The Cognitive and Neural Architecture of Semantic Cognition: Evidence for Dissociable Distributed Systems from Multiple Methods.

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Doctor of Philosophy (PhD)

University of York,

Psychology

January 2015

Abstract

This thesis aimed to dissociate temporoparietal contributions to semantic cognition and investigate the wider semantic control network using behavioural experiments, fMRI, and TMS. Chapter 2 investigated patients with semantic aphasia (SA) and healthy participants under conditions of divided attention and found that the selection of associative knowledge, specifically for weaker associations is reliant on semantic control processes. Chapter 3 utilised TMS to dissociate two sites in the temporoparietal region implicated in semantic cognition (posterior middle temporal gyrus, pMTG; and angular gyrus, AG), which are co-activated in semantic contrasts and often damaged together in SA. pMTG was involved in semantic control whereas the response in AG suggests that it is involved in reflexive orientation to semantic concepts. Chapter 4 examined whether the network involved in the control of semantic information overlapped with the network involved in action selection, as both semantic selection and action selection activate overlapping regions demonstrated by previous fMRI studies. Significant overlap was observed between semantic control and action selection in the left inferior frontal gyrus (LIFG) and pMTG suggesting that flexibility in semantic retrieval and action selection rely on partially overlapping architecture. In Chapter 5 we extended previous work demonstrating an involvement of different parts of LIFG in different aspects of semantic control. Dorsal LIFG showed engagement in goal-driven selection while anterior ventral LIFG showed a response compatible with flexible content-driven retrieval. This distinction extended to posterior temporal cortex with pMTG recruitment only observed for context-driven retrieval demands and ITC involvement in goal-driven semantics. The findings of this thesis further elucidate the role of distinct regions within temporoparietal cortex in semantic cognition and the apparent overlap between semantic control and event/action understanding.

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Acknowledgements

The work in this thesis could have not been completed without my supervisor Beth Jefferies. She was always reassuring and collected, providing excellent advice and guidance even after many confused emails and conversations. I would not be the scientist I am today we it not for her support, leadership, and ensuring that we covered all possible bases and interpretations during the course of my research. I would also like to extend my thanks to Silvia Gennari and Shirley-Ann Rueschemeyer for being members of my thesis advisory panel. I always felt nervous before meetings but they were a great opportunity for personal growth and feedback, and I'm glad to have had your knowledge and advice during the course of my PhD.

The work presented here in this thesis could not have been complete without the help of Katya Krieger-Redwood, who trained me to use TMS and helped me to find my feet in the early days of my PhD, and also for being my friendly face during talks/presentations. I would like to thank all the members of Semantics lab over the course of my PhD. They were always a good source of advice and were always willing to rate and test stimuli, alongside listen to talks and presentations in a friendly setting. I wish them all the best in their future research and careers.

The research contained within this thesis could not have been complete without the numerous people who helped collect data, design tasks, and pilot the stimuli. Those individuals helped to lift great weights off my shoulders and allow me to focus my efforts towards more pressing matters!

A special mention goes to my wife Kirsty Davey, who was always there to provide encouragement and a motivating kick whenever I felt overwhelmed. I would also like to thank my friends and family for providing that little escape from academia, and for always being up for a pint.

Finally I would like to express my sincere gratitude to the participants, patients, and their carers. Without their contributions none of this research could have been conducted.

Declaration

I hereby declare that the work presented in this thesis has been completed by the candidate under the supervision of Professor Elizabeth Jefferies. The candidate was supported by departmental teaching scholarship awarded to the candidate from the Psychology department of the University of York. Additional financial support was obtained from the Stroke Association (Chapter 2), the European Research Council (ERC; Chapter 2, 3, 4), and the Biotechnology and Biological Sciences Research Council (BBSRC; Chapter 3 and 4), awarded to Professor Elizabeth Jefferies.

Part of the work contained in this thesis has been presented at the following conferences:

Chapter 4; Davey, J., Rueschemeyer, S., Costigan, A., Murphy, N., Krieger-Redwood, K., Hallam, G. & Jefferies, E. (2014) Shared neural processes support semantic control and action understanding. Poster presented at the British Neuropsychological Society (BNS) spring meeting, Clinical Neurosciences Centre, London.

Chapter 4; Davey, J., Rueschemeyer, S., Costigan, A., Murphy, N., Krieger-Redwood, K., Hallam, G., & Jefferies, E. (2014) Shared neural processes support semantic control and action understanding. Poster presented at Neurobiology of Language Annual Meeting, Amsterdam.

Part of the work contained in this thesis has been submitted for publication:

Chapter 3; Davey, J., Cornelissen, P. L., Thompson, H. E., Sonkusare, S., Hallam, G., Smallwood, J. Jefferies, E. (Submitted). Shaping and orientating to semantic space, TMS reveals distinct contributions of posterior middle temporal gyrus and angular gyrus.

Part of the work contained in this thesis has been accepted for publication:

Chapter 4; Davey, J., Rueschemeyer, S., Costigan, A., Murphy, N., Krieger-redwood, K., Hallam, G., & Jefferies, E. (2015). Shared neural processes support semantic control and action understanding. *Brain and Language*, *142*, 24–35.

Parts of this thesis were conducted in collaboration with others:

Chapter 2; the dual task study in Chapter 2 was conducted in collaboration with third year BSc students, as part of their empirical project; Rebecca Kosinski, Sarah Howkins, Emma Wooffindin, and Rebecca Gabbitas. The students helped design the tasks, selected suitable stimuli from an existing experimental task, collected data, and helped in processing the behavioural data collected from healthy undergraduate participants under my supervision. Dr. Glyn Hallam and Dr. Hannah Thompson provided data the data from the stroke patients, with Dominic Arnold and Emily Ball collecting data from the healthy control sample.

Chapter 3; the research in Chapter 3 was partially conducted in as an MSc in Cognitive Neuroscience dissertation project, and the students (Saurabh Sonkusare and Nafeesa Yaqoob) helped design the experimental tasks, observed TMS data collection and helped to pre-process the behavioural data under my supervision. Dr. Hannah Thompson and Dr. Katya Krieger-Redwood aided in the stimulation of TMS to participants, with Professor Piers Cornelissen contributing to the analysis of the project using hierarchical linear modelling. Resting state connectivity data was provided by Dr. Jonathan Smallwood, and the connectivity map was produced by Dr. Glyn Hallam. The thesis Chapter is the same as the manuscript of the paper described above.

Chapter 4; the research in Chapter 4 was conducted as an MSc in Cognitive Neuroscience dissertation project co-supervised by Professor Elizabeth Jefferies and Dr. Shirley-Ann Rüeschemeyer. The students (Alison Costigan, Nikolas Murphy, Pavel Gololev, and Yannan Liu) helped design the experimental tasks, oversaw fMRI data collection, and helped to pre-process the behavioural fMRI data under my supervision. The thesis Chapter is the same as the manuscript of the paper described above.

Chapter 5; The research in Chapter 5 was aided by Dr. Hannah Thompson who helped design the experiment task, pilot the stimuli, and aided in fMRI data collection and pre-processing.

Chapter 1 - Thesis introduction and review of the literature

Semantic cognition and its controversies

Semantic cognition describes the control processes and stored representations which allow us to understand the meanings of words, identify and correctly use objects, remember the identities of people, and recall facts (Jefferies and Lambon Ralph, 2006; Patterson et al., 2007). It allows us to be flexible in our responses and retrieve task-relevant knowledge appropriate to our goals or the current environment (Noonan et al., 2010). It can be further broken down into several different independent components: First, widely distributed modality specific sensory/motor areas (referred to as spokes), involved in the processing of particular aspects of objects and events, play a critical role in our understanding of verbal and non-verbal material (Sim and Kiefer, 2005; Pobric et al., 2010; Chouinard and Goodale, 2012). Secondly, these modality-specific aspects of knowledge are thought to be combined in one or more ‘hubs’ in heteromodal cortex (Binder et al., 2009; Binder and Desai, 2011). These brain regions may play a key role in binding together the different aspects of our knowledge of objects and events, allowing for deep conceptual similarities to emerge and preventing conceptual similarities to be driven by a single input/output modality. Finally, this relatively stable store of multimodal conceptual knowledge may not be sufficient to permit successful semantic cognition, at least under some circumstances, because automatic spreading activation between related concepts would be expected to activate the most dominant features and associations, and these may not be relevant to ongoing goals or the task (Poldrack et al., 1999; Devlin et al., 2003; Whitney et al., 2012). Under these circumstances, top-down control processes are thought to shape the way in which activation flows through the semantic system, increasing the activation of task-relevant information and supressing irrelevant information. For example, to retrieve knowledge about how to move a piano, semantic control processes might be involved in selecting relevant features, such that it has wheels and that it is heavy, rather than the precise mechanical hand movements required to play the instrument which are irrelevant in this context (Saffran, 2000).

Despite these advances in understanding the mechanisms that support conceptual processing, numerous controversies remain. First while the roles of some brain regions are relatively well supported in the automatic and controlled semantic retrieval networks, the contributions of sites such as the posterior middle temporal gyrus (pMTG) and Angular gyrus (AG) in the temporoparietal cortex are still controversial and highly debated in the literature. Some research has implicated the AG in the automatic retrieval of semantic features (Binder et al., 2009) and the pMTG in the controlled retrieval of semantic information (Noonan et al., 2013). Another argument is whether the mechanisms which allow us to (i) retrieve associations between objects – for example, that 'helmet' goes with 'racing car' because these objects are used together, and (ii) identify objects – for example, knowing that an aerodynamic vehicle with four wheels and a powerful engine is a racing car are separate. Some researchers have argued that these different aspects of semantic knowledge draw on different hub mechanisms, which separately capture the multimodal physical features of objects and their associations (Schwartz et al., 2011; Kalénine et al., 2012; Mirman and Graziano, 2012a; de Zubicaray et al., 2013). Alternatively, the features that predict object identity do not vary substantially across time and context, while associations in different contexts can be highly variable. It is possible that retrieving knowledge about associations draws on executive control processes to a greater degree than retrieving knowledge about identity under some circumstances, and whether different networks are recruited depending on the current demands of the semantic task. Previous fMRI studies have suggested that feature selection, specified by task instructions executive and controlled retrieval can be separated (Badre et al., 2005); however this was not explored within the context of the wider semantic control network. These issues were explored in a number of studies contained in this thesis; firstly we examined patients with semantic aphasia/mild semantic impairment, who have deregulated semantic processing associated with executive deficits, and in healthy participants under conditions of divided attention (Chapter 2) for decisions taxing association and identity knowledge. We also specifically examined the roles of the AG and pMTG using inhibitory transcranial magnetic stimulation (TMS; Chapter 3) using the same tasks in Chapter 2. Finally we examined the possibility of separable components of semantic control and the possibility that they can be separated in the wider semantic control network in Chapter 5, comparing tasks which require executive or context based aspects of semantic control.

A second controversy surrounds the potential overlap between event/action semantics and semantic control, that processing non-dominant associations requires greater executive control of attention within the semantic system, and that the brain areas that contribute to this process overlap with those that are linked to event and action knowledge. Comparisons between previous studies investigating event (Kim, 2011) and action (Kellenbach et al., 2003; Noppeney et al., 2006; Liljeström et al., 2008; Noppeney, 2008) semantics produce networks similar to the one implicated in semantic control (Noonan et al., 2013). However event/action semantics and semantic control have not been directly contrasted within a single experimental paradigm. This led to the second research question, which asks whether the neural mechanisms that underpin the selection of contextually relevant semantic information overlap with mechanisms that are important for understanding events and actions, since events/actions are inherently flexible and can only be understood in relation to the context in which they are produced. To answer this we examined the performance of semantic aphasia (SA patients in Chapter 2, who have damage to some of the regions implicated in both action/event semantics and semantic control networks, on easy and harder tasks which involve identity and association matching. We also examined healthy participants under high cognitive load (Chapter 2) and following TMS (Chapter 3) in retrieving different semantic associations, which have been implicated to activate these overlapping networks. Direct contrasts between event/action knowledge and semantic control was performed in Chapters 4 and 5 using fMRI; in Chapter 4 we used experimental tasks which involved attending to visual or action features depending on the task instructions providing a direct contrast between event/action knowledge and semantic control. This was expanded in Chapter 5 where we investigated the overlap of the different networks implicated in goal-driven and context-driven semantic selection, examining how the brain areas implicated in event/action knowledge compare with the networks for goal-driven and context-driven semantic selection.

Outline

This literature review is divided into two main sections. The opening section, is concerned with how are concepts represented, and will cover different models of semantic cognition/representation before moving onto how different sensory and motor areas are recruited depending on semantic category, examining the contributions of different regions in identity judgements and in identifying semantic associations between items of same and different categories. Evidence supporting the role of the anterior temporal lobe (ATL) as a key storage component for both semantic associations and identity will be discussed, followed by evidence of a distributed semantic selection network explaining why automatic spreading activation is not enough to generate semantic associations. The discussion will turn to competing alternatives of semantic representation which suggests that there are two subsystems; one for association knowledge and one for identity, each of which is supported by an independent hub.

The second section addresses the issue of how retrieval is shaped by task demand. It will examine how the recruitment of the spokes and possibly hubs is affected by task demands, looking at the regions involved in semantic control alongside the evidence for a distributed semantic control network. The existing body of work has focused primarily on motor features which are important for language tasks in certain contexts. This notion will be linked to semantic control, examining the relationship between these functional networks and their possible involvement in flexible semantics.

How are concepts represented?

Models of semantic cognition/representation

There are many models attempting to explain the complex field of semantic representation. These have been represented on a continuum by Meteyard et al. (2012b), and placed depending on their degree of embodiment referring to their level of integration with sensory-motor systems. The continuum ranges from unembodied, secondary embodiment, weak embodiment, and strong embodiment. Across all theories there is a broad agreement on 'convergence' zones in semantic representation; however they differ in how they define both their locations and modal natures. One thing is certain is that semantic cognition/representation is not an unembodied process due to the interactions between language and sensory motor processes (Hauk and Pulvermüller, 2004; Carota et al., 2012), however the semantic network cannot consist of purely primary sensory/motor regions as some degree of abstraction from these regions is required in order to facilitate conceptual representation (Meteyard et al., 2012b). This section will consider how concepts are represented, and which brain areas are involved in representing different types of semantic feature (e.g., visual vs. action) and different types of concepts (tools vs. animals), since in the thesis we consider how conceptual processing is gated by task demands, such as the requirement to pay attention to a specific feature.

Pulvermüller (2005) suggests that information flow between the systems responsible for language and action underpins semantic representation. Action words are defined by abstract semantic links, between the language and motor regions. This is because in infancy action words are learned alongside action performance (Pulvermüller, 2005), thus in the cortex the motor and neural representation occur at the same time, leading to stronger synaptic links between the language and motor areas. This leads on to a prediction that the perception of action/motor words will activate the regions involved in action control/execution of that particular body part. Imaging studies have found support for this prediction, demonstrating cortical overlap between the areas involved in producing movements and the comprehension of action words (Hauk and Pulvermüller, 2004). These areas are also activated during early action word comprehension;

Hauk and Pulvermüller (2004) found evoked responses with a latency of 210-230 milliseconds, reflecting early semantic access/processes, in an ERP study involving reading of limb related words (arm, leg, face). According to Pulvermüller, words describing actions automatically activate the system for action processing and this activation is a reflection of the understanding of that concept.

On the other hand Patterson, Nestor and Rogers (2007) suggest that while the same regions involved in action and perception are involved in semantics, this explanation is not sufficient to fully explain semantic memory as such a system would be incapable of generating higher-order generalisations, if the system only consisted of the modality-specific content of objects and the links between them (Patterson et al., 2007). They suggest that the semantic network is distributed throughout the cortex but in addition, there is an amodal hub, allowing the system to generalise across concepts with similar features overall but which differ in specific attributes (Hodges and Patterson, 2007). Direct neuroanatomical pathways connect the sensory, motor and language regions, but the 'hub' in the anterior temporal lobe (ATL) supports the activation of representations in all modalities and categories.

A direct prediction of this model is that damage to the hub should result in semantic impairments independent of the type of semantic information to be retrieved. This pattern matches the impairments in semantic dementia (SD) patients who are impaired across semantic tasks tapping the full range of input and output modalities (Bozeat et al., 2000; Patterson et al., 2007; Corbett et al., 2009b), and have focal damage to the ATL. The model is also supported by transcranial magnetic stimulation (TMS) studies; Pobric et al. (2010) found inhibitory TMS stimulation to ATL produced a category general deficit, whereas stimulation to one of the spokes in the network (inferior parietal lobule [IPL]) resulted in a category specific defect specifically for concepts regarding praxis information, in line with the hub and spoke model. The elegance of this model is that it explains how we are able to create higher order generalisations linking information from different modalities and to differentiate between conceptually similar items that differ greatly in their modality specific knowledge.

It is worth noting here that in the latest version of Pulvermüller's theory (Pulvermüller, 2013), Hebbian learning between sensory and motor regions still underpins single item comprehension, however five hub like zones are responsible for drawing information together across modalities. The description of these hub zones primarily focusses on their contribution to the relay of information across modalities when there is no evidence of direct connections. Thus, influential theories of semantic representation convergently suggest both multimodal and unimodal regions play a crucial role in semantic representation, but the division of labour between these systems is not well-understood.

Semantic knowledge can be divided among a number of different dimensions, one such dimension is the difference between taxonomic/identity representations and thematic/association knowledge (Schwartz et al., 2011; de Zubicaray et al., 2013). A third model of semantic representation suggests that there are two separate hubs (Schwartz et al., 2011), with the ATL regions supporting taxonomic associations, and the AG supporting thematic associations. This model explains the impairments of semantic aphasia patients who due to damage to the frontotemporal regions (excluding ATL) have specific impairments for thematic decisions, suggesting the existence of two hub regions, yet however this explanation does not explain the deficits of SD patients.

In the sections below, we consider how these aspects of semantic representation contribute to our knowledge of objects from different categories, and to tasks with different instructions or top-down goals. Following this the discussion will move on to discuss the evidence for specific hub regions, and whether there are multiple hubs or a single amodal semantic hub.

Different recruitment of sensory and motor regions according to semantic category

Different semantic categories activate different regions of the cortex depending on the features which are more prominent to their identification. For example visual features are more important for correct animal identification whereas tools are identified according to their specific motor features (Chouinard and Goodale, 2010). In the following section evidence will be presented supporting the notion that different brain regions support different semantic categories.

Manipulations of modality: The contribution of sensory and motor features

While semantic concepts are amodal, they are constructed through the interaction of modality specific features. For example using a fork requires visual identification of the object, and matching the hand to its volumetric properties, followed by retrieving the action properties behind the object (Mahon et al., 2010). Different manipulations of modality reveal the contributions of modality specific/preferential regions and how they represent information in their preferential modality to support amodal semantic representation. fMRI has revealed adaptation effects for words denoting different artefacts and objects which share overlapping manipulation (IPS and left precentral gyrus), function(left precentral, IPS, and pMTG), and shape (left precentral and IPS) (Yee et al., 2010). Research has also revealed that tool preference in IPL, IPS and posterior superior parietal lobule (pSPL) develops independent of visual experience and respond to tool size judgements in sighted and congenitally-blind participants (Mahon et al., 2010) suggesting that tool responses in this region are not reliant on visual input.

These findings demonstrate that information in one modality (e.g. vision) is capable of activating information in a different modality (motion/praxis) supporting the formulation of amodal semantic representations across distributed modality specific/preferential brain regions, consistent with the predictions of the hub and spoke model surrounding the multimodal nature of category preferential brain regions supporting semantic representation.

Manipulations of semantic category

Different semantic categories are dependent on different sets of features for their correct identification and information retrieval; for example identification of animals is reliant on their perceptual processes and emotional content whereas for tools, correct identification is reliant on other factors such as function (Chouinard and Goodale, 2012). This implies that different semantic categories will activate different networks of brain regions. Positron emission tomography (PET) has revealed different contributions for animals and tools, with animal words activating the left superior temporal sulcus and the left precuneus/lingual gyrus, whereas artefact words activated the left posterior middle temporal gyrus (pMTG; Devlin et al., 2002). Later work using fMRI has revealed animal naming to activate left prefrontal cortex, left anterior cingulate and visual regions in the occipital lobes, whereas naming tools exhibited greater activation in the left MTG, bilateral medial fusiform, left motor areas and the left anterior parietal lobe (Chouinard and Goodale, 2010).

Differences in functional connectivity have also been measured using fMRI during the generation of animal and tool names. Generating tool names was associated with an increase in connectivity within the left hemisphere, in the inferior prefrontal and premotor cortex, IPL and the temporo-occipital junction. Animal naming on the other hand caused a greater degree of coupling between the left visual association regions such as the left lateral/medial fusiform gyrus and superior/inferior occipital gyrus (Vitali et al., 2005), demonstrating different connectivity and network recruitment depending on category retrieval. Adaptation studies have also demonstrated differences between animals and tools with the right frontal operculum (Known to be involved in processing emotional content, Chouinard and Goodale, 2012) demonstrating adaptation for animals, and IPL (reflecting the three dimentional structure of the object during grasping, Chouinard and Goodale, 2012) involvement for tools.

Focusing specifically on tools, multi-voxel pattern analyses have revealed overlapping responses in the lateral occipitotemporal cortex for hands and tools when contrasted to other visual stimuli (Bracci et al., 2012). TMS, capable of demonstrating functional relationships between a brain region and task performance (Watkins and Devlin, 2008) has been used to demonstrate picture naming performance for tools following stimulation to the IPL (Pobric et al., 2010; Ishibashi et al., 2011b) supporting previous fMRI results into tool knowledge.

This collection of studies demonstrate that semantic processing can be specifically focused on specific modalities and categories via task instructions, resulting in different contributions of brain regions supporting that semantic category, however it is still unclear how this process occurs. This is one facet of semantic control i.e. one situation in which automatic spreading activation throughout the semantic system might not be sufficient for success, with control aspects guiding the activation of task relevant areas depending on the current task context.

Manipulations of both semantic category and modality

Pulvermüller (2013) suggested that there are modality invariant semantic hubs supported by modality specific/preferential areas used in the representation of modality specific information for a given concept. Adaptation studies have revealed that the left superior temporal gyrus responds to both tool sounds and animal vocalisations, while the pMTG demonstrates adaptation effects for tool sounds only (Doehrmann and Naumer, 2008), consistent with Pulvermüller's (2013) interpretation. Similar effects to Doehrmann and Naumer (2008) have been observed using word-picture matching for visually presented animals and tools. Both animals and tools activated the ventral occipito-temporal cortex but they activated different regions; animals activated lateral areas whereas tools activated areas more medial visual areas (Zannino et al., 2010).

Words representing objects are associated with different degrees and types of manipulability; some objects must be picked up to be used (functional e.g. cup) whereas others are picked up to be moved but it is not dependent on their use (volumetric e.g. clock). Words denoting functionally manipulable objects elicited greater activation in sensory motor regions such as the ventral premotor cortex (vPMC). This suggests that specific action information for an object is represented neutrally and that specifically how an object can be used rather than its function drives the representations of objects in these regions (Rueschemeyer et al., 2010).

Manipulations of both semantic category and modality suggest that alongside modality invariant areas, modality *and* category specific areas represent a narrow set of features for that category/concept. It also suggests that concept specific information is stored in these modality specific regions, consistent with a distributed set of regions supporting semantic representation, storing information consistent with that areas specific modality preference.

Recruitment of sensory motor regions for semantic cognition - Interim summary

The body of material above demonstrates that different regions of the cortex are recruited for different categories and features, with some regions demonstrating category and/or modality specificity. This pattern is consistent with both the approaches of Pulvermüller (Pulvermüller, 2005; Pulvermüller, 2013) and the hub and spoke model (Patterson et al., 2007), with large networks of brain regions involved in representing category or modality specific information. However what is unclear is whether there are multiple hubs for drawing together information for different categories of modalities, or whether these functions are sub served by a single amodal semantic hub. Damage to one of these multiple hubs would result in a category/modality specific impairment for a concept or feature represented in that region; whereas damage to a single hub would disrupt performance for all categories and modalities, as the links across these different features would be lost.

The work in this section directly relates to the roles of the AG and pMTG in semantic cognition as they have been implicated as a potential hub for the storage of associative knowledge (Schwartz et al., 2011), but also in other aspects of semantic cognition (Binder et al., 2009; Noonan et al., 2013). This directly relates to the research in Chapter 3, where we will use TMS to dissociate the contributions of AG and pMTG, and also to Chapter 2 where we will examine both associative and identity judgements in a sample of patients who have damage to regions implicated in associative knowledge. The evidence presented here proposes that pMTG is a tool selective ‘spoke’, and we will compare its responses and other tool specific regions, whilst manipulating semantic control in Chapter 4 to determine the degree of overlap between these networks. This section also highlights possible category specific responses between animals and tools in Chapter 5, but also whether responses in pMTG are tool specific or dependent on the control demands of the task irrespective of semantic category.

In the next section evidence will be presented for an amodal hub. We will first discuss semantic dementia (SD) patients who suffer from a progressive loss of stored semantic knowledge, alongside research which proposes that there are two separate hubs representing the distinction between taxonomic and thematic knowledge observed in SA patients.

Evidence for the ATL as a single amodal semantic hub

Semantic dementia is a form of frontotemporal dementia (Hodges et al., 1999; Mummery et al., 2000; Hodges and Patterson, 2007) causing a progressive loss of stored semantic knowledge (Snowden et al., 1989; Hodges et al., 1999; Mummery et al., 2000; Hodges and Patterson, 2007). The atrophy in this condition is the most extensive in the anterior temporal (ATL) regions of the brain (Snowden et al., 1989; Mummery et al., 2000; Rogers et al., 2006; Davies et al., 2009). This condition causes a multimodal semantic impairment that affects all features (e.g. sounds, actions, visual recognition) and all tasks, characterised by a reduction in expressive vocabulary, deterioration of receptive vocabulary, anomia, and deficits in person knowledge (Hodges and Patterson, 2007). These patients score poorly on simple naming tasks demonstrating a characteristic decrease in performance as the disease progresses (Patterson et al., 2006). Initially patients demonstrate a specific pattern of impairment failing to recognise atypical items which do not share many corresponding features characteristic of other exemplars in that category (Jefferies et al., 2010) (for example failing to recognise that a Penguin is a bird as it does not fly) as well as producing regularisation errors for atypical items (Patterson et al., 2006). A characteristic impairment in SD is the presentation of specificity effects (Hodges et al., 1995) whereby items are reproduced at the domain-general level rather than producing their specific level term (e.g. calling a ‘swan’ a ‘bird’). This demonstrates that SD patients initially retain the shared features between exemplars of a category but lose the ability to specifically name examples. This specificity impairment is consistent across many other tasks; patients will consistently demonstrate a naming deficit for an item irrespective of the nature of the task and across different modalities (Bozeat et al., 2000; Jefferies and Lambon Ralph, 2006), suggesting a degradation of stored amodal concepts is present in SD.

The deficit in SD is not just limited to the verbal domain with patients demonstrating impairments in non-verbal comprehension (Bozeat et al., 2000) and in naturalistic tool use

(Corbett et al., 2009b). SD patients demonstrate impairments on both verbal (semantic association tasks) and non-verbal semantic tasks (sound recognition), again demonstrating item consistency across modalities and performance graded by concept and sound familiarity (Bozeat et al., 2000). Similar findings have been observed for tool use; SD patient performance is strongly correlated with item familiarity with response omissions more likely when compared to SA patients (Corbett et al., 2009b) .

As a whole the body of evidence on SD highly implicates that there is an amodal semantic store supporting semantic representation across different modalities, allowing us to form links between different items to shape semantic categories (Patterson et al., 2007). The ATL is the most likely candidate for this ‘hub’ as atrophy is greatest in this region, however as SD is a progressive dementia, atrophy spreads to other regions in the frontotemporal area. Neuroimaging studies have the potential to localise and investigate the role of the ATL in semantic representation. However the notion of the ATL in semantic representation has proven to be controversial as it is often omitted from reviews and theories due to its proximity to air-bone interfaces and susceptibility to magnetic inhomogeneity in standard fMRI paradigms, creating signal-drop out in the ATL (Visser et al., 2010c; Visser et al., 2010a).

Early studies investigating semantic representation in healthy populations used positron emission tomography (PET) and found ATL involvement across a variety of semantic tasks when compared to non–semantic tasks (Vandenberghe et al., 1996; Noppeney and Price, 2002). ATL activation has also been observed when contrasting unintelligible verses against intelligible speech (Scott et al., 2000) suggesting that the ATL region projects to higher-order association areas which contain semantic information consistent with it being a hub for semantic representations.

PET has largely been substituted by fMRI with semantic cognition studies using fMRI failing to implicate the ATL in semantic memory (Visser et al., 2010c; Visser et al., 2010a). A meta-analysis of the literature found four factors which affected the likelihood of observing ATL activation; the use of PET versus fMRI, as PET is not susceptible to distortion artefacts near the temporal poles caused by inhomogeneity in the magnetic field (Visser et al., 2010c), ensuring whole brain coverage, use of a baseline task to prevent subtraction of semantic activation, and finally the inclusion of ATL as a ROI (Visser et al., 2010a). It is possible to use fMRI and observe activation in the ATL if distortion correction is implemented; Visser et al. (2010c) used a gradient reversal technique to correct for the magnetic field inhomogeneity and utilising the same semantic tasks employed in Devlin et al. (2002), they demonstrated significant ATL activation for semantic memory. Similar findings were observed for both verbal and non-verbal semantic tasks (pictures and words) further demonstrating ATL involvement in multimodal semantic processing (Visser et al., 2012b).

