.

By modelling and estimating the error covariance structure from the data, SPM2 does not only provide a better estimation of the autocorrelation structure for fMRI data but also enables second level analyses that encompass more than one parameter per subject.

3.3.3 Classical inference and the theory of Gaussian Random Fields

Inferences about the parameter estimates are made using their estimated variances. This allows for two types of statistical tests. One can test the null hypothesis that all the estimates are zero using the F statistic to give a SPM$\{F\}$ or, alternatively, that some particular linear combination or a "contrast" (e.g. a subtraction) of the estimates is zero using a SPM$\{T\}$. The T statistic is calculated by dividing the contrast (specified by contrast weights) of parameter estimates by the standard error of that contrast. This error term is estimated using the variance of the residuals about the least squares fit.

There are basically two classes of inferences using SPMs: (1) If we test an anatomically specific hypothesis about effects in a particular voxel, we can use an uncorrected p-value. (2) If we test an anatomically open hypothesis, we have to correct for multiple comparisons within the entire brain or a more restricted search volume of interest.

The adjustment of p values in SPM is based on Gaussian Random Field Theory. GRF theory is a methodological approach that corrects for multiple comparisons in the context of continuous, spatially extended statistical fields (analogous to Bonferroni correction for discrete data). GRF theory thus controls for the expected number of false positive regions rather than false positive voxels. The expected number of regions is estimated with a topological measure called the Euler characteristic, which is a function of the EC density for the particular statistic and the number of RESELs (hence it depends on the search volume and the smoothness of the normalised residual fields).

The GRF correction is based on two main assumptions: (1) The error fields are a reasonable lattice approximation to an underlying random field with a multivariate Gaussian distribution and (2) they are continuous with a differentiable and invertible autocorrelation function. These assumptions can be violated if the data are not sufficiently smooth or the errors are not normally distributed.

Unless stated otherwise, activations in this thesis are reported when surviving a threshold of p<0.05 corrected for the entire brain or the search volume of interest based on a priori hypotheses.

3.3.4 Random vs. Fixed Effects Analyses

The statistical inference drawn from fMRI time series may be of two types (Friston et al., 1999).

1. A Fixed Effects Analysis considers the subject variable as fixed. It makes the inference about the effect relative to the within subject variability, in other words the precision, with which the response was measured. Therefore, fixed effects analyses do not allow inferences at the population level but only to the group of subjects measured. It is therefore used to report results as case studies.

2. A Random Effects Analysis considers the subjects as randomly drawn from a large population. It makes the inference about the effect relative to the between subject variability and therefore allows generalization to the population level. In SPM, the random effects analysis is implemented in a two-stage procedure (the "summary statistics" approach) where contrasts of parameter estimates from a first level (=fixed effects) analysis are entered into a second level (=random effects) analysis. Inferences are then made at the second level. A full mixed effects analysis, where the within and

between subject variances are explicitly estimated, can be implemented using an EM algorithm (Friston et al., 2002). However, in the case of balanced designs, the "EM approach" and the "summary statistics approach" are equivalent.

In this thesis, the PET studies where the within- and between-subject variabilities are similar were analysed with a Fixed Effects Model, the fMRI studies with a Random Effects Model.

3.4 Effective Connectivity analysis

Effective connectivity is defined as the influence that one region exerts over another. In this thesis, effective connectivity amongst brain regions was investigated using psycho-physiological interactions (PPI) and dynamic causal modelling (DCM).

3.4.1 Psycho-physiological interaction

In a psycho-physiological interaction analysis (Friston et al., 1997), the physiological response in one area of the brain is regressed on the activity of a second region (or of any voxel within the brain) under at least two psychological contexts. A significant psycho-physiological interaction means that the contribution of one area to another changes significantly with the psychological context.

3.4.2   Dynamic Causal Modelling

The aim of DCM (Friston et al., 2003) is to make inferences about the coupling among brain areas within a simple but reasonably realistic neuronal model. DCM is simply a generalization of the linear convolution model used in conventional analyses of regionally specific effects. Both use exactly the same data and stimulus functions encoding experimental design. However, in a conventional analysis, the experimental effects are expressed through a direct or extrinsic influence on each region. In contrast, DCM allows for interactions among brain regions and, critically, the expression of experimental manipulations at the level of connections between brain regions.

DCM treats the brain as a dynamic input-state-output system. The inputs correspond to the conventional stimulus functions encoding experimental manipulations. The state variables encompass the neuronal activities and other biophysical variables that specify the haemodynamics. The outputs are the regional haemodynamic responses measured with fMRI. Effective connectivity is parameterised in terms of the coupling among the unobserved regional states (i.e. neuronal activity). Using a bilinear approximation, the connectivity parameters are reduced to three sets controlling: (i) the intrinsic connections in the absence of experimental perturbation, (ii) the direct or extrinsic influence of inputs on brain states and (iii) the changes in coupling induced by experimental manipulation (corresponds to the psycho-physiological interaction term above). The third set of bilinear parameters allows us to explain –for instance- context-sensitive category-selective activations by changes in coupling among brain areas. The parameters are estimated using a fully Bayesian approach.

4 Task-dependent selectivity for action in the left posterior middle temporal cortex

4.1 Introduction

There is converging evidence that the left posterior temporal area (LPMT) plays a role in action semantics (see Chapter 1). In this chapter, we address three outstanding questions:

1) Does LPMT respond generally to actions or more specifically to hand actions that might be more closely related to tools and utensils?

2) Does LPMT respond to action words irrespective of input-modality or are there modality-specific subregions?

3) Is LPMT action-selectivity determined solely by the semantic content of the stimuli or does it depend upon the cognitive operation that is performed on the stimuli?

In the following, these three questions will be discussed in turn:

LPMT selective response to hand actions

LPMT action selectivity has previously been inferred from an increased response evoked by action relative to visual semantics (Martin et al., 1995;Phillips et al., 2002b). In this study, these findings are extended further by comparing action semantics to a range of other semantic types such as body movements, auditory or abstract semantics. In particular, a comparison between words referring to hand actions and whole body movements might enable us to further specify LPMT response-selectivity. Although hand actions and body movements are both classified as actions, they differ in terms of their semantic and perceptual characteristics. At the semantic level, hand actions are more strongly linked with tools and utensils, while body movements are associated with

humans and animals. At the perceptual level, body movements are characterized by more complex motion trajectories. Different neural substrates for these two action types at the perceptual level have recently been suggested by a study showing increased LPMT activation for observation of moving tools relative to moving humans (Beauchamp et al., 2002). While the right STS showed an enhanced response to whole body movements, LPMT responded preferentially for hand movements. Using words rather than pictures or movies, this study investigates whether LPMT responds more strongly to hand actions than whole body movements at the semantic level.

The effect of input modality on LPMT action selective response

LPMT action selectivity has previously been demonstrated using pictures and written words. Given its anatomical proximity to the MT/V5 complex and satellites (*e.g.* KO) that process biological motion, the effect of input modality on the LPMT response needs to be further investigated. For instance, a recent study comparing words referring to actions and pictures with implied actions demonstrated that pictures enhanced activation in motion area MT/V5, while words increased activation in an area slightly anterior to MT/V5 (Kable et al., 2002). These results suggest that the area referred to as LPMT might actually encompass several distinct functionally specialized areas. In this study, we investigate the effect of input modality (auditory, visual) by presenting written and spoken action words.

The effect of task context on LPMT action selective response

It is an established theme in cognitive neuroscience that stimulus-selective brain responses might also depend upon the task context in which they were elicited. For example, (Friston et al., 1996) demonstrated that object-specific (object versus non-

object) inferotemporal responses were only expressed during tasks that required phonological retrieval (of the stimulus name or colour). This task by stimulus-type interaction raises the fundamental question of whether the specificity or selectivity of evoked brain responses are better understood in terms of the nature of the stimulus being operated upon, or in terms of the cognitive operation induced by the stimulus in a particular context. For example, is the action-selective LPMT response a function of the stimulus or does the selectivity arise from an interaction between stimulus and cognitive set (*i.e.* a stimulus-specific operation in a particular context). Empirically, this question can be answered by investigating the action-selective LPMT response in multiple task contexts.To address these questions, three experiments are reported in which subjects processed stimuli with different semantic contents using two types of tasks that did and did not involve semantic decisions.

This chapter reports three experiments using auditory and visual input modalities respectively. In the first fMRI experiment, subjects made semantic decisions on heard words referring to hand actions, body motions, visual and auditory features. In the second fMRI experiment, subjects were engaged in a semantic association task on triads of written words referring to hand actions, abstract concepts, visual and auditory features. In the third PET experiment, subjects simply read and repeated the same stimuli without being engaged in an explicit semantic decision. Experiments 1 and 2 therefore allow us to investigate the LPMT response to a range of semantic types. In addition, Experiment 1 enables us to test whether LPMT responses distinguish between hand actions and whole body movements. Collectively, the series of experiments allows us to investigate the effect of stimulus-bound characteristics i.e. input modality and task context.

4.2 Methods

4.2.1 Design

Three experiments were conducted (two fMRI and one PET) with different subjects in each experiment. In all three experiments, subjects were presented with blocks of (a) spoken or written words with different types of meaning (matched for word frequency and number of syllables); and (b) a non-lexical baseline condition that controlled for non-linguistic sensori-motor processing. The task, however, varied with experiment. Subjects engaged in decisions that explicitly focused their attention on the semantic content of each word (Experiment 1), made semantic similarity judgements on triads of words (Experiment 2), and were engaged in auditory repetition or reading (Experiment 3). Details of each experimental design are given below.

Experiment 1: fMRI. Semantic decisions on heard words.
During the activation conditions, subjects listened to words with four different types of meaning and performed a semantic decision task that explicitly directed their attention to the semantic content of each word:

1) Words referred to hand actions (e.g. tickling). Subjects decided if the hand action involved a tool.

2) Words referred to body motion (e.g. jumping). Subjects decided if the body movement was slow/involved jumping.

3) Words referred to visual features (e.g. blue). Subjects decided if the visual form was curved/dark.

4) Words referred to auditory features (e.g. loud). Subjects decided if the sound was usually loud/quiet.

For each semantic condition, there was a matched baseline condition that employed the same recorded stimuli after digital reversal, to remove lexical and semantic content. Subjects decided if they were recorded in a male voice. For all 8 (4 semantic and 4 baseline) conditions, 1/3rd of the stimuli were targets (i.e. the correct response was yes). All stimuli were presented at a rate of one per four seconds with five stimuli per block (20s per block) and each block was preceded by a short instruction period (5sec). Yes/No responses to all conditions were indicated (as quickly and as accurately as possible) by a two-choice key press. The order of semantic conditions was counterbalanced within and across subjects and each semantic condition was followed or preceded by its matched baseline condition.

Experiment 2: fMRI. Semantic associations on triads of written words.

In the activation conditions, triads of words were visually presented (one word above / two words below). The words referred to (i) hand actions, (ii) abstract concepts, (iii) visual attributes and (iv) sounds; the task was to decide which of the two words below was more similar in meaning to the word above. The baseline condition used triads of false fonts (non-linguistic symbols matched to the letters for average number and complexity of visual components) and subjects decided which of the stimuli below was the same as the stimulus above. Left/Right responses to all conditions were indicated by a two-choice key press (as quickly and as accurately as possible). There were 7 stimuli per block presented at a rate of one per 3.2 seconds (22.4s blocks). The activation and

baseline blocks were alternated. The order of conditions was counterbalanced within and between subjects.

Experiment 3: PET. Read /Repeat words and think of the meaning

The experimental design comprised 8 activation conditions and four baseline conditions (each presented twice). The activation stimuli were the same as in Experiment 1 but presented in both visual and auditory modalities (with visual and auditory stimuli counterbalanced over subjects). The baseline for the written conditions used the same words after transforming each letter into its corresponding false font (as in Experiment 2). The baseline for the heard conditions entailed the presentation of noise bursts, matched to the words for stimulus duration, frequency and power spectrum. Subjects were instructed to read or repeat the words and "think about their meanings"; or say "OK" in response to the baseline stimuli to partially control for articulation. Stimuli were presented at a rate of one per four seconds. All responses were articulated silently (mouthing) to prevent the subjects from processing the sound of their own voice. Conditions were counterbalanced between and within subjects.

4.2.2   Subjects

12 subjects (8 male, mean age 23.5, range 20-30) participated in Experiment 1, 15 (10 male, mean age 30, range 21-46) in Experiment 2 and 13 (13 male, mean age 27.2 years,

range:20-36) in Experiment 3. All subjects were right-handed, with English as their native language and no history of neurological or psychiatric disorders.

4.2.3   Data acquisition

fMRI (Experiments 1 and 2)

A 2 T Siemens Vision system was used to acquire both T1 anatomical volume images and T2*-weighted axial echoplanar images with blood oxygenation level-dependent (BOLD) contrast (gradient echo, Cartesian k-space sampling, TE=40ms, TR 2.9 s, slices acquired sequentially in descending direction, matrix 64X64, spatial resolution 3X3X3 mm^3 voxels, interslice gap 1.2 mm, slice thickness 1.8 mm, 38 slices covering nearly the whole brain). To avoid Nyquist ghost artefacts a generalized reconstruction algorithm was used for data processing (Josephs et al., 2000). A total of 520/500 volume images were acquired in Experiment 1 and 2 respectively. The first six volumes were discarded to allow for T1 equilibration effects.

PET (Experiment 3)

Each subject underwent 12 PET scans (whole brain coverage, 2X2X2 mm^3 voxels) performed on a Siemens CTI III camera which measured rCBF (regional cerebral blood flow) using a bolus infusion of radioactively-labelled water ($H_2^{15}O$). The dose received was 9 mCi per measurement. The study was approved by the UK Administration of Radioactive Substances Advisory Committee (ARSAC).

4.2.4   Data analysis

The data from all three experiments were analysed with statistical parametric mapping (using SPM99 software from the Wellcome Department of Imaging Neuroscience, London; http//www.fil.ion.ucl.ac.uk/spm) implemented in Matlab (Mathworks Inc. Sherborn, MA). Scans from each subject were realigned using the first as a reference, spatially normalised (Friston et al., 1995) into standard space (Talairach and Tournoux, 1988), resampled to $3X3X3mm^3$ voxels in fMRI and $2X2X2\ mm^3$ in PET. They were spatially smoothed with a Gaussian kernel of 8mm FWHM in the fMRI experiments and 16 mm FWHM in the PET experiments.

fMRI

The timeseries (fMRI) in each voxel was highpass filtered to 1/100 Hz. Experiments 1 & 2 were modelled in an event related fashion with regressors entered into the design matrix after convolving each event-related stick function with a canonical haemodynamic response function (and its first temporal derivative in Experiment 2). In addition to modelling each condition, the statistical model for Experiment 1 included instructions and errors. The model for Experiment 2 accommodated non responses and categorised each activation event as either subsequently remembered or not. In both experiments, nuisance covariates included the realignment parameters (to account for motion artefacts) and reaction times collapsed over (i) all activation conditions and (ii) all control conditions. Condition-specific effects were estimated according to the general linear model (Friston et al., 1995) and passed to a second-level analysis as contrasts. This involved creating contrast images (hand actions> all other semantic conditions) for each subject which were entered into a second level ANOVA to test for differences in activations. Inferences were made at the second level to allow a random effects analysis and generalization to the population level (Friston et al., 1999). The second level

analysis tested whether the hand action effects were common to both fMRI studies and therefore irrespective of input modality (conjunction of Experiment 1 & 2). We also compared each word condition to the baseline(s) using appropriate contrasts at the first level to illustrate the relative effects in terms of averages at the second level.

PET

The PET data were analysed with a conventional fixed effects analysis with 10 conditions. The linear contrasts compared: hand action to all other semantic conditions (the baselines were excluded). Since there were no replications within subject for the activation conditions, there is no distinction between a fixed or a random effects analysis.

4.3 Results

4.3.1 Behavioural

The mean and standard deviation of reaction times (RTs) and the number of errors for Experiments 1 and 2 are provided in Table 4.1 (Experiment 1 & 2 only).

One-way ANOVAs (task with 5 levels, Greenhouse-Geisser corrected) identified a main effect of task for RT (Experiments 1: $F(1,11)=24.5$; $p < 0.001$; Experiment 2: $F(1,14)=110.8$; $p < 0.001$) and errors (Experiments 1: $F(1,11)=5.67$, $p< 0.01$; Experiment 2: $F(1,14)=11.3$ $p<0.001$).

Bonferroni corrected pairwise comparisons of RTs demonstrated significant differences ($p<0.05$) for all word conditions relative to control (Experiment 1 and 2), for hand action relative to motion and visual (Experiment 1 only), sound relative to motion (Experiment

1 only) and for abstract relative to visual and hand action (Experiment 2 only).

Bonferroni pairwise comparisons of errors demonstrated a significant difference between hand action and baseline condition (Experiment 1) and for abstract relative to visual and the hand action (Experiment 2) and baseline relative to sound/abstract (Experiment 2).

Since hand action conditions produced the highest reaction times and errors in Experiment 1 but the lowest in Experiment 2, functional imaging effects that are specific to hand action over experiments are unlikely to be due to differences in task difficulty. Furthermore, reaction times were entered as covariates in the design matrix.

Experiment 1

	Control	Hand	Sound	Visual	Body
Reaction time (ms)	1298	1791	1633	1504	1507
SD	135	225	227	241	214
Errors	0.05	0.12	0.07	0.06	0.06
SD	0.02	0.06	0.05	0.05	0.06

Experiment 2

	Control	Hand	Sound	Visual	Abstract
Reaction time (ms)	826	1405	1502	1439	1614
SD	190	205	262	223	238
Errors	0.07	0.08	0.11	0.08	0.17
SD	0.06	0.04	0.05	0.06	0.07

Table 4.1 Behavioural data
Reaction times and Errors from Experiments 1 & 2.

4.3.2　Imaging

Hand action relative to other word conditions during semantic decisions (Experiments 1 & 2)

During semantic decisions on both seen and heard words, LPMT was significantly more activated for words depicting hand action than all other conditions. The peak activation for the conjunction of hand action relative to sensory semantics in both Experiments 1 and 2 was at [x= -57, y= -63, z= -3] with a Z score of 5.13 (p<0.01 corrected for the entire brain). The same area was also activated for hand action relative to body action [Experiment 1 only: x= -54, y= -63, z= -3; Zscore = 3.0] and hand action relative to abstract concepts [Experiment 2 only: x= -57, y= -66, z= 0; Zscore = 3.1]. The location of these effects corresponds almost exactly to the area [x= -56, y= -62, z= 0] found by Phillips *et al.* (2002) to be activated for hand action decision (Do you twist it?) than real life size decisions (Is it bigger than a hammer?) on pictures and written names of objects. Figure 4.1 shows the activation size for each word condition relative to baseline.

Hand action relative to other word conditions during reading and repeating (Experiment 3)

There was no effect of semantic type in LPMT (p>0.05 uncorrected) for either read/repeat or both combined. Critically, this was not because LPMT failed to respond during the hand action condition but because it responded to all the semantic conditions relative to baselines (see Figure 4.1). Indeed, LPMT activation (x=-52 y=-60 z=6) for reading sensory words relative to baseline was highly significant (z=4.3, p=0.08, corrected). The lack of action specificity in Experiment 3 therefore contrasts with the findings of Experiments 1 & 2.
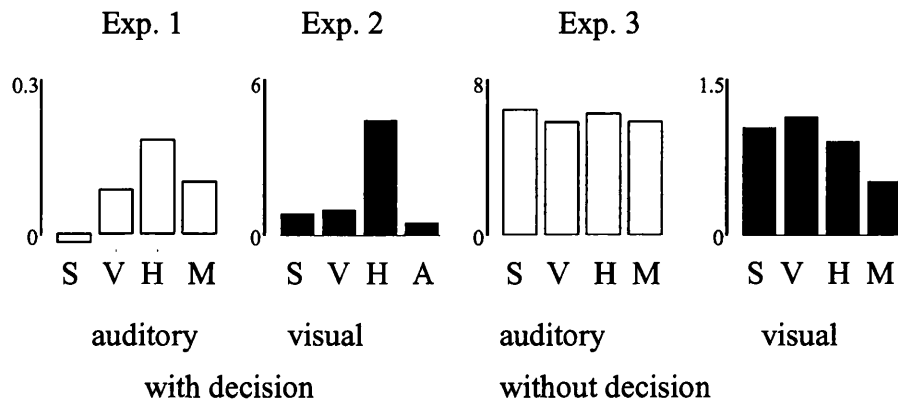
Figure 4.1 Parameter estimates in LPMT

Plot of parameter estimates (each semantic > baseline) in the left posterior middle temporal cortex (-57 –63 –3) for the three experiments; S=Sound, V=Visual, H=Hand action, M=body Motion, A=Abstract semantics. Black= visual, White= auditory

Summary of results

In summary, LPMT responds (i) more to words depicting hand actions than sensory attributes or body movements during semantic decisions irrespective of whether the stimuli are seen or heard (Experiments 1 & 2) and (ii) to sensory as well as action words during semantic tasks without decision (reading/repetition) relative to low level baselines with no lexico-semantic components (Experiments 3). Consequently, LPMT activation is modulated by the semantic content of the stimuli and by the task. Action-selectivity for LPMT emerges only during semantic decision (see Figure 4.2).

Semantic Decision
action>non-action

Read>Baseline &
Repeat>Semantic Decision
non-action
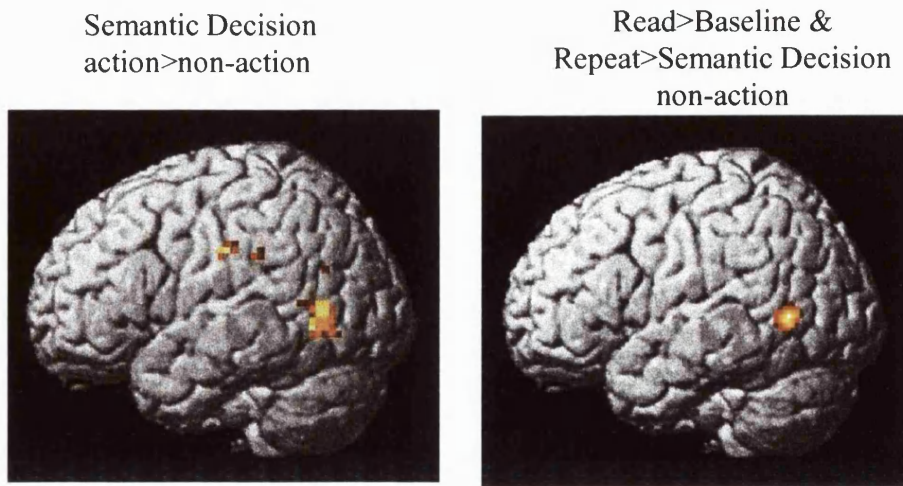
Figure 4.2 Activations in LPMT
Activations in LPMT are rendered on a template of the whole brain:
1. Hand action relative to other types of semantics (Experiment 1 & 2; height threshold = p<0.05 corrected)
2. Overlap between (i) reading of non-action words relative to baseline and (ii) repetition of non-action words relative to semantic decision on the same words (Experiment 3 & previous experiment; height threshold = p<0.001 uncorrected)

4.4   Discussion

This series of studies had three main aims: First, to further characterize the LPMT response by comparing action semantics to a range of other semantic types. Second, to investigate the effect of input modality and third examine the effect of task-context.