Converging evidence has also been demonstrated using TMS to stimulate the ATL. Using TMS it is possible to selectively disrupt picture naming performance for animals and tools. Stimulation to the ATL caused a category general semantic deficit (Pobric et al., 2010). Looking specifically at tool judgements ATL stimulation disrupted tool function judgements whereas IPL stimulation specifically disrupted tool manipulation judgements (Ishibashi et al., 2011b), consistent with the hub and spoke model and the role of the ATL in semantic cognition.

ATL as a single amodal hub - Interim summary

The role of the ATL in automatic semantic representation is controversial. The review of Martin (2007) suggests that the posterior temporal lobe is the critical site for stored semantic representations for concrete objects, not the ATL based on a review of the neuroimaging literature, and looking at the projections between left inferior frontal gyrus (LIFG) a site implicated in control and the posterior temporal lobe consistent with its involvement in selection (Martin, 2007). Atrophy in SD is not localised to the ATL regions and is observed throughout the temporal lobe (Mummery et al., 2000) weakening the proposed critical role of the ATL. Patients can also present with multimodal semantic deficits but have no ATL lesions such as semantic aphasia (SA) patients (Jefferies and Lambon Ralph, 2006; Jefferies et al., 2008), suggesting that the key site for semantics might not be the ATL. However aphasiology work with stroke patients suggests that their deficit is not one of representation but of control which accounts for their particular pattern of semantic impairment, alongside distortion corrected fMRI and TMS evidence supporting the conclusions for the role of ATL in semantic representation.

The research in this section relates to the work in Chapter 2, as our sample of patients have an intact ATL, and should demonstrate a minimal impairment to judgements which can be resolved by automatic semantic activation when compared to harder tasks requiring greater degrees of semantic control (Jefferies and Lambon Ralph, 2006; Jefferies et al., 2010). The ATL was also included as a stimulation site to the TMS experiment in Chapter 3 and should disrupt automatic semantic retrieval irrespective of semantic category or judgement.

The two hubs hypothesis

The difference between SD and SA has been interpreted in two different ways; representation vs. control of retrieval, or a loss of different identity and association hubs. Picture naming studies have implicated damage to the ATL in the production of category errors whereas damage to the temporoparietal junction (TPJ) causes association/thematic errors (Schwartz et al., 2011; Mirman and Graziano, 2012b). Other SA naming studies have demonstrated that SA patients produce a greater proportion of associative errors (Jefferies et al., 2010), for example producing “nuts” when presented with the task of naming a Squirrel. These patterns of impairment have been interpreted in different ways; Schwartz et al. (2011) suggests that this pattern is due to damage to the associative hub with an intact identity hub, but the same pattern of impairment is interpreted as a loss of semantic control by Jefferies and Lambon Ralph (2006). It is worth noting that SD patients are impaired on both identity and association tasks as are SA patients, however it is possible that the balance of these problems might be different in these conditions but again, it can be explained in one of two ways. This account is highly controversial and inconsistent with current accounts of SD (Jefferies and Lambon Ralph, 2006; Jefferies et al., 2010; Jefferies, 2013).

The vast body of neuroimaging studies suggest that there is a common network for association (thematic) and identity (taxonomic) matching with only very subtle differences between them. fMRI studies have revealed that thematic and taxonomic decisions activate common regions; left inferior frontal, middle temporal and occipital lobes (Sachs et al., 2008a). Differences between taxonomic and thematic judgements have been observed in priming studies with taxonomic priming effects observed in the right precuneus, right post central gyrus, middle frontal and superior frontal gyri, and thematic priming observed in the right middle frontal gyrus and anterior cingulate (Sachs et al., 2008b). Other fMRI studies have also demonstrated differences during audio-to-visual semantic priming with thematically related words with left lateralised temporal activation (STS), and taxonomic related words activating right frontal and hippocampal regions (Sass et al., 2009b).

The literature covered so far suggests that there are shared and distinct regions involved in the processing of thematic and taxonomic associations however are these associations inherent in the representation of different semantic categories? Behavioural results suggest that taxonomic associations are identified faster for natural objects whereas thematic associations are identified faster for manipulable objects (Kalénine et al., 2009). Differences were also revealed with fMRI; taxonomic relations activated bilateral visual areas for natural objects, with thematic associations activating IPL and pMTG for manipulable objects (Kalénine et al., 2009), consistent with previous work looking at category differences.

One of the likely candidates for the second thematic hub is the AG, as it is a part of the temporoparietal junction and is damaged in patients who display an impairment when performing taxonomic judgements (Schwartz et al., 2011), and is specifically activated for thematic relations compared to the pMTG, which is activated for both taxonomic and thematic relationships (de Zubicaray et al., 2013). The two hubs hypothesis proposes that categorical relationships are stored in the ATL, and thematic relationships are stored in the AG. These two different amodal hubs fit well with the impairments in SD patients who display a greater proportion of categorical errors compared to thematic ones (Jefferies and Lambon Ralph, 2006), and also with SA patients who can present with only temporoparietal damage along with other patients who suffer from damage to the TPJ producing more thematic than categorical errors (Jefferies and Lambon Ralph, 2006; Schwartz et al., 2011) consistent with a second hub in the AG. This pattern also supports ventral AG activation in response to semantic tasks (Binder, et al., 2009; Seghier et al., 2010; Noonan et al., 2013). However the role of the AG is still unclear as areas display deactivation in response to semantic demands when no task is present (Binder et al., 2008) and it has been implicated in the DMN (Seghier et al., 2010; Wirth et al., 2011), suggesting the possibility of a graded specialisation for semantics within AG.

The two hubs hypothesis - Interim summary

The two hubs idea is based on the knowledge that events, verbs, and actions activate overlapping regions, with a different set of regions activated for knowledge of objects, nouns, and visual features. Under this view the ATL is the end of the ventral visual stream for object identity, with the temporoparietal/AG hub linked to the dorsal route due to its role in concept integration (Hickok and Poeppel, 2004). While this model attempts to explain the associative deficits observed in SA it fails to explain the identity effects observed in this population, and how SD patients are observed for both types of knowledge, with damage to only the hypothesised identity/taxonomic hub. This model suggests that it would be possible to dissociate these aspects of semantic representation within a single paradigm; this is what is explicitly tested in Chapters 2 and 3. In Chapter 2 we investigated decisions which weigh heavily on semantic control and representation in both semantically impaired patients and healthy participants under dual-task conditions to determine which interpretation best explains the deficits in this population. Furthermore in Chapter 3 we used TMS to stimulate both AG and pMTG, two sites in the temporoparietal cortex which are co-activated in semantic contrasts but cannot be dissociated in patients due to the perfuse damage to this region, to determine whether one of these sites demonstrates evidence of a second semantic hub, and to pull apart their individual contributions to semantic cognition within a single paradigm.

How is retrieval shaped by task demand?

Automatic spreading activation is not sufficient for successful semantic cognition under some circumstances, for example when the relationship relates to a specific semantic feature (e.g. colour or shape), or when comparisons are made between ambiguous and unambiguous words

(Jefferies, 2013). Top down control is required to focus attention to specific features and might be required to maintain a ‘context’, to bias processes within the system to allow for the retrieval of distant semantic associations.

The LIFG has been heavily implicated in the control of semantic associations/knowledge. However it has been suggested that there is a distributed semantic network including both pMTG and AG; this section will unpack the processes involved in ‘semantic control’ and examine the evidence for the role of the LIFG and for a distributed semantic control network in both patients and using neuroimaging in healthy populations. This will provide the groundwork for Chapters 4 and 5, investigating the attentional allocation to specific features. Allocating attentional resources requires the LIFG and modulation in feature specific areas (potentially pMTG). It’s possible that the interaction between LIFG and pMTG is required to maintain context for accurate semantic retrieval, whereas AG is involved in distant associations or encoding unexpected sequences.

Evidence for a distributed semantic control system - Semantic Aphasia

Semantic aphasia (SA) is the result of a left prefrontal or temporoparietal infarct creating a multimodal semantic deficit (Jefferies and Lambon Ralph, 2006) in the presence of an intact ATL. In contrast to SD patients, neuropsychological testing reveals that SA patients are insensitive to the effects of familiarity and frequency and only show test-test correlations between tasks which require similar levels of control (Jefferies and Lambon Ralph, 2006). This suggests that the deficit is due to the variations in the level of control required across tasks rather than a degradation or loss of stored semantic knowledge. Picture naming is also impaired; SA patients produce a greater number of associate errors rather than categorical errors (a greater proportion of categorical errors are reported in SD, Jefferies and Lambon Ralph, 2006) demonstrating a failure to control semantic retrieval. Naming in SA can be improved though the presentation of phonemic cues, which reduce the control demands whereas cues are of little to no benefit for SD patients suggesting that the deficit in SD is one of concept degradation compared to the control deficit in SA (Jefferies et al., 2008). SA patients are also less sensitive to word typicality, item frequency, and when naming items they produce less regularisation errors but a greater number of unrelated, semantic and preservative errors (Jefferies et al., 2010).

Like the SD patients, the semantic deficit in SA is not limited to the verbal domain with patients demonstrating impairments in real world object use (Corbett et al., 2009b). Patients are impaired in their ability to a perform picture matching task for object use and were also impaired in demonstrating the correct actions for these objects. Performance was intrinsically linked to control demands, as patients were able to demonstrate single object use but have impaired performance on a mechanical puzzle which places greater demands on the control network. It is worth pointing out at this point that it is possible that there is an overlap between ideational apraxia and the multimodal comprehension problems in SA, suggesting a similar/shared network for action understanding and controlled semantic retrieval. This observation is directly linked to the research outcomes for Chapters 4 and 5 which examine the overlap between semantic control and action selection, which are heavily implicated to be overlapping as both semantic information and actions need to be constrained within a context under selection pressures.

Semantic aphasia - Interim summary

SA patients suffer from inflexible semantic retrieval and disordered sequential behaviour in both verbal and non-verbal domains suggesting that semantic deficits can result from intact knowledge but impaired control mechanisms. Damage in SA always encompasses either or both the left inferior frontal gyrus (LIFG) and posterior middle temporal gyrus (pMTG) implicating these regions in the controlled selection and recall of stored semantic information.

Evidence for a distributed semantic control system – Neuroimaging

The LIFG has been classically implicated in domain general control alongside semantic control. Studies manipulating controlled semantic retrieval across a variety of different paradigms have found LIFG recruitment specifically for more demanding tasks and judgements (Thompson-Schill et al., 1997; Wagner et al., 2001a; Badre et al., 2005), as well as for comparisons between demanding semantic and non-semantic tasks (Poldrack et al., 1999; Wagner et al., 2001b), and that both selection and retrieval activate shared regions within LIFG (Snyder et al., 2007; Snyder et al., 2011). The LIFG is also recruited in semantic decisions even when the decision is implicit, such as when contextual cues guide activation to a given word meaning (Grindrod et al., 2008). fMRI meta-analyses also heavily implicate the LIFG in semantic processing (Binder et al., 2009; Noonan et al., 2013), across a variety of different semantic paradigms manipulating both verbal and non-verbal knowledge. It is possible that the LIFG operates like the biased completion model of attention (Duncan, 2010), whereas the locus of attention is focused towards internal representations in order to achieve the task at hand.

TMS has also been used to demonstrate that the LIFG is involved in demanding semantic judgements. Similar to existing fMRI studies the LIFG has demonstrated the possibility of having functional subdivisions with stimulation to anterior LIFG selectively disrupting semantic judgements (Gough et al., 2005), and that LIFG stimulation causes greater disruption to more demanding semantic judgements (Whitney et al., 2011b). Contextual processing of abstract words compared to concrete words has also been disrupted using TMS resulting in longer reaction times when abstract words are presented out of context (Hoffman et al., 2010).

Evidence has also been presented, suggesting that there is a wider distributed semantic control network. The pMTG alongside the LIFG has also been implicated in semantic control (Jefferies, 2013), as SA can present from pMTG damage alone (Jefferies and Lambon Ralph, 2006; Jefferies et al., 2010), suggesting the existence of a temporoparietal contribution to semantic control. Meta analyses often report pMTG activation as well as LIFG in semantic control paradigms (Binder et al., 2009; Noonan et al., 2013), supporting the notion that there is a distributed semantic control system beyond LIFG. Distortion corrected fMRI has revealed a gradient of convergence in the temporal lobe suggesting that posterior regions are graded in their responses with stronger responses to verbal information but also responding to pictures consistent with it being involved in semantic processing (Visser et al., 2012b). This pattern has also been supported through the use of TMS, with stimulation to pMTG causing equal disruption when compared to LIFG for demanding semantic judgements (Whitney et al., 2011b; Whitney et al., 2012). pMTG stimulation also causes a deficit for verbal and pictorial semantic processing consistent with its involvement in semantic cognition (Hoffman et al., 2012).

Angular gyrus (AG) has also been linked to semantic associations (Binder et al., 2009; Seghier et al., 2010; Noonan et al., 2013), however unlike pMTG and LIFG which overlap with SA patient lesions, the AG demonstrates task-related deactivation for difficult tasks compared to easy tasks (Binder et al., 2003a; Sabsevitz et al., 2005; Hairston et al., 2008) suggesting its involvement in gating attention between internal representations and external information. Alongside semantics the AG has been implicated in the default mode network (DMN); a combination of brain regions which display deactivation in response to externally cued cognitive demands (Seghier et al., 2010; Wirth et al., 2011). It is possible that there is graded specialisation within the AG with mid-to-ventral parts of AG demonstrating greater activity for semantic tasks (Binder, et al., 2009; Seghier et al., 2010; Noonan et al., 2013) with other regions demonstrating deactivation when contrasting semantics to rest periods (Binder et al., 2008), again suggesting that AG gates the allocation of attention between internal and external stimuli depending on task context. However other sites in the parietal lobe (IPS) close to the AG have been implicated in semantic selection demands using TMS (Whitney et al., 2012) suggesting that there is parietal component in the distributed semantic control system.

Evidence for a distributed semantic control system - Interim summary

Neuroimaging and neurostimulation evidence in healthy populations support the involvement of the regions damaged in SA in semantic control, suggesting that semantic control has a distributed control system with shared components between semantic control and domain-general control mechanisms, implicated in both conflict resolution and retrieval of non-dominant features. The pMTG displays similar patterns when compared with LIFG in neuroimaging studies; however its contributions currently remain unclear. It’s possible that these areas interact in maintaining or identifying the current semantic context to bias incoming information. This is specifically relevant when trying to understand weak associations where automatic spreading activation based on dominant, stable features is unlikely to uncover the information in an efficient manner. The role of the AG/parietal lobe is semantic control still unclear as some regions respond to semantic selection demands, despite widespread deactivation for semantic/cognitive tasks.

The role of the pMTG and AG will be further examined in Chapter 3 through the utilisation of TMS to stimulate pMTG and AG during semantic tasks designed to tax associative and identity knowledge, to see if the contributions of these sites can be dissociated, and to determine whether these sites are implicated in controlled or automatic aspects of semantic retrieval. The use of fMRI in Chapters 4 and 5 will further elucidate the role of the pMTG by investigating contributions to semantic control whilst different types of representational knowledge are manipulated according to task context, and whether different selection demands activate different control networks. Badre et al. (2005) found different areas of LIFG responding to different aspects of semantic selection, with posterior aspects responding to goal-driven selection and anterior aspects implicated in context-based selection. One of the aims of Chapter 5 is to extend this work to observe whether dissociable contributions to different types of semantic selection can be observed in the wider semantic control network.

Flexible recruitment of the 'spokes'

Research has previously demonstrated that reading action words activates the corresponding region of the motor cortex (Hauk and Pulvermüller, 2004) and that this is required in understanding the word's meaning (Pulvermüller, 2005; Pulvermüller, 2013). However research has indicated that areas can be flexibly recruited based on context rather than automatic spreading activation. Action words presented in isolation activate the motor cortex, but when presented in a context defining sentence activation shifts to fronto-temporal areas (post-central gyrus and MTG). These areas are involved in language processing suggesting that activation in motor areas is context dependent and not automatic (Raposo et al., 2009). Objects that are also semantically related to actions (e.g. tennis ball) reliably activate motor regions (left IPS/IPL, pMTG) when presented in an action context and demonstrate activation in visual regions (fusiform gyrus) when the context emphasises object colour (van Dam et al., 2012). This has also been demonstrated behaviourally; presenting words in the context of their dominant versus non-dominant action features creates facilitation when the features are congruent with the prepared movement only when the context emphasised motor properties (van Dam et al., 2010).

The above body of literature supports the notion that the spokes of the network are flexibly recruited according to task context, suggesting that there are processes which allow for the selection of context and task relevant semantic retrieval. The question is does this process involve control processes which allocate attention in a flexible way to the relevant aspects of meaning. The recruitment of the spokes, and possibly hubs will depend on concurrent task demands. Thus feature selection tasks (Chapters 4 and 5) might involve the LIFG (and possibly pMTG) modulating activity in visual and action areas when they are appropriate to the current task or context. This feeds into Chapters 4 and 5 whereby we would expect different spokes to activate depending on the specific animal or tool feature being retrieved.

Action understanding

The studies above investigating categorical and association decisions have revealed similar networks, however understanding actions and events (which are linked to associations) have been associated with the pMTG, LIFG, and IPL. These areas share a great deal of overlap with the areas of damage in SA and are implicated in semantic cognition (Binder et al., 2009; Noonan et al., 2013), suggesting the possibility of a functional overlap between action/event understanding and semantic cognition. This overlap has been suggested based on observations of the inability of SA patients to match tools based on similar functions (Corbett et al., 2009b), and that there is cortical overlap between the areas involved in movement and comprehension of action words (Hauk and Pulvermüller, 2004). However the nature of this overlap is uncertain, it could be similar to semantic control (maintaining context to guide retrieval), or it could be related to both the necessary flexibility required for successful semantic cognition and action implementation.

Research looking action observation in fMRI has revealed that the left pre-motor cortex, IPS, and posterior superior temporal sulcus (pSTS) are activated in response to dances (Ballet and Capoeira) only when the participants themselves were trained in the style of dance they observed

(Calvo-Merino et al., 2005). A different study found that activation in the STS and left anterior fronto-median cortex (aFMC) was in response to unusual actions in a plausible context (using one's knee to flick a light switch whilst holding a box) compared to an implausible context (operating the light switch when the hands are free; Brass et al., 2007). These fMRI findings suggest that the STS is involved in action understanding, supported by other motor and frontal regions, but it also hints that the activation in these regions is not automatic but a function of context and training.

Objects differ in the degree of manipulability and this is reflected in the words used to describe them; some objects are associated with functional information (e.g. *cut*) whereas others have volumetric associations (how they are moved e.g. *carry*). These objects are represented differently in the brain with presentation of functional objects (e.g. scissors) compared to volumetric objects (e.g. cup) generating greater activation in the ventral pre-motor cortex (vPMC), IPL and pre supplementary motor area (pre-SMA) (Rueschemeyer et al., 2010). Similar findings have been found when participants were presented with two different sets of images in a naming experiment; each image included an object but one of the images presented the object in the context of its associated action. Images with the associated action irrespective of naming condition generated strong activation in the middle temporal cortex, left TPJ and left frontal cortex compared to object only images (Liljeström et al., 2008). These studies suggest that the representation of objects is different depending on the properties of the objects, and that activation in action areas is affected by task context.

TMS evidence has also implicated regions in the parietal lobe in action understanding; praxis judgements are disrupted following stimulation to the IPS (Pobric et al., 2010; Ishibashi et al., 2011b), suggesting that action decisions/understanding is supported by a temporal and parietal network, similar to the network involved in semantic control and consistent with previous fMRI evidence on the nature of these regions in action understanding.

Action understanding - Interim summary

There is a potential overlap between the areas involved in action understanding and the areas implicated in semantic control highlighted in the meta-analysis of Noonan et al. (2013), alongside other fMRI, TMS and data from SA cases. It is possible based on the evidence presented that the ability to flexibly use our tool knowledge rather than relying on automatic spreading activation is similar to our ability to flexibly alter and attend to our representations in a task dependent manner. This suggests that there is possibly a unifying function or computation in these regions which is important for flexible tool use and flexible semantics underpinning the apparent overlap between these two cognitive faculties. This will be investigated in Chapter 4 where we directly contrast action knowledge and semantic control in a single paradigm using fMRI, to determine the potential overlap between action knowledge and semantic control as indicated by the material in this section.

Event and verb knowledge/understanding

The previous section addressed how the areas implicated in semantic control have also been heavily been implicated in the understanding of tool actions, the same network of brain regions (specifically the temporal and parietal components of the distributed semantic control network) have also been implicated in the representation and encoding of events and also for verb knowledge.

The medial temporal lobes have been implicated in the encoding of new events, whereas areas typically implicated in control (e.g. LIFG) are implicated in the recollection of old events compared to new events (Kim, 2011). The pMTG has also demonstrated a greater response to telic verbs (referring to events with a set endpoint, e.g. *reaching*) compared to atelic verbs (referring to events with a no set endpoint, e.g. *chasing*), further strengthening the role of the pMTG in event knowledge, alongside a preference to verbs (Romagno et al., 2012).

It is hypothesised that the verb-specific responses in pMTG are based on the nature of verbs and nouns; verbs often refer to actions (for which pMTG displays a specific affinity for), whereas nouns often refer to objects (Peelen et al., 2012). However fMRI revealed that pMTG responded equally to verbs with or without an action component (events vs. states) suggesting that verb responses in pMTG and the lateral temporal cortex are independent of action representation (Peelen et al., 2012). It is possible that the effect of context affects verb responses in pMTG, with greater responses to motion verbs when they are presented in a story driven context (Wallentin et al., 2011), similar to previous findings of motor system activation for object names when the context emphasises the action associated with the object (van Dam et al., 2010; van Dam et al., 2012). The semantic system (including LIFG and pMTG) has also been implicated in the retrieval and processing of abstract verbs (less imagable) compared to concrete verbs, and has been demonstrated using fMRI (Rodríguez-Ferreiro et al., 2011), supporting the role of the pMTG in verb knowledge, and strengthening the existence of a distributed semantic control/retrieval system.

Event and verb knowledge/understanding - Interim summary

The distributed semantic control system (specifically LIFG and pMTG) is heavily implicated in the representation and processing of verbs and event knowledge specifically when the verbs or events include either an action or abstract component. However the specific relationship between these functional networks described here and in other sets of literatures and semantic control is not yet fully understood, and will be investigated further in this thesis. Chapters 4 and 5 will directly contrast these networks whilst manipulating both aspects of semantic control and event knowledge to observe where the overlap is and how the system deals with both aspects being manipulated simultaneously.

Summary

Going back to the research questions of the networks involved in automatic and controlled aspects of semantic retrieval and how the systems implicated in event/action knowledge overlap with the semantic control network, based on this review of the literature it is clear that these questions have yet to be satisfactorily addressed. The problem is that whilst research has investigated these facets of semantic cognition they have done so independently and have failed to manipulate both aspects within a single paradigm.

While semantic cognition is supported by a large network of brain regions implicated in automatic and controlled aspects of semantic retrieval, it is still unclear about which sites contribute to these networks. Both AG and pMTG are co-activated in semantic contrasts and have been implicated in automatic (AG) and controlled (pMTG) aspects of retrieval; however due the perfuse damage in SA and the lack of studies manipulating both aspects of semantic retrieval it is currently unclear about the precise contributions these sites make to semantic cognition. A third aspect is whether there are separable components of semantic control, as selection demands can be shaped depending on whether there is a predetermined goal (e.g. matching features) relying heavily on executive processes and whether there are selection processes unique to semantics, relying on the manipulation of spatiotemporal context. Previous work has implicated differences in selection demands in the LIFG (Badre et al., 2005); however it is unclear about the division in the wider semantic network.

Two concurrent sets of literature points towards an overlap between the systems involved in semantic control and event/action understanding, but partially distinct from the areas implicated in object knowledge and visual features. However until both are systematically manipulated within a single paradigm we cannot conclusively conclude that an overlap exists, and whether there is a shared process unique to semantics and event/actions knowledge. The relationship between these functional networks described here is important to understand as it (i) directly relates to the roles of the AG and pMTG, specifically pMTG as it has been specifically implicated in both sets of literatures, which have never been directly contrasted. It is possible that there is a shared process between these aspects of cognition (e.g. events, actions and some aspects of semantic selection require the manipulation of spatiotemporal context). Secondly, manipulating both within a single paradigm allows for a more coherent view of the role of these brain areas to emerge, i.e. providing a unifying function or computation that is important for flexible semantics.

This thesis aims to address these issues to examining the networks involved in automatic and controlled aspects of semantic retrieval, and to investigate the degree of functional overlap between event semantics and semantic control. This will be achieved through paradigms which manipulate both representational *and* control demands within a single paradigm utilising either TMS or dual-task methodology, and using fMRI to examine how the control network responds when faced with decisions on semantically related/unrelated items which match for fixed (visual characteristics) or context dependent (actions/global semantic associations) aspects of their representation. In Chapter 2 we investigated patients with semantic aphasia (SA) and healthy participants under conditions of divided attention, utilising tasks which tax associative and identity knowledge. Chapter 3 utilised TMS to dissociate two sites in the temporoparietal region (pMTG and AG), which are co-activated in semantic contrasts and often damaged together in SA using the same tasks in Chapter 2. Chapter 4 examined whether the network involved in the control of semantic information overlapped with the network involved in action selection, as both semantic selection and action selection and activate overlapping regions demonstrated by previous fMRI studies. In Chapter 5 we extended previous work demonstrating an involvement of different parts of LIFG in different aspects of semantic control.

Chapter 2 – Characterising the deficits in Semantic Aphasia: loss of thematic knowledge of impaired control of semantic retrieval?

Abstract

Semantic deficits that cannot readily be explained in terms of expressive and/or receptive language problems are common in patients with aphasia following frontoparietal stroke; however, their explanation remains controversial. By one view, inferior parietal and posterior temporal lesions affect brain regions implicated in understanding events and semantic associations – while a separate hub for categorical knowledge in ventral medial anterior temporal cortex remains largely intact. In addition, in previous case-series of such patients, these deficits were linked to deficient control over the retrieval of (intact) knowledge, following damage to semantic control processes in left inferior and posterior temporal areas (Jefferies & Lambon Ralph, 2006). We tested these competing accounts by manipulating both knowledge type (thematic associations vs. identity matching) and the difficulty of each type of semantic judgement in (i) patients with left frontoparietal stroke and (ii) healthy controls under dual-task conditions that depleted the capacity for cognitive control. The patients were impaired on both identity and thematic matching tasks, yet their deficits for thematic judgements were restricted to non-dominant associations which required greater control over semantic retrieval. Healthy participants showed the same pattern under conditions of divided attention. These findings support the view that conceptual deficits in the patients reflected impaired control processes rather than damage to a thematic hub, resulting in disorganised and inadequately-constrained retrieval of both identity and association knowledge.

Introduction

Across our lifetimes we acquire a vast body of conceptual knowledge; as a consequence, we must constrain retrieval of our knowledge and select only those aspects that are relevant for the current task or context (Badre et al., 2005; Noonan et al., 2010; Jefferies, 2013). Our knowledge captures contextual associations between different concepts (e.g., knowing that 'spoon' goes with 'sugar' in the context of drinking tea, often referred to as thematic knowledge), as well as the capacity to recognise and categorise objects (e.g., identifying an animal that barks, has a wet nose and has spots as a 'Dalmatian', i.e., taxonomic knowledge). It has been proposed that these different aspects of semantic knowledge can be selectively impaired due to their representation in different cortical areas (Schwartz et al., 2011). An alternative hypothesis is that, at least under some circumstances, identifying associations requires greater control over semantic retrieval, since associations vary depending on the context – e.g., spoon also goes with soup in the context of lunch (hereby refered to as the control hypothesis; Jefferies and Lambon Ralph, 2006; Jefferies et al., 2008; Jefferies et al., 2010).

These theories – referred to below as the "two hubs" and "semantic control" accounts – offer different explanations of conceptual deficits in aphasia that follow frontoparietal stroke and that are not explained by expressive and/or receptive language problems. They also have a different account of why these semantic deficits are qualitatively different from the impairment in semantic dementia (SD). SD follows bilateral atrophy of the inferior anterior temporal lobes (ATL) and is characterised by a multimodal degradation of semantic information which is highly consistent when the same concepts are tested in different tasks (Bozeat et al., 2000; Mummery et al., 2000; Simons et al., 2001; Jefferies and Lambon Ralph, 2006; Patterson et al., 2006). This semantic deficit erodes the distinction between specific concepts first, such that patients can no longer identify a Dalmatian from other breeds of dog; but can identify that this item is an animal (Mummery et al., 2000; Rogers et al., 2006; Hodges and Patterson, 2007). In contrast, conceptual deficits in semantic aphasia (SA) are associated with non-overlapping damage to left inferior frontal and/or posterior temporoparietal cortex. SA patients show inconsistent performance when tested on the same concepts in tasks with differing control demands (e.g., word-picture matching and judgements of semantic association; Jefferies and Lambon Ralph, 2006). They are highly sensitive to manipulations of the executive demands of semantic tasks, including the strength of distracters (and verbal domain; Noonan et al., 2010; in both the non-verbal domain; Corbett et al., 2011) and show strong effects of cues and miscues that modulate the requirement for internally-generated semantic control (Soni et al., 2009; Noonan et al., 2010), alongside a general executive deficit beyond the semantic domain which correlates with their semantic performance (Jefferies and Lambon Ralph, 2006).