Consistent with results from previous studies investigating retrieval of action knowledge (Phillips et al., 2002a), we demonstrate that LPMT responds more to semantic decisions about hand actions than to decisions about visual, sound and abstract knowledge. Furthermore, there was a trend for increased activation when comparing hand actions to body motions, which might be explained by its semantic associations to tools and utensils (see also Beauchamp et al., 2002). Most importantly, an action-selective LPMT response was observed irrespective of whether the words were seen or heard. These

results suggest that although LPMT action-selectivity might be engendered by its functional relation to action/motion perception possibly mediated by afferents from area MT/V5 (Martin et al., 2000), it plays the role of an amodal semantic region that can be activated via auditory as well as visual input.

Although LPMT is more active for action than non-action stimuli during semantic decisions, it responds equally to action and non-action semantics when subjects repeat and read the words (Experiment 3). Collectively, the three studies demonstrate that the response in LPMT depends jointly on the task and the semantic content of the stimulus and an action-selective LPMT response evolves only during semantic decision tasks. Therefore, the action-specificity of LPMT lies in the interaction between task and stimulus-bound factors. More intuitively, responses in this region are not determined by the semantic content of the *stimuli* themselves, but by the *operations* they evoke within the cognitive set established by task instructions. To further characterize this interaction, a future study is required that manipulates stimulus type (action vs non-action) and task (decision vs no decision) within one experiment. This would enable us to investigate whether LPMT action-selectivity results in part from attenuated responses to non-action words during semantic decisions. Indeed, in a previous experiment (Noppeney and Price, 2002) we observed that activation elicited by non-action words decreased for semantic decision relative to repetition (see Figure 4.2, right).

The contrasting effects of stimuli and task can be viewed from two distinct perspectives: cognitive function and neural mechanisms. From the perspective of cognitive function, our data demonstrate the fallacy of assigning brain regions with specific functions that are either stimulus-bound or task-bound. Although LPMT responses to stimuli and tasks tapping action knowledge indicate functional specialisation for action, Experiment 3 in this chapter shows that it is also engaged when subjects read and repeat non-action

words. In terms of neural mechanisms, the finding that action selective responses in LPMT are dependent on the task requirements is consistent with well established notions that functional specialisation emerges from changes in the interactions among brain areas that serve different functions (Mesulam, 1990b;McIntosh, 2000b;Friston and Price, 2001). Accordingly, the functional role played by any neuronal system is defined by its interactions with other neuronal systems. Interactions can either be via forward connections (from lower to higher areas) or via backward connections (from higher to lower areas; see Friston and Price 2001). Backward connections may mediate top-down effects of task. The present study suggests that the experimental set/task may alter the top down influences on LPMT responses to action and non-action stimuli. There are many ways in which this task modulation might be mediated. For instance, LPMT responses to action/non-action words might be enhanced/curtailed by inputs from areas engaged during semantic decisions (e.g. the anterior cingulate or the left inferior frontal cortex). Alternatively, LPMT responses to action/non-action words might be decreased/enhanced by afferents from areas engaged when subjects repeat and think about the word meaning.

In summary, the data reported in this chapter replicate previous results by demonstrating increased LPMT activation for hand actions and extend these findings by comparing hand actions to a range of other semantic types during semantic decision and association tasks. Moreover, this action-selectivity was observed irrespective of the stimulus modality (i.e. spoken or written words). However, when subjects were instructed to read and repeat the same stimuli, significant LPMT activation was elicited by all stimuli irrespective of semantic content, and in this context action selectivity was completely

abolished. These results suggest that modulation of LPMT responses to neuronal inputs are determined by the experimental task and the semantic nature of the stimulus. Although further investigation is required to determine the nature of the interaction between LPMT and other areas during different semantic tasks, our results demonstrate that the function of LPMT is defined by the task requirements and the link between LPMT and action semantics only emerges in a limited set of contexts.

5 Effects of visual deprivation on the organisation of the semantic system

5.1 Introduction

The studies presented in the previous chapter suggested that LPMT action-selectivity depends on the task context, but can be observed for words irrespective of their input modality during semantic decision tasks. In this chapter, early blindness is used as a lesion model to investigate whether LPMT action-selectivity depends on experience-dependent mechanisms, in particular early visual input. In addition, it aims to characterize the common semantic retrieval system that is activated irrespective of the semantic content in sighted and blind subjects.

Early onset blindness allows one to study the effects of visual deprivation on the neuro-development of remaining sensory modalities and higher cognitive systems. Visual deprivation induces abnormal developmental neuroplasticity due to lack of visual experience and altered cross-modal integration among the spared sensory modalities (Rauschecker, 1995;Bavelier and Neville, 2002;Roder et al., 1999;Lessard et al., 1998). Previous studies have demonstrated that this leads to developmental changes in polymodal association and primary cortices of the visual and spared modalities. In animal studies, visual deprivation results in cross-modal reorganisation of extrastriate cortex (Hyvarinen et al., 1981;Heil et al., 1991), primary visual areas (Price et al., 1994;Hubel and Wiesel, 1977) and hypertrophy of auditory cortex (Ryugo et al., 1975;Gyllensten et al., 1966). Similarly, functional imaging studies in humans have reported extrastriate activation bilaterally for tactile discrimination relative to a non-discrimination task (Sadato et al., 1998;Sadato et al., 1996) and in the right hemisphere (BA18) for location of sounds relative to rest (Weeks et al., 2000). Developmental

changes in higher cognitive systems have been investigated through functional imaging studies of Braille reading. In blind subjects, additional extrastriate and inconsistently primary visual activation was observed for Braille reading relative to rest (Cohen et al., 1999;Melzer et al., 2001;Sadato et al., 2002), tactile non-discrimination tasks (Sadato et al., 1996;Sadato et al., 1998), auditory processing (Buchel et al., 1998a;Buchel et al., 1998b) and reading non-lexical Braille strings (Burton et al., 2002).

The present study investigated the effects of visual deprivation on the neural systems underlying semantic retrieval. Basically, two types of semantic processes can be distinguished, which might be affected differentially by visual deprivation: First, semantic retrieval involves general stimulus-driven or executive semantic processes that are invoked irrespective of the type of semantic information retrieved. Visual deprivation might affect these non-specific semantic retrieval processes vicariously by altering related systems (e.g. access to the semantic system from Braille orthography). Second, semantic retrieval involves processes that depend on the specific content of semantic information that is retrieved. The 'sensori-motor theory' of semantics predicates the functional anatomy of semantic memory on the organisation of sensory systems. From this perspective, one might expect that sensory deprivation that leads to the restructuring of sensory systems will also modify the neural systems underlying semantic representations. Thus, visual deprivation might alter retrieval of semantic information related to colour, form, action and motion that is learnt via visual experience, while sparing semantic information related to sounds that is acquired predominantly via the auditory sense. In particular, we hypothesized that visual deprivation, which enforces action experience via somatosensory-motor associations rather than visual motion perception, might reduce the action-selective response in LPMT, which might be engendered by afferents from area MT/V5.

In summary, we used early onset blindness as a lesion model that selectively alters experience-dependent developmental plasticity to ask whether "experience-dependent" mechanisms specify the functional anatomy of semantic retrieval. Within this general question, we embedded a more focussed one: "If experience-dependent mechanisms do play a role, is this more pronounced in parts of the semantic system that depend on visual experience?" We hypothesised that LPMT responds selectively to action features in sighted but not in blind subjects i.e. action-selectivity of LPMT depends on visual experience. Conversely, if semantic responses are not affected by experience-dependent plasticity, we can infer that the organisation of the semantic system is innate and specified epigenetically.

To investigate the effect of visual deprivation on semantic processes that are (i) invoked irrespective of, or (ii) dependent on the semantic content of stimuli, the present study used the following design: Blind and sighted subjects made semantic decisions on heard words referring to auditory, visual, hand action and body motion features. In baseline conditions, they performed an auditory decision on reversed words that had no lexical or semantic content. Differences in neurophysiological correlates of semantic processing were measured with fMRI. We characterized differences in the functional anatomy of semantic retrieval in two ways. First, by comparing regional activations (i.e. group x condition interaction) and secondly in terms of effective connectivity using psychophysiologic interactions (i.e. group x semantic activation). The psychophysiologic analyses represent a natural way to characterize differences in functional architecture in the brain because they refer explicitly to changes in coupling between classical semantic and visual regions that may reflect differences in developmental plasticity.

5.2 Methods

5.2.1 Subjects

Eleven blind (6 male, mean age 50, range 23-69) and 12 sighted control subjects (8 male, mean age 23.5, range 20-30) participated in the study. Four subjects were congenitally blind, 6 were blind before the age of 2 (early onset). One subject had very weak residual light perception. The causes of blindness were peripheral and included retinopathy of prematurity, retinoblastoma, anopthalmos and injury. Apart from one ambidextrous blind subject, all subjects were right-handed. All subjects had English as their first language and no history of further neurological or psychiatric disorder. Each gave informed consent to participate in the study.

5.2.2 Design

Stimuli and design were identical to Experiment 1 (see Chapter 4).

5.2.3 Data acquisition

Data acquisition was identical to Experiment 1 (see Chapter 4).

5.2.4 Data analysis

The data were analysed with statistical parametric mapping (using SPM99 software from the Wellcome Department of Imaging Neuroscience, London; http//www.fil.ion.ucl.ac.uk/spm). Scans from each subject were realigned using the first as a reference, spatially normalised into a standard space (Talairach and Tournoux,

1988) and spatially smoothed with a Gaussian kernel of 8mm FWHM. Data were highpass filtered to 1/100 Hz and were globally normalized with proportional scaling. The conditions were modelled in an event related fashion with regressors entered into the design matrix after convolving each event-related stick function with a canonical hemodynamic response function. In addition to modelling each condition, the statistical model included instructions and errors. Nuisance covariates included the realignment parameters (to account for motion artefacts) and reaction times that were modelled in an event-related fashion separately for (i) all activation conditions and (ii) all control conditions (to account for differences in reaction times across conditions). Condition-specific effects for each subject were estimated according to the general linear model (Friston et al., 1995) and passed to a second-level analysis as contrasts. This involved creating contrast images for each subject and a second level ANOVA, which modelled the group effect (sighted or blind) on the contrast of interest. Inferences were made at the second level to emulate a random effects analysis and allow generalization to the population (Friston et al., 1999).

Analysis of the data tested for

general semantic effects

- semantic decision on words > auditory decision on reversed words

specific semantic effects

- hand action relative to all other semantic conditions (and vice versa)

- motion relative to all other semantic conditions (and vice versa)

- visual relative to all other semantic conditions (and vice versa)

- auditory relative to all other semantic conditions (and vice versa)

Our analysis of specific semantic effects was restricted to voxels that were activated in the semantic condition relative to its baseline (p<0.001).

At the second level, we tested whether (i) general or (ii) specific semantic effects were common to both groups (conjunction of blind and sighted) or dependent on group (i.e. by testing for a significant condition by group interaction). Unless otherwise stated, we only discuss activations that are significant after correction for the entire brain volume.

Regression analysis testing for psychophysiologic interactions

To investigate whether regions from the semantic retrieval system were differentially connected to different brain areas in blind and sighted subjects, a psychophysiologic analysis (Friston et al., 1997) was performed where the BOLD signal timecourse in one semantic region was the physiological factor and the group was the psychological factor. For this, we first identified one left temporal (peak co-ordinates: -54 –54 –18) and one frontal reference region (peak co-ordinates: -45 18 27) that were activated for semantic relative to baseline tasks in both groups. For each subject, we created a new statistical model that used the BOLD signal timecourse of this frontal (or temporal) region as a regressor in a first level analysis, while not modelling the condition effects.

For each subject, one contrast image (positive regression slope) was entered into a second level ANOVA that modelled the group effect (blind vs. sighted). At the second level, we tested for a psychophysiologic interaction by simply comparing the regression slopes between blind and sighted subjects. A significant difference reflects changes in coupling or effective connectivity between the semantic system and the region identified.

5.3 Results

5.3.1 Behavioural

The mean and standard deviation of reaction times and the number of errors for sighted (s) and blind (b) subjects are displayed in Table 5.1.

For reaction times, a two-way ANOVA (task with 5 levels, group with two levels, Greenhouse-Geisser corrected) identified a main effect of task ($F(2,50)=39.9$; $p < 0.001$) and an interaction between task and group ($F(2,50)=3.3$; $p<0.05$). Bonferroni corrected pairwise comparisons demonstrated significant differences ($p<0.05$) for all word conditions relative to baseline, for hand action relative to all other conditions and for sound relative to motion. To account for activation differences due to reaction time differences across tasks, reaction times were modelled as covariates in the analysis of the imaging data.

For errors, a two-way ANOVA (task with 5 levels, group with two levels, Greenhouse-Geisser corrected) identified a main effect of task ($F(3,61)=10$; $p < 0.001$). Bonferroni corrected pairwise comparisons demonstrated significant differences ($p<0.05$) for sound, motion and hand relative to baseline and for hand action relative to sound and motion.

	Control		Sound		Visual		Hand		Body	
	S	B	S	B	S	B	S	B	S	B
RT (ms)	1298	1240	1633	1786	1504	1783	1791	1873	1507	1630
SD	153	194	227	218	241	394	225	276	214	227
Errors	0.05	0.04	0.07	0.09	0.06	0.12	0.12	0.19	0.06	0.10
SD	0.02	0.02	0.05	0.06	0.05	0.11	0.06	0.12	0.06	0.05

Table 5.1 Behavioural data for semantic decision tasks (sighted = S, blind = B)

5.3.2 Imaging (see Table 5.2 & Figures 5.1, 5.2)

General semantic retrieval effects common to blind and sighted subjects: In blind and sighted subjects, semantic decisions relative to baseline activated an extensive left-lateralized fronto-temporal system encompassing the left inferior and middle frontal, the middle and inferior temporal gyri, intraparietal sulcus, the paracingulate and the cerebellum.

General semantic retrieval effects: Differences between blind and sighted subjects (condition by group interaction): A direct comparison of the differences between the semantic and baseline conditions for the two groups revealed stronger activation for the blind in visual association areas including the left fusiform, middle and superior occipital gyri (see Figure 5.1). These activation differences are unlikely to be due to age effects because (i) an additional analysis that modelled the age effect as a covariate in addition to the group effect (sighted or blind), confirmed the enhanced extrastriate activation in the blind subjects and (ii) previous studies have shown increased

extrastriate activation during similar tasks for blind relative to control subjects even when age was controlled (Roder et al., 2002;De Volder et al., 2001).

There were no areas where sighted subjects showed greater activation than blind subjects.

Specific semantic effects common to blind and sighted subjects: Both blind and sighted subjects activated the left posterior middle temporal gyrus (LPMT) for action retrieval relative to all other semantic types (see Figure 5.2). Notably, this effect was present in congenitally blind, early blind subjects and the patient with very weak residual light perception. For visual relative to other semantic types, blind and sighted subjects activated the left inferior temporal gyrus and the cerebellum. There were no other significant effects.

Specific semantic effects differences between blind and sighted subjects (condition by group interaction): There were no brain areas where sighted subjects showed greater or less activation than the blind subjects for one semantic type relative to others.

Psychophysiologic interaction

In the blind relative to the controls, the BOLD signal time-courses of the left inferior frontal (or temporal) region showed higher correlations with those in several primarily left-hemispheric occipital regions including the lateral occipital sulcus and the lingual gyrus. These results demonstrate that frontal as well as temporal regions from the common semantic retrieval system exerted a stronger influence on, or were more strongly coupled with, regions in the occipital cortex in the blind than in the sighted subjects. The results of the PPI analysis, using the left frontal region, are shown in

Figure 5.1 (bottom) at a threshold of p<0.05 (corrected). Note the similarity of these results with the regions identified by the conventional group by condition interaction in Figure 5.1 (middle). Equivalent results were seen for the temporal PPI (results not shown).

Table 5.2 Functional imaging results of general semantic effects in blind and/or sighted

General semantic effects

- common to blind and sighted subjects

Region	Coordinates x y z	Z-score
L. inferior frontal sulcus	-45 18 27	7.79
L. inferior frontal gyrus, triangular part	-51 30 3	7.14
L. inferior temporal gyrus	-54 -54 -18	6.79
L. middle temporal gyrus	-63 -51 -6	6.09
L. anterior inferior temporal gyrus	-39 3 –48	4.80
Paracingulate	-3 30 39	6.72
L. intraparietal sulcus	-27 -69 48	6.69
R. middle frontal gyrus	54 30 33	5.95
Cerebellum, Vermis	3 -78 -27	7.77
Midbrain	-9 –24 -15	4.78

Spatial extent threshold: > 20 voxels

- more active for blind than sighted

Region	Coordinates x y z	Z-score	Sem>Aud blind	Sem>Aud sighted
L. fusiform gyrus	-36 –63 -18	5.88	6.33	ns at 0.9
	-24 –72 -12	5.64	5.99	ns at 0.9
L. inf. occipital sulcus	-36 –81 -15	5.64	5.94	ns at 0.9
L. middle occipital gyrus	-27 –93 6	5.29	5.72	ns at 0.9
	-30 –90 0	5.08	5.45	ns at 0.9
L. superior occipital g.	-21 –99 15	4.80	4.35	ns at 0.9

5.4 Discussion

The current study investigated how early visual deprivation affects the brain systems involved in semantic processing. First, we examined the effect of visual deprivation on the responses that were common to all types of semantic features and primarily reflect semantic retrieval processes. Second, we investigated whether the selectivity of brain responses to one specific semantic type (e.g action) is modulated by or is dependent on early visual experience.

In brief, semantic retrieval evoked left-lateralized fronto-temporal activations in both blind and sighted subjects with activation in the blind group extending beyond the normal semantic retrieval regions to encompass extra-striate regions. To our surprise, selective responses to semantics that are normally learnt with visual experience were not affected by blindness. The remarkable resilience of LPMT action-selectivity to profound perturbation of visual experience suggests a considerable degree of innate and epigenetic specification of the semantic system.

The differences in non-specific semantic activations and the preservation of action semantic selectivity can be reconciled by noting the differences were only expressed in extrastriate visual regions. These can be understood, most simply, from the perspective afforded by the psychophysiologic interaction analysis. In short, blind subjects expressed exuberant effective connectivity between the semantic and visual regions. This over-expressed coupling is consistent with the abnormal pruning of synaptic connections during neurodevelopment that depends on experience (Huttenlocher, 1990;Huttenlocher et al., 1982;Batardiere et al., 2002;Burkhalter, 1993;Price et al., 1994). This pruning normally leads to sparser connectivity, a more refined architecture and a greater degree

of functional specification (for example, children with early unilateral lesions show a relatively normal language development, Nass, 1997).

The "core" semantic retrieval system

In both blind and sighted subjects, semantic retrieval commonly activated a widespread predominantly left-lateralized neuronal system encompassing the inferior/middle frontal and temporal gyri, the intraparietal sulcus, the paracingulate and the cerebellum. In addition to this well-documented semantic retrieval/executive system (Petersen et al., 1990;Vandenberghe et al., 1996;Price et al., 1997;Binder et al., 1997;Noppeney and Price, 2002a;Fiez, 1997), blind subjects activated left hemispheric visual association areas that extended into the left fusiform and inferior/middle occipital gyri. Previously, left hemispheric occipito-temporal activation in blind subjects has been demonstrated for (i) reading Braille (Sadato et al., 1998;Sadato et al., 2002) relative to rest, (ii) tactile discrimination relative to a non-discrimination task (Sadato et al., 1996; Sadato et al., 1998) (iii) sound imagery relative to listening to noise stimuli (De Volder et al., 2001) and other verbal tasks such as verb generation and sentence processing (Amedi et al., 2002;Roder et al., 2002). Although our study does not allow us to assign a specific or necessary function to the semantic regions, it demonstrates a potential role for polymodal extrastriate cortices in higher level semantic retrieval processes following early visual deprivation. To ascertain whether extrastriate regions are necessary for semantic processing, future experiments using TMS with blind and control subjects would be required (see Cohen et al., 1997;Cohen et al., 1999) for related TMS experiments on tactile perception and Braille reading).

The functional role of the visual association cortex in blind subjects may depend on its task-dependent connections with other brain regions. This was characterized by the psychophysiologic interaction analysis (Friston et al., 1997) using, as reference regions, the frontal and temporal areas that were identified as the key players during semantic retrieval. This analysis revealed a significant interaction between the physiological factor, the left prefrontal/temporal activation, and the psychological factor, blindness (see methods and Chapter 3). An interaction of this sort can be construed as (i) a contribution to extrastriate responses from the prefrontal/temporal regions that is augmented by blindness or (ii) group differences in extrastriate responses that are enhanced by prefrontal/temporal activation. From a neurobiological perspective, the first interpretation is consistent with the notion that backwards connections from higher order fronto-temporal brain areas to extrastriate areas have greater efficacy in the context of visual deprivation. In other words, it characterizes extrastriate brain areas as regions that are more tightly coupled with higher order fronto-temporal regions in blind subjects. This may reflect a recruitment of extra-striate regions into the semantic retrieval system. The second, complementary interpretation implies that -possibly due to crossmodal reorganisation (Rauschecker, 1995;Bavelier and Neville, 2002) - the extrastriate cortex response is enhanced in the blind when prefrontal/temporal activation is high.
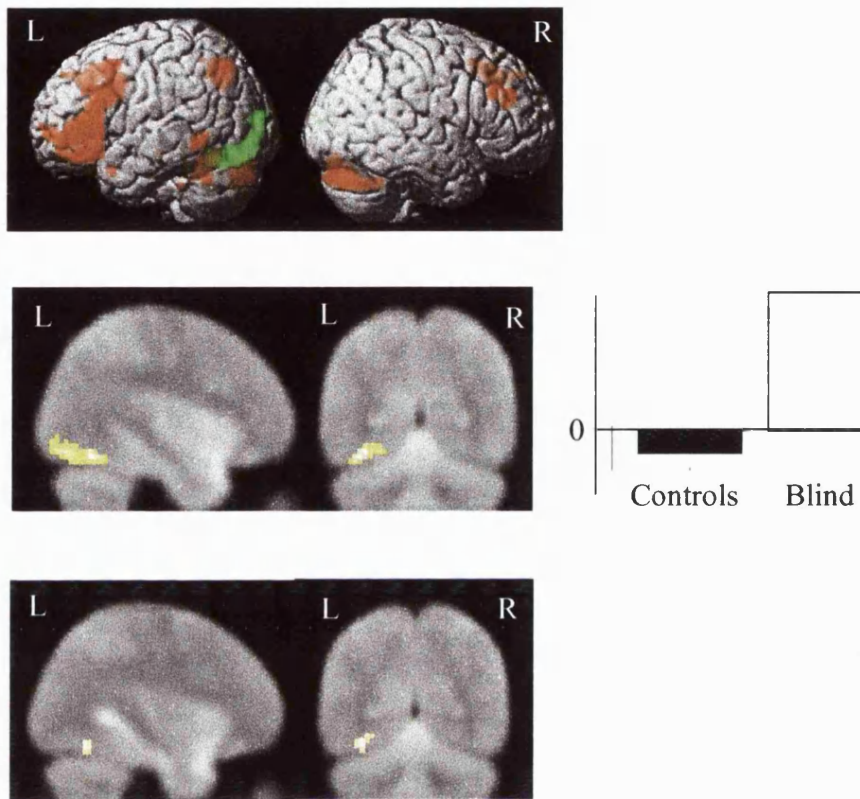
Figure 5.1 General semantic activations in blind and/or sighted

Top: General semantic activations (i) common to blind and sighted subjects (red); and (ii) increased for blind subjects (green) are rendered on an averaged normalised brain. Height threshold = p<0.05 corrected.