The dissociation between SA and SD is clear but the explanation is not. The ventral anterior temporal lobes damaged in SD are thought to contribute to the conceptual identification of visually-presented objects (Moss and Tyler, 2000; Devlin et al., 2002) and also multimodal feature binding such that the deep conceptual similarities between objects can be extracted across colour, shape, texture, motion, action, sound, smell, taste and verbal information (Rogers et al., 2004; Rogers et al., 2006; Patterson et al., 2007). In contrast, semantically-impaired stroke patients with frontoparietal lesions have damage to areas that have been associated with event understanding in neuroimaging studies (Mirman and Graziano, 2012a; de Zubicaray et al., 2013; Kalénine et al., 2013). In line with these findings, Schwartz et al. (2011) proposed that there are two semantic hubs for categorical/identity information and thematic/associative knowledge, in ATL and temporoparietal cortex respectively (Schwartz et al., 2011; Kalénine et al., 2013). Key neuropsychological evidence so far comes from picture naming, with ATL damage associated with category co-ordinate or superordinate errors (e.g., apple – ‘orange’) and temporoparietal lesions associated with thematic errors (e.g, Squirrel - "nuts"; Jefferies et al., 2008; Schwartz et al., 2011). Under the two-hub explanation, damage gives rise to noisy processing that elicits these specific types of errors. However, it is not entirely straightforward to understand why damage to a representational hub for thematic knowledge would elicit associative errors – since saying “nuts” for Squirrel reveals that this association is still intact. An alternative proposal is that these errors reflect the activation of strong but currently *irrelevant* associations, suggesting deficient control over semantic retrieval (Jefferies and Lambon Ralph, 2006; Jefferies et al., 2010). The two hub account also predicts clear differences in neuroimaging studies between the areas of activation for thematic and categorical semantic tasks in healthy participants (de Zubicaray et al., 2013). However other neuroimaging studies have failed to observe a distinction between thematic and categorical knowledge in these proposed hub regions (Kotz, 2002; Sachs et al., 2008a; Kalénine et al., 2009; Sass et al., 2009b).

While frontal, inferior parietal and posterior middle temporal regions are linked to event understanding by one set of studies (see above), overlapping regions are implicated in the flexible control of semantic retrieval (Thompson-Schill et al., 1997; Badre et al., 2005; Whitney et al., 2011b; Whitney et al., 2012; Noonan et al., 2013). Semantic control processes are thought to be required when dominant aspects of meaning are not sufficient for successful semantic cognition because knowledge is being probed in an unusual way; relatively weak associations or specific non-dominant features are required or there is strong competition from non-target concepts. A recent meta-analysis of the neuroimaging literature showed that a distributed network of cortical regions is recruited by a range of semantic control manipulations, including left inferior frontal gyrus (LIFG; Wagner et al., 2001b; Wagner et al., 2001a; Badre et al., 2005; Whitney et al., 2011b; Whitney et al., 2012; Noonan et al., 2013), posterior middle temporal gyrus (pMTG; Whitney et al., 2011a; Whitney et al., 2011b; Whitney et al., 2012; Noonan et al., 2013), and dorsal angular gyrus/intraparietal sulcus (dAG/IPS; Binder et al., 2009; Whitney et al., 2012; Noonan et al., 2013). Patients with SA have damage to one or more of these regions following frontoparietal or temporoparietal stroke (Jefferies and Lambon Ralph, 2006; Jefferies et al., 2010; Noonan et al., 2010).

Thus, in this study, we examined whether semantic deficits following left frontoparietal stroke are best characterised as reflecting (i) damage to a associative hub (Schwartz et al., 2011) or (ii) deficient semantic control (Jefferies and Lambon Ralph, 2006). We compared two word-picture matching tasks – requiring retrieval of thematic relationships and object identity respectively. We also manipulated difficulty in each of these tasks, by comparing weak and strong thematic relationships, and identity matching at different levels of specificity. These manipulations are thought to have different effects on the control requirements of thematic and identity judgements. Weak associations (e.g., 'dog' with 'beach') rely more heavily on control mechanisms since strong but irrelevant associations must be ignored (e.g., dog-bone and beach-sand; Badre et al., 2005). In contrast, we would not necessarily expect identification at a specific level to require greater control than general identification, unless the task structure introduces strong competition by requiring participants to select between similar response options in the specific task (e.g. photos of different breeds of dog; Crutch and Warrington, 2008). In the object identity matching task where the task is to match objects to either a specific (low frequency) or superordinate (high frequency) labels, we would predict higher control demands in the superordinate condition. This is because high frequency superordinate terms have greater *contextual diversity*; they are used in a greater range of contexts, to mean slightly different things (Hoffman and Lambon Ralph, 2011). The word "animal" may refer to pets, or badly-behaving humans, for example, while "Alsatian" always refers to a specific type of dog. Thus, matching tasks employing superordinate as opposed to basic or specific labels might require more executive control over semantic processing, in line with reports of reverse specificity effects in picture naming in dysexecutive patients (Humphreys and Forde, 2005).

In summary, if aphasic patients with semantic deficits following frontoparietal stroke have prominent damage to a thematic/associative hub, they should be poor at retrieving thematic associations, irrespective of association strength, and unimpaired on identity matching decisions as the areas implicated in identity knowledge are undamaged. In contrast, if they have control deficits which lead to uncontrolled and inflexible semantic retrieval, we would predict strong effects based on the strength of the thematic association with decreased performance for weakly associated items, alongside deficits on identity matching tasks that again reflect the control demands of each decision (potentially over-riding the increased difficulty in terms of the degree of detail required during semantic retrieval for specific trials, at least for some cases). To further test these hypotheses, we induced SA-like deficits through the use of a secondary task in healthy young volunteers. Previous studies have shown that SA-like deficits can be mimicked using dual-task methodology to divide attention (Soni et al., 2009; Almaghyuli et al., 2012). Participants performed a semantic task concurrently with a secondary task that either required a high degree of executive control over the retrieval of memory representations (1-back) or little executive control (saying numbers in order). A similar dual-task interference paradigm disrupted processing of high-ambiguity sentences in comparison to low-ambiguity sentences. This pattern is similar to deficits in SA, and consistent with the view that semantic disambiguation and response selection share cognitive and neural mechanisms (Rodd, Johnsrude & Davis, 2010). Therefore, we would expect healthy controls to perform similarly to the SA patients under dual-task conditions.

Experiment 1 – Identity and association matching in semantic aphasia

Method

Participants: 9 volunteers with aphasia (mean age = 65 years, s.d. = 9.2 years; mean age of leaving education = 17 years, s.d. = 1.92) were recruited through stroke and aphasia groups across Yorkshire, UK. Ethical approval was obtained from the local health research ethics committee. Patients were native English speakers and had chronic aphasia from a left hemisphere cardiovascular accident (CVA) at least 1 year previously. They were selected to show semantic deficits across a variety of standard assessments that could not be readily explained in terms of their expressive and/or receptive language deficits and scored less than 95% in the experimental task across all conditions. Six patients fell below the normal range on both word and picture versions of the Camel and Cactus test (CCT) from the Cambridge semantic battery (Bozeat et al., 2000). Eight patients showed impairment on the word version of this test and all of the patients fell below the normal range on measures of picture naming and category fluency. Background neuropsychology and aetiology is provided in Table 2.2. The patients were not specifically selected to show semantic control deficits; nevertheless, as can be seen in Table 2.2, every case replicated the pattern reported by Noonan et al. (2010) for a case-series of SA patients, in that they had greater difficulty retrieving the non-dominant meanings of ambiguous words, yet an ability to retrieve the appropriate information when provided with sentence cues that reduced the requirement for internally-generated control over semantic retrieval. All of the patients were impaired at retrieving the dominant and non-dominant meanings of ambiguous words and showed a higher level of performance (although they were significantly impaired compared to controls) when retrieving their dominant interpretations, suggesting a deficit of semantic control like the SA cases reported by Noonan et al. (2010). Other neuropsychological deficits were variable across the group, with three cases showing severe impairment of speech production beyond semantic tasks (i.e., in word repetition: SSR; NNF; HNA). Five patients showed evidence of executive dysfunction beyond the semantic domain; patients SSR, NNZ, and NTG demonstrated significant impairment on the Raven's Matrices, while RDE and LHN were significantly impaired on the Brixton Spatial Rule Attainment test.

Structural MRI scans were obtained for all cases; example axial slices can be seen in Figure 2.1. Lesion analysis can be seen in Table 2.3. Areas of lesion overlap were observed in inferior parietal cortex (damaged in 8/9 cases, not NNZ) and parietal-occipital-temporal cortex (POT; damaged in 8/9 cases, not LHN). The majority of cases also had damage to the posterior inferior frontal cortex (7/9; not NTG and RDE).

10 healthy age-matched controls (mean age = 69 years, s.d. = 24.0, mean age of leaving education = 18 years, s.d. = 2.54), who had no neurological impairment, were compared with the patients. There were no differences between these groups in terms of age (*t*(8) = 1.22, p = .26) and years of education (*t*(7) < 1).

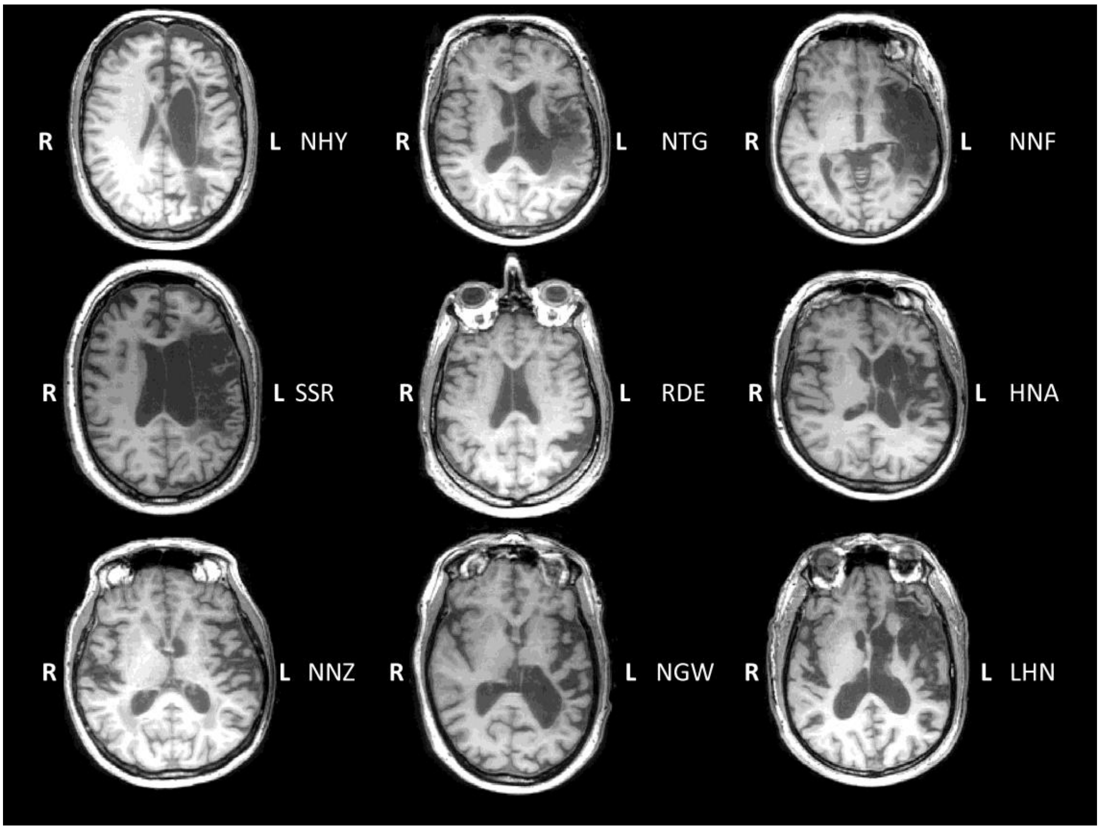


Figure 2.1 - Axial slices for the nine stroke patients centred on the largest area of cortical damage

Task overview: There were four conditions in a 2x2 design, involving two different semantic tasks (identity vs. association matching), each with two levels of difficulty. All of the judgements involved picture-word matching with three written response options (3AFC). For identity matching, participants matched a photograph of a probe object with the superordinate category label (“animal”, “weapon”, “food”, “vehicle”, “plant”, “clothes”, “household item”, “footwear”, “tree”, “Instrument”, and “sports equipment) or with its specific name, requiring finer-grained semantic analysis (see Figure 2.2 for an example). For thematic association matching, participants were instructed to select the word which had the strongest link to the picture: easier decisions were based on strong thematic associations; while harder decisions were based on weak thematic associations (see Figure 2.2). The same probe photographs were presented in the easy and harder versions of both tasks.

Stimuli: The probes were pictures and the response options were words. Picture stimuli consisted of 134 colour photographs (60 photos per judgement, with an extra 12 items in a practice block). All were resized to 200 x 200 pixels whilst maintaining the aspect ratio. In the superordinate identity matching trials, distracters were other superordinate labels. In the specific matching trials, distracter words were specific level names from the same basic category, i.e., two different, incorrect dog breeds were given as distractors when the target was ‘Dalmatian’. For association matching trials, distracter items were semantically unrelated words with no discernible relationship with the picture. All words were nouns. Familiarity and imageability were matched across conditions using published ratings (familarity and imagablity statistics were taken from the MRC Psycholingustic Database; Coltheart, 1981, and were extracted using the program N-Watch; Davis, 2005), supplemented by additional ratings from 22 participants not included in the experiment. We also matched word length and number of words (see Table 2.1). The final set of matched words was identified using the match program (Van Casteren and Davis, 2007). Two pairs of trials (i.e., across easy and hard versions) that did not permit a match were removed prior to analysis, leaving 56 trials per condition.

Table 2.1 - *Word statistics for the trials used in both experiments*

Condition	Word length		Imageability		Familiarity	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Categorical – specific	7.07	2.22	4.71	.88	6.00	.85
Associative – easy	6.97	2.11	4.78	1.03	6.00	.78
Associative - difficult	6.98	2.22	4.73	.92	6.22	.58

Note: Data for trials entered into final analysis. Word length = number of letters. Imageability = on a 7-point scale, where 7 indicates highly imageable. Familiarity = on a 7-point scale, where 7 indicates highly familiar.

Procedure: During the experiment, four patients (NTG, NNZ, CPi, and RDE) spontaneously read the words independently and accurately, while the response options were read aloud to the other patients by the researcher. There were 120 trials in total (60 trials in each condition, across 6 blocks). Trials were presented in mini-blocks, each containing 10 trials from one of the conditions. The order of Individual trials within a block was randomized across subjects, and the order of blocks and judgements was counterbalanced across participants. There was also a practice block of 12 trials per judgement type (not from in the main experiment). The task was presented using E-prime 2.0 (Psychology Software Tools, Inc., 2014). Participants made their responses by pressing 1, 2, or 3 on the keyboard to indicate which of three response options matched the picture. The researcher pressed these buttons for two patients (NNF and HNA) who found this difficult but could respond by pointing at the screen. Patients performed one half of the experiment, and then rested before completing the remaining trials.

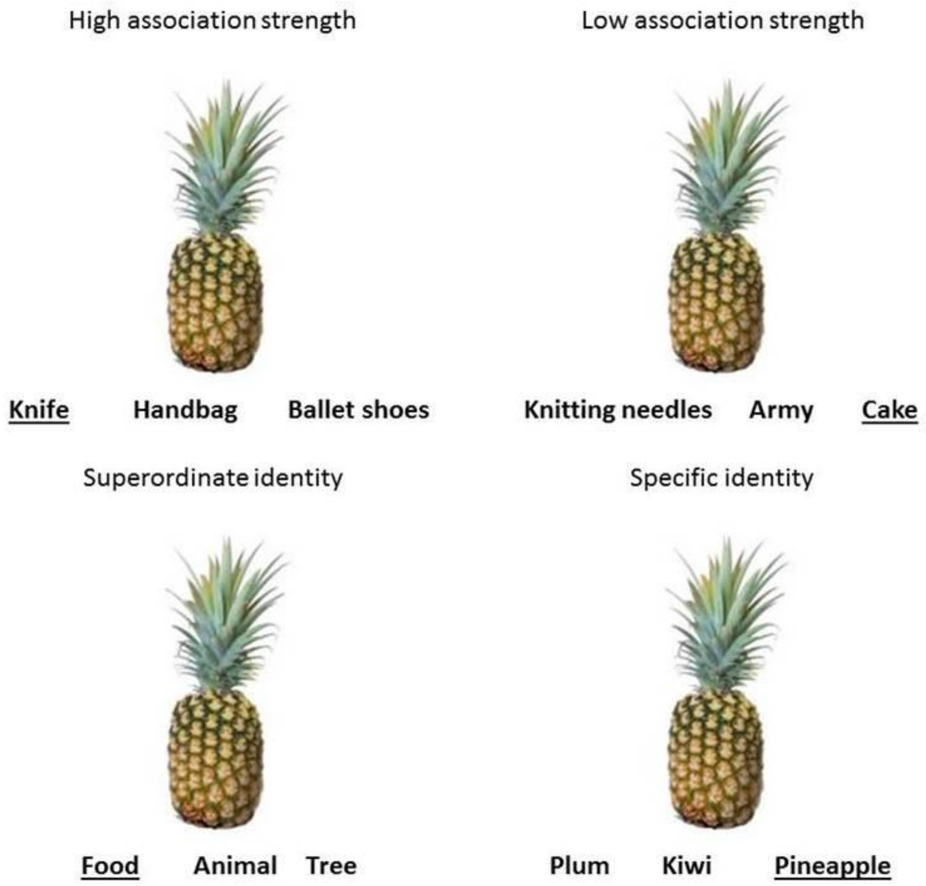


Figure 2.2 - Examples of association and identity matching trials for both levels of difficulty. The target word is underlined in each case.

Table 2.2 - *Neuropsychological test performance for the patient sample*

Test category	Test	Max	Control mean	Control Stdev.	SA mean	Patients								
						NHY	**SSR**	**NNZ**	**NTG**	**RDE**	**NGW**	**NNF**	**HNA**	**LHN**
Experimental task accuracy across all conditions (%)	N/A	100	.98	.02	.88	.95***	.94***	.94***	.90***	.88***	.87***	.85***	.84***	.79***
Semantic	Ambiguity test, written probe; dominant meaning	30	29.50	.53	24	26***	27***	28*	NT	26***	22***	24***	22***	18***
	Ambiguity test, written probe; non-dominant meaning	30	28.875	.64	16	17***	19***	21***	NT	21***	14***	14***	11***	9***
	Picture CCT	25	22.70	1.5	17	21	18**	20	22	9***	19*	17***	8***	16***
	Word CCT	25	23.30	1.3	17	9***	18***	24	19**	18***	19**	15***	13***	15***
	Word-picture matching	16	15.90	0.3	14	15**	13***	12***	16	15**	16	12***	16	15**
	Picture naming	16	16.00	0.0	8	3*	0*	12*	10*	13*	10*	8*	0*	13*
	Category fluency	N/A	20.80	6.0	6	7*	0**	17	9*	7*	4**	5*	0**	7*
Fluency	Verbal letter fluency	N/A	15.50	3.6	2	2***	0***	3**	3**	3**	1***	0***	0***	3**
	Cookie theft (WPM)	N/A	N/A	N/A	19	37	0	54	29	NT	12	9	0	18
Repetition	Word repetition	16	16.00	0.0	12	16	2*	15*	15*	15*	15*	12*	0*	14*
	Digit span	N/A	6.80	0.6	4	4***	0***	5**	3***	5**	5**	2***	0***	4***
Executive processing	Brixton spatial rule attainment *(a)*	54	31.60	7.7	22	23	31	31	36	5**	26	18	21	7**
	Raven's coloured progressive matrices	36	32.90	2.4	27	30	22***	21***	21***	NT	33	32	31	29
	Raven's coloured progressive matrices, set B	12	10.4	1.6	8	8	11	5**	7*	6**	8	10	10	6**

*Patients are organised in order of severity based on their performance on the experimental task, with the more impaired cases to the right of the table.NT = not tested. We used the 'singlims' procedure (Crawford & Garthwaite, 2002) to examine the extent to which the patient sample was impaired when compared to a control group on the battery of neuropsychological tests. Singlims uses a modified t-statistic to work out whether an individual is impaired, accounting for group size and standard deviation. Significant impairment is indicated as follows: * = p<.05, ** = p<.01, *** = p<.001. Singlims was not run on tasks where the accuracy for controls was at ceiling with no standard deviation, however, patients lower than this are marked as impaired (*). (a) - standardised task with pre-existing norms used to define which patients were impaired (*). Ambiguity task (Noonan, Jefferies, Corbett & Lambon Ralph, 2010). (CCT = Camel and Cactus test (Bozeat, Lambon Ralph, Patterson, Garrard, & Hodges, 2000). Word picture matching and picture naming used black and white line drawings (Snodgrass & Vanderwart, 1980). Category/verbal letter fluency - the number of words produced in a minute from a given category (animals) or letter ('s'), digit span – span length (Wechsler, 1987). Brixton spatial rule attainment – number of correct responses for prediciting a location based on a pattern (Burgess & Shallice, 1996). Raven's coloured progressive matrices – measure of non-verbal IQ (Raven, 1962), set B is a subset which requires analogical reasoning in order to match the correct pattern..*

Table 2.3- *Details of SA lesions*

		Prefrontal						Anterior temporal	Posterior temporal					Inferior Parietal	
Patient	**Total lesion size (%)**	**DLPFC**	**DLPFC**	**orbIFG**	**trIFG**	**opIFG**	**PMC**	**sTP**	**pSTG**	**pMTG**	**pITG**	**pFG**	**pOT**	**AG**	**SMG**
		BA 9	**BA46**	**BA47**	**BA45**	**BA44**	**BA 6**	**BA 38**	**BA22**	**BA21**	**BA20**	**BA36**	**BA37**	**BA39**	**BA40**
NHY	7	-	-	-	1	2	1	-	-	-	-	-	1	1	1
SSR	15	-	-	2	1	2	2	-	2	-	-	-	1	1	1
NNZ	4	-	-	-	-	1	1	-	1	1	-	-	1	-	-
NTG	12	-	-	-	-	-		-	2	-	-	-	2	-	1
RDE	1	-	-	-	-	-	-	-	-	-	-	-	1	1	-
NGW	8	-	-	-	-	1	2	-	2	1	-	-	2	-	1
NNF	12	-	-	2	1	1	2	-	2	1	-	-	2	1	2
HNA	12	1	1	-	1	1	1	1	2	-	-	-	1	1	2
LHN	15	2	-	2	2	2	2	-	2	-	-	-	-	-	1

Damage to the posterior temporal areas did not extend into anterior temporal cortex. Quantification of lesion: 2 = complete destruction/severe damage to cortical grey matter; 1 = partial destruction/mild damage to cortical grey matter. Anatomical abbreviations: DLPFC = dorsolateral prefrontal cortex; orbIFG = pars orbitalis in inferior frontal gyrus; trIFG,= pars triangularis in inferior frontal gyrus; opIFG = pars opercularis in inferior frontal gyrus; PMC = premotor cortex; sTP = superior temporal pole; pSTG = posterior superior temporal gyrus; pMTG = posterior middle temporal gyrus; pITG = posterior inferior temporal gyrus; FG = fusiform gyrus; POT = posterior occipitotemporal area; SMG = supramarginal gyrus; AG = angular gyrus. Total lesion size was estimated by overlaying a standardised grid of squares onto each patient's template to determine the percentage that were damaged relative to the complete undamaged template, using MRI data acquired at the York Neuroimaging Centre.

Results

For both patients and controls, incorrect trials and outlying responses more than two standard deviations away from an individual's mean for that condition were removed prior to RT analysis.

Healthy controls – response efficiency: To characterise the overall performance of the healthy controls, we examined response efficiency (reaction time divided by accuracy). Behavioural results for RT and accuracy can be seen in Table 2.4. The control participants showed highly significant main effects of semantic task (associations vs. identity; $F(1,9) = 105.03$, $p <.001$, $eta^2 = .921$) and difficulty (easy vs. hard; $F(1,9) = 267.72$, $p <.001$, $eta^2 = .967$). Response efficiency was significantly lower for associative compared to identity judgements, and for the harder judgements compared to the easy judgements. A highly significant interaction was observed; $F(1,9) = 50.01$, $p <.001$, $eta^2 = .847$. This indicated that the manipulation of difficulty had a greater effect on response efficiency for the association than the identity matching task. However, both tasks showed lower efficiency for more difficult judgements (weak vs. strong association matching: Bonferroni $t(9) = 13.02$, $p <.001$; specific vs. general identity matching: Bonferroni $t(9) = 2.46$, $p = .036$).

Patients vs. controls: Behavioural results for the patients (RT and accuracy) can be seen in Table 2.4. For the patients, the key dependent measure was accuracy although we also provide analyses of RT and response efficiency to expedite comparison with the healthy controls. For each of these three measures, we computed 2x2x2 omnibus ANOVAs, which included the factors of group (aphasia vs. controls), task (thematic association vs. identity matching) and difficulty (manipulated via associative strength and specificity). These analyses revealed highly similar effects for the three measures (see Table 2.5). There were significant main effects of group, task and difficulty. Significant two-way interactions were observed between group and task (patients were more impaired at thematic associations than identity matching), and task and difficulty (reflecting a bigger effect of strength of association than specificity) in all three measures. There was also an interaction between group and difficulty for accuracy, with patients showing larger effects of difficulty overall. Finally, there was a three way interaction between patient/group, task, and difficulty, which was significant for RT and response efficiency and approaching significance for accuracy.

To explore these interactions, we investigated the interaction between difficulty and group in the association and identity matching tasks separately. For association matching, the effect of difficulty (manipulated via associative strength) was larger for patients than controls: the group by difficulty interaction was significant for accuracy (F(1,8) = 23.11, p = .001, eta² = .743) and response efficiency (F(1,8) = 24.19, p = .001, eta² = .751) and was approaching significance for RT (F(1,8) = 3.85, p = .086, eta² = .325). In contrast, there was no difficulty by group interaction for any of the measures in the identity matching task. This pattern is shown in Figure 2.3, which reveals a small difference between the patients and controls in response efficiency for strong associations, specific and superordinate identity matching, and a substantially larger difference for weak associations.

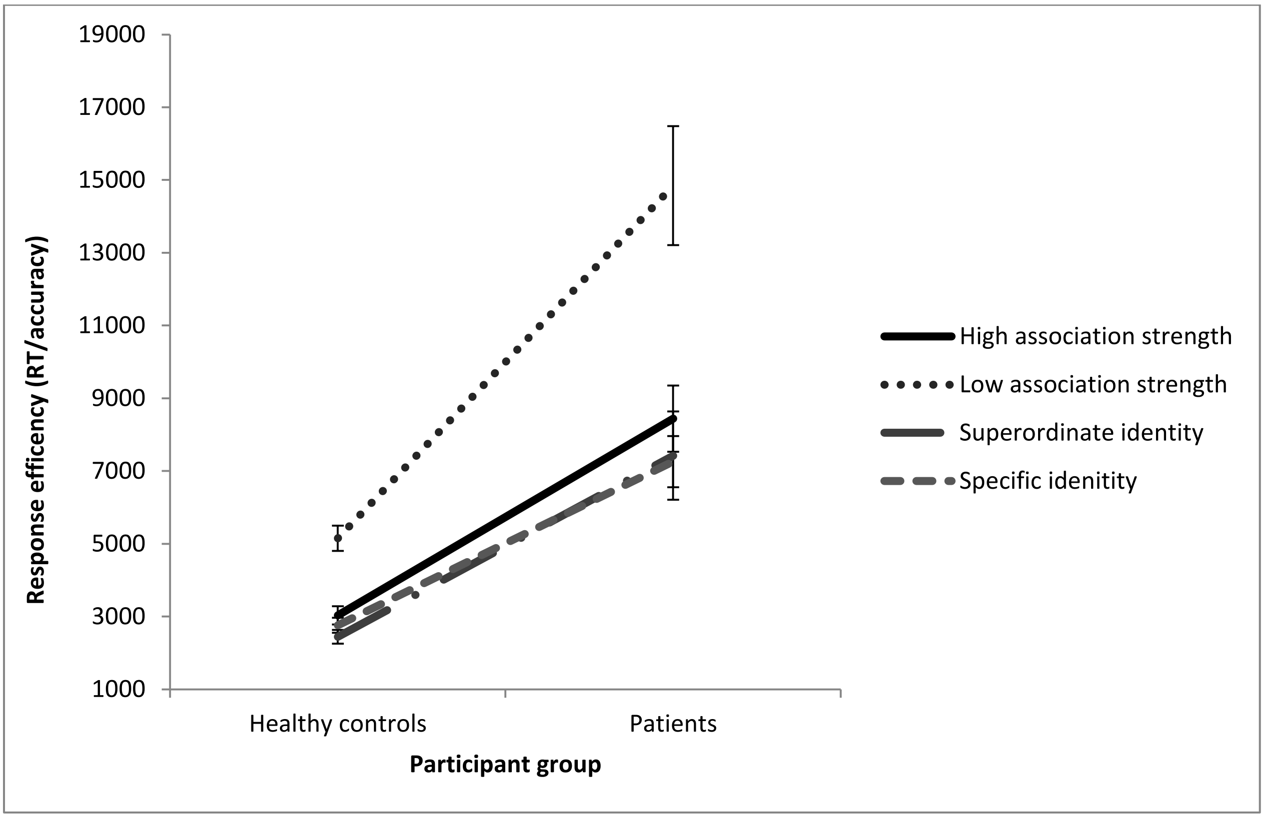


Figure 2.3 – Response efficiency for both healthy controls and patients. Error bars represent the standard error.

Table 2.4 – *Behavioural results for the healthy controls and patients*

	Reaction time		Accuracy	
Condition	Mean (milliseconds)	Standard deviation	Mean (proportion correct)	Standard deviation
Healthy controls				
High association strength	3002.58	845.66	1.00	.01
Low association strength	4956.50	1136.15	.96	.02
Superordinate identity	2354.14	657.07	.97	.03
Specific identity	2731.50	659.25	.98	.01
Patients				
High association strength	7722.70	2275.60	.93	.06
Low association strength	11308.58	3864.95	.77	.12
Superordinate identity	6622.33	2710.67	.92	.08
Specific identity	6577.61	1814.60	.91	.06

Table 2.5 – *Omnibus ANOVA results comparing patients and controls*

	Response efficiency (RT/accuracy)			Accuracy			Reaction time		
	F	Sig.	effect size (partial eta^2)	F	Sig.	effect size (partial eta^2)	F	Sig.	effect size (partial eta^2)
Group	**35.22**	**<.001**	**.815**	**28.39**	**.001**	**.780**	**31.47**	**.001**	**.797**
Task	**53.03**	**<.001**	**.869**	**6.48**	**.034**	**.447**	**47.84**	**<.001**	**.857**
Difficulty	**31.24**	**.001**	**.796**	**11.67**	**.009**	**.593**	**17.59**	**.003**	**.687**
Group by task	**25.59**	**.001**	**.762**	**11.15**	**.010**	**.582**	**9.07**	**.017**	**.531**
Group by difficulty	**6.88**	**.030**	**.462**	**16.91**	**.003**	**.679**	0.85	.383	.096
Task by difficulty	**37.62**	**<.001**	**.825**	**9.60**	**.015**	**.545**	**33.89**	**<.001**	**.809**
Group by task by difficulty	**14.90**	**.005**	**.651**	4.02	.080	.335	**7.63**	**.024**	**.490**

Individual patient analysis: Table 2.6 shows the individual task performance for each of the nine patients. Chi-squared tests revealed that the two most impaired cases (HNA and LHN) produced more errors for the association than the identity judgements; HNA χ^2 (1) = 6.17, p = .013, LHN χ^2 (1) = 14.69, p < .001. The other seven cases showed no significant overall difference between tasks. Six of the nine patients made more errors on weak than strong associations; NNF χ^2 (1) = 8.70, p = .003, NTG χ^2 (1) = 4.26, p = .039, LHN χ^2 (1) = 8.93, p = .003, HNA χ^2 (1) = 12.69, p < .001, NNZ χ^2 (1) = 12.15, p < .001, with marginally significant results for patient RDE; χ^2 (1) = 3.37, p = .066. For identity matching, there were more mixed effects of specificity: four patients made more errors on the specific trials (resembling the normal pattern): NNY χ^2 (1) = 12.15, p < .001; LHN χ^2 (1) = 7.02, p = .008; CPi χ^2 (1) = 7.45, p = .006; NGW χ^2 (1) = 4.92, p = .027, while three patients demonstrated reverse specificity effects (resembling patients with dysexecutive syndrome): this effect was significant for NNF χ^2 (1) = 12.15, p < .001 and NTG χ^2 (1) = 5.95, p = .015, with an effect for patient HNA that was approaching significance; χ^2 (1) = 3.35, p = .067.

To circumvent ceiling effects in the controls and to account for individual variation in both accuracy and RT, we further examined the response sensitivity data at a single-subject level. We tested whether the effects of associative strength and specificity were larger in any of the patients than would be expected from the distribution of test scores seen in the controls using the revised standardised difference test (RDST; Crawford et al., 2010). This test uses a modified t-statistic to compare individual patients with a control group, taking into account the variability of the control data and the sample size. For associative strength, seven out of the nine patients demonstrated bigger differences between strong and weak trials than controls. This difference approached significance for two patients: NTG $t(9)$ = 2.16, p = .059 and RDE $t(9)$ = 2.13, p = .062, and was significant for a further five cases: NHY $t(9)$ = 8.19, p < .001; NNZ $t(9)$ = 2.62, p = .028; NGW $t(9)$ = 8.14, p < .001; NNF $t(9)$ = 5.97, p < .001; HNA $t(9)$ = 2.91, p = .017. For specificity, four of the nine cases showed reverse specificity effects that were greater than the effect observed in controls. This difference was marginal for patient NTG; $t(9)$ = 2.22, p = .053, and significant for RDE $t(9)$ = 5.88, p <.001; NNF $t(9)$ = 10.67, p <.001; and HNA $t(9)$ = 6.14, p <.001. However, three cases showed an exaggeration of the normal pattern (i.e., greater response efficiency for superordinate than specific items): NHY *t*(9) = 3.60, p = .005; NNZ *t*(9) = 2.90, p = .017; and NGW *t*(9) = 5.00, p < .001.

Table 2.6 - *Individual patient performance*

Patients	High association		Low association		uperordinate identit		Specific identity	
	Mean	Stdev	Mean	Stdev	Mean	Stdev	Mean	Stdev
Accuracy								
NHY	0.97**	0.18	0.91**	0.28	0.97	0.18	0.93**	0.26
SSR	0.97**	0.18	0.91**	0.28	1	0	0.88***	0.33
NNZ	1	0	0.81***	0.4	0.98	0.13	0.95*	0.22
NTG	0.95***	0.22	0.83***	0.38	0.83***	0.38	0.97	0.18
RDE	0.91***	0.28	0.79***	0.41	0.91*	0.28	0.90***	0.31
NGW	0.88***	0.33	0.78***	0.42	0.97	0.18	0.84***	0.37
NNF	0.93***	0.26	0.72***	0.45	0.78***	0.42	0.97	0.18
HNA	0.91***	0.28	0.64***	0.48	0.84***	0.37	0.95*	0.22
LHN	0.81***	0.4	0.55***	0.5	0.97	0.18	0.81***	0.4
Patient average	0.93	0.24	0.77	0.4	0.92	0.24	0.91***	0.27
Control average	1	0.01	0.96	0.02	0.97	0.03	0.98	0.01
Reaction time								
NHY	6846.70**	3717.19	15248.65*	11167.39	4594.40**	1495.91	6662.81**	4140.14
SSR	4698.23*	1327.66	7573.53*	2945.37	4296.61**	922.7	4723.13**	1461.86
NNZ	6947.62**	2336.82	9808.51**	3566.45	4479.59**	1382.85	6211.48**	2187.69
NTG	4629.12*	1747.1	7423.19*	3435.44	3889.00*	1169.38	3951.53	1804
RDE	10050.25*	4632.02	11834.65*	4345.64	9249.41**	5032.44	7004.68**	3610.76
NGW	10327.23*	4360.88	17895.64*	6136.88	7463.89**	2736.14	9486.42**	6853.64
NNF	10636.39*	3026.46	14966.39*	4505.64	11875.44*	3300.81	9102.50**	3112.02
HNA	7115.37**	3943.45	8579.69**	3176.94	7841.67**	2536.07	6376.30**	2912.75
LHN	8253.39**	3708.75	8446.97**	1953.29	5910.98**	1695.98	5679.64**	1745.85
Patient average	7722.7	3200.04	11308.58*	4581.45	6622.33**	2252.47	6577.61**	3092.08
Control average	3028.02	801.35	4957.73	1071.18	2365.06	620.45	2708.45	625.81

Patients are organised by order of severity in descending order. We used the ‘singlims’ procedure (Crawford & Garthwaite, 2002) to examine the extent to which the patient sample was impaired when compared to a control group on the battery of neuropsychological tests. Singlims uses a modified t-statistic to work out whether an individual is impaired, accounting for group size and standard deviation. Significant impairment is indicated as follows: * = p<.05, ** = p<.01, *** = p<.001

Summary of Experiment 1 – Identity and association matching in aphasia

The semantically-impaired stroke cases were significantly more impaired at matching thematic associations than object identity. However, their difficulties were largely restricted to the retrieval of *non-dominant* associations. Therefore, our findings are not fully consistent with the view that the patients' deficits reflected damage to a "thematic hub", but are instead compatible with the view they had impaired flexible and controlled semantic retrieval (Jefferies & Lambon Ralph, 2006). Weaker associations, like pineapple-cake, are thought to require more control over semantic retrieval to dampen down the spread of activation to highly associated but irrelevant associations (e.g., pineapple-fruit). A deficit in controlled semantic retrieval might also explain the reverse specificity effects seen several patients. High-frequency superordinate labels activate a broader range of semantic associations than low-frequency specific terms since they occur in a wider range of contexts. This is thought to increase demands on semantic control, which might be necessary to shape semantic retrieval towards associations relevant for a particular context (Hoffman et al., 2010). In line with this view, dysexecutive patients with prefrontal damage have shown reverse specificity effects in picture naming tasks (Humphreys and Forde, 2005).

Experiment 2 – Effects of dual task conditions on semantic performance in healthy participants

This experiment investigated whether the pattern observed in stroke aphasia could be reproduced under conditions of divided attention in healthy young participants. Such a finding would support the hypothesis that the deficits in semantically-impaired patients are related to the control demands of different semantic judgements. We used the same semantic tasks before, combined with either a relatively automatic or an attention-demanding secondary task during testing (Almaghyuli et al., 2012). We predicted that divided attention would produce more disruption of association than identity matching, and that the degree of this disruption would reflect associative strength.

Method

Participants: 30 right-handed native English speaking participants (27 females, mean age 20.5 years) were recruited at the University of York. Ethical approval was obtained from the Research Ethics Committee of the Department of Psychology at the University of York. All participants had normal/corrected-to normal vision and were screened for dyslexia through self-report. Two participants with incomplete datasets were removed from the analysis leaving a total of 28 participants.

Design: The study utilised a 2x2x2 within-subjects design, which examined (1) semantic task (categorical vs. associative); (2) semantic task difficulty (manipulated through strength of association and specificity, as before); and (3) dual task difficulty. An easy version of the dual task involved reproducing aurally presented numbers in numerical order (“count sequence”: e.g., 1 – “1”, 2 – “2”, 3 – “3”). A more demanding 1-back condition also involved spoken inputs and outputs, but required participants to supress the most recently-presented item and instead produce the item presented on the *previous* trial (i.e., 1 – “no response”, 6 – “1”, 3 – “6”). Thus, the 1-back condition placed greater demands on working memory, updating and controlled retrieval in the face of potential interference from the most recent input.

Procedure: The semantic tasks and stimuli were identical to Experiment 1; however participants were only given 3000 milliseconds to make their decision. During these semantic decisions, participants were simultaneously engaged in a secondary task, presented, and scored using the N-backer program (Monk et al., 2011). Both the count sequence and 1-back conditions for the secondary task involved spoken numbers every 1.5 seconds, presented over headphones. Participants had to give a spoken response before the next number was presented. The semantic tasks were presented using e-prime on a second computer and involved visual inputs and manual responses; thus participants could attempt these tasks at the same time.

At the beginning of the session, participants practiced both the easy and hard secondary task for 30 seconds in combination with the semantic tasks, allowing participants to become familiar with speed of presentation. Participants were instructed not to make other vocalisations during the task. An experimental session started with a set of 40 practice trials divided equally across association and identity judgements, which were performed three times; under single task conditions, during the count sequence task, and during 1-back. Semantic tasks and secondary tasks were blocked with participants completing 60 trials for each semantic judgement type. After 60 trials the participant stopped all tasks in order to read the instruction slide for the next set of semantic judgements. The order of identity and association judgements and the order of the secondary tasks were counterbalanced across participants.

Results

Table 2.7 shows RT and accuracy for both semantic tasks whilst performing the easy (count sequence) and difficult (1-back) secondary tasks, with the ANOVA analyses of these data provided in Table 2.8. Table 2.9 shows performance on the secondary tasks whilst making the different types of semantic judgement.

Semantic task performance: We present ANOVA results for accuracy and RT in Table 2.8, but focus here on a combined measure of response efficiency (RT/accuracy). All three measures (accuracy, RT and response efficiency) showed a similar pattern. Only correct responses were included in the RT analysis, and outlying responses more than two standard deviations from the mean for each participant were removed prior to analysis. A 2 (semantic task) by 2 (difficulty) by 2 (secondary task) repeated-measures ANOVA for response efficiency (see Table 2.8) showed main effects of semantic task (lower efficiency for association than identity matching), difficulty (lower efficiency for more difficult judgements overall) and the secondary task (1-back resulted in more disruption than the easier count sequence task). There was an interaction between semantic task and difficulty, indicating larger effects of associative strength than specificity (strong vs. weak for association matching task: Bonferroni $t(55) = -9.29$, p < 001; superordinate vs. specific for identity matching task: Bonferroni $t(55) = - 3.09$, p = .025), although difficulty effects were significant for both semantic tasks. There was also a significant interaction between semantic task and secondary task, with greater disruption from 1-back than from count sequences for association matching (Bonferroni $t(55) = -11.05$, p <.001) compared with identity matching (Bonferroni $t(55) =$

-10.41, p = <.001). The difficulty of semantic judgements interacted with the secondary task, reflecting greater disruption from 1-back than count sequences for the harder semantic judgements (dual task effect for easy semantic judgements: Bonferroni *t*(55) = -10.00, p <.001; and for hard semantic judgements: Bonferroni *t*(55) = -11.18, p = <.001). Finally, a significant three-way interaction was observed between semantic task, difficulty and secondary task (Figure 2.4). The weak association judgements were more affected by secondary task difficulty than the other three semantic tasks. Thus, divided attention specifically disrupted the task that was most impaired in the SA patients.

We followed the strategy used in the analysis of Experiment 1 and examined difficulty by secondary task interactions for the two semantic tasks separately. These confirmed that the secondary task (1-back vs. count sequences) interacted with difficulty in the thematic matching task (i.e., the effect of the secondary task depended on associative strength, F(1,27) = 26.29, p <.001, eta^2 = .463). In contrast, there was no interaction between secondary task identity and difficulty for the identity matching task (i.e. effect of specificity did not differ; F(1,27) =.31, p = .584, eta^2 = .011).

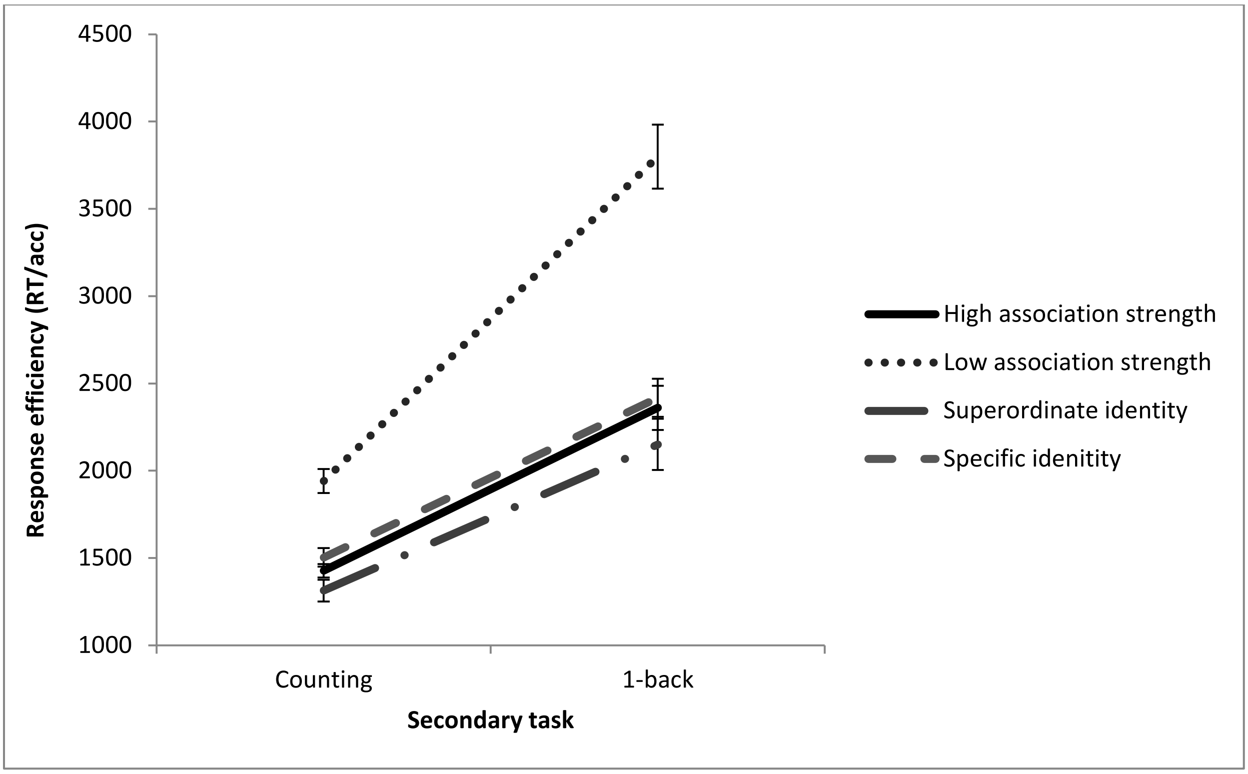


Figure 2.4 - Three-way interaction between semantic task, difficulty and secondary task for response efficiency. Error bars represent the standard error of the mean.

Table 2.7 - *Behavioural performance on the semantic tasks whilst performing the secondary tasks (Exp. 2)*

	Reaction time		Accuracy	
Condition	Mean (milliseconds)	stdev.	Mean (proportion correct)	stdev.
Count sequence secondary task				
High association strength	1315.23	168.23	.91	.07
Low association strength	1543.05	175.78	.79	.14
Superordinate identity	1178.46	205.85	.91	.09
Specific identity	1285.58	225.61	.85	.08
1-back secondary task				
High association strength	1618.45	249.81	.70	.16
Low association strength	1861.25	231.29	.51	.12
Superordinate identity	1574.32	242.86	.76	.16
Specific identity	1568.99	257.38	.67	.11

Table 2.8 - *ANOVA results for reaction time, accuracy, and response efficiency in Exp. 2*

	Response efficiency (RT/accuracy)			Reaction time			Accuracy		
	F	Sig.	effect size (partial eta²)	F	Sig.	effect size (partial eta²)	F	Sig.	effect size (partial eta²)
Semantic task	**100.58**	**<.001**	**0.788**	**95.63**	**<.001**	**0.78**	**43.48**	**<.001**	**0.617**
Difficulty	**102.78**	**<.001**	**0.792**	**49.93**	**<.001**	**0.649**	**92.42**	**<.001**	**0.774**
Secondary task	**132.91**	**<.001**	**0.831**	**97.04**	**<.001**	**0.782**	**143.67**	**<.001**	**0.842**
Task by difficulty	**48.23**	**<.001**	**0.641**	**27.87**	**<.001**	**0.508**	**13.79**	**0.001**	**0.338**
Task by secondary task	**20.27**	**<.001**	**0.429**	0.282	0.6	0.01	**17.14**	**<.001**	**0.338**
Difficulty by secondary task	**14.44**	**<.001**	**0.348**	0.83	0.37	0.03	**11.45**	**0.002**	**0.298**
Task by difficulty by secondary task	**21.39**	**<.001**	**0.442**	**4.31**	**0.05**	**0.135**	0.951	0.338	0.034

Table reports separate omnibus ANOVAs for each measure

Secondary task performance: Table 2.9 shows the accuracy on the secondary tasks whilst participants were performing the two types of semantic judgements. Correct responses occurred when participants produced the target number within the response window before the next item in the sequence was presented. Performance on the count sequence and 1-back tasks was examined using a 2 (semantic task) by 2 (secondary task) repeated-measures ANOVA. There was a highly significant main effect of secondary task type (F(1,27) = 104.73, p <.001, eta^2 = .795), demonstrating that the 1-back task was less accurate than the count sequence task. In addition, there was a significant interaction between semantic task and secondary task (F(1,27) = 9.23, p =.005, eta^2 = .255) revealing that the harder secondary task was significantly disrupted by the association judgements compared to the identity judgements.

Table 2.9 – *Behavioural performance for the secondary dual tasks*

Condition	Mean proportion correct (%)	Stdev.
Counting secondary task		
Association matching	.94	.02
Identity matching	.93	.01
1 n-back secondary task		
Association matching	.68	.12
Identity matching	.72	.14

Summary of Experiment 2 – secondary task disruption in healthy participants

The 1-back task depleted executive resources for semantic processing more than the production of numbers in order. The requirement to selectively attend to items in memory disrupted association matching more than identity matching, particularly when the associations were weak. Thus, healthy participants tested under conditions of divided attention showed poorer performance on the same condition that was more impaired for the stroke patients in Experiment 1, supporting our earlier conclusion that the patients' difficulties on thematic matching tasks reflect a deficit in the control of semantic retrieval, as opposed to loss of knowledge per se.

General Discussion

This study compared the explanatory power of two different accounts of conceptual deficits in semantic aphasia. Semantic deficits in SA patients may reflect deficient semantic control or a specific impairment in thematic knowledge. According to one view, damage to a “thematic hub” in temporoparietal cortex impairs knowledge about events and semantic associations, while a hub for categorical knowledge in ventral anterior temporal cortex remains largely intact. An alternative framework proposes that inferior ATL captures knowledge of associations as well as concrete features of objects, and emphasises deficient semantic control as opposed to damage to representations in SA, since the focus of their damage is not in ventral ATL. To test these accounts, we compared knowledge of thematic associations and object identity in semantically impaired aphasia patients (Experiment 1) and healthy participants under conditions of reduced executive capacity (Experiment 2). In addition, we manipulated the difficulty of these judgements by contrasting strong with weaker associations, and by comparing superordinate and specific identity matching tasks. The retrieval of weak associations is expected to require greater executive control (since semantic retrieval must be focussed on non-dominant links and directed away from strong yet irrelevant aspects of knowledge in these trials; Badre et al., 2005; Whitney et al., 2012; Jefferies, 2013). In contrast, although the retrieval of specific identity is globally harder than the retrieval of superordinate identity because concepts must be specified more precisely, necessitating the retrieval of more information, this manipulation does not have the same impact on control demands – indeed, the control demands of the superordinate decisions are arguably higher because the words in the trials had higher contextual diversity (i.e., they had more variable meanings, across a wider range of contexts).

The data supported the view that the patients’ semantic deficits reflected impaired control. This semantic control deficit (and conditions of divided attention in healthy young participants) specifically disrupted the thematic matching task when the associations being probed were non-dominant (i.e., the weak association condition). In addition, both groups of participants did not show the same degree of disruption for identity matching, even when this task was made more difficult by requiring the retrieval of highly specific concepts. Although healthy young participants and age-matched controls found it easier to match words with pictures on the basis of shared identity when superordinate labels (e.g., “animal”) as opposed to specific labels (e.g., Dalmatian) were presented – presumably because less detailed conceptual retrieval was required – this effect of difficulty was not increased in magnitude by a demanding concurrent 1-back task. Similarly, patients with semantic aphasia showed an exaggerated effect of difficulty in a thematic matching task – but as a group they did not show an exaggerated effect of specificity in identity matching and some cases showed *reverse* specificity effects (i.e., better retrieval of specific than superordinate concepts).

In healthy individuals, categorising items based on their thematic/associative relationships is thought to draw on cognitive control processes; transcranial direct stimulation (tCDS) when applied to the left prefrontal cortex affects whether participants are more likely to categorise items based on weakly associated features, based on whether the current is excitatory or inhibitory (Lupyan et al., 2012). However, making decisions based on thematic links does not necessarily require greater control – instead, the control demands should vary with the strength of the association being probed. When the relevant relationship is between weakly associated items, the target cannot be identified through automatic spreading activation (Badre et al., 2005; Jefferies et al., 2008; Whitney et al., 2011a) – instead, control processes are required to shape semantic processing away from dominant yet currently-irrelevant information in a flexible way to suit the current context and goals. This pattern is observed in SA patients, including the case-series presented here: these individuals are poor at retrieving the non-dominant meanings of ambiguous words, yet are able to retrieve these meanings when provided with external cues such as a sentence that guides retrieval towards relevant information. Similarly, unless the context is highly constraining, their responses during picture naming, fluency tasks, and other associated tasks can be highly disordered and vague (Jefferies and Lambon Ralph, 2006; Jefferies et al., 2008; Corbett et al., 2009b; Soni et al., 2009; Jefferies et al., 2010; Noonan et al., 2010; Corbett et al., 2011). The inability to prevent automatic spreading activation might underpin SA patients’ production of associative errors in picture naming tasks (producing ‘nuts’ when presented with a picture of a Squirrel); these responses are suggestive of a failure to guide semantic retrieval towards knowledge relevant for the task (Jefferies and Lambon Ralph, 2006).

Reduced semantic control in patients with semantic aphasia (and in healthy participants with a concurrent task) did not increase difficulty effects across the board: while the harder, weak-association trials were more disrupted than judgements about strong thematic links, control deficits did not interact with difficulty in the identity matching task in the same way. We manipulated the specificity with which objects were matched with words. Identifying objects at a specific level is generally more difficult (i.e., error rates were higher and response times were longer for controls), and specific-level knowledge is especially vulnerable to neurodegeneration in the ATL in semantic dementia (Bozeat et al., 2000; Mummery et al., 2000; Jefferies and Lambon Ralph, 2006; Patterson et al., 2007). Yet the SA patients investigated here showed a different pattern: in the group analysis, they did not show an increased effect of specificity, relative to controls, and some individuals showed *reverse* specificity effects (i.e., more impairment for superordinate labels). These findings once again might reflect deficient semantic control. Superordinate terms like “animal” have substantially higher frequency than specific labels like “Labrador”, and therefore appear in a greater range of contexts – for example, “animal” might refer to a pet, a farm animal, a zoo animal, a wild animal or a badly behaving human. In contrast, specific terms have very specific uses: “Labrador” is likely to be a pet, and none of the other contexts apply (Hoffman & Lambon Ralph, 2011). In the task used in this study, a single picture was presented with a choice of three words; therefore, when the words that participants could select from were superordinate and high frequency, uncontrolled spreading activation would be expected to activate a broad field of task-irrelevant associations, increasing the need to narrow down semantic retrieval in line with the demands of the task. In contrast, uncontrolled spreading activation from the word “Labrador” would remain relatively narrow and focussed on salient task-relevant features. This pattern is consistent with previous reports of higher control demands for superordinate-level terms affecting picture naming performance in SA (Crutch and Warrington,

2008) and other patients with semantic impairment in the context of dysexecutive syndrome (Humphreys and Forde, 2005). However, this effect was not reliable in every case: three patients showed significant reverse specificity effects and it should also be noted that three of the more mildly impaired cases (overall task accuracy was greater than or equal to 90%) showed an exaggeration of the normal pattern, alongside a non-significant relationship between executive measures and performance on our experimental task, consistent with the view that semantic control and executive control can be independently impaired (Hoffman et al., 2013).

The patients had large frontoparietal lesions affecting the regions associated with the thematic hub in mid AG (50% of cases) and pMTG (100% of cases) (Schwartz et al., 2011; de Zubicaray et al., 2013). However, these regions implicated in knowledge of events and thematic associations overlap with areas in posterior temporal cortex implicated in controlled semantic retrieval in pMTG (Noonan et al., 2013; Davey et al., Submitted). Indeed, the majority of our patient sample had damage to both anterior and posterior components of the distributed network implicated in semantic control, including to dorsal AG/IPS, pMTG and LIFG (Whitney et al., 2012; Noonan et al., 2013). We hypothesise that co-activation in LIFG and pMTG is important for maintaining relevant semantic information which is selected and shaped to suit the current task context (Jefferies, 2013; Noonan et al., 2013). This function was tapped by the weak associative judgements in the current study, which required participants to set up a shared context between items, while ignoring strong automatic but irrelevant relationships between items. Disruption to this semantic "shaping" process might result in patients not being able to recover a non-dominant link between words, and not being able to avoid dominant yet irrelevant features and associations. This proposal is in line with previous suggestions that interactions between ventral pre-frontal cortex (vPFC) and pMTG allow for selected aspects of meaning to be maintained in short term memory before contextual integration (Turken and Dronkers, 2011a).