Middle: General semantic activations for blind subjects only on sagittal and coronal slices of an EPI-image created by averaging the normalized mean images from all 23 subjects. Height threshold=p<0.05 corrected. Parameter estimates for semantic decision relative to baseline for control (black) and blind (white) subjects at x=—36 y=—63 z= —18. Bottom: Psychophysiologic interaction results using the left inferior frontal region as a reference region on sagittal and coronal slices of the average EPI-image from all 23 subjects. Height threshold=p<0.05 corrected.

Semantic activation related to semantic content

Consistent with previous studies investigating retrieval of action knowledge (Martin et al., 1995;Phillips et al., 2002b), our results demonstrate that a posterior region in the left lateral middle temporal cortex (LPMT) responds more during semantic decisions on hand action than semantic decisions on visual, sound or motion knowledge. However, contrary to our hypothesis, we did not observe a significant interaction between LPMT action-selectivity and early onset blindness. Instead, an action-selective LPMT response was observed for both, the blind and sighted subjects. This surprising resilience of LPMT action-selectivity to visual deprivation might rely on its multimodal function - mediating between semantic aspects learnt from several modality-specific experiences of hand actions (e.g. visual, auditory, somatosensory and motor). LPMT is thus integrating converging inputs from many regions, so that its response properties might not be altered substantially by the absence of visual input. However, as blind subjects experience actions predominantly via somatosensory-motor associations, action-selective responses in the blind subjects would be expected in several other regions (e.g. anterior intraparietal sulcus) that integrate somatosensory input and motor output. Alternatively, in both blind and sighted subjects, the LPMT response might primarily be driven by connections from areas involved in hand actions. However, this is unlikely given the close anatomical and potential functional relation between LPMT and V5/MT. Therefore, we suggest that LPMT action-selectivity might be engendered by innately-specified neurobiological mechanisms in addition to experiential factors. In short, the consistent LPMT action-selectivity in blind and control subjects indicates a considerable degree of epigenetic specification of the semantic system.
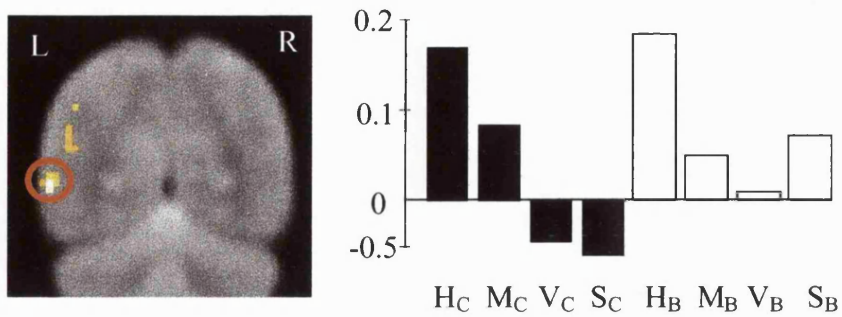
Figure 5.2 Action-selective LPMT response in blind and sighted subjects
Action-specific LPMT activation common to blind and sighted subjects on sagittal and axial slices of the average EPI-image from all 23 subjects. Height threshold=p<0.001 uncorrected. Parameter estimates for semantic decisions on hand action (H), motion (M), visual (V) and sound (S) words relative to their baselines for control (black) and blind (white) subjects at x=-54 y=-66 z=3.

6 Two distinct neural mechanisms for category-selective responses

6.1 Introduction

The last two chapters discussed the effects of task-context, input modality and visual experience on action-selective responses in LPMT. This chapter will now focus on tool-selective responses. Consistent with the feature-based account of semantic memory that links tools with action semantics, previous studies have demonstrated tool-selective responses in a visuo-motor action system encompassing a left posterior middle temporal area (LPMT; Martin et al., 1996;Phillips et al., 2002b;Noppeney et al., 2003;Devlin et al., 2002;Damasio et al., 1996;Kellenbach et al., 2002), the anterior intraparietal sulcus (AIP;Chao and Martin, 2000) and the ventral premotor cortex (Rizzolatti et al., 1996). In addition, tool-selective responses have been found in the medial fusiform gyrus (Chao et al., 1999). However, despite extensive evidence for tool-selective responses in multiple cortical regions, the associated cognitive processes and their neural implementation remain unclear. Thus, the tool-selective responses might emerge at multiple processing levels ranging from structural to semantic (Humphreys and Forde, 2001).

The fMRI study presented in this chapter addresses two questions: First, it asks whether category-selective fMRI responses are differentially modulated by stimulus modality and/or task-context. Using conventional SPM analyses, this enabled us to determine whether category-selectivity emerges primarily at the structural or semantic processing level. Second, using Dynamic Causal Modelling (DCM; Friston et al., 2003), we investigated the neural mechanisms that mediate these context-sensitive, category-selective responses.

The aim of DCM is to make inferences about the coupling among brain areas within a simple but reasonably realistic neuronal model. DCM is simply a generalization of the linear convolution model used in conventional analyses of regionally specific effects. Both use exactly the same data and stimulus functions encoding experimental design. However, in a conventional analysis, the experimental effects are expressed through a direct or extrinsic influence on each region. In contrast, DCM allows for interactions among brain regions and, critically, the expression of experimental manipulations at the level of connections between brain regions. For example, a conventional model would allow fusiform responses to be caused directly by the main effects of stimulus modality, task and category, and any interactions among these factors. In a DCM, fusiform responses could be modelled as responses to inputs from visual areas, with the modality (e.g. pictures vs. written words) or modality x category interaction effects modulating the forward connections from visual to fusiform areas. This modulation effectively increases the sensitivity of the fusiform area to visual afferents.

In this chapter, fMRI was used to investigate category-selective responses while manipulating stimulus modality and task context in a factorial design. Subjects were engaged in a one-back-task on animals and tools that were presented as pictures, written words or spoken words. The one-back-task used either implicit (i.e. stimulus identity) or explicit semantic (i.e. typical action or real life size of the stimulus) attributes. This design allows us to segregate category-selective regions into two classes: In one class, category-selectivity is modality-dependent and primarily observed for pictures. In the other class, it is task-dependent and observed when subjects are engaged in explicit semantic tasks.

DCM was then used to investigate the neural mechanisms underlying category-selectivity in two representative brain regions exhibiting modality-dependent or task-dependent tool-selective responses. Modelling bottom-up input from early visual areas and top-down influences from left prefrontal areas, to both regions allows us to address the following three questions: First, whether modality-dependent tool-selective responses could be mediated by forward connections from early visual areas that are enabled when tools are presented as pictures. Second, whether task-dependent tool-selective activations could be mediated via increased backward influences from left prefrontal regions during explicit semantic tasks. Finally, whether the distinct category-selective activation patterns in the two modality- and task-dependent regions could be explained by differential modulation of forward or backward connections.

6.2   Methods

6.2.1   Subjects

22 healthy right-handed English native speakers (14 males; mean age: 25) gave informed consent to participate in the study. The study was approved of by the joint ethics committee of the Institute of Neurology and University College London Hospital, London, UK.

6.2.2   Design

The activation conditions conformed to a 2 x 3 x 3 factorial design manipulating

(i) Semantic category: animals or tools,

(ii) Stimulus modality: pictures, written words or spoken words

(iii) Task: Subjects were engaged in a one back-task and decided whether subsequent stimuli within a block were identical (= implicit semantic task; e.g. sparrow, sparrow), performed a similar action (=explicit action semantic task; e.g. stork, butterfly) or were of similar size in real life (=explicit visual semantic task; e.g. pigeon, rabbit).

Altogether, there were 90 animals and 90 tools that were matched for word frequency and number of letters. Each stimulus was presented once in each modality and during each task (i.e. three times during the entire experiment) yielding 270 animal and 270 tool events. ~30% of the stimuli were targets. As the identity task inevitably required successive repetitions of the targets, 16 additional target stimuli were used for the implicit condition to avoid repetition priming confounds. Yes/No responses to all conditions were indicated (as quickly and as accurately as possible) by a two-choice key press. The stimuli (SOA = 3.3 s; stimulus duration = 1.2 s) were presented in blocks of 5 stimuli interleaved with 5.5 s fixation. The category and modality factors were manipulated across the activation blocks, the task factor in long periods covering one third of each session. The order of semantic conditions was counterbalanced within and across subjects.

6.2.3 Data acquisition

A 1.5 T Siemens Sonata system was used to acquire both T1 anatomical volume images and T2*-weighted axial echoplanar images with blood oxygenation level-dependent (BOLD) contrast (gradient echo, Cartesian k-space sampling, TE=50ms, TR 2.97 s, 33 slices acquired sequentially in descending direction, matrix 64X64, spatial resolution 3X3X3.4 mm^3 voxels, interslice gap 1.4 mm, slice thickness 2.0 mm, tilted from transverse to coronal orientation by −30 degree to reduce susceptibility artefacts). To

avoid Nyquist ghost artefacts a generalized reconstruction algorithm was used for data processing (Josephs et al., 2000). There were three sessions with a total of 340 volume images per session. The first six volumes were discarded to allow for T1 equilibration effects.

6.2.4   Data analysis

Conventional SPM analysis

The data were analysed with statistical parametric mapping (using SPM2 software from the Wellcome Department of Imaging Neuroscience, London; http//www.fil.ion.ucl.ac.uk/spm; Friston et al., 1995). Scans from each subject were realigned using the first as a reference, spatially normalised into standard space (Talairach and Tournoux, 1988), resampled to $3X3X3mm^3$ voxels and spatially smoothed with a Gaussian kernel of 8mm FWHM. The timeseries in each voxel were highpass filtered to 1/128 Hz and globally normalized with proportional scaling. The fMRI experiment was modelled in an event related fashion with regressors entered into the design matrix after convolving each event-related stick function with a canonical hemodynamic response function and its first temporal derivative. In addition to modelling the 18 conditions in our 2 x 3 x 3 factorial design, the statistical model included instructions, targets during the implicit condition and non-responses. Nuisance covariates included the realignment parameters (to account for motion artefacts). The analysis was performed twice: (i) including all trials, (ii) including only the trials that were equated for reaction times (the excluded trials were modelled as an additional covariate). Condition-specific effects for each subject were estimated according to the

general linear model and passed to a second-level analysis as contrasts. This involved creating contrast images (each of the 18 conditions averaged across the three sessions) for each subject and a second level ANOVA (corrected for departures from sphericity), which modelled the effects in our 2 x 3 x 3 factorial design. Inferences were made at the second level to allow a random effects analysis and inferences at the population level(Friston et al., 1999).

The random effects analysis tested for the main effects of tools relative to animals and animals relative to tools. Interactions between category and stimulus modality (i.e. tool or animal selective responses that were increased or decreased for pictures relative to words) were identified after pooling over written and spoken words. Interactions between category and task (i.e. tool or animal selective responses that were increased or decreased for explicit relative to implicit tasks) were identified after pooling over action and visual explicit semantic tasks.

All effects were inclusively masked with stimulus > baseline (at p<0.001 uncorr.). The interactions were further characterized by masking each contrast with (i) tools > animals or (ii) animals > tools (at p<0.001 uncorr.). The results from the conventional SPM analysis are equated for reaction times. Unless otherwise stated, activations are only reported if they are significant (p<0.05) corrected for the entire brain volume.

DCM analysis

22 subject-specific DCMs were constructed. The regions (see Table 6.3) were selected using the maxima from the random effects analysis. The left posterior medial fusiform and AIP were selected as representative regions for modality- and task-dependent

category-selectivity respectively. Region-specific time series (concatenated for the three sessions and adjusted for confounds) comprised the first eigenvariate of all voxels within a 4 mm radius centred on each location. The DCM (Figure 6.4) included five regions, (i) a left superior temporal area that was activated by spoken words relative to fixation (STG), (ii) a left occipital region that was activated for both written words and pictures and did not show any category-selectivity (OCC), (iii) a task-sensitive left prefrontal region (PF), (iv) tool-selective AIP and (v) the tool-selective left posterior medial fusiform area. The visual input (words$_{written}$ and pictures) was connected to OCC, the auditory input (words$_{spoken}$) to STG. The main effect of task entered directly in the left prefrontal area. Tool pictures, tool words$_{written}$ and pictures were entered bilinearly to modulate the forward connections from OCC to the category-selective regions. Category-effects (tools in all modalities) were entered bilinearly to modulate the backward connection from PF to the category-selective regions.

Region	Co-ordinates
L. inf. frontal sulcus	-45 9 27
L. middle occ. g.	-30 -93 6
L. sup. temp. g.	-60 -15 3
L. medial fusiform	-27 -63 -12
L. anterior intraparietal sulcus	-60 -30 42

Table 6.3 DCM Regions

The subject-specific bilinear effects were entered into t-tests at the subjects level (see Table 6.4). First, the analysis tested whether tool pictures relative to tool words increased the strength of forward connections (i.e. for a bilinear effect of the category x modality interaction on forward connections). Second, it tested whether tools (pooled over modalities) increased the backward connections from the left prefrontal to the category-selective regions. As the left prefrontal response is caused primarily by the main effect of task, this effectively tests for a category x task interaction mediated by backward connections. Finally, we tested for differences in bilinear effects between connections to the fusiform and AIP regions using a paired t-test.

6.3   Results

6.3.1   Behavioural

For performance accuracy, a three-way ANOVA with category (tools, animals), stimulus modality (pictures, spoken words, written words) and task (identity, action, real life size) identified a significant main effect of modality ($F_{(1.7, 36.5)}=9.6$; $p < 0.01$) and of task ($F_{(1.8, 39)}=247$; $p < 0.001$) after Greenhouse-Geisser correction. Importantly, there was no significant effect of category or interaction between category and task/modality. For reaction times, the three-way ANOVA identified (i) main effects of category ($F_{(1, 21)}=66$; $p < 0.001$), modality ($F_{(1.5, 31)}=597$; $p < 0.001$) and task ($F_{(1.7, 35)}=203$; $p < 0.001$) and (ii) significant interactions of category X modality ($F_{(1.9, 41)}=7$; $p < 0.01$) and category X task ($F_{(1.8, 38)}=13$; $p < 0.001$) following Greenhouse-Geisser correction (see Table 6.1).

Table 6.1 Behavioural data

Reaction-Times

Task	Implicit	Action	Size
Words written			
Tools	624(99)	944(118)	951(96)
Animals	617(86)	920(104)	897(98)
Words spoken			
Tools	1057(138)	1432(159)	1419(125)
Animals	1017(136)	1353(174)	1317(97)
Pictures			
Tools	635(77)	1014(132)	953(92)
Animals	638(73)	905(102)	870(80)

Response-Accuracy

Task	Implicit	Action	Size
Words written			
Tools	0.99(0.03)	0.91(0.06)	0.85(0.07)
Animals	0.99(0.02)	0.90(0.07)	0.87(0.07)
Words spoken			
Tools	0.99(0.04)	0.89(0.07)	0.86(0.06)
Animals	0.98(0.09)	0.89(0.07)	0.84(0.09)
Pictures			
Tools	0.99(0.03)	0.87(0.05)	0.81(0.08)
Animals	0.98(0.06)	0.87(0.06)	0.81(0.06)

Values are across-volunteer means (SD)

6.3.2   Imaging

Conventional SPM analysis

The SPM analysis was performed in two steps: First, regions that responded selectively to tools or animals were identified. Second, category-selective responses were identified where they were significantly modulated by stimulus modality or task-context. Analyses including all trials or only the trials that were equated for reaction times (see methods) yielded nearly identical activation patterns. Only the results of the latter are reported.

Tools (see Table 6.2, Figure 6.1, 6.2) increased evoked responses relative to animals, in the left posterior medial and anterior fusiform regions ($p < 0.05$ corrected for the entire brain). At a lower significance threshold ($p < 0.001$ uncorrected), increased responses were observed in the right medial fusiform (co-ordinates: [27 –42 –21]; $z = 4.4$; $p < 0.001$ uncorr.). In addition, tools evoked selective responses in a visuo-motor system encompassing a left posterior middle/inferior temporal area (LPMT), the anterior intraparietal sulcus (AIP) and several left prefrontal regions ($P < 0.05$ corrected for the entire brain). Left prefrontal activation was found in the ventral pre-motor area and along the left inferior frontal sulcus extending into the triangular part of the left inferior frontal gyrus. Critically, tool-selective responses in the occipito-temporal areas showed a significant interaction with modality and were greater for pictures. In contrast, responses in LPMT and AIP exhibited a significant interaction with task and were greater for explicit semantic tasks that required retrieval of an associated action or the real life size of the stimulus.

We did not detect any tool-selective activation that was enhanced for (i) words relative to pictures or (ii) implicit relative to explicit semantic tasks.

Animals (see Table 6.2, Figure 6.1, 6.3) increased responses relative to tools in the right middle occipital and the lateral fusiform gyri. Animal-selective responses in both regions and additional left and right lateral occipito-temporal areas interacted with stimulus modality and were greater when the stimuli were presented as pictures. No animal-selective responses were detected that (i) were enhanced for words relative to pictures or (ii) interacted with task context.

In summary, a ventral object recognition system, comprising occipito-temporal regions showed modality-dependent category-selective effects, while a dorsal visuo-motor system showed task-dependent category-effects. Our DCM analysis addressed now how this dissociation was mediated in terms of functional integration:

Table 6.2 Tool-selective activations

Region	Co-ordinates	Z-score	p-value (corr.)	voxels
Tools > Animals				
L. post. middle temporal g.	-51 -66 -6	>8.0	0.0	195
L. medial fusiform	-24 -57 -15	5.9	0.0	14
L. supramarginal g.	-57 -30 39	6.9	0.0	32
L. prefrontal triangular	-48 36 6	6.2	0.0	64
opercular	-54 18 15	5.5		
L. ant fusiform	-33 -33 -24	5.8	0.01	5
Interaction: Tool-selective activation for Pictures > Words				
L. medial fusiform g.	-27 -63 -12	5.5	0.0	4
L. middle occipital g.	-45 -66 -9	4.9	0.0	2
Interaction: Tool-selective activation for Semantic Decision > Implicit task				
L. supramarginal g.	-60 -30 42	5.7	0.0	12
				(at p<0.001 uncorr.)
L. post. middle temporal g.	-54 -57 -12	3.8	0.8	27
L. prefrontal, opercular	-54 12 24	3.4	1.0	14

activation at p<0.05 (corr.); extent threshold > 1 voxel

Table 6.2 Animal-selective activations

Region	Co-ordinates	Z-score	p-value (corr.)	voxels
Animals > Tools				
R. middle occipital g./	51 -78 0	6.2	0.0	17
Lat. occipital sulcus				
R. fusiform g.	39 -60 -21	5.2		5
Interaction: Tool-selective activation for Pictures > Words				
R. middle occipital g./	51 -78 0	>8.0	0.0	26
Lateral occipital sulcus				
R. fusiform g.	45 -48 -27	5.8		22
	42 -57 -21	4.9		
R. sup. occipital sulcus	15 -102 9	5.7		5
R. inf. occipital sulcus	36 -84 -12	5.4		3
L. middle occipital g.	-45 -84 3	5.5		2

activation at p<0.05 (corr.); extent threshold > 1 voxel
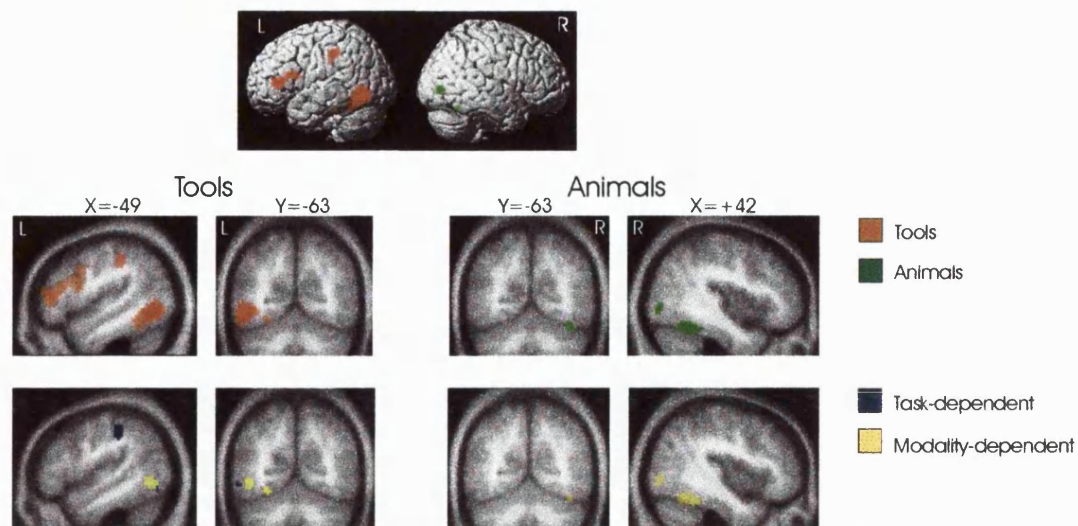
Figure 6.1 Overview of tool- and animal-selective activations

Top: Main effects of category: Tool- and Animal-selective activations are rendered on an averaged normalised brain. Height threshold: p<0.05 corrected. Extent threshold: > 1 voxel, including only voxels that were activated for stimulus > fixation at p < 0.001 (uncorrected).