We used a dual-task method in a second healthy sample to observe whether association matching required more semantic/cognitive control than identity matching. While both semantic judgements were affected by the difficulty of the secondary task, the 1-back task particularly disrupted retrieval of weak associations (compared with identity matching or strong associations). Thus, this work supports the findings of the patient study. The 1-back task reduced general executive capacity and, like the semantic tasks, also required the controlled retrieval of representations from memory in the face of competition from a dominant response (i.e., the item presented in the immediately preceding trial): this may have contributed to its effectiveness. Neuroimaging studies suggest there is partial overlap between brain regions that contribute to semantic control and those that are implicated in domain general cognitive control: anterior LIFG and pMTG are thought to contribute to controlled retrieval of semantic information, but do not form part of the multi-demand executive network, while posterior LIFG/IFS and dorsal AG/IPS are recruited during both difficult semantic judgements and other executively-demanding tasks (Duncan, 2010; Noonan et al., 2013).

In conclusion, this study supports the view that the deficits in SA are the result of impaired control over semantic retrieval (Jefferies and Lambon Ralph, 2006), rather than damage to representations within a hub which supports thematic associations (Schwartz et al., 2011). Our results therefore motivate some modification of the two-hub theory: while there is strong evidence that separable components of semantic cognition are impaired in patients with ATL and frontoparietal damage (Jefferies and Lambon Ralph, 2006; Schwartz et al., 2011), their differences may not reflect loss of two different types of knowledge (e.g., categorical vs. thematic), but rather loss of task- and context-invariant semantic information versus difficulty with the flexible retrieval of knowledge.

Chapter 3 - Shaping and orientating to semantic space: TMS reveals distinct contributions of posterior middle temporal gyrus and angular gyrus

Abstract

The neural processes underpinning the reflexive and controlled orientation of attention to external stimuli have been widely studied, but less is known about how we detect and shape the activation of concepts in our mental world. Two structures in left temporoparietal cortex, angular gyrus (AG) and posterior middle temporal gyrus (pMTG), are thought to be key to this process and are often recruited together during semantic tasks; however, they show strikingly different patterns of functional connectivity at rest (coupling with the 'default mode network' and 'frontoparietal control system' respectively). Here, repetitive transcranial magnetic stimulation (rTMS) was used to establish a causal yet dissociable role for these sites in object identification and the retrieval of thematic associations. TMS to AG disrupted thematic judgements irrespective of the strength of the association between probe and target, while TMS to pMTG only disrupted weak thematic associations when the requirement to guide activation to the linking context was high. In addition, TMS to AG impaired the identification of objects at a specific level (e.g., Dalmatian), while TMS to pMTG only disrupted identity matching for basic and superordinate labels (e.g., dog; animal), which have more variable meanings across contexts and thus higher control demands. Our findings can be accommodated within a new theoretical framework in which mid-AG is necessary for accurate reflexive orientation of internal attention towards activated conceptual representations, while pMTG flexibly shapes conceptual activation such that currently-relevant aspects of knowledge are brought to the fore.

Introduction

Conceptual knowledge drives thought and behaviour through a combination of (i) automatic spreading activation between highly related concepts and (ii) control processes tailoring activation to suit the current context and goals (Badre et al., 2005; Jefferies et al., 2008; Whitney et al., 2012; Noonan et al., 2013). On encountering words and objects, we activate representations in anterior temporal lobes (ATL) capturing 'deep' conceptual similarities across perceptual/motor features (Patterson et al., 2007; Rogers and Patterson, 2007) and *reflexively orient attention* towards these representations. However, we know a myriad of features and associations for any given concept – only some are relevant at any one time, thus executive-semantic processes are recruited to *flexibly shape* retrieval towards relevant but non-dominant aspects (Thompson-Schill et al., 1997; Wagner et al., 2001b; Jefferies and Lambon Ralph, 2006). Thus, the ATL hub interacts with control processes supported by left inferior frontal gyrus (LIFG; Thompson-Schill et al., 1997; Wagner et al., 2001b; Badre et al., 2005; Noonan et al., 2013) in conjunction with the frontoparietal "multiple-demand" system (Duncan, 2010). Greater 'shaping' of conceptual retrieval is required when there is strong competition from alternative meanings and/or when the context only weakly cues the retrieval of relevant information (Badre et al., 2005; Rodd et al., 2005; Bedny et al., 2008; Rodd et al., 2010a; Rodd et al., 2010b; Whitney et al., 2011b; Rodd et al., 2012).

While ATL and LIFG are associated with automatic and controlled semantic retrieval respectively, the contribution of temporoparietal regions remains unclear – even though posterior middle temporal gyrus (pMTG; Visser et al., 2012a; Noonan et al., 2013) and mid-angular gyrus (AG; Binder et al., 2009; Humphreys and Lambon Ralph, 2014) show highly reliable responses to semantic contrasts. Some theories propose a temporoparietal semantic store complementing the information in ATL (Schwartz et al., 2011): ATL integrates knowledge about concrete multimodal features supporting the categorical organisation of knowledge (e.g., apple is similar to banana; Tyler et al., 2003; Rogers et al., 2004), while AG and/or pMTG capture *thematic* *knowledge* (such that apple is linked to pie; Schwartz et al., 2011; Mirman and Graziano, 2012b; de Zubicaray et al., 2013).

Alternatively, pMTG and/or AG might contribute to specific conceptual *retrieval processes* (Cabeza et al., 2011; Humphreys and Lambon Ralph, 2014). Patients with semantic aphasia following left temporoparietal stroke have deficits of controlled semantic access/retrieval: this ‘deregulated’ semantic cognition is also seen following LIFG damage and is qualitatively distinct from degraded semantic knowledge seen in semantic dementia (Jefferies and Lambon Ralph, 2006; Noonan et al., 2010). However, the lesions in these patients prevent the separation of pMTG and AG. Moreover, the retrieval hypothesis remains highly controversial given that both regions are often considered to underpin aspects of semantic representation (Martin, 2007; Binder et al., 2009). Therefore, we used TMS to produce focal ‘virtual lesions’ in pMTG and AG, and explored the impact on identity and association matching tasks to determine whether either of these sites can be characterised as a “thematic hub” or whether they support aspects of semantic retrieval.

Materials and methods

Overview: We used inhibitory offline TMS (pulses at 1Hz for 10 minutes) to produce 'virtual lesions' within left mid-AG and pMTG, and examined the effect of this stimulation on two types of word-picture matching, requiring either (1) object identification e.g., is the picture a DALMATION or a CORGI?) or (2) the retrieval of thematic associations (e.g., does the picture go with BONE or FEATHER). Since stimulation was delivered offline, TMS-induced disruption could not be attributed to distracting jaw contractions or eye blinks following peripheral nerve stimulation. We also included a control task (scrambled picture matching) and a control site (vertex) to test for non-specific effects of TMS. Performance immediately after the application of TMS was compared with baseline data collected either immediately *before* or 30 minutes *after* stimulation, by which time inhibitory TMS effects are no longer expected to be present (Pobric et al., 2010; Whitney et al., 2011b). Thus, the order of TMS and baseline sessions was counterbalanced across participants.

Selection of stimulation sites: The TMS sites (see Figure 3.1) were taken from two complementary meta-analyses of neuroimaging data. Figure 1 displays the TMS stimulation peaks on an inflated surface, accompanied by functional connectivity (the resting state data used in these measures of functional connecitivity was taken from the Enhanced Nathan Kline Institute Rockland Sample and is independent of the TMS data and sites in this study) measures using the TMS sites as seed regions. The left mid AG site was taken from a meta-analysis examining semantic tasks versus difficulty-matched non-semantic tasks (Humphreys and Lambon Ralph, 2014) and is comparable to the peak for semantics reported by Binder et al. (2009). The pMTG site, in contrast, was a peak response in a meta-analysis examining diverse manipulations of semantic control (i.e., effects of strong competition, weak probe-target relationships and improverished contextual constraints, versus lower-control versions of these tasks; Noonan et al., 2013). Thus, while the response to semantic manipulations in neuroimaging studies often encompasses both pMTG and AG within one cluster (Binder et al., 2009), we predicted that these sites would show a functional dissociation, with a greater contribution to automatic aspects of retrieval in AG, and more controlled semantic processes in pMTG. Stimulation of an additional site in ATL (-53 0 -22) did not elicit any inhibitory effects and is not discussed further.

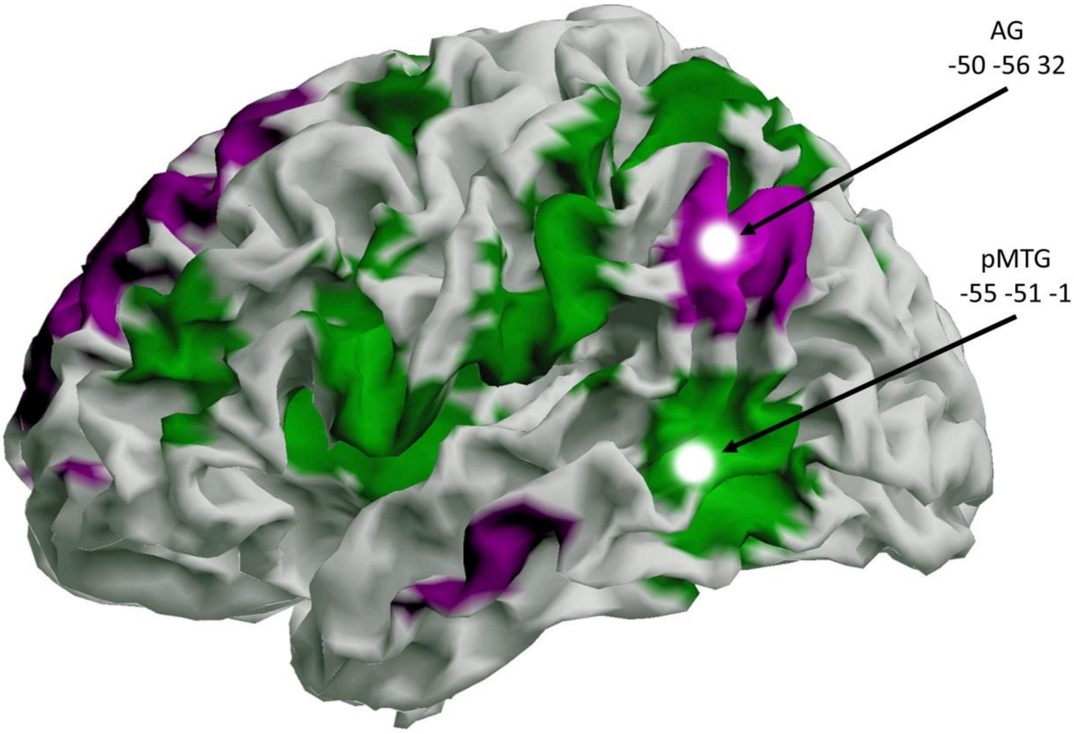


Figure 3.1 - The two TMS stimulation sites and their differing resting state connectivity. The MNI co-ordinates shown are the target sites for TMS application taken from two meta-analyses focused on automatic and controlled semantic retrieval (Noonan et al., 2013; Humphreys and Lambon Ralph, 2014). Resting state scans from 81 individuals from the Enhanced Nathan Kline Institute Rockland Sample (NKI-RS, 1st release) were used. Scans were 5 minutes duration each (TR = 2500 ms; TE = 30ms; 38 slices; voxel size = 3 mm isotropic). Data were processed using DPARFS (v2.3) toolbox (Chao-Gan and Yu-Feng, 2010), implemented in MATLAB (MathWorks, Inc.). Pre-processing steps included slice-time correction, motion correction, normalisation to MNI space using the unified segmentation approach (Ashburner and Friston, 2005), smoothing with FWHM of 4 mm, detrending and band-pass filtering (between .01 and .10 Hz). Nuisance covariates (head motion parameters, white matter and cerebrospinal fluid signal) were also regressed. The connectivity patterns of the two regions of interest were explored by seeding the stimulated regions (AG and pMTG) with a sphere of 6mm radius. The averaged time course was obtained

from each ROI and the correlation analysis was performed in a voxel-wise way to generate the functional connectivity of each region. The correlation coefficient map was converted into z maps by Fisher's r-to-z transform to improve the normality Rosner (2006). Each individual’s connectivity maps for AG and pMTG were then compared against each other in a paired samples t-test, with each contrast masked by a binarised mask of the region's functional connectivity z-map.

Tasks: All tasks involved word-to-picture matching, with a probe picture presented alongside three words (i.e., 3 alternative forced choice design). Figures 3.2 and 3.3 contain an example trial for each condition. We manipulated the requirement to shape the activation elicited by the target word in both the identity and association matching tasks. For association matching, relatively little shaping was required when the probe-target relationship was strong (e.g., DOG-BONE) since activation is thought to spread rapidly and automatically between strongly-related concepts. In contrast, when the probe-target relationship was weaker (e.g., DOG-RAZOR WIRE), semantic processing needed to be “shaped” by control processes that channelled activation towards features relevant for the linking context (e.g., guard dog; Copland et al., 2003; Wible et al., 2006; Sass et al., 2009a) and away from dominant but currently irrelevant associations (e.g., dog as pet). A group of 9 participants who did not take part in the rTMS experiment rated the probe-target pairs for the strength of association on a 7-point scale (0 = no discernible association; 7 = extremely strong link), and these ratings were used to assign trials to conditions. A further set of ratings from 28 participants were entered as a continious variable in the analysis (see analysis section).This contrast of weak vs. strong associations has been used in many investigations of semantic control: it reliably activates pMTG along with LIFG in fMRI investigations (Badre et al., 2005; Noonan et al., 2013), and TMS to both LIFG and pMTG disrupts the retrieval of weak but not strong semantic associations (Whitney et al., 2011b), suggesting they both play a causal role in shaping semantic retrieval. Given these findings, we predicted that the disruptive effect of TMS would be inversely related to the strength of association between the probe and target concepts for pMTG but not AG.

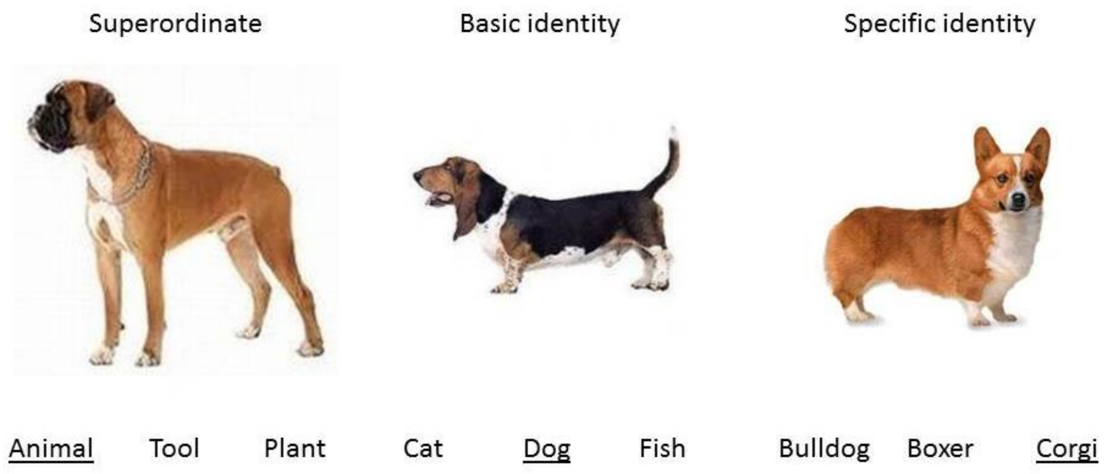


Figure 3.2 - Example of the identity judgements at different levels of specificity. The target word is underlined.

In the identity matching task, we varied the level of specificity at which an item was identified: participants had to match a photograph of an object (e.g., a specific type of dog) to (i) its specific name (i.e., ALSATIAN), (ii) the basic-level name they would typically use to refer to the object (i.e., DOG) or (iii) a superordinate label (ANIMAL). Healthy particiants show a basic-level advantage in word-picture matching tasks because these terms are more frequent (Rogers and Patterson, 2007). However, while higher frequency labels enjoy some processing advantages, there is also a cost in terms of increased semantic control demands. Hoffman and Lambon Ralph (2011) explained this in terms of contextual diversity – i.e., more frequent terms like ANIMAL and DOG are used in a wider range of contexts than specific low-frequency terms like ALSATIAN and thus they tend to activate a wider range of associations that are not relevant to object identification – e.g., the word DOG might elicit activation of the concepts LEAD and KENNEL, which is irrlevent for the task of word to picture matching (see also Almaghyuli et al., 2012). Therefore, if pMTG is involved in shaping semantic retrieval across tasks, inhibitory TMS to this site should disrupt superordinate and basic-level identification more than specific-level matching. However, in other ways, specific-level matching is harder than superordinate/basic level matching, since this task requires highly similar representations with overlapping features to be distinguished – i.e., separation of ALASATIAN from other breeds of dog (Patterson et al., 2007). Patients with semantic dementia (SD) and semantic aphasia (SA) show opposing effects of specificity: SD cases are more impaired when fine-grained concepts are probed, since similar and highly overlapping concepts (ALSATIAN, DALMATIAN) collapse together into a single attractor (DOG) as ATL degenerates. In contrast, the semantic control deficit in SA produces weaker effects of specificity, particularly when the task structure minimises competition, since (1) this condition is not associated with a loss of conceptual knowledge per se, but instead difficulty retrieving it in an appropriate way and (2) deficits of control disproportionately affect understanding of high-frequency superordinate and basic-level terms (Hoffman and Lambon Ralph, 2011). Given our prediction that pMTG and AG differentially contribute to controlled and automatic aspects of semantic retrieval, we might expect stimulation of these sites to maximally disrupt superordinate/basic-level matching and specific matching respectively.

Figure 3.3 - Example of the association judgements. Association strength is in italics under the target word. The target word is underlined.

Given the proximity of pMTG and AG to brain regions supporting aspects of visual processing and attention, we included a non-semantic control task with similar perceptual and decision making demands as the semantic judgments. The stimuli were scrambled black and white images photographs and participants were asked to find a target which was identical to a probe; the distracters were the same images rotated by 180˚ or 270˚ degrees.

Participants: 18 right handed participants were recruited from the University of York, UK (7 females, mean age 23, range 11 years). Three additional participants with incomplete data were removed prior to analysis. All participants had normal or corrected to normal vision and met safety screening requirements for TMS. Ethical approval was given by Ethics Committee of the York Neuroimaging Centre.

Stimuli: 318 colour photographs, collected through an internet search engine (Google), were used in the semantic tasks (with the same probes used across the different judgement types). All images were resized to 200x200 pixels whilst maintaining the aspect ratio of the initial image to prevent distortions. 262 images of faces were pixelated and scrambled (Krieger-Redwood, 2012) for the visual control task. In the semantic tasks, these images were presented alongside target nouns which were either the names of natural/man-made objects at different levels of specificity, or concrete associates of the object. The distracters in the association matching task were associates taken from other trials (carefully selected to ensure they were not linked to the probe). A separate set of participants who did not take part in the TMS experiment provided ratings of familiarity and imagability of the target nouns, with further ratings of lexical frequency obtained from the SUBTLEX-UK database (van Heuven et al., 2014) alongside polysemy ratings collected using WordNet (2010).

Procedure: Structural T-1 MRI scans (3D FSPGR MRI) were co-registered to the scalp using Brainsight (Rogue Research, Montreal Canada, https://www.rogue-research.com) to identify the stimulation targets in each participant's brain. Scalp measurements were taken to determine the location of the vertex. At the beginning of each session, each participant's active motor threshold was established, determined as the lowest stimulation intensity needed to cause a contraction of the first dorsal interosseous (FDI) muscle of the right hand when stimulating left motor cortex (average motor threshold was 61%, with a range of 29%, average stimulator output was 73%). TMS stimulation was delivered using an 8mm figure of eight coil, attached to a MagStim Rapid stimulator (The MAGSTIM Company Ltd). Repetitive trains of TMS were delivered at 1 Hz for 10 minutes changing the coil after 5 minutes. Stimulation intensity was set at 120% of a participant's individual motor threshold and capped at a maximum of 75% of stimulator output. Coil orientation was adjusted to produce the most comfortable stimulation for participants. Tasks were presented on a PC running E-prime 2.0 (Psychology Software Tools). Each session started with a set of 20 practice trials. Per session, there were 4 blocks of trials after TMS and at baseline (in the absence of TMS). The blocks were divided into mini-blocks containing 20 trials for each of the identity and association matching conditions (with both of these split into 10 easy and 10 hard trials), and 10 trials for the visual control task (i.e., 50 trials in all per block; 40 trials per condition across blocks). The order of conditions and stimuli was counterbalanced across participants and experimental sessions. No trials were repeated within a session and 7.5% of trials were repeated across sessions. Tasks started with a prompt to remind the participant what feature they had to match (IDENTITY = match the picture with its name, ASSOCIATION = match the picture to a verbal association, VISUAL = match the top picture to an identical but rotated target picture). For all tasks, the three written response options appeared 900ms before the probe image, which stayed on screen for a maximum of 3000ms after the presentation of the response image or until the participant made their response. Participants pressed 1, 2, or 3 to indicate their selection of targets on the left, middle, and bottom of the screen.

Statistical analysis: Behavioural data was analysed using hierarchical linear modelling (HLM) in SAS 9.3 (SAS Institute Inc., North Carolina, US). Accuracy data was analysed using PROC GLIMIX but this analysis did not reveal significant effects of TMS and is not discussed further. Thus, the analysis below focuses on response time (RT), which was analysed using PROC MIXED with maximum likelihood (ML) as the estimation method and an "unstructured" covariance structure. Incorrect trials were removed prior to analysis, as were outlying responses that fell more than 2 s.d. from each participant's mean for that condition. We report three analyses below: (1) an omnibus model examining effects of TMS for each site and condition; (2) a model of association matching incorporating association strength as a continuous variable; (3) a model examining three levels of specificity – for superordinate, basic and specific-level labels – in the identity matching task. Details of each of these models are provided below.

Results

Analysis 1 – Omnibus model: This model included three categorical fixed effects. (1) There were five conditions: (i) superordinate identity matching (for the over-arching category labels ANIMAL, WEAPON, FOOD, VEHICLE, PLANT, CLOTHES, HOUSEHOLD ITEM, FOOTWEAR, TREE, INSTRUMENT, and SPORTS EQUIPMENT); (ii) more specific identity matching (using the names of individual objects); (iii) thematic association matching for strong probe-target pairings (rated associative strength; mean = 5.46, s.d. = .75); (iv) thematic association matching for weaker probe-target pairings (rated associative strength; mean = 4.70, s.d. = .79); (v) visual matching for meaning images. (2) There were four stimulation sites (1 = AG, 2 = ATL, 3 = pMTG, 4 = vertex). (3) There were two levels of TMS time (0 = baseline, 1 = post TMS). All interactions terms between these effects were included, with participant and target item entered as random effects. We permitted random variation for the intercept at both subject and individual trial level. This represents a fully saturated model which was constructed in order to examine pairwise comparisons of the least squared (LS) means with and without TMS, controlling for multiple comparisons (26001 observations).

Table 3.4 shows mean RT for each condition entered into this analysis, plus response accuracy. Table 3.1 shows the outcomes of the statistical tests. As expected, the pairwise contrasts revealed no significant TMS effects at vertex (the non-semantic control site). AG showed significant TMS effects for specific identity matching, strong and weak associations and visual decisions. pMTG showed significant TMS effects for superordinate and specific level identity matching, visual decisions and a marginal effect for weak associations. Since TMS to both AG and pMTG disrupted identity *and* thematic association matching, neither site showed the profile expected for a thematic hub (i.e., specific disruption of semantic associations). Moreover, since TMS to pMTG and AG disrupted visual matching as well as semantic decisions, it is possible that the functional contribution of these sites is not restricted to the semantic domain, or that neighbouring visual cortical regions were additionally stimulated. For this reason, we included the TMS effect for the visual task (per participant and session) as a covariate of no interest in subsequent analyses examining association strength and specificity.

Table 3.1 - *Paired contrasts examining the TMS effect (no TMS vs. TMS) for each site and each task separately*

Site	**LS means estimate difference**	**Condition**	**t-value**	**Sig.**
AG	-116.59	Superordinate identity	-0.92	0.357
AG	-57.20	More specific identity	**-2.71**	**0.007**
AG	-43.80	Strong association	**-2.13**	**0.034**
AG	-64.28	Weak association	**-3.00**	**0.003**
AG	-41.50	Visual	**-1.99**	**0.046**
pMTG	-43.20	Superordinate identity	**-2.11**	**0.035**
pMTG	-46.06	More specific identity	**-2.19**	**0.028**
pMTG	-20.20	Strong association	-0.98	0.326
pMTG	-38.30	Weak association	-1.76	0.079
pMTG	-53.29	Visual	**-2.54**	**0.011**

Footnote: Comparing LS means for each site and task, with and without TMS. Significant effects of TMS are highlighted in bold text.

Analysis 2 – *Association strength as a continuous variable:* We fitted a fully-saturated model to estimate the effects of TMS on RT for pMTG and AG at different levels of associative strength, entered as a continuous variable. Fixed effects were association strength, site and TMS time, with subject and the target on each trial as random effects (10204 observations). We predicted that TMS to pMTG would only disrupt the weakest association trials, while TMS to AG might disrupt all thematic associations. Consistent with this prediction, we found a statistically significant three-way interaction, *F*(3, 9037) = 2.78, *p* = .040, between TMS, site and associative strength. This justified running separate models for each site to determine the relationship between TMS and associative strength. Each of these models was computed twice, with and without statistically controlling for the effects of TMS on the visual task, by entering the LS means estimates of this non-semantic TMS effect, per participant and per site, as a covariate. In addition, for all four models, lexical frequency, polysemy, familiarity, and imageabilty ratings were entered as covariates to control for the variable nature of associations between items and the psycholinguistic variables of the target words.

Figure 3.4 shows the predicted RT values at different levels of associative strength whilst controlling for all other sources of variance in the model. Point comparisons were computed for the LS means with and without TMS at six different levels of associative strength (ranging from ranging from 1.5 to 6.5 on a 7-point scale). These comparisons, corrected for multiple comparisons, confirmed our predictions. TMS to AG disrupted both strong and weak associations, while stimulation to pMTG caused a specific disruption only for weakly associated items. These effects were observed at both sites even when the disruption to the visual trials was entered as a covariate; i.e. disruption of non-semantic decisions was not sufficient to explain the impairment of semantic performance, as reported in Table 3.2. Moreover, additional models examining the two sites separately revealed a marginally significant interaction (this result is significant when performing a one-tailed test, consistent with our predication of a disruptive effect of TMS on weakly associated items at this site) between TMS time and associative strength for pMTG (*F*(1, 1615) = 1.70, *p* = .087) but not AG (*F*(1, 1606) = 0.21, *p* = .650). Thus, TMS to pMTG elicited the profile associated with the disruption of controlled semantic retrieval, while stimulation of AG did not.

Table 3.2 - *Least squared mean differences for the TMS effect (no TMS vs. TMS) in Analysis 2, modelling associative strength as a continuous variable*

Site	Associative strength	No visual covariate		Visual covariate entered	
		LSmean difference	**Sig.**	**LSmean difference**	**Sig.**
AG	1.5	-55.0	**.002**	-39.0	**.031**
	2.5	-55.0	**.002**	-39.0	**.031**
	3.5	-55.0	**.002**	-39.0	**.031**
	4.5	-55.0	**.002**	-39.0	**.031**
	5.5	-55.0	**.002**	-39.0	**.031**
	6.5	-55.0	**.002**	-39.0	**.031**
pMTG	1.5	-125.4	**.032**	-117.3	**.042**
	2.5	-98.6	**.024**	-85.3	**.049**
	3.5	-71.8	**.017**	-53.33	.076
	4.5	-44.9	**.024**	-21.3	.291
	5.5	-18.2	.355	10.7	.588
	6.5	8.6	.769	42.8	.145

Footnote: Point comparisons of RT with and without TMS at different levels of associative strength. The analysis was performed twice, with and without the inclusion of the TMS effect for the visual task as a covariate. Significant effects of TMS at p<.05 are highlighted in bold text.

Analysis 3 – Identity matching at three levels of specificity: To subdivide the "more specific" trials from Analysis 1 into basic-level and specific-level trials, we asked a separate group of 8 participants to name the probe pictures. When the majority of participants (>80%) spontaneously produced the target label as the name of the object, trials were considered to be basic-level. Trials were considered to be specific-level when fewer participants provided the target label as the name of the object – with the majority of alternative responses corresponding to a more generic label (such as "dog" for ALSATIAN). These three categories (5258 observations in total, 2709 = 'superordinate', 1394 = 'basic', 1155 = 'specific') were entered as a fixed effect alongside site and TMS time, with subject and target as random effects.

Paired contrasts, corrected for multiple comparisons (see Figure 3.5 and Table 3.2, 3.3), revealed that TMS to AG only disrupted identity matching at the specific level, suggesting this site allows precise semantic retrieval that differentiates highly similar concepts that share many features. In contrast, pMTG demonstrated significant disruption for items which were labelled at the superordinate and basic level, suggesting it contributes to retrieval when broad category labels activate potentially irrelevant features. A similar pattern was seen when the visual TMS effect for each participant and each site was added as a covariate of no interest.

Table 3.3 - *Paired contrasts of TMS effect (no TMS vs. TMS) in Analysis 3, at three levels of specificity*

		No visual covariate		**Visual covariate entered**	
Site	**Specificity**	**T-value**	**Sig.**	**T-value**	**Sig.**
AG	Superordinate	-1.01	.312	-0.23	.821
	Basic	-1.07	.284	-0.55	.585
	Specific	**-2.59**	**.009**	**-2.13**	**.033**
pMTG	Superordinate	**-2.49**	**.013**	-1.56	.118
	Basic	**-3.35**	**<.001**	**-2.65**	**.008**
	Specific	-1.39	.166	-0.9	.368

Footnote: Comparisons of LS means with and without TMS for superordinate identity-matching trials (involving category label such as “animal”), basic-level trials (where the target name was produced as the label for the picture by the majority of participants in a picture naming experiment), and specific-level trials (which provided words that participants could recognise as matching the picture yet participants typically produced a more generic label in picture naming). The analysis was performed twice, with and without the inclusion of the TMS effect for the visual task as a covariate. Significant effects of TMS are highlighted in bold text.

Table 3.4 - *Reaction time (RT) and mean proportion correct*

			Site					
			AG		**pMTG**		**Vertex**	
Measure	**Condition**	**Baseline/TMS**	**Mean**	**s.d.**	**Mean**	**s.d.**	**Mean**	**s.d.**
RT (ms)	Superordinate identity	Baseline	1108.4	347.5	1090.9	334.17	1112.3	370.92
		TMS	1123.4	359.16	1134.8	342.57	1103.8	356.55
	More specific identity	Baseline	1073	384.49	1107.7	403.54	1104.3	393.47
		TMS	1129.1	429.15	1147.3	406.1	1143.7	420.72
	Strong association	Baseline	1297.7	460.89	1312.4	447.95	1297.2	440.25
		TMS	1331.4	452.74	1138.7	447.18	1311.9	417.18
	Weak association	Baseline	1528.6	517.36	1582.9	546.06	1593.7	530.27
		TMS	1590.8	544.35	1616	537.65	1605.8	542.56
	Visual	Baseline	1205.7	428.56	1189.8	423.17	1255.1	407.51
		TMS	1247.8	465.81	1249	421.25	1286.5	462.89
Accuracy (proportion correct)	Superordinate identity	Baseline	.96	.052	.97	.025	.97	.033
		TMS	.96	.040	.97	.033	.97	.031
	More specific identity	Baseline	.92	.070	.93	.049	.93	.044
		TMS	.92	.057	.91	.051	.92	.440
	Strong association	Baseline	.96	.033	.95	.035	.97	.035
		TMS	.96	.027	.97	.034	.96	.049
	Weak association	Baseline	.91	.072	.89	.064	.89	.087
		TMS	.92	.056	.89	.091	.89	.071
	Visual	Baseline	.93	.063	.92	.076	.90	.100
		TMS	.93	.076	.93	.050	.92	.080

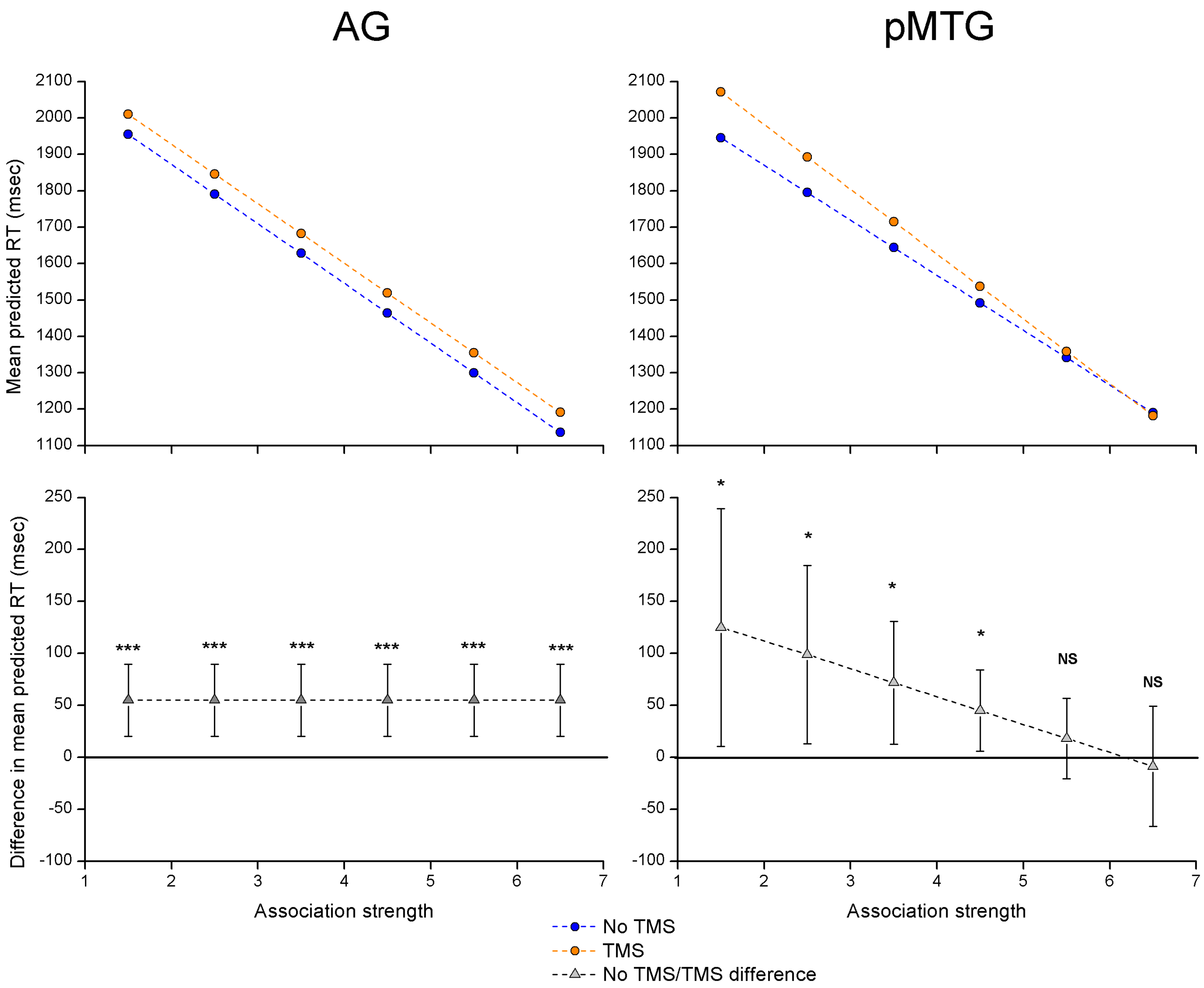


Figure 3.4 - Predicted RT values for AG and pMTG with and without TMS in Analysis 2, modelling association strength as a continuous variable. The top plots show the predicted RT with and without TMS at different levels of associative strength, while the bottom plots show the difference between these conditions. Error bars represent 95% confidence interval.

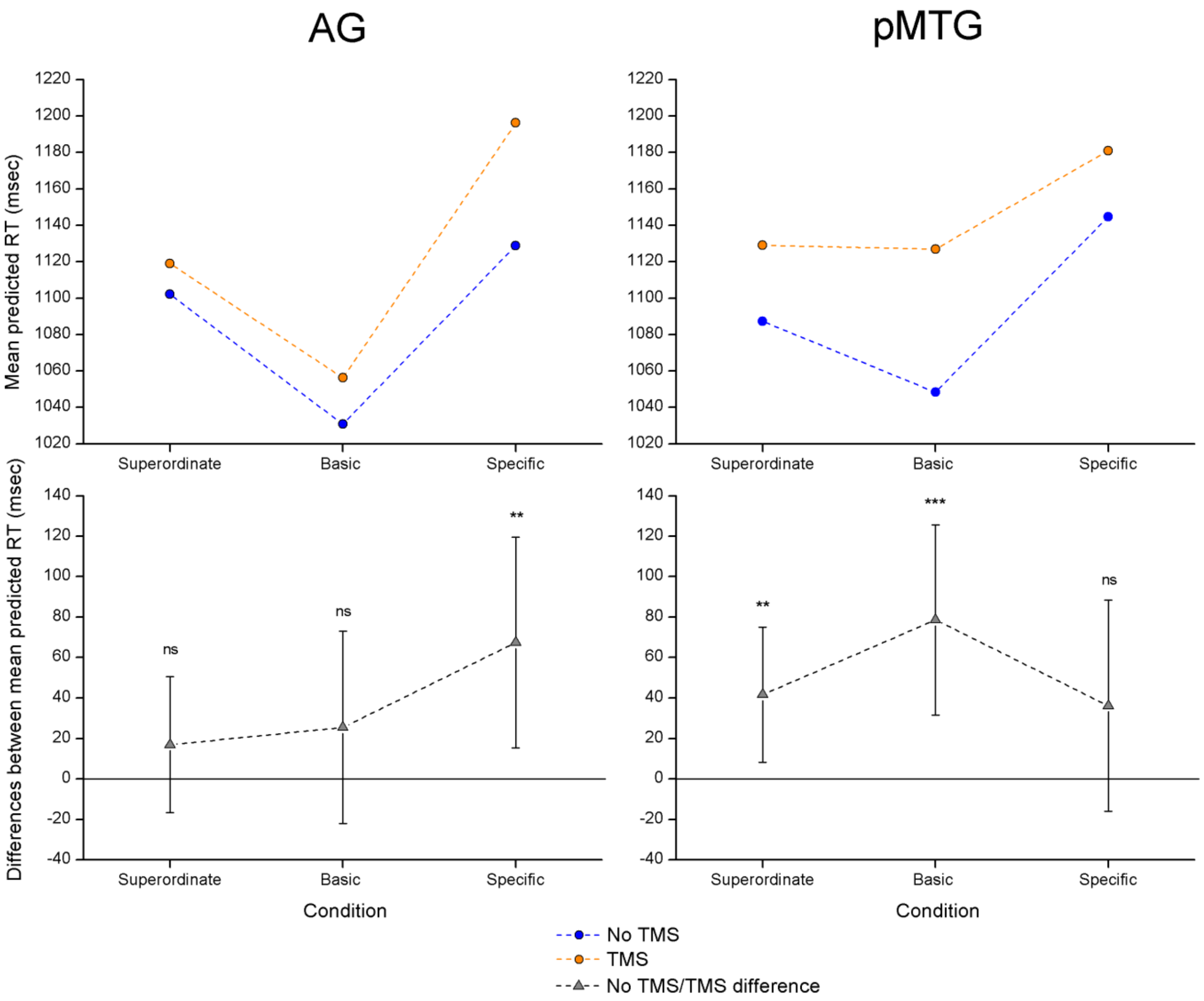


Figure 3.5 - Predicted RT values for AG and pMTG with and without TMS in Analysis 3, comparing identity matching at three levels of specificity. The top plots show the predicted RT with and without TMS at different levels of specificity, while the bottom plots show the difference between these conditions. Error bars represent 95% confidence interval.

Discussion

We examined two contrasting hypotheses about the role of AG and pMTG: (i) these sites store semantic information about thematic associations and events (Kim, 2011; Schwartz et al., 2011; Romagno et al., 2012); (ii) these sites support different aspects of semantic retrieval (Cabeza et al., 2011; Jefferies, 2013; Noonan et al., 2013). We applied TMS to peaks taken from two meta-analyses of semantic cognition examining (i) semantic over non-semantic tasks matched for difficulty (Binder et al., 2009; peak in mid-AG) and (ii) semantic decisions with high control demands over similar decisions with lower control demands (Noonan et al., 2013; peak in pMTG). We measured the effects on identity matching (at different levels of specificity) and association matching (for weak and strong associations). The results show that AG and pMTG make dissociable contributions to semantic cognition. However, neither site showed the predicted pattern for a semantic store supporting thematic associations (i.e., a specific disruption of association matching), since both tasks were impaired by TMS to both regions. The findings are consistent with a theoretical model where pMTG (and LIFG) supports *controlled* aspects of semantic retrieval (i.e., the *shaping* of semantic processing towards knowledge required by the current task/context), while AG (alongside ATL) demonstrated involvement in automatic/reflexive aspects of semantic retrieval (specifically, the orientation of attention internally to activated features). Below, we describe this new framework and consider how it can accommodate our results as well as studies motivating the two-hub hypothesis.

The co-activation of pMTG and LIFG has been linked to *controlled* semantic retrieval (Jefferies, 2013; Noonan et al., 2013). Automatic spreading activation within the semantic system is insufficient for successful semantic cognition since only a subset of features and associations about a given object are relevant at any given time. Without any constraint over the retrieval of knowledge, semantic processing would be dominated by the strongest and most commonly retrieved associations, yet research shows we have a high degree of flexibility in the information we retrieve. For example, when asked to recover an association between weakly associated concepts (e.g., DOG and RAZOR WIRE), the dominant features/associations are largely irrelevant (i.e., pet; sharp) but we can bring these concepts together (by focussing on linking features such as guard dog), and this process activates both pMTG and LIFG (Badre et al., 2005; Whitney et al., 2011a; Noonan et al., 2013) explaining why TMS to pMTG selectively disrupted the retrieval of weak associations. Moreover, when encountering ambiguous words that have different meanings across contexts, we can shape retrieval to focus on features that are currently relevant, which also involves the co-activation of LIFG and pMTG (Badre et al., 2005; Whitney et al., 2011a). In a similar way, high-frequency words activate a broader range of semantic associations than low-frequency words since they occur in a wider range of contexts, increasing their control demands (Hoffman et al., 2010). This effect can explain the greater disruption for superordinate and basic-level identity-matching following pMTG stimulation: unlike specific-level names, which only refer to a narrow range of objects, basic and superordinate terms are used in different ways, increasing the need to shape semantic activation towards task-relevant aspects. In summary, although pMTG activation continues to be interpreted in terms of a semantic store (Binder et al., 2009; Martin et al., 2014), multiple studies using complementary methods have noted responses incompatible with passive storage and have suggested instead that pMTG allows for the controlled *shaping* of semantic activation in line with the current context (Gold et al., 2005; Whitney et al., 2011b; Jefferies, 2013; Noonan et al., 2013). Thus we propose that pMTG maintains *currently-relevant* semantic information, as opposed to long-term and static semantic representations.

The mid-AG site demonstrated a very different response profile from pMTG although once again, the findings are incompatible with a thematic knowledge store. AG has several functional subdivisions (Seghier et al., 2010; Noonan et al., 2013): while dorsal AG is associated with executive-semantic processing, mid-AG is characterised by task-related deactivation (i.e., it forms part of the ‘default-mode network’; Seghier et al., 2010; Wirth et al., 2011; Humphreys and Lambon Ralph, 2014). Moreover, greater deactivation is observed for harder tasks (Binder et al., 2003b; Sabsevitz et al., 2005; Hairston et al., 2008; Wilson et al., 2014). Some authors have suggested this deactivation follows from the subtraction of rich spontaneous semantic processing during rest from more circumscribed semantic processing in a task context (Binder et al., 2009). An alternative view is that AG is involved in the attentional gating of internally and externally-generated activation. By this view, task-related deactivation results from “perceptual decoupling” – i.e., reduced attention to the external world to facilitate conceptual retrieval (Schooler et al., 2011; Smallwood et al., 2011; Smallwood et al., 2013). Inferior parietal cortex is associated with the reflexive orienting of attention to external space driven by salient visual inputs (Corbetta and Shulman, 2002), and plays a role in the allocation of attention to episodic memories (Sestieri et al., 2010; Cabeza et al., 2011). Thus, an emerging view is that this site acts as a hub linking together brain regions which permit reflexive orientation of attention to the external or the internal world, with goals set by medial PFC (Burgess et al., 2007). While TMS to mid-AG had a general effect on the retrieval of both strong and weak associations, there was an effect on identity matching only at the most specific level. In specific-level trials, participants must focus on a restricted part of semantic space to allow fine-grained differentiation of very similar concepts, thus any disruption of reflexive orientation to semantic space would impair these decisions but not necessarily basic/superordinate judgements. This focus on restricted aspects of activated semantic space also explains why TMS disrupts association strength judgements irrespective of their associative strength. Disrupting this narrow focus on a particular concept impairs activations of the associative links between items and concepts across categories irrespective of strength, as focus is now driven towards related but incorrect items belonging to the same category as the intended target.

We propose that AG and pMTG both make necessary, but different contributions to semantic retrieval. Mid-AG may allow for the reflexive orientation of attention to activated regions of ‘semantic space’, analogous to stimulus-driven attention to external space when visual inputs are presented (Corbetta and Shulman, 2002; Anderson et al., 2010). The accurate internal attentional capture by concepts in semantic tasks may depend on the ability to decouple attention from irrelevant external inputs (Schooler et al., 2011; Smallwood et al., 2011; Smallwood et al., 2013). Once concepts are activated, this activation will spread to strongly-associated concepts, but this may be insufficient if weak associations are being probed, or there are many irrelevant associations: under these circumstances, re-representation of *task-relevant* aspects of knowledge may be necessary within pMTG to bring concepts that are normally only weakly linked into a context in which they are strongly linked. Thus, pMTG plays a crucial role whenever semantic processing has to be shaped according to the context in which retrieval is taking place.

This framework can also account for key evidence offered by the two-hub theory (Schwartz et al., 2011; de Zubicaray et al., 2013) in support of the view that temporoparietal regions capture thematic knowledge. This account was motivated by the observation that patients with temporoparietal stroke make thematic errors in picture naming (e.g., SQUIRREL → "nuts"), unlike those with ATL damage (Jefferies and Lambon Ralph, 2006; Schwartz et al., 2011). However, other research has suggested that these patients do not have degraded semantic knowledge, but deficits of controlled semantic retrieval (Jefferies and Lambon Ralph, 2006; Noonan et al., 2010). Thus, their inappropriate production of associations in picture naming might reflect intact thematic knowledge but a deficit in the ability to constrain semantic retrieval. Additional evidence for the two-hub account comes from neuroimaging studies of event semantics, which show peaks in pMTG and AG. However, as our findings emphasise, weak thematic associations require substantial control and flexible semantic retrieval – and this need for flexibility is shared by tasks tapping knowledge of events/actions, since events can have very different meanings in different contexts (e.g., kicking ball: on a field = GAME vs. in a greenhouse = VANDALISM). Therefore, pMTG's contribution to action/event understanding might follow from its role in *shaping* retrieval in line with the current context. Secondly, since a sequence of concepts/representations is retrieved in action, event and autobiographical memory tasks, there is a need to redirect internal attention which activates mid-AG.

The results of the omnibus model indicated that TMS stimulation to both AG and pMTG had an effect on the visual task, demonstrating a disruptive effect on visual processing beyond our intended stimulation site. Previous studies have shown that the roles of these sites are not exclusive to semantics, and this is not necessarily in contradiction with our claims about their role in semantics. The AG has already shown to be engaged in many tasks beyond semantics; there is a continuum in IPL from anterior to posterior with a focus on bottom-up visual attention (Corbetta and Shulman, 2002) and semantics (Binder et al., 2009). Our stimulation site is in the semantic end of the continuum (Humphreys and Lambon Ralph, 2014), but that would not mean that we would exclusively predict a semantic effect. pMTG is located anterior to the visual motion processing visual area MT (Malach et al., 1995; Wallentin et al., 2011). Similar to AG an anterior/posterior continuum is observed in MTG with posterior areas implicated in the frontoparietal control system, whereas anterior areas are implicated in the default mode network (Yeo et al., 2011), with our stimulation site within the semantic/frontoparietal region, similarly to AG we would not predict an exclusive semantic effect.

Thus, although semantic contrasts can activate pMTG and mid-AG as a single cluster (Binder et al., 2009), we propose that these sites should not be interpreted narrowly in terms of supporting specific aspects of semantic knowledge – instead, they are implicated within distinct large-scale cortical networks, which support retrieval processes crucial for semantics and also other aspects of cognition. This view is supported by Figure 3.1 demonstrating our two stimulation sites have different functional connectivity profiles revealed by resting state fMRI. Mid-AG has strong connections to ATL (Ruschel et al., 2013) and to posterior cingulate and ventromedial prefrontal cortex implicated in the default mode network (Uddin et al., 2010). In contrast, pMTG shows strong connectivity to LIFG, implicated in semantic control (Koopmans et al., 2012). These different patterns of connectivity support our conclusions that mid-AG is implicated in automatic aspects of retrieval, while pMTG contributes to controlled, context-appropriate retrieval.

Chapter 4 - Shared neural processes support semantic control and action understanding

Abstract

Executive-semantic control and action understanding appear to recruit overlapping brain regions but existing evidence from neuroimaging meta-analyses and neuropsychology lacks spatial precision; we therefore manipulated difficulty and feature type (visual vs. action) in a single fMRI study. Harder judgements recruited an executive-semantic network encompassing medial and inferior frontal regions (including LIFG) and posterior temporal cortex (including pMTG). These regions partially overlapped with brain areas involved in action but not visual judgements. In LIFG, the peak responses to action and difficulty were spatially identical across participants, while these responses were overlapping yet spatially distinct in posterior temporal cortex. We propose that the co-activation of LIFG and pMTG allows for the flexible retrieval of semantic information, appropriate to the current context; this might be necessary both for semantic control and understanding actions. Feature selection in difficult trials also recruited ventral occipital-temporal areas, not implicated in action understanding.

Introduction

Our conceptual knowledge encompasses a large body of information but only particular aspects of concepts will be useful in any given context or task: as a consequence, executive control processes are engaged to guide conceptual processing in a context-dependent manner (Badre et al., 2005; Noonan et al., 2010; Jefferies, 2013). We can match objects on the basis of specific features, even when these are not prominent aspects of the items, and this is crucial for intelligent behaviour – for example, when trying to pitch a tent, we can understand that a shoe has properties that make it suitable for banging pegs into the ground, even though these properties are not directly related to its dominant associations. Semantic control processes in left inferior frontal gyrus (LIFG) are thought to be critical for this selection of task-relevant attributes (Thompson-Schill et al., 1997) and the controlled retrieval of weak associations (Wagner et al., 2001a; Noonan et al., 2013). However, little is known about *how* control processes are deployed to focus neural activity on specific, task-relevant aspects of knowledge – and whether the same mechanisms are recruited for different types of features (e.g., action vs. visual properties).

Contemporary theories of semantic cognition agree that modality-specific sensory and motor areas, plus multi-modal regions capturing specific features, contribute to semantic representation (Patterson et al., 2007; Pobric et al., 2010; Meteyard et al., 2012a; Pulvermüller, 2013). As a result, semantic judgements about manipulable objects are thought to draw on representations across the cortex, including inferior parietal, premotor and posterior middle temporal (pMTG) regions, which support motor and praxis features (Vitali et al., 2005; Liljeström et al., 2008; Pobric et al., 2010; Rueschemeyer et al., 2010; Yee et al., 2010; Zannino et al., 2010; Chouinard and Goodale, 2012; Watson et al., 2013). Although some research suggests that sensory and motor regions are recruited rapidly and automatically following word presentation (Hauk and Pulvermüller, 2004; Shtyrov et al., 2014), recent neuroimaging studies have examined how activity within modality-specific areas might be modulated on the basis of task demands (Rüeschemeyer et al., 2007; Hoenig et al., 2008; Tomasino and Rumiati, 2013). Action words (e.g., kick) and their semantic associates do not necessarily activate motor regions when presented in isolation; this response is seen more strongly for literal sentences (‘kick the ball’) in which the action properties are relevant to the task (Raposo et al., 2009; van Dam et al., 2012; Schuil et al., 2013). Such findings challenge the assumptions of strong ‘embodied’ accounts of semantic cognition, in which neural connections between distributed sensory and motor features are sufficient for conceptual representation. Furthermore, they raise questions about how semantic representations are applied in a controlled way, to suit the particular task or context.

In addition to the role of distributed visual and motor/praxis representations in object knowledge, some theories suggest these disparate features are drawn together in an amodal semantic ‘hub’ in the anterior temporal lobes (ATL; Patterson et al., 2007). This proposal remains controversial (Simmons and Martin, 2009) because although data from multiple methods – including patients with semantic dementia (Bozeat et al., 2000), TMS (Pobric et al., 2010; Ishibashi et al., 2011a) and PET (Devlin et al., 2002) – reveal a contribution of the ATL in action/tool knowledge, however fMRI is relatively insensitive to signals from ATL due to magnetic susceptibility artefacts that produce signal loss and distortion in this brain region (Visser et al., 2010b; Visser et al., 2012a). Consequently the fMRI literature does not emphasise a role for ATL and instead focuses on the contribution of pMTG to multimodal tool/action knowledge, with some recent studies suggesting pMTG is a semantic hub for tool and action understanding (Martin, 2007; Martin et al., 2014; van Elk et al., 2014).

An alternative view about the contribution of pMTG to semantic cognition is provided by work on semantic control (for reviews, see Jefferies, 2013; Noonan et al., 2013). Although this research has largely focussed on the role of LIFG in selection and controlled semantic retrieval (Thompson-Schill et al., 1997; Wagner et al., 2001a; Badre et al., 2005; Hoffman et al., 2010), a recent meta-analysis revealed that manipulations of the executive demands of semantic tasks activate a distributed cortical network, including left and right inferior frontal gyrus (LIFG; RIFG), medial PFC (pre-SMA), dorsal angular gyrus (dAG) bordering intraparietal sulcus (IPS) and, most notably, pMTG (Noonan et al., 2013). These sites all show greater activation during difficult tasks that tap less prominent aspects of meaning, or require strongly related distracters to be suppressed (Wagner et al., 2001a; Rodd et al., 2010a; Whitney et al., 2011a). Moreover, inhibitory TMS to LIFG and pMTG produces equivalent disruption of semantic tasks tapping controlled retrieval, but has no effect on semantic judgements to highly-associated word pairs, which rely largely on automatic spreading activation (Whitney et al., 2011b). This network for semantic control overlaps with the “fronto-parietal control network” involved in cognitive control across domains – which includes inferior frontal sulcus, intraparietal sulcus and occipital-temporal regions (Duncan, 2010; Woolgar et al., 2011; Yeo et al., 2011), although some sites appear to make a relatively restricted contribution to control processes important for semantic cognition, particularly anterior parts of LIFG and pMTG (Devlin et al., 2003; Whitney et al., 2011a; Whitney et al., 2011b; Whitney et al., 2012; Noonan et al., 2013).

In summary, separate literatures on executive-semantic processing and action understanding have linked similar left hemisphere networks – encompassing IFG/premotor cortex, IPL and pMTG – with diverse aspects of semantic cognition (Noonan et al., 2010; Watson et al., 2013). Since these regions are associated with understanding actions, tools, verbs and events, it has been suggested they might represent motion, action, or praxis features (Liljeström et al., 2008; Chouinard and Goodale, 2010; Spunt and Lieberman, 2012; Watson et al., 2013). However, left IFG, pMTG, and dorsal IPL are also activated during semantic tasks with high executive demands, suggesting they might support controlled retrieval/selection processes that shape semantic processing to suit the current context (Noonan et al., 2013). Damage to this network in semantic aphasia (SA) produces difficulty controlling conceptual retrieval to suit the task or context, both in verbal tasks like picture naming and non-verbal tasks like object use (Jefferies and Lambon Ralph, 2006; Noonan et al., 2010). These deficits can be overcome through the provision of cues that reduce the need for internally-generated control (i.e., phonological cues for picture naming; photographs of the recipients of actions in object use; Corbett et al., 2009b; Corbett et al., 2011), suggesting that damage to this network does not produce a loss of semantic information about words or actions, but instead poor control over conceptual retrieval. However, both neuropsychological studies and neuroimaging meta-analyses have poor spatial resolution, and thus it is not yet known whether semantic control and action understanding recruit adjacent (yet distinct) or overlapping regions in pMTG and LIFG.

We addressed this question in an fMRI study with a 2x2 design that (1) contrasted decisions about action and non-action (visual) features and (2) compared easy, low-control judgements, in which participants selected a globally semantically-related item with more difficult, high-control judgements, in which the target was only related via a specific feature. We predicted that the recruitment of sensory/motor regions would vary according to the feature, with more activity within visual areas for visual decisions (e.g., lateral occipital cortex, occipital pole), and within motor/praxis areas for action decisions (e.g., precentral gyrus; IPL; pMTG). Executive-semantic regions were expected to show stronger responses for more demanding judgements irrespective of the feature to be matched. Furthermore, we examined whether brain regions recruited during the retrieval of action knowledge would overlap with those implicated in semantic control in both group analyses and at the single-subject level.

Method

Participants

20 right-handed, native English speaking participants were recruited from the University of York, UK. All subjects had normal/corrected to normal vision. Three participants had to be excluded from the final analysis due to head movement (> 2mm) and poor accuracy. A total of 17 participants were entered into the analysis (mean age = 22.7 years, 10 females).

Study design

A fully-factorial 2 x 2 within-subjects design was used. The two factors were *judgement type* (action or visual form matching) and *control demands* (contrasting easy decisions about globally related items with difficult decisions based on specific features).