Bottom: Main effects of category and category x task/modality interactions on coronal and sagittal slices of a structural image created by averaging the subjects' normalized images. Red: Tools > Animals; Green: Animals > Tools; Blue: Tools > Animals for Semantic Decision > Implicit task; Yellow: (i) Tools > Animals for Pictures > Words or (ii) Animals > Tools for Pictures > Words. Height threshold: p<0.001 uncorrected for illustration purposes. Extent threshold: > 19 voxels restricted to voxels that showed a significant effect of category-selectivity and stimulus > fixation.

Tool-selectivity: Modality-dependent

L.post.fusiform g. z= -12

Words_spoken

Words_written

Pictures

L.post. temp. g. z= -9
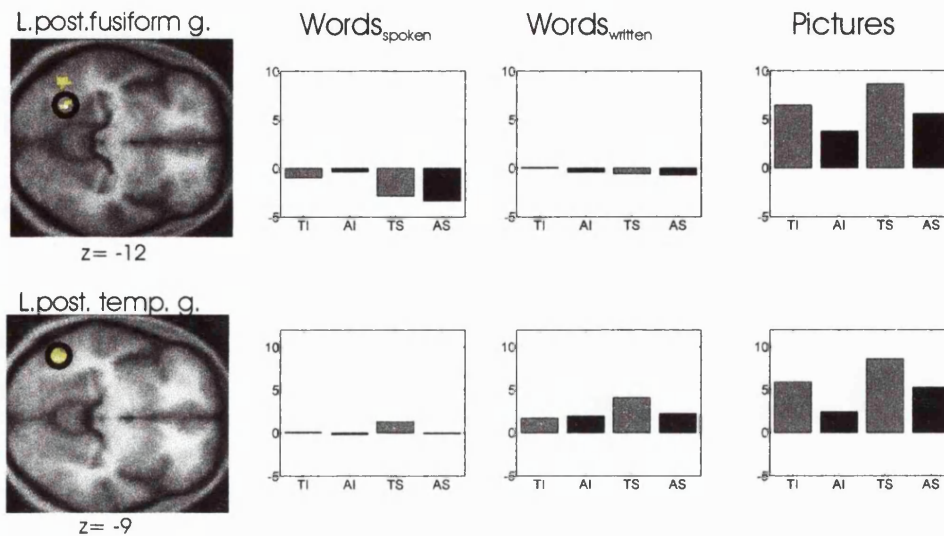
Tool-selectivity: Task-dependent

L.post. middle/inf. temp. g. z= -12

L.ant. intraparietal sulcus z= 42
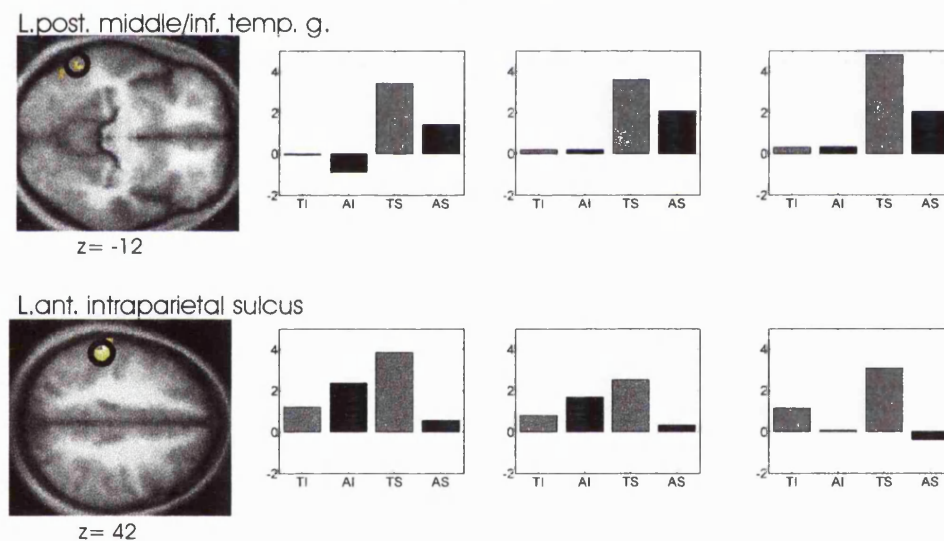
Figure 6.2 Tool-selective activations: Interactions with modality and task

Left: Interactions: Modality- and task-dependent tool-selective activations on transverse slices of a structural image created by averaging the subjects' normalized images. Modality-dependent: Tools > Animals for Pictures > Words. Task-dependent: Tools > Animals for Semantic Decision > Implicit task. Height threshold: $p<0.001$ uncorrected for illustration purposes. Extent threshold: > 19 voxels, restricted to voxels that showed a significant effect of tool-selectivity and stimulus > fixation.

Right: Parameter estimates for Tools (T, grey) and Animals (A, black) relative to fixation during Implict (I) and Explicit Semantic (S) task.

Animal selectivity: Modality-dependent
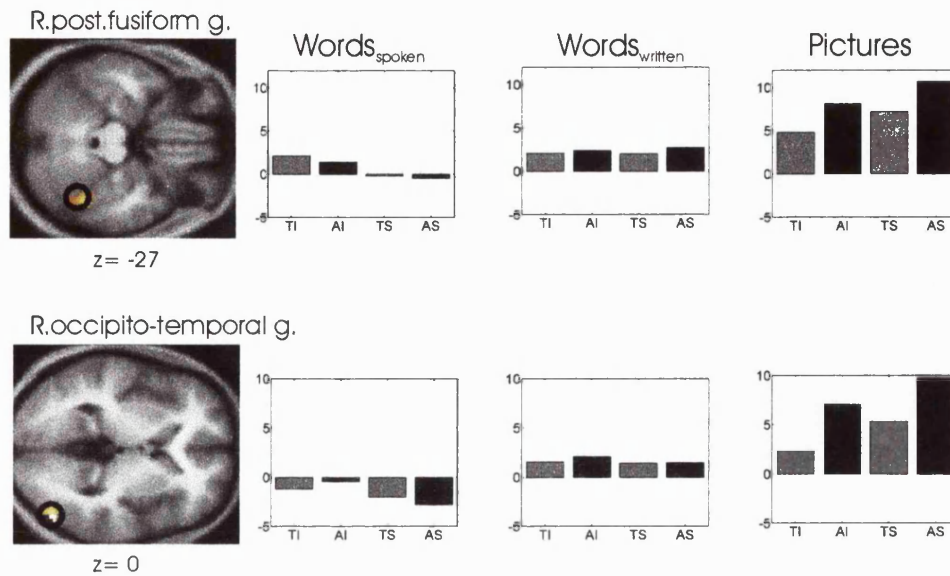

Figure 6.3 Animal-selective activations: Interactions with modality

<u>Left:</u> Interactions: Modality-dependent animal-selective activations on transverse slices of a structural image created by averaging the subjects' normalized images. Animals > Tools for Pictures > Words. Height threshold: $p < 0.001$ uncorrected for illustration purposes. Extent threshold: > 19 voxels, restricted to voxels that showed a significant effect of animal-selectivity and stimulus > fixation.

<u>Right:</u> Parameter estimates for Tools (T, grey) and Animals (A, black) relative to fixation during Implict (I) and Explicit Semantic (S) task.

Dynamic Causal Model analysis

First, tool pictures enabled the forward connections from OCC to the tool-selective left posterior medial fusiform and AIP areas. Furthermore, these effects were significantly greater for tool pictures than tool words i.e. there were significant bilinear effects of the modality x category interaction on the forward connections (Fusiform: $p<0.001$; AIP: $p<0.05$). These results imply that modulation or selective enabling of forward connections, in the context of tool pictures, provides a sufficient explanation for modality-dependent category-selective responses (see Figure 6.4).

Second, left prefrontal areas that showed greater responses during explicit semantic tasks exerted more top-down influence on the fusiform and AIP when subjects were actively engaged in semantic tasks on tools than on animals. These results demonstrate that category-sensitive modulation of backward connections, during explicit semantic tasks on tools provides a sufficient explanation for task-dependent category-selective responses.

Finally, the effect of the modality x category interaction was greater for the forward connections from early visual areas to the fusiform than to AIP ($p<0.01$). Conversely, the task-dependent category-effect of tools was greater for backward connections from the left prefrontal area to the AIP than the fusiform area ($p<0.05$). These results (see Table 6.4) demonstrate that the distinct patterns of category-selectivity over regions can be explained by differences in top-down and bottom-up influences (i.e. differences in bilinear effects between connections to the fusiform and AIP).

In summary, fusiform category-effects can be explained by a modality-dependent increase in bottom-up category-specific influences, whereas AIP regions are subject to category-selective top-down influences of task-related prefrontal activity.

Bilinear Effects		Connections	T-value df=21	p-value
Forward and Backward Bilinear Effects				
Forward	Tool Pictures - Tool Words	Occ => AIP	2.78	0.01
	Tool Pictures - Tool Words	Occ => FG	8.06	0.00
Backward	Tools	PF => AIP	7.31	0.00
	Tools	PF => FG	4.18	0.00
Dorso-ventral Dissociation of Bilinear Effects				
Forward	Tool Pictures - Tool Words	(Occ => FG) - (Occ => AIP)	3.3	0.00
Backward	Tools	(PF => AIP) - (PF => FG)	2.5	0.02

Table 6.4 Bilinear Effects on Forward and Backward connections
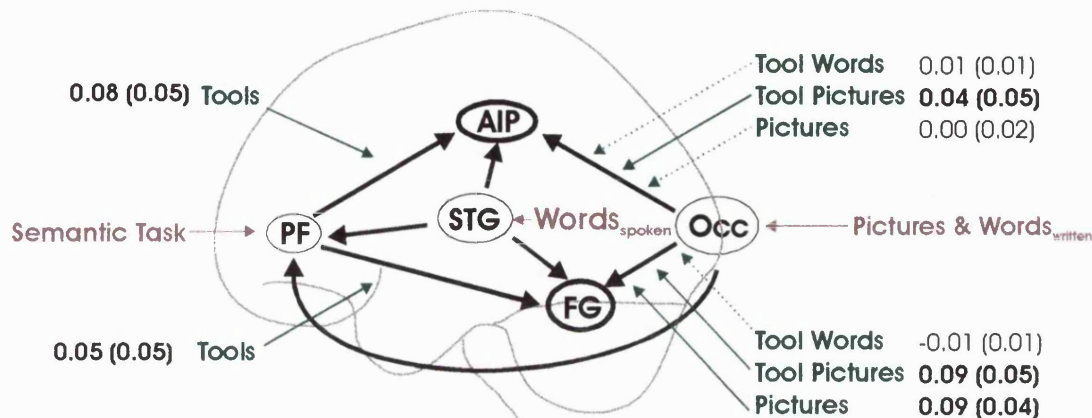
6.3.3 Figure 6.4 Dynamic Causal Model: Bottom up and top-down influences

DCM for left anterior intraparietal (AIP) and left posterior medial fusiform gyrus (FG) responses. Black: Intrinsic connections; Purple: Extrinsic input; Green: Bilinear effects Values are across subject means (SD) of changes in connection strength (at p<0.001 in bold). The bilinear parameters correspond to increases in the rate at which the source area activity causes increases in the target area. For example, a 10% increase in a connection with a time constant of 2 seconds (rate of $0.5 \, s^{-1}$) would give a value of $0.05^{-1} \, s$

6.4 Discussion

The results demonstrate robust category-selective responses in multiple cortical regions:

Within the fusiform gyrus, category-selective activations were found medially for tools

and laterally for animals. In addition, tools elicited increased responses in a left-

lateralized visuo-motor action system encompassing ventral premotor, anterior

intraparietal and posterior middle temporal regions. Importantly, while category-

selective activations in ventral occipito-temporal cortex depended on modality, they were

modulated by task-context in the tool-selective regions of the visuo-motor system.

Therefore, category-selectivity rests on the interaction of semantic content with either (i)

stimulus-bound factors such as modality or (ii) task. From a cognitive perspective, category-selective responses may be better understood in terms of the cognitive operations induced by a semantically invested stimulus in a particular context rather than its semantic content alone. In particular, they might reflect either stimulus-bound structural processing or task-induced semantic operations. In terms of neural mechanisms, our results suggest that the modality- and task-dependent category-selective responses are not properties intrinsic to a region but are mediated by changes in the influence of or the responsiveness to other regions (McIntosh, 2000a;Mesulam, 1990a;Friston and Price, 2001). These two distinct classes of category-selectivity can be explained by differential top-down and bottom up influences for task and modality-dependent effects respectively.

The tool and animal-selective responses within the ventral occipito-temporal cortex are consistent with numerous studies of object recognition demonstrating focal regions with preferential responses to various semantic categories including faces, houses and chairs (Haxby et al., 2001;Spiridon and Kanwisher, 2002;Ishai et al., 1999). In our study, occipito-temporal category-selective responses were modulated by stimulus modality and were evident only for pictures, irrespective of the task context. According to our DCM, these stimulus-bound responses were mediated by increased bottom-up influence of tools during object perception (Mechelli et al., 2003). Collectively, these results suggest that ventral occipito-temporal regions are specialized for processing structural features that permit object categorization and are sufficiently abstract to be shared by different exemplars of the same category. This functional specialization is not an intrinsic property of the category-selective regions, but is mediated via bottom up mechanisms

that render them especially responsive to certain patterns of input from early visual areas.

Additional tool-selective responses were found in a visuo-motor action system encompassing the left inferior/middle temporal area (LPMT), anterior inferior parietal sulcus (AIP) and ventral pre-motor cortex (i.e. the putative homologue of area F5). These three regions correspond to those with the highest lesion overlap in patients with impaired action retrieval (Tranel et al., 2003) and have been previously implicated in tool and action observation by functional imaging studies (Grezes and Decety, 2001). In the macaque, neurons in areas F5 and AIP have been identified that respond selectively to action execution, observation and presentation of graspable objects (Rizzolatti and Luppino, 2001;Rizzolatti and Arbib, 1998). The study reported in this chapter demonstrates that LPMT and AIP in humans respond to both tool pictures and names suggesting a role in semantic processing. However, their responses were not obligatory but strongly context-sensitive with tool-selective responses being enhanced when subjects process stimuli at a deeper semantic level. Consistent with studies in primates and neuropsychology that have implicated the left prefrontal cortex as a key player in top-down control processes (Fuster, 1989;Miller, 2000), the DCM analysis demonstrated that task-dependent tool-selectivity is mediated via increased backward influences from the left prefrontal cortex to AIP during semantic decisions on tools. Thus, tool-related action responses, for instance in AIP, might be enabled during explicit semantic tasks by top-down modulation from the prefrontal cortex.

The DCMs discussed so far have established bottom-up and top-down modulations as sufficient explanations for modality- and task-dependent category-selectivity. Obviously, most brain regions will -to a certain degree- be exposed to both bottom-up and top-down influences. Directly comparing the bilinear components of connections to the left posterior fusiform and AIP demonstrated that (i) modality-dependent bottom-up category effects were greater for the fusiform and (ii) task-dependent top-down category effects were greater for AIP. Thus, distinct classes of category-selectivity in AIP and left posterior medial fusiform can result from differential enabling of ventral and dorsal connections.

In conclusion, the results demonstrate two classes of category-selectivity: In the ventral occipito-temporal cortex, category-selective responses were observed primarily for pictures and mediated by bottom-up effects. In LPMT and AIP, they were observed during semantic decision tasks and mediated by increased top-down modulation from left prefrontal cortex. These distinct activation and connectivity patterns suggest that the two classes of category-selective systems may support different cognitive operations with occipito-temporal regions engaged in structural processing and visuo-motor regions activated during strategic semantic processing. Consistent with current semantic theories, we thus provide evidence that explicit semantic processing of tools relies on re-activating their associated action representations via top-down modulation (Damasio, 1989;Martin and Chao, 2001;Barsalou et al., 2003). Future studies are required to investigate whether other types of semantic retrieval tasks might induce retro-activation of visual structural representations in the ventral occipito-temporal cortex.

7 Retrieval of sensory-experienced and verbally-learnt knowledge

7.1 Introduction

Chapters 4, 5 & 6 focused on the dissociation of action and visual features. In particular, they have identified multiple cortical regions that showed selective responses to tools or/and action semantics. Their response patterns have been characterized using additional manipulations of task, stimulus modality and visual experience. The final two chapters will focus on the dissociation of verbally-learnt and sensory semantics. Sensory semantics is usually learnt via the senses and might therefore be represented in a modality-congruent format and processed close to or even within the regions that are engaged in sensory experience. In contrast, abstract concepts and verbally-learnt facts might be represented in a propositional-based format (Paivio, 1991) and be related to the sentence processing system (Breedin et al., 1994).

The two studies presented in Chapter 7 and 8 used two distinct approaches to delineate the neural systems engaged in retrieving verbally mediated semantics: The study presented in this chapter holds the stimuli constant and manipulates the task instructions to focus the subjects' attention on different semantic aspects of the stimuli i.e. on sensory attributes and verbally-learnt facts. The study reported in the following chapter holds the task constant and manipulates the stimuli, i.e. compares words referring to abstract concepts or to sensory features.

The study reported in this chapter aims to dissociate sensory-experienced attributes and verbally-learnt facts about concrete objects. To differentiate between these two types of knowledge, subjects were engaged in semantic decisions on the attributes of taste (sweet?), colour (red?) and origin (tropical?) of the auditorily presented names of food

items. In a low level baseline condition, auditory input and motor responses were controlled by instructing subjects to detect a specific auditory feature in spoken words which were acoustically reversed to obliterate access to the semantic system. The common semantic system can therefore be revealed by contrasting all semantic tasks with the baseline. The retrieval of colour and taste knowledge, which depends on the visual and gustatory channels, is then compared to retrieval of the origin of the food item, which is verbally-learned. Differences between the sensory and verbally-learnt conditions are then attributed either to differences in retrieval strategies or the semantic representations themselves.

7.2 Methods

7.2.1 Subjects

9 male subjects (mean age: 23; range: 20-30) participated in the study. All subjects were right-handed, with English as their native language and no history of neurological or psychiatric disorders. Each of them gave informed consent to participate in the study.

7.2.2 Design

There were four conditions, three activation conditions and one baseline. The activation stimuli consisted of three lists of digitised auditory words designating food items presented at a rate of one every four seconds. The baseline stimuli consisted of three lists of the same words after they had been digitally reversed to obliterate semantic associations. Stimuli were spoken by either a male or a female voice. The three activation tasks were a semantic decision on the taste (sweet?), the colour (red?) and the

origin (tropical?) of the auditorily presented food items. With their eyes closed subjects listened to the stimuli via earphones and indicated their decision by pressing a button (index finger for "yes", middle finger for "no" of the right hand). Each list of food items was presented once under each of the three semantic task conditions in different orders (i.e 9 activation conditions). For the baseline task, subjects listened to the reversed words as meaningless sounds and decided whether the stimuli were spoken by a male or a female voice. This non-linguistic task was designed to control for activation due to auditory processing and making a button response. In all conditions, subjects were instructed to respond as quickly and as accurately as possible.

The order of the three activation and baseline conditions were counterbalanced within and across subjects. The word lists were also rotated across tasks so that the initial presentation of a word list occurred an equal number of times for each task.

7.2.3 Data acquisition

Subjects were scanned with PET which measured rCBF (regional cerebral blood flow) using bolus infusion of radioactively-labeled water ($H_2^{15}O$) and with MRI to obtain structural images for coregistration with the PET data. Each subject underwent 12 PET scans, performed on a Siemens CTI III camera. The dose received was 9 mCi per measurement. The study was approved of by the UK Administration of Radioactive Substances Advisory Committee (ARSAC). Reaction times and errors were recorded for each judgment.

7.2.4 Data analysis

The data were analysed with statistical parametric mapping (using SPM99 software from the Wellcome Department of Cognitive Neurology, London; http//www.fil.ion.ucl.ac.uk/spm) implemented in Matlab (Mathworks Inc.Sherborn, MA). Scans from each subject were realigned using the first as a reference and transformed into a standard space. The normalisation parameters were determined by matching each scan to a reference PET template that already conformed to the standard space. Finally, all images were smoothed with a Gaussian - kernel of 16 mm FWHM to increase signal to noise. The T1-weighted structural MRI scans were coregistered to the mean PET image for each subject and transformed into the Talairach and Tournoux space (Talairach and Tournoux, 1988).

Statistical analysis involved ANCOVA with subject effects modelled and global activity included as a subject specific covariate. The condition and subject effects were estimated according to the general linear model at each voxel (Friston et al., 1995). To test hypotheses about regionally specific condition effects, the estimates were compared using linear contrasts. The resulting set of voxel values constitutes a SPM of the t statistic (SPMt). The SPMt values were transformed to the unit normal distribution (SPMZ).

Analysis of the data tested for (1) a common semantic system; (2) regions selective for the retrieval of verbally-learnt (origin) and sensory experienced (colour, taste) knowledge; and (3) regions selective for colour or taste:

The *common semantic system* was identified by contrasting all semantic tasks with the baseline task and then (using the inclusive masking option in SPM, which identifies voxels that are commonly activated in a series of contrasts) including only those regions that were activated by each condition relative to control (i.e. taste-control, colour-control, and origin-control).

Regions that were selectively activated by the *retrieval of verbally-learnt knowledge* (origin) were determined by finding those areas that were activated for origin relative to baseline and using inclusive masking to include only those voxels where there was increased activity for origin-taste and origin-colour. In this way, the analysis for differential effects was limited to regions that were activated by the semantic task relative to baseline, i.e. regions that belong to the semantic system.

Regions that were more active for *sensory-experienced knowledge* were assessed by contrasting the colour and the taste tasks with the baseline task and including only those regions where both colour and taste were more active than the control and the origin task (i.e. masked with four contrasts). Regions that were selectively activated by the *retrieval of colour or taste* were determined by finding those areas that were activated for either colour- baseline (or taste- baseline) and using inclusive masking to include only those voxels where there was increased activation for colour (or taste) relative to all other conditions.

Significance level for the main contrast is reported at an uncorrected $p < 0.001$ (Z score greater than 3.1) but activations are only interpreted where they (i) reached a significance level of $p<0.05$, corrected for the number of comparisons; or (ii) were in *a priori* regions of interest (i.e. the fusiform areas previously associated with colour). The

masking threshold for within semantic comparisons was set at p<0.001 for interpretation but effects that are present at p<0.01 are also reported to give a full characterisation of the data.

7.3   Results

7.3.1   Behavioural

The mean and standard deviation of reaction times are displayed in Table 7.1. A one-way ANOVA (task with 4 levels) identified a main effect of task (p = 0.008). Holmes post hoc testing revealed that this result was due to significant differences between each activation task and the baseline task, while the differences between the 3 activation tasks were not significantly different. A one-way ANOVA of the reaction times limited to the three activation tasks did not identify a significant task effect.

	Baseline	*Colour*	*Taste*	*Verbal*
Reaction time (ms)	909	1091	1147	1209
SD	274.47	214.51	305.05	246.82

Table 7.1 Behavioural data

7.3.2 Imaging (see Table 7.2)

1) *Common semantic system* relative to baseline: At a corrected level (p<0.05) the comparison of all semantic tasks relative to the baseline identified activation in the left inferior temporal gyrus including the left medial anterior fusiform gyrus (BA 20/37), the triangular part of the left inferior frontal gyrus and the precuneus. At an uncorrected level (p<0.001), activation was also revealed in the right pons, the right cerebellum and the left superior frontal gyrus (see Figure 7.1).

2) Activations selective for *verbally-learnt (origin) knowledge* were demonstrated in the posterior cingulate spreading widely into the precuneus and the temporo-parieto-occipital junction bilaterally – although more pronounced on the left side. At an uncorrected level, there was also activation in the right cerebellum (see Figure 7.3).

3) Activations selective for *colour and taste*: The triangular part of the left inferior frontal gyrus, which was reported in common for all three semantic tasks, was marginally more active for both taste (Z=2.6) and colour (Z=2.3) relative to origin. There were no significant differences in activation for retrieval of colour or taste. The area we anticipated to see enhanced for colour showed a trend towards increasing activation from taste to colour to verbally-learnt knowledge. A plot of the parameter estimates for the different tasks in this area of interest can be seen in Figure 7.2.
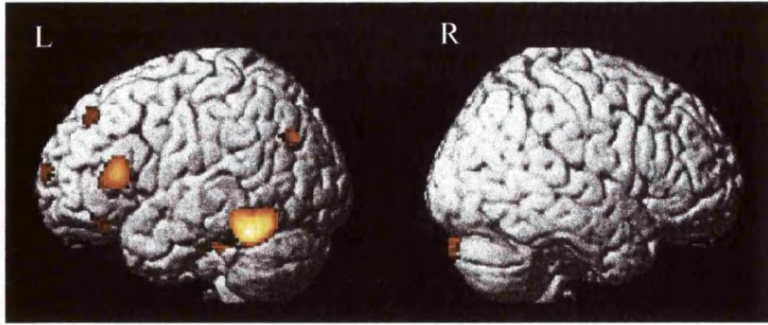
Common semantic system

Region	X Y Z	vtc-3b	P(corr.)	Voxels	v-b	t-b	c-b
Left inferior temporal	-54 -50 -18	5.72	0.00	1017	4.39	4.79	5.14
Left fusiform	-28 -38 -22	4.79	0.014	90	5.13	2.37	4.3
Left inferior frontal	-46 24 12	4.69	0.021	69	2.47	4.68	4.43
Precuneus	0 -60 6	4.62	0.029	15	5.13	2.69	2.55
Right cerebellum	12 -90 -30	3.73	0.525	36	3.9	2.69	3.7
Pons	4 -16 -24	3.79	0.463	31	2.56	3.07	3.7
Left superior frontal	-8 66 12	3.58	0.195	0	3.7	3.84	1.15

Selective for Verbally-learnt knowledge

Region	X Y Z	v-b	P(corr.)	voxels	v-c	v-t
Posterior cingulate	-8 -62 8	6.79	0.00	2384	5.69	4.64
precuneus	12 -56 10	5.6	0.00		4.00	4.75
	-2 -58 26	5.15	0.003		4.29	4.14
Temporo-parieto-occipital junction	-36 -80 36	4.75	0.017	676	3.53	4.73
	-48 -76 26	4.56	0.037		3.88	3.09
	50 -78 26	4.52	0.043		4.04	4.12
Right cerebellum	22 -90 -28	3.61	0.663	7	2.79	2.36

Table 7.2 PET activations
Common to all semantic tasks (top) and selective for retrieval of verbally-learnt knowledge (bottom); v = verbally-learnt; c = colour; t = taste; b = baseline

Figure 7.1 Common semantic activations

Activations for the common semantic system rendered onto a template of the whole brain
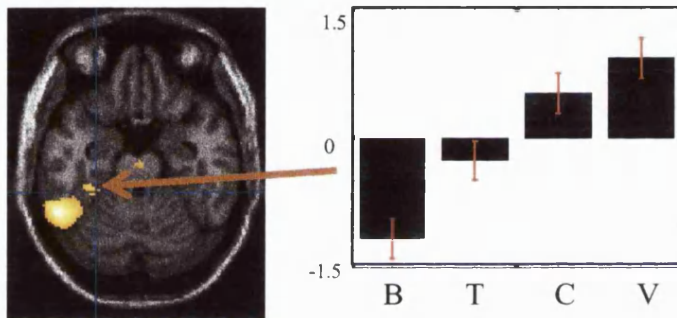
Figure 7.2 Response in the fusiform

Horizontal section through the fusiform gyri and a plot of rCBF in the baseline (B), taste (T), colour (C) and the verbal (V) tasks (right).
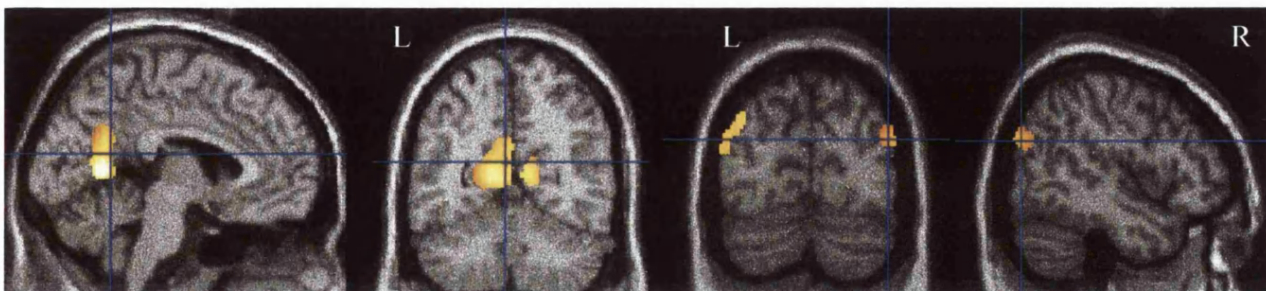
Figure 7.3 Activations selective for verbally-learnt knowledge

Activations specific for retrieval of verbally-learnt knowledge shown on horizontal slices of a standardized MRI template brain.

7.4 Discussion

This study was intended to identify the neural correlates of semantic processing and to further investigate the organisation of the semantic system. In particular, it investigated whether retrieval of verbally-learnt knowledge (origin) and sensory-experienced features (taste, colour) elicit spatially distinct activation patterns due to differences in semantic representations or retrieval strategies. Furthermore, it tested the *a priori* hypothesis that the left anterior fusiform gyrus is particularly involved in retrieval of colour knowledge as has been suggested by the feature-based approach and previous functional imaging studies (Martin et al., 1995;Chao and Martin, 1999;Wiggs et al., 1999; D'Esposito et al., 1997;Thompson-Schill et al., 1999a;Wise et al., 2000).

Consistent with numerous previous studies, the results demonstrate a left lateralized common semantic system encompassing the triangular part of the left inferior frontal gyrus, the posterior inferior temporal and the anterior medial fusiform gyri. These regions have generally been reported to be involved in semantic decisions on objects and words irrespective of whether they were visually (Mummery et al., 1998;Vandenberghe et al., 1996) or auditorily (Demonet et al., 1992;Binder et al., 1997) presented.

Contrary to the feature-based account, no regions were detected that responded selectively to taste, colour or generally sensory-experienced features. Even the left fusiform area, which has previously been associated with visual semantics and imagery, did not show increased activation for visual features. In fact, the study revealed a non-significant activation increase from taste to colour to origin (see Figure 7.2). These divergent findings might be explained by implicit semantic processing. For instance, in some paradigms, visual features might be automatically activated since they are

fundamental to our knowledge of objects at least in sighted people. However, activation in the left fusiform area when congenitally blind people (with no visual experience) read abstract words (Buchel et al., 1998b) indicates that this area is not specific for visual semantics. Furthermore, neuropsychological studies have not linked visual semantics to left fusiform damage (for a review see Caramazza and Shelton, 1998a; Caramazza, 2000) Therefore, the study suggests a common role for the left medial fusiform anterior gyrus in semantic retrieval.

While no selective activation was observed for sensory-experienced features, retrieval of verbally-learnt knowledge was associated with increased activation in the anterior medial parietal cortex and the temporo-parieto-occipital junctions bilaterally. Although these activations might reflect prepositional-based or verbally-mediated semantic representations, based on other functional imaging results, an explanation within the framework of memory retrieval appears more convincing: Thus, joint activation in the TPO and the medial parietal lobe during semantic retrieval tasks has been reported for semantic decision tasks that require the integration of different aspects of semantic information (Mummery et al., 1998;Vandenberghe et al., 1996;Demonet et al., 1992;Binder et al., 1997;Maguire and Mummery, 1999;Cappa et al., 1998). Similarly, during semantic decisions on verbally-learnt knowledge subjects are required to retrieve additional facts about food items and link this multidimensional information with their pre-conceptions about tropical regions. In contrast, in the semantic task on taste and colour, subjects make a decision on one specific over-learnt semantic feature, which defines the core concept of a food item. Therefore, we suggest that activation in the TPO in concert with the anterior medial parietal lobe reflects retrieving semantic facts and linking them with a pre-existing semantic framework rather than reflecting activation of semantic representations per se.

In summary, the enhanced activation in the TPO and the medial parietal lobe during the semantic task on verbally-learnt knowledge may reflect different strategies for semantic processing. In the semantic tasks on sensory-experienced features, subjects make a semantic decision on one specific over-learnt core feature of an object. By contrast, during the task on verbally-learnt knowledge, subjects retrieve additional facts about food items and link them with their preconceptions of a tropical origin.

8 Retrieval of abstract semantics

8.1 Introduction

In the previous chapter, the neural systems processing verbally-mediated semantics were investigated by manipulating the task instructions. Comparing retrieval of verbally-learnt facts with sensory features of food items was associated with increased activation in a memory retrieval system encompassing the medial parietal and the TPO junction bilaterally. The study in this chapter investigates verbally-mediated semantics by contrasting abstract concepts with words referring to sensory features during a semantic association task.

Behavioural and neuropsychological evidence suggests that abstract and concrete concepts might be represented, retrieved and processed differently in the human brain. Consistent with the general notion that concrete words are easier to comprehend, neurologically normal subjects respond faster and more accurately to concrete than to abstract words during lexical decision tasks (James, 1975;Kroll and Merves, 1986). They also show better performance for concrete words during recall and recognition memory tests (Paivio, 1991). Moreover, the advantage for concrete concepts (concreteness effect) is generally amplified in patients with left-hemispheric damage who present with aphasia (Goodglass et al., 1969), deep dysphasia (Katz and Goodglass, 1990;Martin and Saffran, 1992) or deep dyslexia (Coltheart, 1980). Although abstract words are generally more difficult to comprehend than concrete words, several neuropsychological studies have reported patients who were more impaired on concrete than abstract concepts. The advantage for abstract concepts across a range of tasks has been demonstrated in several patients with left inferior anterior-temporal lesions in the context of semantic dementia (Breedin et al., 1994;Cipolotti and Warrington,

1995;Warrington, 1975) or herpes encephalitis (Warrington and Shallice, 1984;Sirigu et al., 1991). Taken collectively, these neuropsychological double dissociations suggest that the neural substrates for abstract and concrete semantics might be distinct in terms of representations or retrieval processes.

Most cognitive theories have been designed to explain the general superiority of concrete words by assuming that concrete concepts contain additional information that renders them easier to process. For instance, the dual coding theory (Paivio, 1991) suggests that concrete words activate a verbal and an additional non-verbal image-based representation, while abstract words are only verbally encoded. Similarly, based on the observation that the concreteness effect can be diminished in the presence of contextual information (e.g. sentence context), the context availability theory (Schwanenflugel et al., 1988) explains the superiority of concrete words by their stronger links to other contextual information. While these theories can account for the concreteness effect observed in normals and aphasics, they have difficulties accommodating the rare neuropsychological findings where the concreteness effect is reversed. To account for the double dissociation, qualitative differences between abstract and concrete words have been postulated with respect to (i) concept acquisition, (ii) representational format and (iii) specification of meaning (see Breedin et al., 1994). *Concept acquisition* differs for concrete and abstract semantics, because only concrete semantics is learnt via sensory experience with physical objects, while abstract concepts are acquired through their use in sentences and their relationship to other concepts. Therefore, the *representational format* varies with concrete semantics being represented in visual, auditory, tactile or gustatory formats and abstract semantics in a propositional format. Finally, *specification of meaning* varies because concrete concepts correspond directly with entities in the physical world and have a fixed core meaning, while the meaning of

abstract concepts is largely specified by the sentence context (e.g. the phase of the moon, the phase of development, see Saffran et al., 1998).

In summary, while the meaning of concrete concepts is supposed to be defined by perceptual features and their relation to physical everyday objects, the meaning of abstract concepts is thought to be verbally-mediated and to emerge from use in sentence contexts. Thus, this distinction explains the difference between abstract and concrete concepts by their associations with different types of semantic knowledge (see also Allport, 1985;Warrington and Shallice, 1984;Shallice, 1988). It links concrete concepts with perceptual features and abstract concepts with verbally-learnt information. It is consistent with the neuropsychological finding that patients with greater deficits for concrete than abstract concepts during synonym tasks were also more impaired on retrieval of sensory-experienced/perceptual properties of everyday objects than verbally-learnt (e.g. 'Does a whale live in water') properties (Breedin et al., 1994;Marshall et al., 1996).

The present study investigates the distinction between abstract and sensory-experienced knowledge, whilst explicitly modelling the factor of task difficulty: Subjects were presented triads of written words (one word above / two words below) referring to abstract concepts, visual attributes, sounds or hand movements. They made a synonym judgement (Breedin et al., 1994) by deciding which of the two words below was more similar in meaning to the word above. While the meaning of visual attributes, sounds or hand actions is at least in part learnt and defined by visual, auditory or sensory-motor experience, the meaning of abstract concepts can only be verbally mediated. Based on the event-specific reaction times, each event was categorized as easy or difficult thus allowing us to investigate the effect of semantic type unconfounded from task difficulty differences.

8.2 Methods

8.2.1 Subjects

15 subjects (10 male, mean age 30, range 21-46) participated in the Experiment. All were right-handed, with English as their native language and no history of neurological disorders. Each gave informed consent to participate in the study.

8.2.2 Design

The basic design was identical to Experiment 2 in Chapter 4. However in addition, task difficulty was introduced as an experimental factor:

There were four activation and one baseline conditions. In the activation conditions, words within a triad were visually presented (one word above / two words below). The words were drawn from four *semantic types* referring to (i) abstract concepts, (ii) hand movements, (iii) visual attributes and (iv) sounds; the task was to decide which of the two words below was more similar in meaning to the word above. Each of these triads was repeated twice during the experiment (*presentations 1 and 2*). The activation conditions were equated with respect to reaction times separately for presentation 1 and 2 by excluding/modelling trials separately with reaction times that were 1.25 std above the mean in the abstract condition, below 2 std in the sound condition, below 2 std in the visual condition and below 2std in the action condition. Each event was then categorized as *easy or difficult* depending on whether the response time was above or below the condition- and presentation specific mean. We thus obtained a 4X2X2 factorial design with the factors: (i) semantic type, (ii) number of presentation and (iii) task difficulty. The factors semantic type and number of presentation were blocked, while the factor task difficulty was randomised. The baseline condition used triads of false fonts (non-

linguistic symbols matched to the letters for average number and complexity of visual components) and subjects decided which of the stimuli below was the same as the stimulus above. Left/Right responses to all conditions were indicated by a two-choice key press (as quickly and as accurately as possible). Across semantic conditions, the stimuli were matched for word frequency and number of letters. There were 7 stimuli per block presented at a rate of one per 3.2 seconds (22.4s blocks). The activation and baseline blocks were alternated. The order of conditions was counterbalanced within and between subjects.

8.2.3 Data acquisition

See Experiment 2 in Chapter 4

8.2.4 Data analysis

The data were analysed with statistical parametric mapping (using SPM99 software from the Wellcome Department of Imaging Neuroscience, London; http//www.fil.ion.ucl.ac.uk/spm) implemented in Matlab (Mathworks Inc. Sherborn, MA). Scans from each subject were realigned using the first as a reference, spatially normalised (Friston et al., 1995) into standard space (Talairach & Tournoux, 1988), resampled to 3X3X3mm^3 voxels and spatially smoothed with a Gaussian kernel of 8mm FWHM. The timeseries in each voxel was highpass filtered to 1/100 Hz. The fMRI experiment was modelled in an event related fashion with regressors entered into the design matrix after convolving each event-related delta function with a canonical hemodynamic response function and its first temporal derivative. Each activation event was categorised according to a 4X2X2 factorial design with the factors (i) semantic type

(ii) presentation and (iii) task difficulty. Additional covariates accommodated for trials that were excluded when reaction times were equated across conditions (see above) or that subjects did not respond to. Nuisance covariates included the realignment parameters (to account for motion artefacts).

Condition-specific effects for each subject were estimated according to the general linear model (Friston et al., 1995) and passed to a second-level analysis as contrasts. This involved creating contrast images (i) abstract > other types of semantics and (ii) difficult > easy events for each subject and a second level ANOVA, which modelled these two effects of interest. Inferences were made at the second level to emulate a random effects analysis and enable inferences at the population level (Friston et al., 1999).

The second level analysis tested for

1) Abstract > Sound, Visual and Hand Movements

2) Sound, Visual and Hand Movements > Abstract

3) Difficult > Easy trials

4) Easy trials > Difficult

The effects pertaining to contrast (1) were tested for only in voxels that were also activated for abstract > baseline (p<0.001 uncorrected) and the effects pertaining to contrast (2) were tested for only in voxels that were also activated for Sound, Visual and Hand Movements > baseline (p<0.001 uncorrected). Likewise, the effects pertaining to contrasts (3) and (4) were tested for only in voxels that were activated for all semantic conditions > baseline (p<0.001 uncorrected).

Unless otherwise stated, activations are only reported if they are significant (p<0.05) corrected for the entire brain volume.

8.3   Results

8.3.1   Behavioural

The mean and standard deviations of the reaction times of the semantic conditions are displayed in Table 2. A 3-way-ANOVA (Factor 1: semantic type with 4 levels, Factor 2: Task difficulty with 2 levels, Factor 3: Presentation with 2 levels, Greenhouse-Geisser corrected) identified only a main effect of task difficulty $(F(1,14)=302; p < 0.001)$ and of presentation $(F(1,14)=23; p < 0.001)$ as well as an interaction between semantics and presentation $(F(3,41)=3.1; p<0.05)$. Importantly, there was no main effect of semantic type or an interaction between semantic type and task difficulty (see Table 8.1).

Reaction Times	Difficult		Easy	
	1 P	2 P	1P	2P
Sound	1886 (288)	1801 (278)	1375 (269)	1270 (215)
Visual	1943 (272)	1729 (344)	1407 (222)	1209 (195)
Hand Action	1880 (295)	1710 (289)	1372 (200)	1238 (186)
Abstract	1835 (304)	1745 (294)	1327 (251)	1266 (217)

Values are across-volunteer means (SD)

Table 8.1 Behavioural data

8.3.2   Imaging (see Table 8.2 & Figure 8.1)

Abstract > Sound, Visual and Hand Movements

Retrieval of abstract semantics relative to other types of semantics enhanced activation in

the left inferior frontal and middle temporal gyrus/superior temporal sulcus and in the

left anterior temporal pole. All of these regions even showed increased activation for

easy abstract trials relative to difficult trials of other semantic types.

Sound, Visual and Hand Movements > Abstract

No significant activations. Even in the left fusiform gyrus that has previously been

reported for concrete vs abstract semantics (D'Esposito et al., 1997), no increased

activation was observed at $p<0.05$ uncorrected (using a 15 mm radius sphere centered on

the peak co-ordinates of D'Esposito et al.; x=-33 y=-48 z= -18).The apparent lack of

consistency with previous studies might be explained by the fact that concrete objects are

characterized by a concatenation of multiple sensory features, while the present study

used stimulus words referring to the single sensory features (such as colour or sound)

themselves. However, activation in the fusiform area [-39 –45 –24] was observed for

both sensory>baseline (z=5.17) and abstract > baseline (z=4.94) suggesting a more

general role during semantic retrieval.

Difficult > Easy trials

Difficult relative to easy trials increased activation in the left insula, thalamus, inferior

frontal sulcus, the anterior cingulate and the cerebellum.