In action judgement trials, participants were asked to match the probe and target words on the basis of shared or similar action features involved in stereotypical use (e.g., selecting SCREWDRIVER for the probe KEY, because both involve a precise twisting action). In visual judgement trials, participants performed a match on the basis of shared visual characteristics (e.g., SCREWDRIVER with PEN, because these objects both have a long, thin rounded shape). We also contrasted 'easy' trials in which the probe and target were taken from the same semantic category and shared either overlapping action or visual properties (i.e., KETTLE and JUG share action properties and are both kitchen items) with 'difficult' trials in which the probe and target were not semantically related and *only* shared an action or visual feature (e.g., KETTLE with HOURGLASS, which only share a tipping action). Moreover, in the difficult trials, there were globally-related distracters which shared category membership with the probe but *not* the relevant feature (e.g., SCALES and TOASTER are categorically related to KETTLE but are not targets because they do not share action features). In both types of trial, there were two response options that were globally-semantically related, and two that were not, but the trials varied as to whether these constituted the target or distracters. A complete list of probes and targets is provided in the Appendix (Appendix 4.1).

A four-alternative forced-choice paradigm was used; participants matched centrally presented probe words to one of four potential items, based on the nature of the association for that block. A reminder of the association being probed was present on every trial, in parentheses underneath the probe word. The experiment was organised into sixteen blocks; eight blocks for each feature type (action or vision) with control demands randomised within a block. An instruction slide stating the relevant feature to be matched (action/vision) appeared before each block for 1000ms. Blocks contained seven or nine events. In blocks with seven events, there were six semantic decisions with one null event (screen was blank for 6000ms). In blocks with nine events, there were seven trials with two null events. Probe words were presented for one second, and then the response options appeared and remained on the screen until the participant responded via a button press, with a maximum duration of 7.5 seconds. There was a jittered inter-trial interval of 4000-6000ms between all events (including null events) with 10-12 seconds of rest between each block. Null events were combined with the rest between blocks to provide a baseline measure for analysis. Before participants took part in the fMRI experiment they were given a practice session, equivalent to one fMRI run.

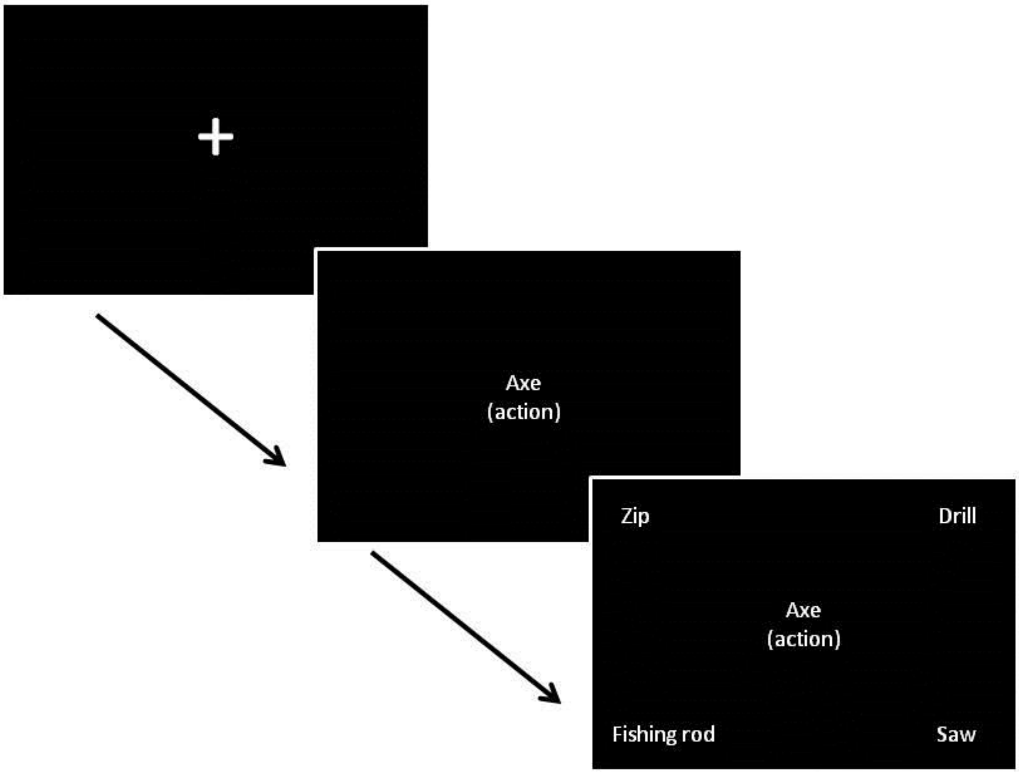


Figure 4.1 - An example of the trial format. Here, “axe” is the probe, and the target is “fishing rod” (both involve a chopping action). Given that axe and fishing rod are not globally related, this is a trial from the difficult, high control action feature condition.

Stimuli

Each condition had 25 targets (100 in total; see Appendix 4.1). In the easy condition, 25 semantically related items were used as distracters, combined with 50 unrelated distracter items. In the hard conditions, 50 semantically related items were used, with the remaining 25 distracters consisting of semantically unrelated items. All of the words were concrete nouns denoting manipulable objects. Individual words were used a maximum of four times throughout the experiment. Target words were matched across conditions for frequency (CELEX database, Max Planck Institute for Psycholinguistics, 2001), number of letters, and imageability, with no significant differences between conditions. Frequency and letter length were obtained using the program N-watch (Davis, 2005). Details of imageability ratings, descriptive statistics and ANOVA results can be found in the Appendix (Appendix 4.2 and 4.3).

Data acquisition

Brain images were acquired using a 3T GE HDx Excite MRI scanner, utilising an 8 channel head coil. We obtained high-resolution structural images for every participant (3D FSPGR MRI). Functional data was recorded from the whole brain using gradient-echo EPI (FOV: 192x192, matrix: 64x64, slice thickness: 4.5mm, voxel size; 3x3x4.5mm, flip angle: 90^0, TR: 2000ms, TE: 30ms) with bottom-up sequential data acquisition. Each session was split into two 14 minute runs, with a total of 420 volumes for each run. Co-registration between structural and functional scans was improved using an intermediary scan (T1 FLAIR) with the same parameters as the functional scan. NBS Presentation version 14 (Neurobehavioral Systems inc., 2012) was used to present stimuli and capture responses (reaction time and accuracy) during fMRI. Stimuli were projected using a Dukane 8942 ImagePro 4500 Lumens LCD projector onto an in-bore screen with a 45x30 visual degree angle. Responses were collected using two Lumitouch two button response boxes, in a custom built case allowing all four buttons to be operated using the left hand.

Data analysis

The analysis used an event-related design to examine the transient responses to each trial separately. fMRI analysis was conducted using FSL 4.1.9 (Analysis Group, FMRIB, Oxford, UK; Smith et al., 2004; Woolrich et al., 2009; Jenkinson et al., 2012). First and higher level analyses were conducted using FEAT (fMRI Expert Analysis Tool). Pre-processing of the data included McFLIRT motion correction (Jenkinson et al., 2002), skull-brain segmentation (Smith, 2002), slice timing correction, spatial smoothing using a Gaussian kernel FWHM of 5mm, and high-pass temporal filtering (100s). Time-series data were modelled using a general linear model (FILM; FMRIB Improved Linear Model), correcting for local autocorrelation (Woolrich et al., 2001). Each experimental variable (EV) was entered as a boxcar function, convolved with a hemodynamic response gamma function, using a variable epoch model (Grinband et al., 2008): the start of each epoch was defined as the onset of the probe word, with epoch duration determined by the response time on each trial. The following EVs were used: correct responses from each of the four conditions, rest (null events and time between blocks, modelled independently since we were initially interested in potential differences between them, driven by the instructions, but these were not observed) and errors (a temporal derivative was added to all variables). Four contrasts were defined from the correct responses; individual conditions > rest (easy action, hard action, easy visual, hard visual).

Whole brain group analysis: A first analysis examined the effect of *feature type* by comparing brain activity to action and visual decisions separately. Analysis of the complete behavioural data from the scanner revealed a small but significant difference in accuracy between the action and visual conditions. Therefore, the whole brain analysis was conducted on a subset of 84 trials (i.e., 21 trials per condition, using the same probe words across conditions). All of the trials related to four specific probe words were removed across all conditions and participants, and entered as a covariate of no interest. The trials in the analysis were matched for psycholinguistic properties, accuracy, and RT (see Appendix 4.1, 4.2 and 4.3). Contrasts of each of the conditions over rest were entered into a higher level contrast of action decisions (hard action > rest + easy action > rest) vs. visual decisions (hard visual > rest + easy visual > rest) and vice versa. To control for multiple comparisons, cluster-based thresholding was applied to all analyses. Voxel inclusion was set at $z = 2.3$ with a cluster significance threshold at FWE $p < .05$. The minimum cluster size for significance at $p = .05$ was 615 contiguous voxels.

In a second analysis, the manipulation of *difficulty* was maximised by selecting 60/100 trials with accurate responses which generated the fastest and slowest decisions for each participant. This was done in order to maximise sensitivity to the effects of this variable as initial analyses using the matched subset of trials failed to produce reliable difficulty effects. These trials were divided evenly between the action/visual conditions (15 easy action; 15 easy visual; 15 hard action; 15 hard visual). The fastest trials were based on global semantic similarity while the slowest were based on a specific feature in the presence of globally-related distracters. The same contrasts described above were repeated using these 60 trials. Voxel inclusion was set at $z = 2.3$

with a cluster significance threshold at $p < .05$. The minimum cluster size for significance at $p = .05$ was 561 contiguous voxels.

Regions of interest (ROI) group analysis: We examined 8mm spherical ROIs placed at key coordinates taken from the literature. The coordinates used in this analysis are shown in Figures 4.4 and 4.5. The FEATquery tool in FSL was used to extract unthresholded percentage signal change for each ROI and each of the four conditions using the matched set of 84 items. The average change across all voxels within the ROI was computed and subjected to ANOVA to examine the effects of difficulty and task, and their interaction at each location.

(i) The first set of ROIs focussed on regions implicated in executive-semantic control by a recent meta-analysis of neuroimaging studies (Noonan et al., 2013). This highlighted a distributed network, involving left posterior and anterior IFG (corresponding to BA44 and BA47 respectively), right posterior IFG (RBA44), medial PFC (pre-SMA), pMTG and dAG/IPS.

(ii) In addition, we included peaks designed to localise additional brain responses involved in understanding actions. These were taken from a study which contrasted responses to action and object pictures (Liljeström et al., 2008) and from a meta-analysis investigating action concepts in the brain (Watson et al., 2013). In the Liljeström et al. (2008) study, the strongest action-selective peak was in left precentral gyrus, motivating the choice of this site as an ROI. We also examined the strongest peak in left IPL identified from the same contrast. Finally, we examined a pMTG site for actions identified in a recent meta-analysis (Watson et al. (2013), which was similar to the pMTG peak identified in the semantic control meta-analysis of Noonan et al. (2013).

(iii) We examined a left fusiform peak implicated in the retrieval of visual features (Thompson-Schill et al., 1999). This was transformed to the right hemisphere to investigate bilateral fusiform contributions to visual and action judgements.

Individual analysis

Overlap between the *feature* and *difficulty* contrasts in the whole-brain group analysis would be consistent with a shared functional system for the executive control of semantic processing and action understanding. However, it is still possible that these contrasts activate non-overlapping voxels in individual subjects, due to variability in functional organisation and anatomy (Fedorenko et al., 2013). We therefore repeated these analyses at the individual level, within two anatomical masks that examined regions implicated in semantic/cognitive control (e.g., by the meta-analysis of Noonan et al., 2013): LIFG (including adjacent precentral gyrus) and left pMTG/ITG. Both masks were created using the Harvard-Oxford structural atlas (Frazier et al., 2005; Desikan et al., 2006; Makris et al., 2006; Goldstein et al., 2007) and transformed into each individual's native brain space (Appendix 4.4 and 4.5). Each voxel within these masks in each individual was classified as responding to either (i) a conjunction of both contrasts of feature type (action > visual) and difficulty (hard > easy); (ii) feature type only; (iii) difficulty only and (iv) neither contrast. This was done by using the Cluster command in FSL to extract the total number of voxels that were above threshold for the conjunction term, feature type, and difficulty effects separately – and then subtracting these activated voxel counts from the total number of voxels in each mask for each participant. Following Fedorenko et al. (2013), we used a voxel inclusion threshold of $p < 0.05$ ($z = 1.96$), which was uncorrected for multiple comparisons, since we were not seeking to establish whether *any* of the voxels in the mask showed significant effects (which would require correction for multiple comparisons), but instead *which* voxels responding to one contrast also responded to the other contrast. We also used MANOVA to establish whether there were any differences in the location of peak responses for the feature and difficulty contrasts within LIFG and posterior temporal cortex across individuals (Woo et al., 2014), again using the Cluster command in FSL.

Results

Behavioural results

Descriptive statistics are provided in the Appendix (Appendix 4.6). A repeated-measures ANOVA on the set of 84 trials revealed significant main effects of difficulty for both reaction time and accuracy (RT: $F(1,16) = 61.70$, $p < .001$, eta^2 = 0.79; accuracy: $F(1,16) = 35.86$, $p < .001$, eta^2 = 0.69). Participants took longer and were less accurate in the hard conditions compared to the easy conditions, irrespective of feature type. There were no significant main effects of feature type (RT: $F(1,16) = 1.261$, $p = .278$, eta^2 = 0.07; accuracy: $F(1,16) = 1.207$, $p = .288$, eta^2 = 0.07) and no interactions (RT: $F(1,16) = 0.407$, $p = .533$, eta^2 = 0.03; accuracy: $F(1,16) = 0.095$, $p = .762$, eta^2 = 0.01).

Whole brain analysis: Action vs. visual decisions

To examine differences between action and visual feature judgements, direct contrasts of these two tasks were performed. Figure 4.2 shows the activation maps for the contrasts of action > visual judgements and visual > action judgements. Cluster maxima and sub-peaks are in the Appendix (Appendix 4.9). A contrast of actions > rest and visual > rest can be found in Appendix 4.7 and 4.8. The action > visual contrast revealed large clusters in left hemisphere areas previously implicated in action processing and semantic cognition, including LIFG, premotor cortex, IPL and pMTG. The opposite contrast of visual over action judgements revealed bilateral areas involved in visual processing, including right supramarginal gyrus, left lateral occipital cortex (LO) and left occipital pole.

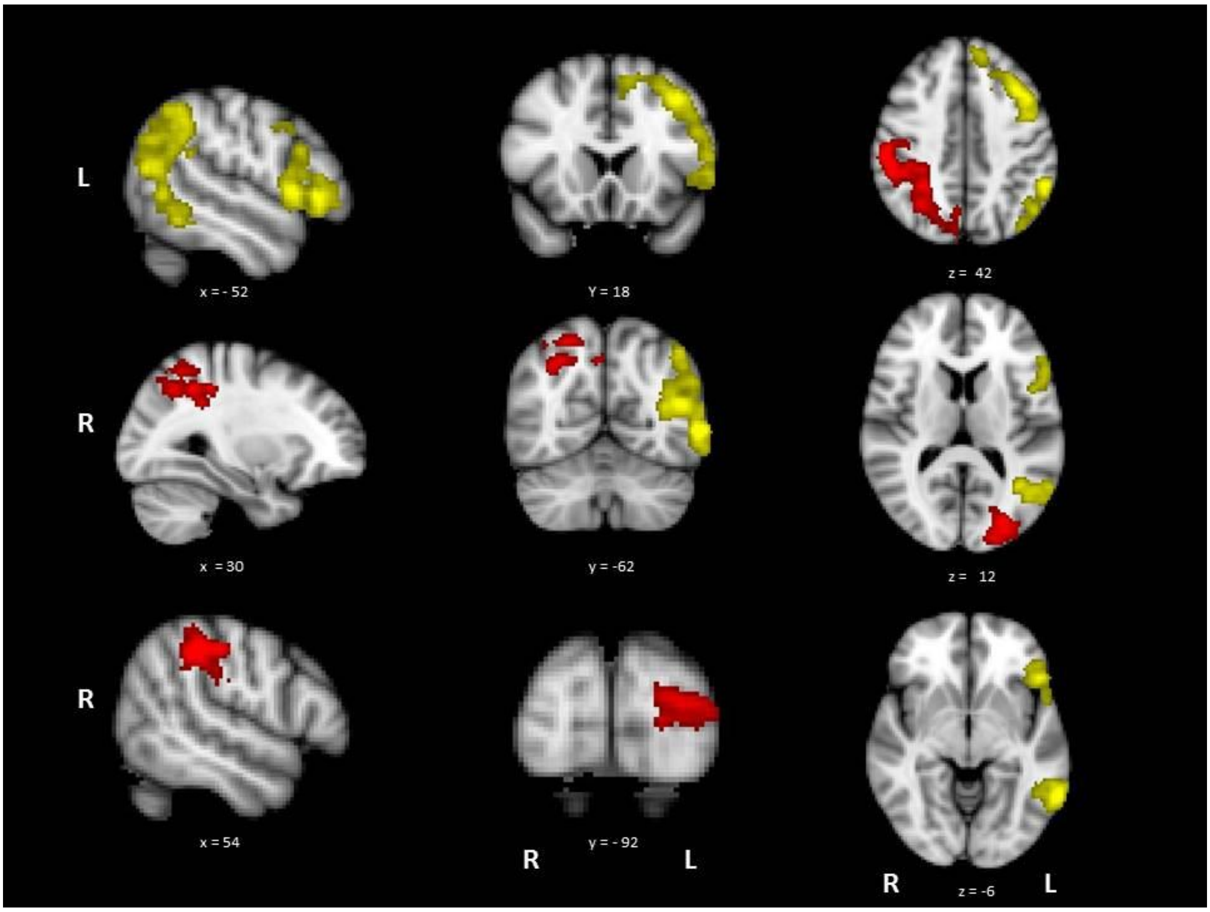


Figure 4.2 - Activation maps for action > visual (yellow) and visual > action (red), presented on the MNI-152 standard brain with cluster correction applied (voxel inclusion threshold z = 2.3, cluster significance threshold *p* < .05). Image is presented using radiological convention (left hemisphere on the right-hand side).

Whole brain analysis: The effects of task difficulty

The activation map for the contrast of hard > easy decisions is shown in Figure 4.3. Coordinates for cluster maxima and sub-peaks can be found in the Appendix (Appendix 4.10). Consistent with our predictions, the manipulation of difficulty for the semantic judgements produced activation in a distributed network associated with executive control of semantic decisions. The most extensive and strongest activity was in LIFG, but the network was bilateral, extending to RIFG, medial PFC/anterior cingulate/paracingulate and posterior temporal areas in left posterior ITG/MTG/fusiform gyrus.

Activation revealed by the hard > easy contrast partially overlapped with several regions also activated by action > visual judgements (see Figure 4.3). These areas of overlap were found in LIFG, extending into left precentral gyrus and superior frontal gyrus (site 1), pMTG (site 2) and left paracingulate gyrus/medial PFC (site 3). In contrast, there was no overlap between the difficulty and visual > action contrasts. These findings suggest common brain regions are involved in action understanding and in dealing with the executive demands of semantic tasks.

We explored the possibility of an interaction between task (action vs. visual) and difficulty; however this effect was not significant: the effect of difficulty was largely equivalent across the two feature types.

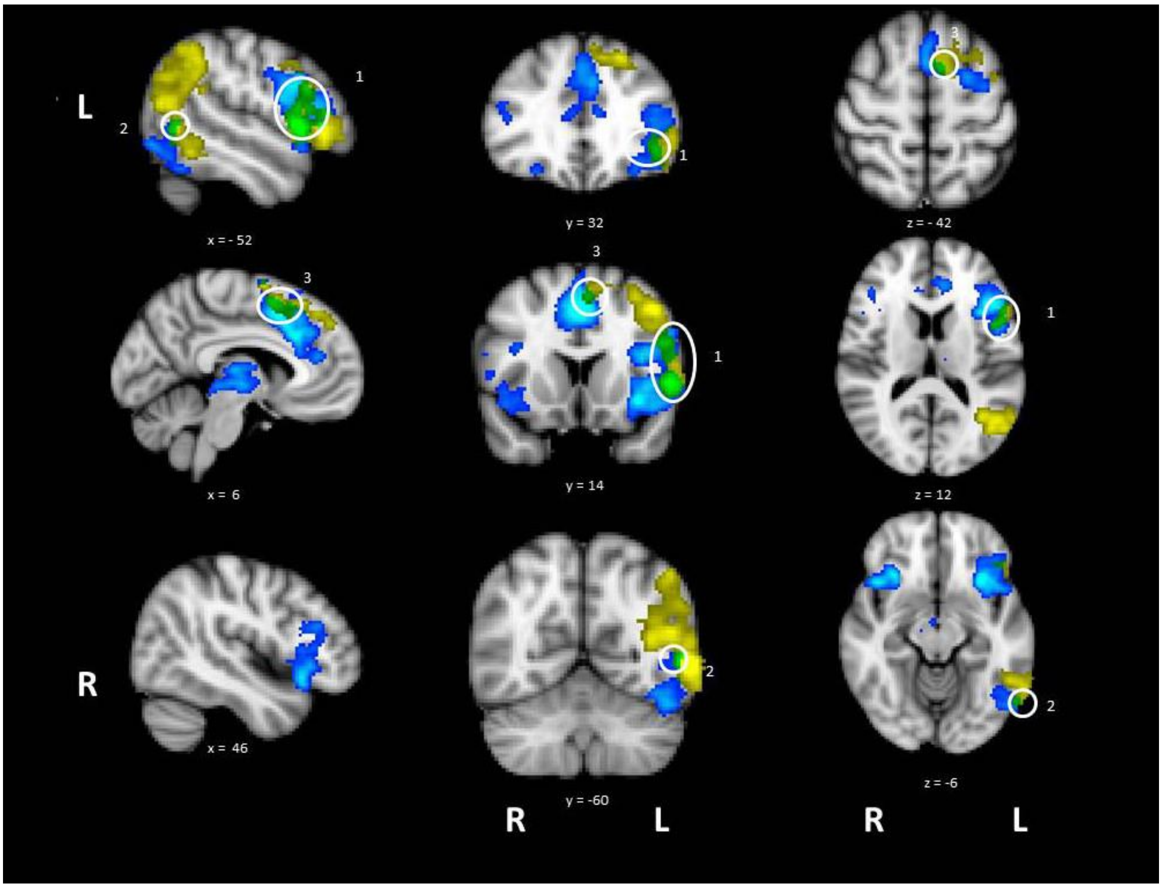


Figure 4.3 - Activation maps for high difficulty > low difficulty (blue/light blue) and action > visual (yellow), with the overlap in green. White circles have been placed around the overlap foci; [1] LIFG, [2] pMTG and [3] anterior cingulate. Data is presented on MNI-152 standard brain with cluster correction applied (voxel inclusion threshold z = 2.3, cluster significance threshold $p < .05$). Image is presented using radiological convention (left hemisphere on the right-hand side).

ROI analysis

Within each ROI, we extracted the mean percentage signal change for the four conditions (easy action, hard action, easy visual, and hard visual) for each participant and submitted the data to a 2x2 repeated-measures ANOVA, examining the factors of task (action vs. visual judgements) and difficulty (easy vs. hard). ANOVA results are shown in Table 4.1, while Figures 4.4 and 4.5 display ROI locations on a rendered 3D brain, plus graphs displaying mean percentage signal change for each condition.

Executive-semantic control peaks: The ROI analysis revealed significantly greater signal change for difficult vs. easy trials for all left hemisphere PFC/IFG sites (there were no significant effects in right BA44). In addition, left BA 47 showed a near-significant effect of task, reflecting somewhat greater signal change for action than visual trials. No other effects of task were observed and there were no significant interactions.

Left dorsal AG/IPS showed a highly significant interaction between control demands and task. While difficult visual feature decisions involved increased recruitment of left dAG/IPS, this site showed deactivation for hard action decisions: there was a highly significant difference between *hard* action and visual trials ($t(16) = -5.32$, uncorrected $p < .001$) but no difference between *easy* action and visual judgements.

Left pMTG displayed significant effects of task and difficulty, with a greater response for action trials compared to visual trials, and for difficult trials compared to easy trials, with no interaction.

Action peaks: Left precentral gyrus demonstrated a significant effect of control, with a stronger response to hard judgements compared to easy judgements. There were no significant effects or interactions with task: therefore, although this site has been previously implicated in action understanding, it is also involved in executive-semantic control, even when the task involves visual feature matching.

Left SMG, a site implicated in hand praxis, showed a stronger response to action than visual trials. No significant main effects or interactions with difficulty were observed, indicating that this site is recruited by action judgements irrespective of difficulty.

The pMTG peak from Watson et al. (2013) demonstrated significant effects of both task and category, with no interaction. Greater signal change was observed for action trials relative to visual trials, and for harder trials relative to easy trials. The pattern of results mirrors those observed for the semantic control peak in pMTG from Noonan et al. (2013), and indeed, these two ROIs selected from different literatures were highly overlapping.

Visual peaks: The fusiform gyrus bilaterally demonstrated significant effects of control with stronger responses to hard than easy trials, irrespective of task.

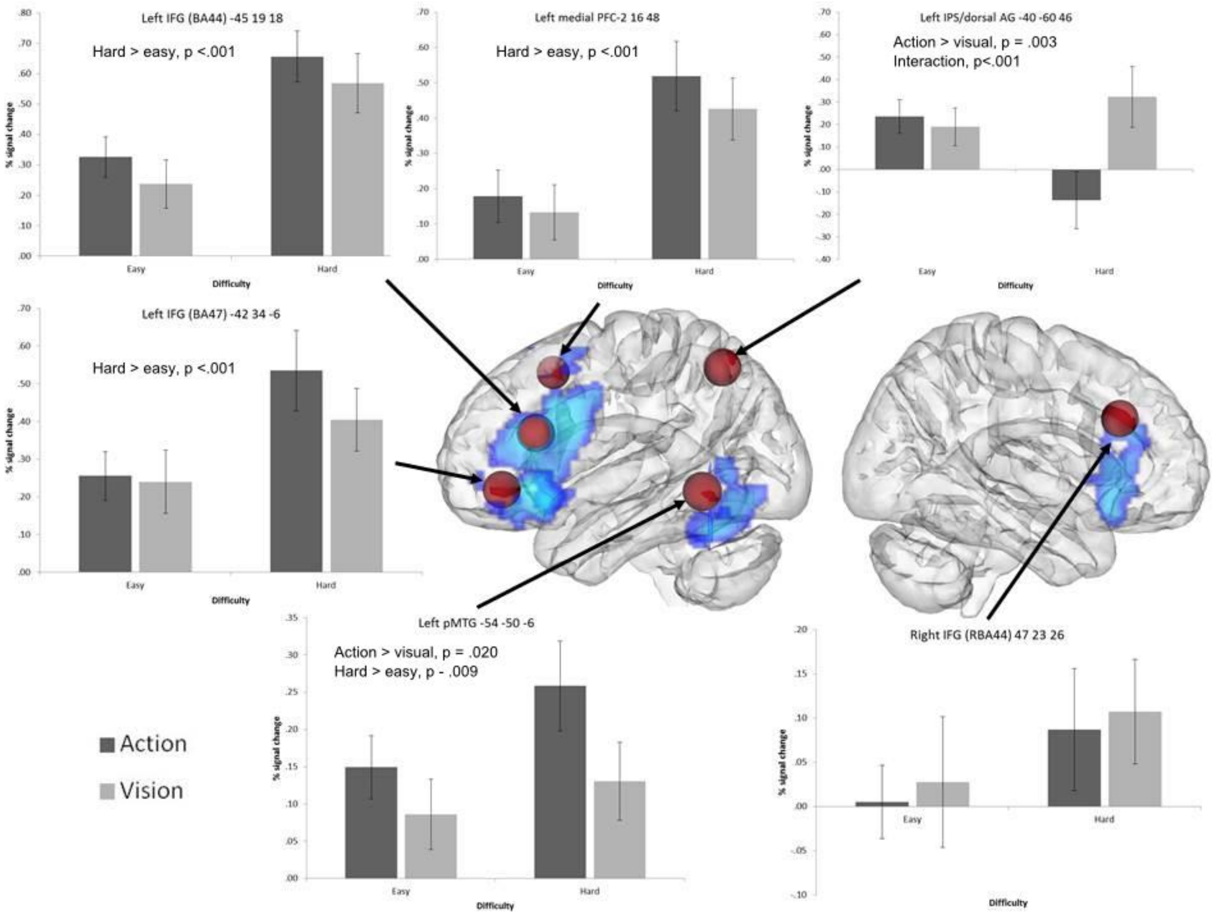


Figure 4.4 - 8mm ROI spheres placed around peaks from a ALE meta-analysis examining executive-semantic demands (Noonan et al., 2013). To allow the location of the ROIs to be compared with the independent whole-brain contrast for hard > easy trials (in blue), they are displayed together on a glass brain using DV3D, with depth information characterised by transparency (Gouws et al., 2009). Graphs show the mean percentage signal change for each condition at each ROI; error bars represent the standard error of the mean. All significant effects are noted on each graph. The left hemisphere is shown on the left side of the image. ROI coordinates are given in MNI space.