Easy trials > Difficult:

No significant activations

Abstract > other types of semantics

	Co-ordinates	Z-score
L. inferior frontal g.	-54 21 -6	5.7
L. ant. temporal pole	-51 18 -27	4.9
	-51 9 –24	4.9
L. middle temporal g. / STS	-60 –42 -6	5.2

Effect of task difficulty

	Co-ordinates	Z-score
L. insula	-30 18 -6	5.6
Ant. cingulate	-6 24 48	5.6
L. thalamus	-9 –6 3	5.4
L. inf. frontal sulcus	-42 9 27	4.9
Cerebellum	0 –57 -45	5.3

Table 8.2 fMRI activations
Selective for abstract concepts (top) and increased with task difficulty (bottom)
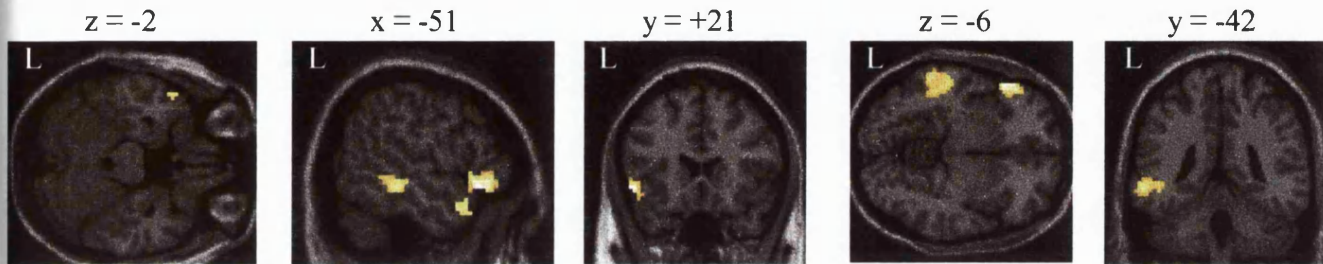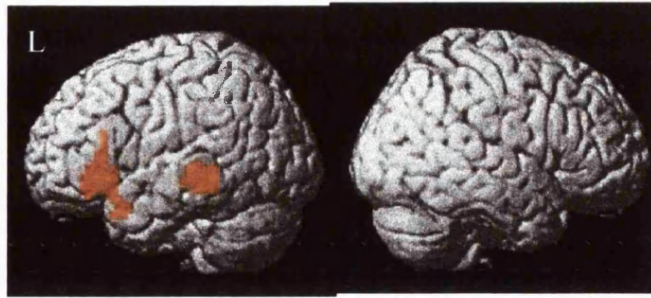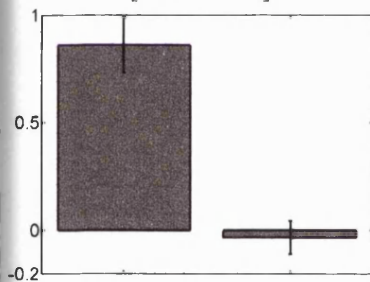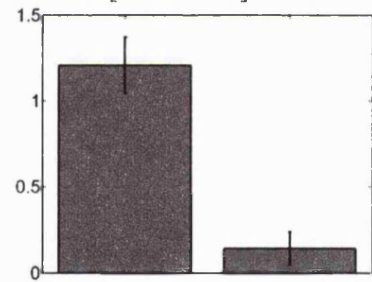
Figure 8.1 Activations for abstract > Visual, Sound & Hand movement semantics
Top: Activation for Abstract > Visual, Sound, Hand Movement semantics is rendered on a canonical brain. Height threshold: p<0.0001 uncorrected in areas also activated for Abstract > Baseline at p<0.001 uncorrected. Spatial extent threshold: > 15 voxels.
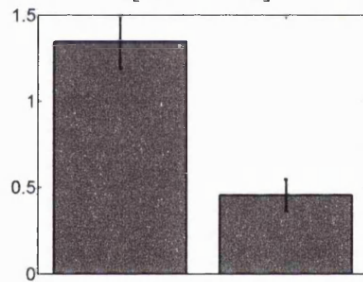Middle: Activation for Abstract > Visual, Sound, Hand Movement semantics in the (i) left temporal pole, (ii) left inferior frontal gyrus, (iii) left middle temporal gyrus on coronal, axial and sagittal sections of a canonical brain. Height threshold: p<0.0001 uncorrected in areas also activated for Abstract > Baseline at p<0.001 uncorrected.
Bottom: Parameter estimates for (i) Abstract > Visual, Sound, Hand Movement semantics and (ii) Difficult > Easy trials in: Left temporal pole [x=-51 y=9 z=-24]; Left inferior frontal gyrus [x=-54 y=21 z=-6]; Left middle temporal gyrus [x=-60 y=42 z=-6]. Note that the main effect of abstractness is greater than the main effect of task difficulty, which is equivalent to demonstrating that these regions showed increased activation for easy abstract trials even relative to difficult trials of other semantic types.
A=Abstract, SVH=Sound Visual and Hand Movement, D=Difficult, E=Easy

8.4　Discussion

The current study intended to dissociate the neuronal systems that sustain retrieval of abstract semantics from those used in the retrieval of sensory-based semantics. In brief, we demonstrate that retrieval of abstract relative to sensory-based semantics in a synonym task increased activation in a left fronto-temporal system that has been associated with semantic processing particularly at the sentence level. Since activation increases were observed irrespective of the degree of difficulty, they might reflect a particular retrieval mechanism or strategy for accessing abstract semantics.

The left inferior frontal, middle temporal and anterior temporal pole areas that were activated for abstract concepts relative to visual, sound or hand movement features can be interpreted in terms of (i) increased processing demands, (ii) semantic representations and (iii) retrieval mechanisms or strategies, which will be discussed in turn:

Previous behavioural results (e.g. longer reaction times for abstract words) suggested that *increased processing resources* might be required for abstract concepts. However, the present study modelled task difficulty as measured by reaction times as an additional experimental factor that was orthogonal to the manipulation of semantic type. This analysis revealed that easy trials on abstract concepts increased activation in the same fronto-temporal regions even relative to difficult trials of other semantic types (see Figure 7.1). In contrast, comparing all difficult to all easy trials revealed activation in the bilateral thalami, insulae and the brainstem which is consistent with increased processing demands and level of arousal (Paus et al., 1997;Coull et al., 1997;Sturm and Willmes, 2001). Taken collectively, these results make an interpretation in terms of increased

difficulty and length of duty cycle for abstract concepts unlikely. Instead, they suggest that synonym judgements on abstract concepts and perceptually-based features are different either in terms of underlying neural representations or retrieval mechanisms.

If verbally-learnt/abstract and perceptual features have different *neural representations*, they should show distinct patterns of activation irrespective of the task. In contrast to this conjecture, only one study has previously revealed increased activation in the left middle temporal gyrus for abstract concepts relative to animals or tools in a pleasantness judgement (Grossman et al., 2002), while several other studies reported activations in various other brain regions (D'Esposito et al., 1997; Beauregard et al., 1997; Wise et al., 2000) during reading, passive listening or lexical decision tasks (Kiehl et al., 1999). In addition, Chapter 7 has demonstrated that retrieval of verbally-learnt facts relative to perceptual semantic features about food items increased activation in bilateral and medial parietal regions that are usually found for memory retrieval functions. These different activation patterns across studies that all investigate verbally-mediated/abstract semantics but use different tasks are more consistent with an interpretation in terms of *retrieval mechanisms or strategies* than in terms of different neural representations.

While the meaning of abstract concepts is variable and mostly defined by and learnt through the context in which they are used, perceptual features directly correspond to distinct qualities of everyday objects. Therefore, to fully elucidate the meanings of the abstract concepts during synonym judgements subjects might have created an appropriate meaningful, possibly sentential, context that integrates and defines the specific semantic aspects of the three words. Consistent with this hypothesis, abstract concepts enhanced activation in fronto-temporal regions that are generally engaged in semantic processing and form part of a sentence comprehension system (Vandenberghe et al., 2002;St George et al., 1999;Mazoyer et al., 1993;Stowe et al., 1998;Stowe et al.,

1999;Humphries et al., 2001;Bavelier et al., 1997;Chee et al., 1999b;Chee et al., 1999a).

In summary, the study reported in this chapter demonstrates that although facts about everyday objects and abstract concepts have both been suggested to be verbally-mediated, they do not engage the same neuronal system. This may reflect different retrieval mechanisms or strategies: Semantic decisions on verbally-learnt facts about physical objects activated medial and lateral parietal areas of a memory retrieval system (Chapter 7), while synonym judgements on abstract concepts activated areas that are involved in sentence comprehension. Nevertheless, to demonstrate that abstract word and sentence level processing activate the same set of regions, further studies are required that manipulate (i) sentence versus single words and (ii) abstract versus concrete content independently within the same group of subjects.

Finally, the functional imaging findings will be discussed within the context of the current neuropsychological data. The strongly left lateralized fronto-temporal activation that was observed for abstract concepts is consistent with and might explain the vulnerability of abstract concepts to lesioning left hemispheric areas engaged in language processing. Thus, most aphasic patients with left-hemispheric damage are generally more impaired on abstract than concrete words. In contrast, a reversal of the concreteness effect (i.e. greater impairment for concrete words) was observed in several patients with lesions primarily to the temporal poles in the context of herpes encephalitis (Warrington and Shallice, 1984;Sirigu et al., 1991) and semantic dementia (Breedin et al., 1994;Cipolotti and Warrington, 1995;Warrington, 1975). However neither the present nor previous studies have revealed increased left anterior temporal activation for concrete relative to abstract concepts. These inconsistencies between functional imaging

and neuropsychological results might in part be attributed to fMRI susceptibility artefacts in the temporal poles (Lipschutz et al., 2001).

In conclusion, this chapter demonstrates that retrieval of abstract relative to sensory concepts during synonym judgements activates a left-lateralized fronto-temporal system that is usually involved in semantic processing especially at the sentence level. The results suggest that these differential activations might reflect a particular retrieval mechanism or strategy for abstract concepts: As abstract concepts do not correspond to physical objects in the external world, subjects might generate an appropriate semantic context that fully explores and specifies their meanings. The widespread left lateralized fronto-temporal activation might explain the vulnerability of abstract concepts to left hemispheric lesions within the language system.

9   General Conclusions

9.1   Summary of the thesis

The work in this thesis aimed to identify the organisational principles of semantic memory. Based on the feature-based account, it investigated whether there are cortical regions that are specialized for processing different types of semantic information. In particular, the studies focused on action and verbally-mediated semantics. To identify regions that were selective for a particular semantic type, the studies compared (1) semantic features (e.g. action vs. visual), (2) object categories that were strongly associated with a particular semantic type (e.g. animals vs. tools) or (3) tasks that required retrieval of different types of semantic information. The response selectivity was then further characterized by manipulating additional factors such as stimulus modality, task instruction/context, task difficulty and visual experience. In the following, the results of each chapter will be summarized briefly:

Chapter 4 investigated the response selectivity in the left posterior middle temporal area (LPMT) by (1) comparing action features to a range of other semantic features and manipulating (2) input modality and (3) task context. Irrespective of input modality, LPMT was more responsive for semantic decisions on words referring to hand actions (e.g. "TWIST") than on words referring to body motions, sensory qualities or abstract concepts. Taken alone, these results support and extend previous conclusions that LPMT is involved in retrieving semantic knowledge about hand actions. However, Chapter 4 also demonstrates that during word repetition and reading, LPMT responds irrespective of the type of semantics (sensory or action) and in this context there was no advantage for action words. These seemingly conflicting results demonstrate that the function of

LPMT is defined by the task requirements and the link between LPMT and action semantics only emerges in a limited set of contexts.

The study presented in Chapter 5 used early onset blindness as a lesion model to investigate whether experience-dependent mechanisms subtend the functional anatomy of semantic retrieval. In particular, Chapter 5 investigated whether visual deprivation alters the action-selective LPMT response that might be mediated by afferents from motion area V5/MT. In brief, semantic retrieval evoked left-lateralized fronto-temporal activations in both blind and sighted subjects with activation in the blind group extending beyond the normal semantic retrieval regions to encompass extra-striate regions that were coupling with frontal and temporal semantic regions. This exuberant functional connectivity between extrastriate and "core" semantic retrieval regions might be explained by abnormal pruning processes during early neurodevelopment. To our surprise, the action-selective LPMT response was not affected even in the congenitally blind where action experience develops via somatosensory-motor associations rather than visual motion perception. This remarkable resilience of LPMT action-selectivity to profound perturbation of visual experience suggests (1) a considerable degree of innate and epigenetic specification of the semantic system or (2) a multimodal function for LPMT e.g. mediating between semantic aspects learnt from several modality-specific experiences of hand actions (e.g. visual, auditory, somatosensory and motor).

Chapter 6 returned to the questions raised in Chapter 4 but focussed on tool- rather than action-selectivity. Thus, it investigated the effects of task context and stimulus modality on animal and tool-selective responses in a multi-factorial design manipulating stimulus modality (pictures vs. words) and task (implicit vs. explicit semantic one-back task). Furthermore, it combined functional imaging with Dynamic Causal Modelling, to investigate the neural mechanisms that mediate the tool-selective responses that were

observed in multiple cortical regions. This approach allowed us to dissociate two distinct mechanisms that engender tool-selectivity: (1) a ventral object recognition system showing modality-dependent category-selective effects mediated by bottom up effects; (2) a dorsal visuo-motor system showing task-dependent category-effects mediated by increased top-down influences of task-related prefrontal activity. From a cognitive perspective, category-selective responses therefore reflect either stimulus-bound structural processing or task-induced semantic operations. In terms of neural mechanisms, category-selective brain responses emerge from the patterns of interactions among brain regions. The results suggest that the two distinct classes of category-selectivity can be explained by differential top-down and bottom up influences for task and modality-dependent category-selective effects respectively.

Chapter 7 and 8 report studies that aimed to delineate the neural systems engaged in representing and processing verbally mediated knowledge. Chapter 7 showed that retrieval of verbally-learnt facts relative to the colour and taste of food items increased activation in a memory retrieval system encompassing the medial parietal and the temporo-parieto-occipital junction bilaterally.

In contrast, Chapter 8 demonstrated that synonym judgements on abstract concepts relative to sensory features increased activation in a left fronto-temporal system that has been associated with semantic processing particularly at the sentence level. Since activation increases were observed irrespective of the degree of difficulty, the results suggest that these differential activations might reflect a particular retrieval mechanism or strategy for abstract concepts. In contrast to sensory-based semantics, the meaning of abstract concepts is largely specified by their usage in language rather than by their relations to the physical world. Subjects might therefore generate an appropriate semantic sentential context to fully explore and specify the meaning of abstract concepts.

Collectively, the inconsistent results of Chapter 8 & 9 that both supposedly investigated verbally-mediated/abstract semantics but used different tasks and stimuli suggest an interpretation in terms of *retrieval mechanisms or strategies* rather than in terms of different neural representations.

9.2 The organisation of semantic memory

The following revisits several of the themes that have emerged from the series of experiments in this thesis. The first section emphasizes that category-selective activations can arise at multiple processing levels. The second section evaluates the positive evidence for the feature-based account of semantic memory that is provided by this thesis. The third section reviews inconsistencies and null-results that raise problems for the feature-based account and discusses their underlying causes from the perspective of structure-function relationships.

9.2.1 Multiple levels of object processing: Structural and semantic processing

Neuropsychological studies have suggested that category-selective impairments can emerge at multiple processing levels ranging from structural to semantic(Humphreys and Forde, 2001). Similarly, Chapter 6 has demonstrated that tool-selective activations in multiple cortical regions can be further dissociated using a multi-factorial design that manipulates stimulus modality and task context. While tool-selective activations depended on modality and were only observed for pictures in the ventral occipito-temporal cortex, they were modulated by task-context and greater for explicit semantic tasks in the dorsal visuo-motor system. In terms of neural mechanisms, the ventral tool-selective responses could be explained by a modality-dependent increase in bottom-up

tool-selective influences, whereas dorsal regions were subject to tool-selective top-down

influences of task-related prefrontal activity. These distinct activation and connectivity

patterns suggest that there are two classes of category-selective systems supporting

different cognitive operations during object processing: While the occipito-temporal

regions might be engaged in structural processing, the visuo-motor regions are activated

during "strategic" semantic processing.   This dorso-ventral dissociation is further

supported by two other recent functional imaging studies investigating category-selective

responses: The first study manipulated visual experience (i.e. priming) and demonstrated

that priming decreased activation in a tool-selective fashion only in the dorsal regions

(i.e. LPMT), but not in ventral occipito-temporal tool-selective regions (Chao et al.,

2002). The second study compared tool and human body motion in the context of real

and point light display (Beauchamp et al., 2003). The ventral occipito-temporal

responses were profoundly sensitive to the particular stimulus characteristics and tool-

selectivity emerged only in the context of real display. Collectively, these three studies

provide converging evidence that tool-selectivity in the ventral occipito-temporal cortex

is strongly modality-dependent.

To summarize, neuropsychological studies have suggested that there are multiple

processes involved in object recognition that can be impaired in a category-selective

fashion. Consistent with this view, functional imaging has provided evidence that

multiple category-selective regions in the ventral occipito-temporal cortex and the dorsal

visuo-motor system sustain dissociable processes in object processing. In particular, a

distinction has been drawn between structural processing that is modality-dependent and

semantic strategic processing that is modulated by task-context. In conclusion,

neuropsychology and functional imaging suggest that some sort of category-selective

organisation might be realized at both, structural and semantic strategic processing levels.

9.2.2   The feature-based model

The feature-based model of semantic memory was primarily developed to account for category-selective impairments of semantic memory (Shallice, 1988;Warrington and Shallice, 1984;Warrington and McCarthy, 1987). Rather than assuming a category-specific organisation, it explains seemingly category-specific deficits by (1) a functional segregation for different types of semantic features and (2) differential contributions of semantic features to distinct object categories. Translated into functional imaging, the feature-based model of semantic memory postulates that (1) there are brain regions with selective responses to different types of semantic features and (2) these brain regions overlap with those that show a category-selective response. For instance, we would expect that tools and action features show increased activation in the same brain regions. More closely related to the functional brain architecture, it has further been suggested that the neural substrates underlying semantic features are (i) related to or (ii) even identical with the regions that were engaged when the particular type of semantic knowledge was acquired during primary sensory-motor experience (Martin et al., 2000;Martin and Chao, 2001). Thus, tools and action semantics were linked to the visuo-motor action system.

The series of studies reported in this thesis provide partial evidence for the feature-based model of semantic memory with respect to action and verbally mediated semantics.

Action and tool semantics

Chapters 4 to 6 collectively demonstrated that semantic decisions on words referring to action features and to tools increased activation the left posterior middle temporal gyrus (LPMT) and the anterior inferior parietal sulcus that have previously been implicated in action imagery, observation and execution. Hence, in the case of action semantics, the functional imaging results showed the expected congruency of (1) feature: action semantics, (2) category: tool semantics and (3) sensori-motor region: visuo-motor system. Furthermore, using effective connectivity analyses, Chapter 6 demonstrated that the function of a visuo-motor region such as AIP is defined by the particular cognitive and neural context. For example, during tool perception the tool-selective AIP response was mediated by forward connections from early visual areas. During semantic decision tasks, it was in part mediated primarily by backward connections from the left prefrontal cortex.

Verbally-mediated semantics and sentence processing

Chapter 8 demonstrated that abstract semantics relative to sensory features activates a left-lateralized fronto-temporal system that is usually engaged for sentence reading and listening. This activation was attributed to the association of abstract concepts with propositional-based semantics and sentence processing. While the meaning of concrete concepts is supposed to be defined by perceptual features and their relation to physical everyday objects, the meaning of abstract concepts is thought to be verbally-mediated and to emerge from use in sentence contexts (Breedin et al., 1994). Hence, in a wider and more tentative sense, the selective activation elicited by abstract concepts in the sentence reading system might also be taken as weak functional imaging evidence for the feature-based model of semantic memory.

So far, the emphasis has been on the consistencies between the functional imaging results and the predictions generated from the feature-based model of semantic memory. However, the results also exhibit several results that were not predicted by the feature-based account.

First, although the action- and tool-selective responses in the visuo-motor action system were consistently observed during explicit semantic tasks, they were profoundly context-sensitive and were not detected during repetition, reading or implicit semantic tasks. The question therefore emerges, whether these action-selective activations are truly essential for "daily" semantic processing and simply too small to be detected by functional imaging during implicit semantic processing tasks. Alternatively, they might reflect particular task-induced strategies such as action imagery, which are not necessarily involved in semantic processing. Transient lesion methods such as TMS might help us to distinguish between these two possibilities: Applying TMS to LPMT should be associated with impaired semantic processing and comprehension only if LPMT makes a critical functional contribution to action retrieval.

Second, in contrast to action semantics, other semantic types such as visual, taste or auditory features could not be associated consistently with particular cortical regions. These inconsistencies and null-results question but do not necessarily refute the feature-based model of semantic memory as a general explanatory framework. Instead, task-dependent effects, inconsistencies and null-results raise multiple fundamental issues about structure-function relationships, which will be further explored in the following section.

9.2.3   Task-dependency, Inconsistencies and Null-results

This section will discuss how task-dependent effects, inconsistencies and null-results in functional imaging studies of semantic processing can emerge from structure-function-relationships that do not conform to a simple one-to-one mapping. Instead structure-function relationships may be of a more complicated nature. They might either be "one to many" (= pluripotentiality) or "many to one" (= degeneracy; Friston and Price, 2003;Price and Friston, 2002b;Wilkinson and Halligan, 2004;Tononi et al., 1994;Tononi et al., 1999;Edelman and Gally, 2001).

Task-dependent selectivity and Pluripotentiality

Both Chapter 4 and 6 were concerned with the context-sensitivity of action- and tool-selective brain responses. This semantic content by task context interaction might simply reflect that semantic selectivity is enhanced during explicit semantic tasks for instance due to attentional top-down modulation. In this case, a region sustains only one process that is enhanced in a particular cognitive context. Alternatively, there is a one-to-many structure –function mapping and one brain structure fulfils multiple functions. In this case of pluripotentiality, selectivity of evoked brain responses is better understood in terms of the cognitive operation induced by the stimulus in a particular context. Context might thereby be defined as (i) cognitive set in cognitive terms or (ii) the integration of activity in distributed brain regions in neural terms. For instance, a "semantic" brain region (e.g. LPMT in Chapter 4) might take part in phonological processing during repetition and reflect specific retrieval strategies (e.g. action imagery) that are relevant only for one type of semantic feature during focussed semantic decisions. Hence, LPMT

would sustain multiple functions and action-selectivity emerges only in particular cognitive contexts. Pluripotentiality or many-to-one structure-function-mappings preclude investing a region with functional specificity e.g. action-selectivity in a simple and straightforward fashion. Instead, semantic selectivity needs to be fully characterized in terms of stimulus and task context. Understanding semantic selectivity as an interaction between stimulus and cognitive set might enable us to resolve the inconsistencies across functional imaging studies of semantic organisation where identical semantic stimuli evoked distinct activation patterns in different task contexts.

Null-results and Degeneracy

This thesis has focused on action and verbally-mediated semantics – one reason being that other types of semantics did not elicit any selective brain responses. The introduction has already discussed how implicit semantic processing can decrease or even abolish activation differences between different semantic stimuli or tasks. This section will briefly introduce the concept of degenerate structure-function relationships as a potential explanatory mechanism for these "null-results". Degenerate structure-function mapping refers to the situation where multiple structural or anatomical brain systems can produce the same behavioural response. For instance, there might be multiple processing systems, each sufficient for performing a semantic task but reflecting different strategies. Hence, if subjects engage in different strategies to perform the same task, no single system will be consistently activated across subjects and we will not be able to identify a specialized system (e.g. action retrieval system) at the random effects level. To summarize, degenerate structure-function relationships might be an important mechanism that can explain "null-results" particularly for complex cognitive tasks such as semantic processing that can be performed by engaging different cognitive strategies.

9.3 Future directions

What does this discussion imply for future studies investigating the organisational principles of semantic representations? This section will conclude by briefly highlighting four proposals:

Context-sensitive response selectivity: Task by stimulus interactions and multi-factorial designs

Previous functional imaging studies of semantic organisation have focussed on semantic-selective responses independent of the particular task-context. This approach has primarily produced inconsistent results. The studies in this thesis have highlighted that semantic-selective activations are profoundly sensitive to the context as defined by the task-type (e.g. repetition, semantic decision) and the specific task-instructions (e.g. different instructions used for action retrieval). Therefore, semantic segregation needs to be considered within different task-contexts. For this, multi-factorial designs are required that allow us to (i) dissociate context-independent from context-sensitive effects and (ii) characterize the interactions between semantic type and task-context. This approach will reveal "semantic selectivity" as a semantic type/category by task interaction whereby the semantic-selective role of a brain area is defined and modulated by the specific task-context. Investigating the retrieval of a particular semantic type in a series of task-contexts and redefining semantic selectivity as stimulus by task interaction might help us to explain and resolve the inconsistent results in the current literature. Furthermore, characterizing the regional response pattern in multiple contexts will enable us to further characterize and segregate the particular functional contributions of different regions to object and semantic processing.

The neural mechanisms of semantic processing

In terms of neural mechanisms, task by stimulus interactions are consistent with the well established notion that functional specialisation emerges from changes in the interactions among brain areas that serve different functions (McIntosh, 2000b;Mesulam, 1990b;Horwitz, 2003). Accordingly, the functional role played by any neuronal system is defined by its interactions with other neuronal systems. Chapter 6 has presented one study that explained tool-selective activations by context-sensitive modulation of forwards and backwards connections. Clearly, further studies combining functional imaging with effective connectivity analyses are needed to investigate how regionally semantic-selective responses emerge from interactions amongst brain regions (see also (Mechelli et al., 2003)). Effective connectivity analyses will also enable us to formally address the predictions made by the "sensori-motor" theory of semantics. That is they will allow us to test whether identical brain regions can sustain sensory functions when activated via forward connections but semantic representational functions when activated via backward connections

Inter-subject variability: Condition by subject interactions

The task-dependent LPMT action/tool-selectivity suggested that selectivity of evoked brain responses is better understood in terms of the cognitive operations or strategies induced by the stimulus in a particular task context. However, if subjects engage different strategies, the context is not entirely defined by the task-instructions but also depend on the individual subjects. To account for these subject-specific strategies, future studies will need to evaluate inter-subject variability rather than simply focussing on consistent activations across subjects. Inter-subject variability can be investigated using

multiple methodological approaches: For instance, one might characterize the remaining structure in the residuals in a random effects analysis. Alternatively, one could formally test for condition by subject interactions or consistent variations in regional activations across subjects (e.g using subject-specific activations as a regressor in a random effects analysis)

Integration of object features

Previous research has focussed on the cortical regions that showed selective responses to modality-specific object features. Obviously, multiple modality-specific features collectively characterize objects and semantic concepts. Thus, the question emerges whether there are particular regions that are specialized for integrating modality-specific features into a semantic or object concept. Only few functional imaging studies have investigated cross-modal integration at the semantic level using familiar objects characterized by one or multiple modality-specific features. By presenting multiple features separately and together and manipulating their semantic congruency, recent fMRI studies (Gottfried and Dolan, 2003;Beauchamp et al., 2004), revealed a crossmodal integration effect in the left intraparietal, superior temporal sulci and the respective early sensory areas for auditory-visual and olfactory-visual integration of features at the semantic level. In addition, the left anterior hippocampus showed an effect of semantic congruency (Gottfried and Dolan, 2003). Clearly, further studies are needed to investigate the neural mechanisms that solve the "binding" problem of semantic features.

Conclusions for future work

In conclusion, future functional imaging studies of semantic organisation will need to (1) redefine semantic selectivity as stimulus by task interactions using multi-factorial designs, (2) determine the underlying neural mechanisms by combining functional imaging with modelling approaches e.g. Dynamic Causal Modelling, (3) identify particular subject-specific strategies by testing for subject by condition interactions and (4) investigate how object features are integrated into semantic or object concepts.

10 References

1. Allport DA (1985) Distributed memory, modular subsystems and dysphasia. In: Current perspectives in Dysphasia (Newman SK, Epstein R, eds), pp 32-60. Edinburgh: Churchill Livingstone.

2. Amedi, A., Raz, N., Pianka, P., Hendler, T., Malach, R., and Zohary, E. Language related activation in the occipital cortex following early onset blindness. SFN 32nd annual meeting [418.14]. 2002.
   Ref Type: Abstract

3. Barsalou LW, Kyle SW, Barbey AK, Wilson CD (2003) Grounding conceptual knowledge in modality-specific systems. Trends Cogn Sci 7: 84-91.

4. Batardiere A, Barone P, Knoblauch K, Giroud P, Berland M, Dumas AM, Kennedy H (2002) Early specification of the hierarchical organization of visual cortical areas in the macaque monkey. Cereb Cortex 12: 453-465.

5. Bavelier D, Corina D, Jezzard P, Padmanabhan S, Clark VP, Karni A, Prinster A, Braun A, Lalwani A, Rauschecker JP, Turner R, Neville H (1997) Sentence Reading: A functional MRI study at 4 Tesla. Journal of Cognitive Neuroscience 9: 664-686.

6. Bavelier D, Neville HJ (2002) Cross-modal plasticity: where and how? Nat Rev Neurosci 3: 443-452.

7. Beauchamp MS, Lee KE, Argall BD, Martin A (2004) Integration of Auditory and Visual Information about Objects in Superior Temporal Sulcus. Neuron 41: 809-823.

8. Beauchamp MS, Lee KE, Haxby JV, Martin A (2002) Parallel visual motion processing streams for manipulable objects and human movements. Neuron 34: 149-59.

9. Beauchamp MS, Lee KE, Haxby JV, Martin A (2003) FMRI responses to video and point-light displays of moving humans and manipulable objects. J Cogn Neurosci 15: 991-1001.

10. Beauregard M, Chertkow H, Bub D, Murtha S, Dixon R, Evans A (1997) The neural substrate for concrete, abstract, and emotional word lexica: A positron emission tomography study. Journal of Cognitive Neuroscience 9: 441-461.

11. Binder JR, Frost JA, Hammeke TA, Cox RW, Rao SM, Prieto T (1997) Human brain language areas identified by functional magnetic resonance imaging. J Neurosci 17: 353-62.

12. Bonda E, Petrides M, Ostry D, Evans A (1996) Specific involvement of human parietal systems and the amygdala in the perception of biological motion. J Neurosci 16: 3737-44.

13. Breedin SD, Saffran EM, Coslett HB (1994) Reversal of the concreteness effect in a patient with semantic dementia. Cognitive Neuropsychology 11: 617-660.

14. Buccino G, Lui F, Canessa N, Patteri I, Lagravinese G, Benuzzi F, Porro CA, Rizzolatti G (2004a) Neural circuits involved in the recognition of actions performed by nonconspecifics: an FMRI study. J Cogn Neurosci 16: 114-126.

15. Buccino G, Vogt S, Ritzl A, Fink GR, Zilles K, Freund HJ, Rizzolatti G (2004b) Neural circuits underlying imitation learning of hand actions: an event-related fMRI study. Neuron 42: 323-334.

16. Buchel C, Price C, Frackowiak RS, Friston K (1998a) Different activation patterns in the visual cortex of late and congenitally blind subjects. Brain 121 (Pt 3): 409-419.

17. Buchel C, Price C, Friston K (1998b) A multimodal language region in the ventral visual pathway. Nature 394: 274-7.

18. Burkhalter A (1993) Development of forward and feedback connections between areas V1 and V2 of human visual cortex. Cereb Cortex 3: 476-487.

19. Burton H, Snyder AZ, Conturo TE, Akbudak E, Ollinger JM, Raichle ME (2002) Adaptive changes in early and late blind: a fMRI study of Braille reading. J Neurophysiol 87: 589-607.

20. Buxbaum L, Veramonti T, Schwartz M (2000) Function and manipulation tool knowledge in apraxia: Knowing 'what for' but not 'how'. Neurocase 6: 83-97.

21. Capitani E, Laiacona M, Mahon B, Caramazza A (2003) What are the facts semantic category-specific deficits? A critical review of the clinical evidence. Cognitive Neuropsychology 20: 213-262.

22. Cappa SF, Perani D, Schnur T, Tettamanti M, Fazio F (1998) The effects of semantic category and knowledge type on lexical-semantic access: a PET study. Neuroimage 8: 350-9.

23. Caramazza A (2000) Minding the facts: a comment on Thompson-Schill et al.'s "A neural basis for category and modality specificity of semantic knowledge" [comment]. Neuropsychologia 38: 944-9.

24. Caramazza A, Shelton JR (1998b) Domain-specific knowledge systems in the brain the animate-inanimate distinction. J Cogn Neurosci 10: 1-34.

25. Caramazza A, Shelton JR (1998a) Domain-specific knowledge systems in the brain the animate-inanimate distinction. J Cogn Neurosci 10: 1-34.

26. Carbonnet S, Charnallet A, David D, Pellat J (1997) One or several semantic system(s)? Maybe none: Evidence from a case study of modality and category-specific 'semantic' impairment. Cortex 33: 391-417.

27. Carpenter PA, Just MA, Keller TA, Eddy WF, Thulborn KR (1999) Time course of fMRI-activation in language and spatial networks during sentence comprehension. Neuroimage 10: 216-24.

28. Chao LL, Haxby JV, Martin A (1999) Attribute-based neural substrates in temporal cortex for perceiving and knowing about objects. Nat Neurosci 2: 913-9.

29. Chao LL, Martin A (1999) Cortical regions associated with perceiving, naming, and knowing about colors. J Cogn Neurosci 11: 25-35.

30. Chao LL, Martin A (2000) Representation of manipulable man-made objects in the dorsal stream [In Process Citation]. Neuroimage 12: 478-84.

31. Chao LL, Weisberg J, Martin A (2002) Experience-dependent modulation of category-related cortical activity. Cereb Cortex 12: 545-551.

32. Chee MW, Caplan D, Soon CS, Sriram N, Tan EW, Thiel T, Weekes B (1999a) Processing of visually presented sentences in Mandarin and English studied with fMRI. Neuron 23: 127-37.

33. Chee MW, Tan EW, Thiel T (1999b) Mandarin and English single word processing studied with functional magnetic resonance imaging. J Neurosci 19: 3050-6.

34. Cherry SR, Phelps ME (1995) Imaging brain function with Positron Emission Tomography. In: Brain Mapping (Toga AW, Mazziotta JC, eds), pp 191-218. San Diego: Academic Press.

35. Cipolotti L, Warrington EK (1995) Semantic memory and reading abilities: a case report. J Int Neuropsychol Soc 1: 104-10.

36. Cohen LG, Celnik P, Pascual-Leone A, Corwell B, Falz L, Dambrosia J, Honda M, Sadato N, Gerloff C, Catala MD, Hallett M (1997) Functional relevance of cross-modal plasticity in blind humans. Nature 389: 180-183.

37. Cohen LG, Weeks RA, Sadato N, Celnik P, Ishii K, Hallett M (1999) Period of susceptibility for cross-modal plasticity in the blind. Ann Neurol 45: 451-460.

38. Cohen MS (1998) Theory of Echo-Planar Imaging. In: Echo-Planar Imaging, Theory, Technique and Application (Schmitt R, Stehling MK, Turner R, eds), pp 11-30. Berlin: Springer-Verlag.

39. Coltheart M (1980) Deep dyslexia: A review of the syndrome. In: Deep dyslexia (Coltheart MPKEMJC, ed), pp 22-48. London: Routledge and Kegan Paul.

40. Contreras, V. Category-specific effects: segregation of semantic knowledge and degree of feature processing in the brain. 2002.
Ref Type: Thesis/Dissertation

41. Coull, J. T., Frith, C. D., Dolan, R. J., Frackowiak, R., and Grasby, P. M. The neural correlates of the noradrenergic modulation of human attention, arousal

and learning. Eur J Neurosci 9, 589-598. 1997.
Ref Type: Abstract

42. D'Esposito M, Detre JA, Aguirre GK, Stallcup M, Alsop DC, Tippet LJ, Farah MJ (1997) A functional MRI study of mental image generation. Neuropsychologia 35: 725-30.

43. Damasio AR (1989) Time-locked multiregional retroactivation: a systems-level proposal for the neural substrates of recall and recognition. Cognition 33: 25-62.

44. Damasio H, Grabowski TJ, Tranel D, Hichwa RD, Damasio AR (1996) A neural basis for lexical retrieval [see comments] [published erratum appears in Nature 1996 Jun 27;381(6595):810]. Nature 380: 499-505.

45. Damasio H, Grabowski TJ, Tranel D, Ponto LL, Hichwa RD, Damasio AR (2001) Neural correlates of naming actions and of naming spatial relations. Neuroimage 13: 1053-1064.

46. De Volder AG, Toyama H, Kimura Y, Kiyosawa M, Nakano H, Vanlierde A, Wanet-Defalque MC, Mishina M, Oda K, Ishiwata K, Senda M (2001) Auditory triggered mental imagery of shape involves visual association areas in early blind humans. Neuroimage 14: 129-139.

47. Demonet J-F, Chollet F, Ramsay S, Cardebat D, Nespoulos J-D, Wise R, Rascol A, Frackowiak RSJ (1992) The anatomy of phonological and semantic processing in normal subjects. Brain 115: 1753-1768.

48. Devlin JT, Moore CJ, Mummery CJ, Gorno-Tempini ML, Phillips JA, Noppeney U, Frackowiak RS, Friston KJ, Price CJ (2002) Anatomic constraints on cognitive theories of category specificity. Neuroimage 15: 675-85.

49. Edelman GM, Gally JA (2001) Degeneracy and complexity in biological systems. Proc Natl Acad Sci U S A 98: 13763-13768.

50. Evans, A. C., Collins, D. L., and Milner, B. An {MRI}-based stereotactic atlas from 250 young normal subjects. SNA . 1992.
Ref Type: Abstract

51. Farah MJ, McMullen PA, Meyer MM (1996) The living nonliving dissociation is not an artefact: Giving an a priori implausible hypothesis a strong test. Cognitive Neuropsychology 13: 137-154.

52. Fiez JA (1997) Phonology, semantics, and the role of the left inferior prefrontal cortex. Hum Brain Mapp 5: 79-83.

53. Frackowiak R, Friston K, Frith CD, Dolan R, Price C, Zeki S, Ashburner J, Penny W (2004) Human Brain Function. 2nd Edition. London. Academic Press.

54. Friston KJ, Buchel C, Fink GR, Morris J, Rolls E, Dolan RJ (1997) Psychophysiological and modulatory interactions in neuroimaging. Neuroimage 6: 218-229.

55. Friston KJ, Harrison L, Penny W (2003) Dynamic causal modelling. Neuroimage 19: 1273-1302.

56. Friston KJ, Holmes A, Worsley KJ, Poline JB, Frith CD, Frackowiak R (1995) Statistical parametric mapping: a general linear approach. Hum Brain Mapping 2: 189-210.

57. Friston KJ, Holmes AP, Price CJ, Buchel C, Worsley KJ (1999) Multisubject fMRI studies and conjunction analyses. Neuroimage 10: 385-96.

58. Friston KJ, Penny W, Phillips C, Kiebel S, Hinton G, Ashburner J (2002) Classical and Bayesian inference in neuroimaging: theory. Neuroimage 16: 465-483.

59. Friston KJ, Price CJ (2001) Generative models, brain function and neuroimaging. Scand J Psychol 42: 167-177.

60. Friston KJ, Price CJ (2003) Degeneracy and redundancy in cognitive anatomy. Trends Cogn Sci 7: 151-152.

61. Friston KJ, Price CJ, Fletcher P, Moore C, Frackowiak RS, Dolan RJ (1996) The trouble with cognitive subtraction. Neuroimage 4: 97-104.

62. Fuster JM (1989) The prefrontal cortex. New York: Raven Press.

63. Gabrieli JD, Poldrack RA, Desmond JE (1998) The role of left prefrontal cortex in language and memory. Proc Natl Acad Sci U S A 95: 906-13.

64. Gainotti G, Giustolisi L, Daniele A, Silveri MC (1995) Neuroanatomical correlates of category-specific semantic disorders: A critical survet. Memory 3: 247-264.

65. Gainotti G, Silveri MC (1996a) Cognitive and anatomical locus of lesion in a patient with a category-specific semantic impairment for living beings. Cognitive Neuropsychology 13: 357-389.

66. Gainotti G, Silveri MC (1996b) Cognitive and anatomical locus of lesion in a patient with a category-specific semantic impairment for living beings. Cognitive Neuropsychology 13: 357-389.

67. Gerlach C, Law I, Gade A, Paulson OB (2000) Categorization and category effects in normal object recognition. A PET study [In Process Citation]. Neuropsychologia 38: 1693-703.

68. Gerlach C, Law I, Gade A, Paulson OB (2002a) The role of action knowledge in the comprehension of artefacts--a PET study. Neuroimage 15: 143-152.

69. Gerlach C, Law I, Paulson OB (2002b) When action turns into words. Activation of motor-based knowledge during categorization of manipulable objects. J Cogn Neurosci 14: 1230-1239.

70. Gjedde A (2001) Brain energy metabolism and the physiological basis of the haemodynamic responses. In: Functional MRI, An introduction to methods (Jezzard P, Matthews PM, Smith SM, eds), pp 37-66. Oxford: Oxford University Press.

71. Goodglass H, Hyde MR, Blumstein S (1969) Frequency, picturability and availability of nouns in aphasia. Cortex 5: 104-19.

72. Gottfried JA, Dolan RJ (2003) The nose smells what the eye sees: crossmodal visual facilitation of human olfactory perception. Neuron 39: 375-386.

73. Grabowski TJ, Damasio H, Damasio AR (1998) Premotor and prefrontal correlates of category-related lexical retrieval. Neuroimage 7: 232-43.

74. Grafton ST, Fadiga L, Arbib MA, Rizzolatti G (1997) Premotor cortex activation during observation and naming of familiar tools. Neuroimage 6: 231-6.

75. Grezes J, Costes N, Decety J (1998) Top-down effect of strategy on the perception of human biological motion: A PET investigation. Cognitive Neuropsychology 15: 553-582.

76. Grezes J, Costes N, Decety J (1999) The effects of learning and intention on the neural network involved in the perception of meaningless actions. Brain 122: 1875-87.

77. Grezes J, Decety J (2001) Functional anatomy of execution, mental simulation, observation, and verb generation of actions: a meta-analysis. Hum Brain Mapp 12: 1-19.

78. Grezes J, Decety J (2002) Does visual perception of object afford action? Evidence from a neuroimaging study. Neuropsychologia 40: 212-22.

79. Grezes J, Fonlupt P, Bertenthal B, Delon-Martin C, Segebarth C, Decety J (2001) Does perception of biological motion rely on specific brain regions? Neuroimage 13: 775-85.

80. Grossman M, Koenig P, DeVita C, Glosser G, Alsop D, Detre J, Gee J (2002) The neural basis for category-specific knowledge: an fMRI study. Neuroimage 15: 936-948.

81. Gyllensten L, Malmfors T, Norrlin ML (1966) Growth alteration in the auditory cortex of visually deprived mice. J Comp Neurol 126: 463-469.

82. Hauk O, Johnsrude I, Pulvermuller F (2004) Somatotopic representation of action words in human motor and premotor cortex. Neuron 41: 301-307.

83. Haxby JV, Gobbini MI, Furey ML, Ishai A, Schouten JL, Pietrini P (2001) Distributed and overlapping representations of faces and objects in ventral temporal cortex. Science 293: 2425-30.

84. Heil P, Bronchti G, Wollberg Z, Scheich H (1991) Invasion of visual cortex by the auditory system in the naturally blind mole rat. Neuroreport 2: 735-738.

85. Hillis AE, Caramazza A (1991) Category-specific naming and comprehension impairment: a double dissociation. Brain 114: 2081-94.

86. Horwitz B (2003) The elusive concept of brain connectivity. Neuroimage 19: 466-470.

87. Howard RJ, ffytche DH, Barnes J, McKeefry D, Ha Y, Woodruff PW, Bullmore ET, Simmons A, Williams SC, David AS, Brammer M (1998) The functional anatomy of imagining and perceiving colour. Neuroreport 9: 1019-1023.

88. Hubel DH, Wiesel TN (1977) Ferrier lecture. Functional architecture of macaque monkey visual cortex. Proc R Soc Lond B Biol Sci 198: 1-59.

89. Humphreys GW, Forde EM (2001) Hierarchies, similarity, and interactivity in object recognition: "category-specific" neuropsychological deficits. Behav Brain Sci 24: 453-76.

90. Humphries C, Willard K, Buchsbaum B, Hickok G (2001) Role of anterior temporal cortex in auditory sentence comprehension: an fMRI study. Neuroreport 12: 1749-52.

91. Huttenlocher PR (1990) Morphometric study of human cerebral cortex development. Neuropsychologia 28: 517-527.

92. Huttenlocher PR, de Court, Garey LJ, Van der LH (1982) Synaptogenesis in human visual cortex--evidence for synapse elimination during normal development. Neurosci Lett 33: 247-252.

93. Hyvarinen J, Carlson S, Hyvarinen L (1981) Early visual deprivation alters modality of neuronal responses in area 19 of monkey cortex. Neurosci Lett 26: 239-243.

94. Ishai A, Ungerleider LG, Martin A, Schouten JL, Haxby JV (1999) Distributed representation of objects in the human ventral visual pathway. Proc Natl Acad Sci U S A 96: 9379-84.

95. James CT (1975) The role of semantic information in lexical decisions. Journal of experimental Psychology 104: 130-136.

96. Jezzard P, Clare S (2001) Principles of nuclear magnetic resonance and MRI. In: Functional MRI, an introduction to methods (Jezzard P, Matthews PM, Smith SM, eds), pp 67-92. Oxford: Oxford University Press.

97. Jones RA, Brookes JA, Moonen CTW (2001) Ultra-fast MRI. In: Functional MRI, an introduction to methods (Jezzard P, Matthews PM, Smith SM, eds), pp 93-108. Oxford: Oxford University Press.

98. Joseph JE (2001) Functional neuroimaging studies of category specificity in object recognition: a critical review and meta-analysis. Cogn Affect Behav Neurosci 1: 119-136.

99. Josephs, O., Deichmann, R., and Turner, R. Trajectory measurement and generalized reconstruction in rectilinear EPI. ISMRM meeting , 1517. 2000.
Ref Type: Abstract

100. Just MA, Newman SD, Keller TA, McEleney A, Carpenter PA (2004) Imagery in sentence comprehension: an fMRI study. Neuroimage 21: 112-124.

101. Kable JW, Lease-Spellmeyer J, Chatterjee A (2002) Neural substrates of action event knowledge. J Cogn Neurosci 14: 795-805.

102. Katz RB, Goodglass H (1990) Deep Dysphasia: Analysis of a rare form of repetition disorder. Brain and Language 39: 153-185.

103. Kellenbach ML, Brett M, Patterson K (2001) Large, colorful, or noisy? Attribute- and modality-specific activations during retrieval of perceptual attribute knowledge. Cogn Affect Behav Neurosci 1: 207-221.

104. Kellenbach M, Brett M, Patterson K (2002) Action speak louder than functions. The importance of manipulability and action in tool representation. Journal of Cognitive Neuroscience. J. of Cognitive Neuroscience 15:30-46.

105. Kiehl KA, Liddle PF, Smith AM, Mendrek A, Forster BB, Hare RD (1999) Neural pathways involved in the processing of concrete and abstract words. Hum Brain Mapp 7: 225-33.

106. Kohler E, Keysers C, Umilta MA, Fogassi L, Gallese V, Rizzolatti G (2002) Hearing sounds, understanding actions: action representation in mirror neurons. Science 297: 846-848.

107. Kourtzi Z, Kanwisher N (2000) Activation in human MT/MST by static images with implied motion. J Cogn Neurosci 12: 48-55.

108. Kroll JF, Merves JS (1986) Lexical access for concrete and abstract words. Journal of experimental Psychology 12: 92-107.

109. Lessard N, Pare M, Lepore F, Lassonde M (1998) Early-blind human subjects localize sound sources better than sighted subjects. Nature 395: 278-280.

110. Lipschutz B, Friston KJ, Ashburner J, Turner R, Price CJ (2001) Assessing study-specific regional variations in fMRI signal. Neuroimage 1: 1-7.

111. Lueck CJ, Zeki S, Friston KJ, Deiber MP, Cope P, Cunningham VJ, Lammertsma AA, Kennard C, Frackowiak RS (1989) The colour centre in the cerebral cortex of man. Nature 340: 386-9.

112. MacLeod CM (1991) Half a century of research on the Stroop effect: an integrative review. Psychol Bull 109: 163-203.

113. Maguire EA, Mummery CJ (1999) Differential modulation of a common memory retrieval network revealed by positron emission tomography. Hippocampus 9: 54-61.

114. Marshall J, Pring T, Chiat S, Robson J (1996) Calling a salad a federation: An investigation of semantic jargon. Part I - Nouns. Journal of Neurolinguistics 9: 237-250.

115. Martin A, Chao LL (2001) Semantic memory and the brain: structure and processes. Curr Opin Neurobiol 11: 194-201.

116. Martin A, Haxby JV, Lalonde FM, Wiggs CL, Ungerleider LG (1995) Discrete cortical regions associated with knowledge of color and knowledge of action. Science 270: 102-5.

117. Martin A, Ungerleider LG, Haxby JV (2000) Category-specificity and the brain: The sensory / motor model of semantic representations of objects. In: The cognitive neurosciences (Gazzaniga MS, ed), pp 1023-1037. Cambridge, MA: MIT Press.

118. Martin A, Wiggs CL, Ungerleider LG, Haxby JV (1996) Neural correlates of category-specific knowledge. Nature 379: 649-52.

119. Martin N, Saffran EM (1992) A computational account of deep dysphasia. Brain and Language 43: 240-274.

120. Matthews PM (2001) An introduction to functional magnetic resonance imaging of the brain. In: Function MRI (Jezzard P, Matthews PM, Smith SM, eds), pp 3-35. Oxford: Oxford University Press.

121. Mazoyer BM, Tzourio N, Frak V, Syrota A, Murayama N, Levrier O, Salamon G, Dehaene S, Chohen L, Mehler J (1993) The cortical representation of speech. J of Cognitive Neuroscience 5: 467-479.

122. McIntosh AR (2000b) Towards a network theory of cognition. Neural Netw 13: 861-70.

123. McIntosh AR (2000a) Towards a network theory of cognition. Neural Netw 13: 861-870.

124. Mechelli A, Price CJ, Noppeney U, Friston KJ (2003) A dynamic causal modeling study on category effects: bottom-up or top-down mediation? J Cogn Neurosci 15: 925-934.

125. Mecklinger A, Gruenewald C, Besson M, Magnie MN, von Cramon DY (2002) Separable neuronal circuitries for manipulable and non-manipulable objects in working memory. Cereb Cortex 12: 1115-1123.

126. Melzer P, Morgan VL, Pickens DR, Price RR, Wall RS, Ebner FF (2001) Cortical activation during Braille reading is influenced by early visual experience in subjects with severe visual disability: a correlational fMRI study. Hum Brain Mapp 14: 186-195.

127. Mesulam MM (1990b) Large-scale neurocognitive networks and distributed processing for attention, language, and memory. Ann Neurol 28: 597-613.

128. Mesulam MM (1990a) Large-scale neurocognitive networks and distributed processing for attention, language, and memory. Ann Neurol 28: 597-613.

129. Miller EK (2000) The prefrontal cortex and cognitive control. Nat Rev Neurosci 1: 59-65.

130. Moore CJ, Price CJ (1999) A functional neuroimaging study of the variables that generate category-specific object processing differences. Brain 122: 943-62.

131. Mummery CJ, Patterson K, Hodges JR, Price CJ (1998) Functional neuroanatomy of the semantic system: divisible by what? J Cogn Neurosci 10: 766-77.

132. Mummery CJ, Patterson K, Hodges JR, Wise RJ (1996) Generating 'tiger' as an animal name or a word beginning with T: differences in brain activation [published erratum appears in Proc R Soc Lond B Biol Sci 1996 Dec 22;263(1377):1755-6]. Proc R Soc Lond B Biol Sci 263: 989-95.

133. Nass R (1997) Language development in children with congenital strokes. Semin Pediatr Neurol 4: 109-116.

134. Noppeney U, Friston K, Price C (2003) Effects of visual deprivation on the organisation of the semantic system. Brain 126: 1620-1627.

135. Noppeney, U., Josephs, O., Kiebel, S., Winterburn, D., Friston, K., and Price, C. Action selectivity in left posterior middle temporal cortex. submitted . 2002.
Ref Type: Unpublished Work

136. Noppeney U, Phillips JA, Price C (2004a) The neural areas that control the retrieval and selection of semantics. Neuropsychologia 42: 1269-1280.

137. Noppeney U, Price C (2004) Retrieval of abstract semantics. Neuroimage 22: 164-170.

138. Noppeney U, Price C, Penny W, Friston K (2004b) Two distinct neural mechanisms for category-selectivity. submitted.

139. Noppeney U, Price CJ (2002a) A PET study of stimulus- and task-induced semantic processing. Neuroimage 15: 927-35.

140. Noppeney U, Price CJ (2002b) Retrieval of visual, auditory, and abstract semantics. Neuroimage 15: 917-26.

141. Noppeney U, Price CJ (2003) Functional imaging of the semantic system: Retrieval of sensory-experienced and verbally-learnt knowledge. Brain and Language.

142. Paivio A (1991) Dual coding theory:retrospect and current status. Can J Psych 45: 255-287.

143. Paus, T., Zatorre, R. J., Hofle, Z., Caramanos, J., Gotman, M., Petrides, M., and Evans, A. Time-changes in neural systems underlying attention and arousal

during the performance of an auditory vigilance task. J.Cogn Neurosci. 9, 392-408. 1997.
Ref Type: Abstract

144. Perani D, Cappa SF, Schnur T, Tettamanti M, Collina S, Rosa MM, Fazio F (1999a) The neural correlates of verb and noun processing. A PET study. Brain 122: 2337-44.

145. Perani D, Fazio F, Borghese NA, Tettamanti M, Ferrari S, Decety J, Gilardi MC (2001) Different brain correlates for watching real and virtual hand actions. Neuroimage 14: 749-58.

146. Perani D, Schnur T, Tettamanti M, Gorno-Tempini M, Cappa SF, Fazio F (1999b) Word and picture matching: a PET study of semantic category effects. Neuropsychologia 37: 293-306.

147. Petersen SE, Fox PT, Snyder AZ, Raichle ME (1990) Activation of extrastriate and frontal cortical areas by visual words and word-like stimuli. Science 249: 1041-4.

148. Phillips JA, Humphreys GW, Noppeney U, Price CJ (2002a) The neural substrates of action retrieval:
An examination of semantic and visual routes to action. Vision and Cognition.

149. Phillips JA, Noppeney U, Humphreys GW, Price CJ (2002b) Can segregation within the semantic system account for category- specific deficits? Brain 125: 2067-2080.

150. Price C, Friston K (2002a) Functional imaging studies of category specificity. In: Category Specificty in Brain and Mind (Forde EM, Humphreys GW, eds), Psychology Press.

151. Price C, Moore C, Humphreys G, Wise R (1997) Segregating semantic from phonological processing. Journal of Cognitive Neuroscience 9: 727-733.

152. Price, C., Noppeney, U., Phillips, J. A., and Devlin, J. T. How is the fusiform gyrus related to category-specificity? Cognitive Neuropsychology in press. 2003.
Ref Type: Abstract

153. Price CJ, Friston KJ (1997) Cognitive conjunction: a new approach to brain activation experiments. Neuroimage 5: 261-70.

154. Price CJ, Friston KJ (2002b) Degeneracy and cognitive anatomy. Trends Cogn Sci 6: 416-421.

155. Price CJ, Wise RJ, Frackowiak RS (1996) Demonstrating the implicit processing of visually presented words and pseudowords. Cereb Cortex 6: 62-70.

156. Price DJ, Ferrer JM, Blakemore C, Kato N (1994) Postnatal development and plasticity of corticocortical projections from area 17 to area 18 in the cat's visual cortex. J Neurosci 14: 2747-2762.

157. Rauschecker JP (1995) Compensatory plasticity and sensory substitution in the cerebral cortex. Trends Neurosci 18: 36-43.

158. Reiman E, Lane R, Van Petten C, Bandettini PA (2000) Positron Emission Tomography and Functional Magnetic Resonance Imaging. (Cacioppo J, Tassinary L, Berntson G, eds), pp 85-188. Cambridge: Cambridge University Press.

159. Rizzolatti G, Arbib MA (1998) Language within our grasp. Trends Neurosci 21: 188-94.

160. Rizzolatti G, Craighero L (2004) THE MIRROR-NEURON SYSTEM. Annu Rev Neurosci 27: 169-192.

161. Rizzolatti G, Fadiga L, Matelli M, Bettinardi V, Paulesu E, Perani D, Fazio F (1996) Localization of grasp representations in humans by PET: 1. Observation versus execution. Exp Brain Res 111: 246-52.

162. Rizzolatti G, Fogassi L, Gallese V (2002) Motor and cognitive functions of the ventral premotor cortex. Curr Opin Neurobiol 12: 149-154.

163. Rizzolatti G, Luppino G (2001) The cortical motor system. Neuron 31: 889-901.

164. Roder B, Stock O, Bien S, Neville H, Rosler F (2002) Speech processing activates visual cortex in congenitally blind humans. Eur J Neurosci 16: 930-936.

165. Roder B, Teder-Salejarvi W, Sterr A, Rosler F, Hillyard SA, Neville HJ (1999) Improved auditory spatial tuning in blind humans. Nature 400: 162-166.

166. Roskies AL, Fiez JA, Balota DA, Raichle ME, Petersen SE (2001) Task-dependent modulation of regions in the left inferior frontal cortex during semantic processing. J Cogn Neurosci 13: 829-843.

167. Ruby P, Decety J (2001) Effect of subjective perspective taking during simulation of action: a PET investigation of agency. Nat Neurosci 4: 546-550.

168. Rushworth MF, Ellison A, Walsh V (2001) Complementary localization and lateralization of orienting and motor attention. Nat Neurosci 4: 656-661.

169. Rushworth MF, Johansen-Berg H, Gobel SM, Devlin JT (2003) The left parietal and premotor cortices: motor attention and selection. Neuroimage 20 Suppl 1: S89-100.

170. Ryugo DK, Ryugo R, Globus A, Killackey HP (1975) Increased spine density in auditory cortex following visual or somatic deafferentation. Brain Res 90: 143-146.

171. Sacchett C, Humphreys GW (1992) Calling a squirrel a squirrel but a canoe a wigwam: A categry-specific deficit for artifactual objects and body parts. Cognitive Neuropsychology 5: 3-25.

172. Sadato N, Okada T, Honda M, Yonekura Y (2002) Critical period for cross-modal plasticity in blind humans: a functional MRI study. Neuroimage 16: 389-400.

173. Sadato N, Pascual-Leone A, Grafman J, Deiber MP, Ibanez V, Hallett M (1998) Neural networks for Braille reading by the blind. Brain 121 (Pt 7): 1213-1229.

174. Sadato N, Pascual-Leone A, Grafman J, Ibanez V, Deiber MP, Dold G, Hallett M (1996) Activation of the primary visual cortex by Braille reading in blind subjects. Nature 380: 526-528.

175. Saffran EM (2000) The organization of semantic memory: in support of a distributed model. Brain Lang 71: 204-12.

176. Saffran EM, Schwartz MF, Linebarger MC (1998) Semantic influences on thematic role assignment: evidence from normals and aphasics. Brain Lang 62: 255-97.

177. Sartori G, Job R, Miozzo M (1993) Category-specific naming impairments? Yes. Quarterly Journal of Experimental Psychology 46 A: 489-504.

178. Schwanenflugel PJ, Harnishfeger KK, Stowe LA (1988) Context availability and lexical decisions for abstract and concrete words. J of Memory and Language 27: 499-520.

179. Senior C, Barnes J, Giampietro V, Simmons A, Bullmore ET, Brammer M, David AS (2000) The functional neuroanatomy of implicit-motion perception or representational momentum. Curr Biol 10: 16-22.

180. Shallice T (1988) From neuropsychology to mental structure. Cambridge: Cambridge University Press.

181. Sirigu A, Duhamel JR, Poncet M (1991) The role of sensorimotor experience in object recognition. A case of multimodal agnosia [published erratum appears in Brain 1992 Apr;115(Pt 2):645]. Brain 114: 2555-73.

182. Spiridon M, Kanwisher N (2002) How distributed is visual category information in human occipito-temporal cortex? An fMRI study. Neuron 35: 1157-1165.

183. St George M, Kutas M, Martinez A, Sereno MI (1999) Semantic integration in reading: engagement of the right hemisphere during discourse processing. Brain 122: 1317-25.

184. Stowe LA, Broere CA, Paans AM, Wijers AA, Mulder G, Vaalburg W, Zwarts F (1998) Localizing components of a complex task: sentence processing and working memory. Neuroreport 9: 2995-9.

185. Stowe LA, Paans AM, Wijers AA, Zwarts F, Mulder G, Vaalburg W (1999) Sentence comprehension and word repetition: a positron emission tomography investigation. Psychophysiology 36: 786-801.

.

186. Sturm W, Willmes K (2001) On the functional neuroanatomy of intrinsic and phasic alertness. Neuroimage 14: S76-S84.

187. Talairach J, Tournoux P (1988) Co-planar stereotaxic atlas of the human brain. Stuttgart: Thieme.

188. Thompson-Schill SL, Aguirre GK, D'Esposito M, Farah MJ (1999a) A neural basis for category and modality specificity of semantic knowledge. Neuropsychologia 37: 671-6.

189. Thompson-Schill SL, D'Esposito M, Aguirre GK, Farah MJ (1997) Role of left inferior prefrontal cortex in retrieval of semantic knowledge: a reevaluation. Proc Natl Acad Sci U S A 94: 14792-7.

190. Thompson-Schill SL, D'Esposito M, Kan IP (1999b) Effects of repetition and competition on activity in left prefrontal cortex during word generation. Neuron 23: 513-22.

191. Thompson-Schill SL, Gabrieli JD (1999) Priming of visual and functional knowledge on a semantic classification task. J Exp Psychol Learn Mem Cogn 25: 41-53.

192. Tononi G, Sporns O, Edelman GM (1994) A measure for brain complexity: relating functional segregation and integration in the nervous system. Proc Natl Acad Sci U S A 91: 5033-5037.

193. Tononi G, Sporns O, Edelman GM (1999) Measures of degeneracy and redundancy in biological networks. Proc Natl Acad Sci U S A 96: 3257-3262.

194. Tranel D, Kemmerer D, Adolphs R, Damasio H, Damasio AR (2003) Neural Correlates of conceptual knowledge. Cognitive Neuropsychology 20: 409-432.

195. Tyler LK, Moss HE (2001) Towards a distributed account of conceptual knowledge. Trends Cogn Sci 5: 244-252.

196. Tyler LK, Moss HE, Durrant-Peatfield MR, Levy JP (2000) Conceptual structure and the structure of concepts: A distributed account of category-specific deficits. Brain and Language 75: 195-231.

197. Vandenberghe R, Nobre AC, Price CJ (2002) The response of left temporal cortex to sentences. J of Cogn Neursoscience 14: 550-560.

198. Vandenberghe R, Price C, Wise R, Josephs O, Frackowiak RS (1996) Functional anatomy of a common semantic system for words and pictures [see comments]. Nature 383: 254-6.

199. Warburton E, Wise RJ, Price CJ, Weiller C, Hadar U, Ramsay S, Frackowiak RS (1996) Noun and verb retrieval by normal subjects. Studies with PET. Brain 119: 159-79.

200. Warrington EK (1975) The selective impairment of semantic memory. Q J Exp Psychol 27: 635-57.

201. Warrington EK, McCarthy RA (1987) Categories of knowledge. Further fractionations and an attempted integration. Brain 110: 1273-96.

202. Warrington EK, Shallice T (1984) Category specific semantic impairments. Brain 107: 829-54.

203. Weeks R, Horwitz B, Aziz-Sultan A, Tian B, Wessinger CM, Cohen LG, Hallett M, Rauschecker JP (2000) A positron emission tomographic study of auditory localization in the congenitally blind. J Neurosci 20: 2664-2672.

204. Wiggs CL, Weisberg J, Martin A (1999) Neural correlates of semantic and episodic memory retrieval. Neuropsychologia 37: 103-18.

205. Wilkinson D, Halligan P (2004) The relevance of behavioural measures for functional-imaging studies of cognition. Nat Rev Neurosci 5: 67-73.

206. Wise RJ, Howard D, Mummery CJ, Fletcher P, Leff A, Buchel C, Scott SK (2000) Noun imageability and the temporal lobes. Neuropsychologia 38: 985-94.

11 Appendix

Example stimuli for Chapters 4 and 5

SOUND
Is it usually quiet/loud?
Bark
Bang
Siren
Whisper

VISUAL
Is it always curved?
Angle
Cone
Pyramid
Oval

Is it usually dark?
Brown
Dusk
Glow
Flash

HAND ACTION
Is it a hand action with/without a tool?
Chisel
Knit
Tapping
Tickle

MOTION
Is it a jumping movement?
Leap
Swimming
Climb
Springing

Is it a slow movement?
Tiptoeing
Dawdle
Gallop
Run

Stimuli for Chapters 4 and 8

Visual (5.8 letters per word)

silver, gray, gold
blue, indigo, maroon
burgundy, purple, orange
green, pink, red
turquoise, cream, yellow
pale, beige, violet
brown, bronze, transparent

beige, brown, pink
red, turquoise, blue
purple, yellow, orange
gray, burgundy, maroon
silver, golden, transparent
indigo, violet, green
bronze, pale, cream

angle, cylinder, column
round, pyramid, triangle
cross, ellipsoid, oval
globe, sphere, cube
dot, cone, circle
convex, crescent, hexagon
parallel, arc, curve

parallel, cube, oval
sphere, circle, pyramid
cross, cone, cylinder
ellipsoid, crescent, dot
convex, arc, angle
hexagon, triangle, round
column, curve, globe

mean KFFRQ: 38.05   NLET: 5.74   NSYL: 1.74

Sounds (5.9 letters per word)
humming, buzzing, howl
voice, chime, gong
thunder, bang, quiet
hooting, honk, song
crackle, whistle, siren
tooting, shot, pop
loud, ticking, clicking

hooting, clicking, crackle
bang, pop, whistle
chime, howl, siren
song, voice, gong
buzzing, honk, tooting
thunder, quiet, ticking
shot, loud, humming
sound, music, bark
ringing, talking, speaking

tone, melody, noise
tinkling, drumming, drone
clamour, din, clinking
murmur, shouting, bellow
whisper, chatter, blaring

music, drone, din
talking, clamour, shouting
ringing, whisper, murmur
noise, tone, sound
speaking, chatter, blaring
melody, bellow, bark
drumming, clinking, tinkling

mean KFFRQ: 35.9 NLET: 5.86 NSYL: 1.64

Hand movement (5.8 letters per word)
picking, sew, stitch
knit, draw, scrawl
scribble, write, wring
pinch, dusting, cleaning
hold, wipe, polish
squeeze, comb, brush
raking, sweep, twist

raking, sew, knit
scribble, scrawl, picking
sweep, write, draw
wipe, dusting, hold
stitch, polish, cleaning
comb, wring, twist
squeeze, pinch, brush

tickle, cut, pruning
carve, chisel, tearing
grind, crushing, screw
thrust, hammer, nailing
drilling, pierce, ripping
touch, chopping, sawing
tossing, throw, hitting

pierce, tickle, touch
tearing, ripping, grind
tossing, carve, cut
thrust, throw, chopping
crushing, screw, nailing
pruning, drilling, chisel
hammer, hitting, sawing

mean KFFRQ: 36.5 NLET: 5.86 NSYL: 1.45

Abstract words
aim, goal, cause
motive, intent, attempt
skilled, adept, clever
smart, shrewd, dextrous
mistake, flaw, defect

wicked, evil, wrong
venture, trial, target

adept, clever, smart
skilled, dextrous, shrewd
cause, aim, intent
goal, target, motive
attempt, venture, sin
wrong, defect, trial
flaw, mistake, evil

deceit, swindle, fake
counterfeit, embezzlement, fraud
glory, victory, triumph
renown, fame, success
esteem, respect, smug
conceit, arrogance, pride
impact, influence, haughty

swindle, counterfeit, fake
embezzlement, deceit, fraud
glory, fame, respect
esteem, renown, arrogance
smug, conceit, influence
pride, haughty, triumph
success, victory, impact

mean KFFRQ: 35.9 NLET: 6.17   NSYL: 1.79

Example stimuli for Chapter 6

Action conditions: Underlined words refer to objects that perform similar actions
Tools: <u>sword dagger</u> spoon <u>calculator typewriter</u> pump mug <u>drill screwdriver</u>
Animals: <u>lobster spider</u> dragonfly <u>goat wolf</u> starfish <u>mosquito pigeon</u>

Real Life Size conditions: Underlined words refer to objects that are of similar size
Tools: <u>pencil nail file</u> rake <u>bucket basket</u> screw <u>safety pin pencil sharpener</u>
Animals: <u>toad hamster</u> wasp <u>rhinoceros hippopotamus</u> mosquito <u>frog sparrow</u>

Example stimuli for Chapter 7

apricot
garlic
mango
parsley
banana
squash