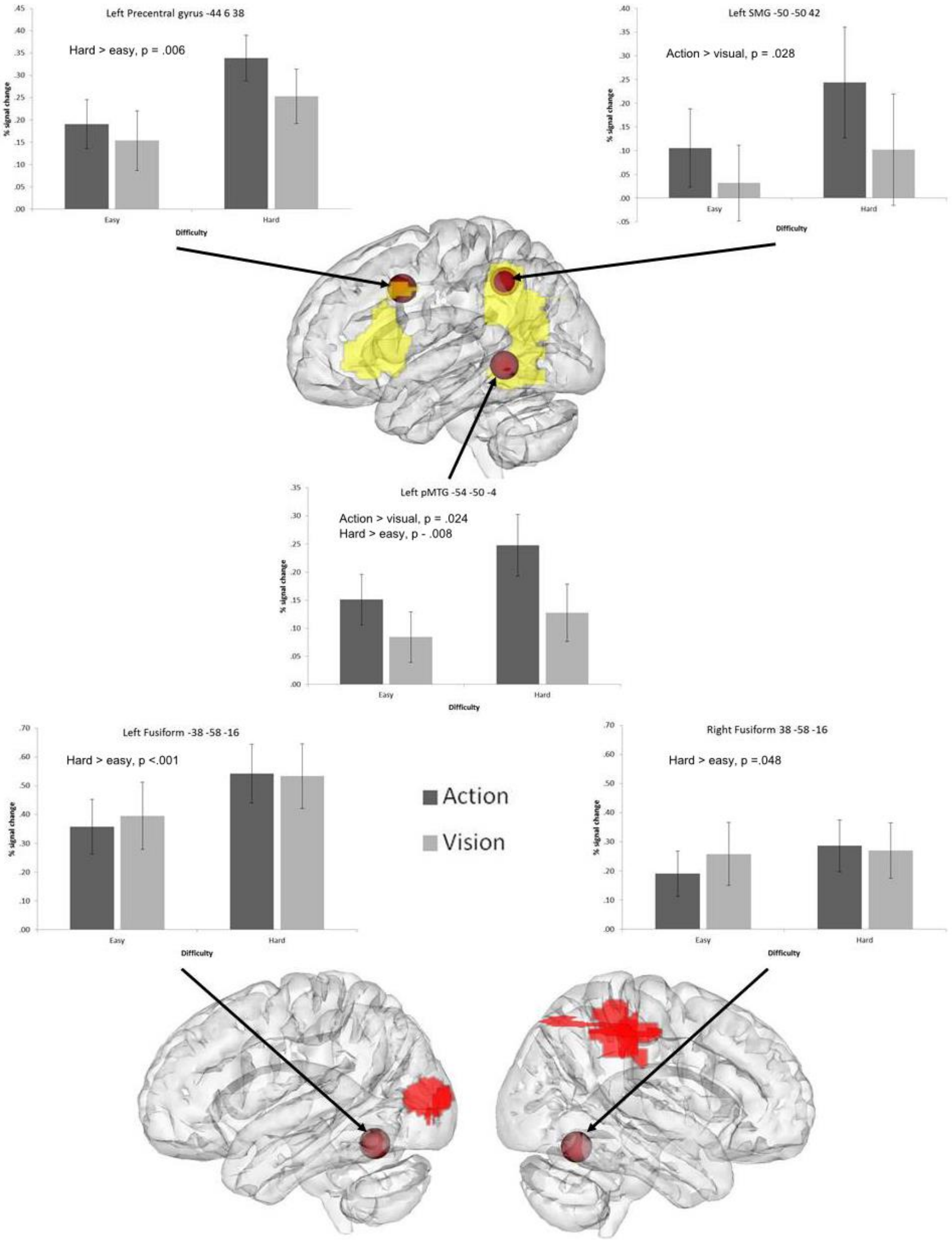


Figure 4.5 - 8mm ROI spheres placed around peaks from the literature implicated in action knowledge (from Liljeström et al., 2008), and visual semantics from Thompson-Schill et al. (1999). Activation from the whole-brain contrast for action > visual trials is projected onto a glass brain in yellow, while the visual > action response is shown in red, using DV3D, with depth information characterised by transparency (Gouws et al., 2009). Graphs display the mean percentage signal change for each condition at each ROI; error bars represent the standard error of the mean. All significant effects are noted on each graph. ROI coordinates are given in MNI space.

Table 4.1 – *ANOVA results for the ROI analysis*

Location	Task			Difficulty			Interaction		
	F	Sig.	effect size (eta²)	F	Sig.	effect size (eta²)	F	Sig.	effect size (eta²)
Action ROIs									
Left precentral gyrus	2.01	.175	.120	**10.13**	**.006**	**.380**	.693	.417	.040
Left SMG	**5.81**	**.028**	**.270**	4.22	.057	.210	.805	.383	.050
Left pMTG (Watson et al., 2013)	**6.18**	**.024**	**.280**	**9.22**	**.008**	**.360**	1.10	.309	.070
Visual ROIs									
Left fusiform gyrus	.265	.614	.010	**33.68**	**<.001**	**.690**	1.49	.240	.080
Right fusiform gyrus	.537	.474	.030	**4.85**	**.048**	**.220**	3.35	.086	.170
Control ROIs									
Left IFG (BA 44)	2.42	.139	.132	**53.58**	**<.001**	**.770**	.000	.984	.000
Left IFG (BA 47)	3.45	.082	.117	**21.11**	**<.001**	**.559**	1.59	.225	.091
Left medial PFC	1.59	.226	.090	**46.97**	**<.001**	**.750**	.629	.439	.040
Left IPS/dorsal AG	**12.80**	**.003**	**.450**	3.02	.101	.160	**19.06**	**<.001**	**.540**
Left pMTG (Noonan et al., 2013)	**6.71**	**.020**	**.300**	**8.69**	**.009**	**.350**	1.59	.226	.090
Right IFG (BA 44)	.191	.668	.012	3.12	.096	.163	.001	.976	.000

Table reports results for 2x2 repeated measures ANOVAs examining the effects of task (visual vs. action feature selection) and difficulty (easy vs. hard) plus their interaction. All significant effects are reported in bold text.

Individual overlap between contrasts examining task difficulty and action retrieval

LIFG: 88% of participants (N=15) showed a response for both feature type (action > visual) and difficulty (hard > easy). For these participants, we counted the number of voxels within the mask responding to (i) both contrasts, (ii) feature type only, (iii) difficulty only and (iv) neither contrast, in order to establish whether the number of voxels showing effects of *both* contrasts was greater than would be expected by chance (Appendix 4.11). Nine participants (60% of the sample) showed a significant conjunction between the two contrasts when each contrast was thresholded at $p = 0.05$ ($z = 1.96$) (i.e., number of voxels > 0; mean cluster size 47.6 voxels, s.d. = 60.6, mean MNI coordinates; -50 22 6, pars triangularis); however, the number of voxels showing a conjunction was highly variable across subjects. Loglinear analysis examined the frequencies of voxels responding to difficulty and feature type in the 15 participants who showed both effects, with participant identity included as an additional predictor. The final model retained all three effects and their interaction terms (for k=3, $\chi^2(14) = 369.7$, $p < .001$), with a significant partial association between voxels responding to difficulty and those responding to feature type ($\chi^2(1) = 55.9$, $p < .001$). Follow-up chi-square analyses confirmed that across subjects, more voxels responded to *both* difficulty and feature type than would be expected by chance ($\chi^2(1) = 9.19$, $p = .002$ with continuity correction; see Appendix 4.11). In addition, within-subjects MANOVA was used to examine the coordinates of the peak responses for each contrast across participants (N=15). Descriptive statistics are provided in Appendix 4.12. There was no difference in the location of the peaks associated with difficulty and action feature retrieval, $F(3,12) = 1.89$, $p = .19$, suggesting overlapping responses.

Posterior temporal cortex: 94% of participants (N=16) showed a response to both feature type and difficulty. 8 individuals (50%) showed a significant conjunction between the two contrasts that reached $p = 0.05$ (mean cluster size 42.1 voxels, s.d. = 57.1, mean MNI coordinates; -50 -60 0 pMTG); however, as for LIFG, the number of voxels showing a conjunction was highly variable across subjects. Loglinear analysis was conducted using the model described above for LIFG. The final model retained all three effects and their interaction terms (for k=3, $\chi^2(15) =$

1011.6, *p* < .001), with a significant partial association between voxels responding to difficulty and those responding to feature type ($\chi^2(1) = 41.6$, *p* < .001). Follow-up chi-square analyses confirmed that across subjects, significantly more voxels responded to *both* difficulty and feature type than would be expected by chance ($\chi^2(1) = 209.6$, *p* = .002 with continuity correction; see Appendix 4.11). Within-subjects MANOVA was used to examine the coordinates of the peak responses for each contrast across participants (N=16). Descriptive statistics are provided in Appendix 4.12. This analysis revealed that difficulty and action retrieval elicited overlapping yet spatially distinct peaks, F(3,13) = 4.75, p = .02, with significant differences in the x (F(1,15) = 8.83, p = .01) and the z dimension (F(1,15) = 6.98, p = .02). The peak for difficulty was more ventral and medial than the peak for action retrieval.

In conclusion, overlapping voxels responded to difficulty and feature type (action > visual) in both LIFG and pMTG. The location of the peak responses for these two contrasts across individual participants did not differ within LIFG yet was spatially distinct in posterior MTG/ITG.

Discussion

Neuropsychological studies (Corbett et al., 2009a; Corbett et al., 2011) and neuroimaging meta-analyses have identified apparently overlapping left-hemisphere sites which respond to both action knowledge (Watson et al., 2013) and semantic tasks with high executive demands (Noonan et al., 2013), yet both of these methods lack spatial resolution. In the current study, group-level and single-subject analyses examined the extent to which the brain regions implicated in difficult semantic judgements also responded to the requirement to retrieve action as opposed to visual features. We established that there is significant overlap between these contrasts in both LIFG and posterior temporal cortex (with peaks in pars triangularis and pMTG respectively). However, while the response to these contrasts in LIFG was spatially identical, there were overlapping yet distinct responses to difficulty and action retrieval in posterior temporal cortex. These findings suggest that there is a common distributed functional system for executive control over semantic processing and action understanding, involving both prefrontal and posterior temporal components; however, the data also point to differences in the roles and organisation of these regions.

First, the study revealed differential activation in modality-specific areas during action and visual feature judgements, which was flexibly driven by the task instructions. The retrieval of action features over visual features revealed an exclusively left-hemisphere network, including left inferior frontal and precentral cortex, inferior parietal lobule (IPL) and pMTG – regions linked to action processing and representation (Liljeström et al., 2008; Ghio and Tettamanti, 2010; Sasaki et al., 2012; Yoon et al., 2012; Watson et al., 2013). Left IPL has been implicated in the planning of tool use (Johnson-Frey et al., 2005) and in tool-action observation and naming (Liljeström et al., 2008; Peeters et al., 2009), while pMTG is thought to be important for action, tool and event knowledge and responds across a variety of modalities (Chao et al., 1999; Noppeney et al., 2006; Liljeström et al., 2008). In contrast, visual > action decisions yielded bilateral activation in lateral occipital (LO) cortex implicated in object perception (Grill-Spector et al., 1999; Grill-Spector et al., 2001), while right IPL and occipital pole were recruited during visual judgements (Liljeström et al., 2008). These findings confirm that participants were able to selectively focus their semantic processing for tools on *task-relevant* sensory and motor areas: activation was enhanced in sensory/motor areas relevant to the decision being performed (van Dam et al., 2010; Schuil et al., 2013).

An interesting question to emerge from these findings is *how* participants are able to focus attention on specific semantic features in a flexible way, depending on the task. There was little evidence that sites specifically implicated in processing visual and action features showed a selective response to task difficulty for those features. In fact, posterior fusiform cortex, associated in previous studies with visual-semantic processing (Thompson-Schill et al., 1999), showed an increased response when hard trials were contrasted with easy trials for both visual and action features; possibly reflecting increased use of visual imagery in both visual and action trials, and/or an increased response linked to word reading when the decision was hard. Instead, the goal-driven retrieval of both visual and action features in difficult trials recruited a network of regions implicated in controlled semantic processing (and, in many cases, other aspects of cognitive control), including LIFG, RIFG, medial PFC, pMTG and ventral temporal-occipital cortex. Trials in the 'easy' condition were relatively undemanding of executive-semantic processes, because the target items that shared the relevant action or visual feature were *globally semantically* related to the probe word. In contrast, for more difficult decisions, participants had to identify a target word on the basis of the task-relevant features and inhibit globally-related distracters that shared task-irrelevant features. This required the application of a varying 'goal set' to control the allocation of attention and to bias selection processes in a task-appropriate way.

Posterior MTG has been implicated in executive-semantic control, along with LIFG, by convergent lines of evidence: first, patients with semantic aphasia show deregulated semantic cognition in the absence of degraded semantic knowledge following either left prefrontal or left temporoparietal lesions (Jefferies and Lambon Ralph, 2006; Noonan et al., 2010); secondly, TMS to both LIFG and pMTG specifically disrupts semantic decisions that maximise controlled retrieval/selection but not automatic aspects of semantic retrieval (Whitney et al., 2011b); (iii) a recent meta-analysis of fMRI studies found that left IFG and pMTG were reliably activated across different manipulations of executive-semantic demands (Noonan et al., 2013). However, the proposal that pMTG helps to support executively-demanding semantic decisions remains controversial, because differing theoretical perspectives ascribe alternative roles to pMTG, including the view that pMTG captures aspects of semantic *representation* linked to action/event/tool knowledge (Kellenbach et al., 2003; Martin, 2007; Kilner, 2011; Peelen et al., 2012; Romagno et al., 2012). Moreover, prior to this investigation, the role of pMTG in action/event knowledge and in semantic control has always been examined in separate studies.

Given this controversy, perhaps the most significant finding to emerge from the current study was the overlap between the regions implicated in executive-semantic judgements and retrieving actions (as opposed to visual features). In the whole-brain analysis, areas of overlap were observed in left IFG/precentral gyrus, medial PFC (pre-SMA) and pMTG. Significant overlap was also confirmed for individual participants in LIFG and left posterior temporal lobe. In contrast, there were *no* areas of overlap between executive-semantic processing and the retrieval of visual features. To explain these findings, we tentatively suggest that action retrieval and executively-demanding semantic tasks may share some cognitive processes that are supported by the network revealed here. Representations of actions and events must be flexibly controlled to suit the context or task – for example, we can retrieve very different actions for the object 'shoe' if the task is to bang in tent pegs rather than fasten our laces. The action decisions in this experiment required participants to establish contexts in which the probe and target objects could be used in a similar way, and in many trials this would have involved linking actions to their recipients (e.g., easy action trials involved recognising that both a highlighter and a felt tip are drawn across a sheet of paper; hard action trials involved recognising that a similar action is made when drawing a match across the box). Arguably, the matching of visual features for tools in the easy condition did not involve retrieval of a spatiotemporal context to the same degree – e.g., when thinking about the shape of a "TV remote", it is perhaps not necessary to think about the object interacting with other objects within its environment to see the shape similarity with "mobile phone". However, for more difficult trials loading semantic control, even those involving visual decisions, there was a requirement to match items on a specific feature and disregard a globally-related distracter (e.g., "TV remote" with "soap bar" not "radio"): thus, activation within the semantic system had to be tailored to suit the context specified by the instructions within each block. Manipulations of semantic control demands generally have this quality: they require participants to retrieve specific associations and features which may be non-dominant but which are required for that trial or task (e.g., associations such as "slippery" and "mud" must be retrieved for the word "bank", in the context of "river"). This might explain why action retrieval (in both easy and hard trials) and specific feature matching on harder trials (irrespective of feature type) recruited an LIFG-pMTG network. We propose that this network shows activation when semantic cognition is tailored in a flexible way to suit the context in which retrieval occurs. These sites may be involved in the creation and maintenance of a task set or semantic 'context' which facilitates the controlled and flexible retrieval of stored multimodal semantic information such that it is appropriate to ongoing goals. This proposal is compatible with Turken and Dronkers's (2011b) suggestion that interactions between ventral PFC and pMTG allow selected aspects of meaning to be sustained in short-term memory such that they can be integrated into the overall context.

Although we propose that the sites within this functional network are recruited together, and that controlled aspects of semantic cognition emerge from their interaction, it is also likely that they each make a unique contribution to our flexible retrieval of concepts. Indeed, there were some differences in their responses in the current study. ROIs in posterior LIFG and medial PFC demonstrated strong effects of control demands irrespective of the semantic feature to be retrieved. This pattern was observed not only for LIFG (within ROIs determined by the semantic control literature) but also in left premotor cortex (within an ROI associated with action understanding). Moreover, individual participants' peak responses to contrasts examining difficulty and action retrieval were not spatially distinct in LIFG, suggesting that the same voxels were recruited in both action understanding and difficult feature selection. In contrast, in our pMTG ROI, there was a main effect of *both* difficulty *and* feature type – i.e., pMTG showed greater activity for hard relative to easy trials, and for action decisions compared with visual decisions. Individual participants' peak responses to these contrasts were overlapping in LIFG yet spatially distinct within posterior temporal cortex, suggesting that LIFG co-activates with somewhat different neuronal populations during action retrieval and difficult feature selection. One possibility is that while LIFG and pMTG both contribute to the shaping of semantic retrieval in line with a semantic context (driving their engagement in both action understanding and difficult trials across feature types, according to the arguments above), posterior ITG is additionally recruited during difficult feature selection: resting-state functional connectivity analyses show coupling of this region with networks implicated in semantic control (Spreng et al., 2010; Yeo et al., 2011), and there is common recruitment of this site across executively-demanding tasks involving visual inputs (Duncan and Owen, 2000). This could potentially pull the peak for the difficulty contrast posterior to the peak for the action contrast in single subject analyses, in line with our observations. Interestingly, in this way, our data hints at the possibility that there may be more than one response in posterior temporal cortex associated with semantic control: a region in pMTG within Yeo et al.'s (2011) 'frontoparietal control system' which might support the retrieval of contextually-appropriate but non-dominant semantic information, and an adjacent region in ITG within the 'dorsal attention network', which may support more demanding semantic judgements more generally and/or which may be recruited to resolve competition during feature selection (Hindy et al., 2012; Hindy et al., 2013).

Sites within left inferior parietal cortex are also variably implicated in knowledge of events and semantic associations, praxis for tools, and semantic control (Humphries et al., 2007; Binder et al., 2009; Pobric et al., 2010; Kim, 2011; Kim, et al., 2011; Wirth et al., 2011; Noonan et al., 2013). However, a common area of activation across contrasts examining action retrieval and semantic control was not observed in this study, presumably because there are multiple regions within left IPL with different response profiles (Seghier et al., 2010; Noonan et al., 2013). Anterior SMG/IPS is associated with action observation and tool praxis (Caspers et al., 2010; Watson et al., 2013), while dorsal AG/IPS emerged as part of the semantic control network in the meta-analysis of Noonan et al. (2013). In contrast to both of these sites, more ventral/posterior aspects of AG show a stronger response to semantic than non-semantic tasks, particularly for concrete concepts (Binder et al., 2005; Wang et al., 2010), yet no effect of control demands (Noonan et al., 2013).

Dorsal AG/IPS, unlike other regions showing a response to semantic control demands, showed an increased response with difficulty for visual features, but task-related deactivation for hard action trials. This interaction between difficulty and task is a novel finding which speaks to the role of dorsal AG within and beyond semantic cognition. By some accounts, AG plays a key role in semantic representation and integration (Binder, et al., 2009): deactivation of AG is often observed when demanding tasks are contrasted with rest, and these effects have been interpreted in terms of semantic processing within self-generated thought, which is reduced in a task context (Binder, Swanson, Hammeke, & Sabsevitz, 2008). In addition, IPL has been proposed to play a crucial role in reflexive visual attention (Corbetta and Shulman, 2002; Nobre et al., 2003;

Konen et al., 2004). Left IPL may therefore show deactivation when participants perform demanding tasks which would be disrupted by allocating attention to changing visual inputs. The interaction that we observed between difficulty and task suggests that dorsal AG/IPS shows above-baseline activation when increased attention to visual features is necessary to perform a task. In contrast, it shows deactivation when attention is increased to non-visual features (e.g., actions). In short, this site might play an important role in allocating attention towards different types of features according to the task requirements, even when these features are not present.

In conclusion, we manipulated semantic control demands and the feature to be matched in the same experiment, revealing overlapping responses to semantic control demands and action knowledge in left IFG/precentral gyrus, medial PFC (pre-SMA) and pMTG at both the group and single-subject level. We also identified a distinct response to semantic selection but not action retrieval in pITG.

Chapter 5 - Large-scale cortical networks supporting context-driven and goal-driven semantic retrieval

Abstract

Previous work on the contribution of left inferior frontal gyrus (LIFG) to semantic control has suggested a functional subdivision within this region; fMRI activation was observed in dorsal/posterior IFG by tasks which required participants to selectively focus on specific non-dominant information in line with task instructions or current goals, while ventral/anterior IFG plays a role in "controlled retrieval" – i.e., when a global association must be recovered between two distantly related words (e.g., salt – road) by establishing a *context* in which they are linked (icy conditions). However, a recent meta-analysis indicated that semantic control is supported by a wider network, drawing on posterior temporal areas alongside LIFG. This study therefore examined whether the dissociation between goal-driven feature selection and context-driven retrieval would extend to other areas in this network. In addition, the cognitive operations that elicit recruitment of the "controlled retrieval" network are not fully understood. We used fMRI conjunctions between experimental tasks which encapsulated two aspects of flexible semantic retrieval: (1) goal-driven retrieval (a conjunction of colour and action feature matching tasks, which yielded activation in and around inferior frontal sulcus/gyrus and ventral occipital-temporal cortex); (2) context-driven retrieval (a conjunction of global associations and action features within a spatiotemporal context, which yielded activation in ventral anterior IFG and posterior middle temporal gyrus). Thus, we identified two spatially similar yet distinct networks responding to context-driven and goal-driven semantic retrieval.

Introduction

Across our lifetime we acquire a large body of conceptual knowledge; however only a subset of this information is relevant for a given task or context. Automatic spreading activation is thought to elicit the retrieval of features and associations that are *dominant* for a particular concept. When semantic retrieval needs to be focussed on aspects of knowledge that are *not* the strongest response for the inputs, we need additional control mechanisms to flexibly guide our semantic retrieval. Previous studies have implicated different brain regions in the controlled selection of different features (e.g. action and visual features for tools) for items from the same semantic category (Chapter 4; Davey et al., 2015), with other studies demonstrating differing networks supporting the naming and categorisation of exemplars within different semantic categories (Chouinard and Goodale, 2010, 2012). These findings suggest that control mechanisms flexibly recruit different networks of brain regions which support different semantic categories or different attributes of the same semantic category. However the nature of the mechanism is unclear as this degree of flexibility can be achieved in several ways. First, we can use top-down goals such as task instructions to drive the selection of specific features or associations. For example, if you are instructed to think about the texture of a piano, you can recall that it is smooth, even though the musical sounds made by the piano are more central to this concept. To achieve this type of goal-driven flexibility, control mechanisms are needed to bias the flow of activation within the semantic system away from dominant features and associations, and towards aspects of knowledge that are relevant to these goals. Secondly, we can flexibly shape retrieval to suit the context, in the absence of specific goals or instructions. For example, we retrieve different actions for the concept “piano” in the context of playing the instrument (pressing keys) and moving house (strenuous pushing) (Saffran, 2000). In this latter type of stimulus-driven control, the combination of concepts occurring together defines what is relevant, and features relevant to this context are brought to the fore.

Previous work has implicated different areas within the left inferior frontal gyrus (LIFG) in distinct aspects of semantic control. Badre et al. (2005) found that posterior/dorsal LIFG responded to semantic “selection” demands, while anterior/ventral IFG was implicated in “controlled retrieval”. Selection demands elicit peak responses in posterior/dorsal LIFG across different language domains, including phonology (Poldrack et al., 1999; Nixon et al., 2004; Gough et al., 2005). This response overlaps with the multiple demand system, which supports executive control across different aspects of cognition, in inferior frontal sulcus (IFS) and dorsal IFG bordering the inferior frontal junction. Controlled retrieval, in contrast, might be driven by processes that shape semantic retrieval to suit the current task or context, and has been localised to ventral IFG. Since this process is specific to memory retrieval, ventral IFG is engaged in semantic but not phonological control. It is worth mentioning that these studies failed to examine whether the different subdivisions of the LIFG play a larger role in the selection of information for different features of the same items; as demonstrated in the previous chapter anterior LIFG demonstrated effects of action feature selection that were approaching significance, in contrast to other aspects of the LIFG which demonstrated no evidence of feature specific effects (Chapter 4; Davey et al., 2015). It is also unclear whether these same brain regions are involved in the selection of information for all semantic categories or whether their contributions are influenced by semantic category. These studies reveal functional dissociations within LIFG but further work is needed to establish what constitutes controlled retrieval. Badre et al.’s (2005) “controlled retrieval” task involved semantic *associations* between two weakly-related words, which required identification of a linking context which might differ between different types of features, while the “selection” task involved the goal-driven retrieval of *specific features* specified by the task. Specifically, we examined brain activation for the conjunction of (1) global associations and action feature retrieval within a spatiotemporal context (i.e., two different tasks that both involved context-driven retrieval) and compared this with (2) goal-driven selection (a conjunction of colour and action feature matching tasks) to establish if dorsal and ventral parts of LIFG are recruited during these different modes of flexible semantic retrieval. The first conjunction (see the results section for how we define a conjunction in the context of this study, further details can be found in Nichols et al., 2005) takes advantage of the fact that the actions associated with tools are typically retrieved within a spatiotemporal context. To understand that KEY and SCREWDRIVER are associated with similar actions, participants report that they retrieve information about these objects within their environment (e.g., an ‘opening the door’ context for key and a ‘tightening a screw’ context for screwdriver), and then compare the similarities of the actions in these contexts. This is perhaps necessary because the actions associated with tools vary according to the context: for example, we can use the same KNIFE to *spread* butter and *slice* cheese. A similar process is required to establish a link between weakly-associated words: for example, to understand that TAP (faucet) goes with PLUG, participants might retrieve information that these items are used and talked about together in the context of the concept SINK. The retrieval of other types of object features is arguably less dependent on spatiotemporal context: for example, it is not helpful to retrieve a spatiotemporal context for GOLDFISH (e.g., swimming in the pond) and CARROT (e.g., vegetable in the kitchen) to establish that these objects have a similar colour. Although objects do show some variation in their colour features according to context (e.g., muddy vs. clean carrots), people report that they tend not to retrieve contextual information when making matching objects according to their canonical colour (see below).

A second aim of this study was to examine evidence for contributions of brain regions *beyond* LIFG to these potentially dissociable goal-driven and context-driven components of flexible semantic retrieval. There is growing evidence for a distributed network that underpins semantic control, which draws on IFG and adjacent IFS but also posterior temporal cortex. A recent meta-analysis of neuroimaging studies that manipulated semantic control demands in various ways (through the strength of probe-target relationships, the presence of strong vs. weak distracters, and use of ambiguous words etc.) found a common response in LIFG, RIFG, left pMTG and left dorsal angular gyrus/intraparietal sulcus (Noonan et al., 2013). Although posterior bilateral IFG/IFS and IPS are implicated in cognitive control beyond semantics, anterior IFG and pMTG appear to make a more selective contribution to controlled semantic processing. This conclusion is supported by neuropsychological studies, since patients with semantic aphasia (SA) have poor control over semantic retrieval following infarcts focussed on LIFG and pMTG (Jefferies and

Lambon Ralph, 2006; Jefferies et al., 2008; Jefferies et al., 2010; Thompson and Jefferies, 2013). Semantic cognition in these patients is dominated by strong but currently irrelevant aspects of knowledge, and they are highly sensitive to the need to internally shape retrieval to suit the task or context: they show much better performance when semantic retrieval is constrained by the provision of cues. Although SA patients have large lesions potentially affecting multiple processes and brain regions, parallel findings have also been demonstrated using transcranial magnetic stimulation (TMS) in healthy participants. TMS to LIFG and pMTG produces equivalent disruption of tasks requiring semantic control (e.g., retrieval of weak associations) but no disruption of tasks largely relying on automatic semantic retrieval (e.g., strong associations) (Whitney et al., 2011b; Whitney et al., 2012). However the responses in posterior temporal cortex are not restricted to semantic cognition. In the previous chapter it was demonstrated that two regions implicated in the semantic control literature (LIFG and pMTG) demonstrated overlapping activation for tool action decisions (Chapter 4; Davey et al., 2015) and historically activation in pMTG has been observed in response to tool stimuli/decisions (Liljeström et al., 2008; Watson et al., 2013). It is also important to note that previous studies manipulating semantic cognition have failed to manipulate semantic category, thus it is unclear whether the control profile of pMTG is driven by category specific effects, specifically for tools. This study will investigate whether the responses in pMTG are driven by semantic category, or whether responses in pMTG are invariant of semantic category but are driven by a shared process between tool processing and semantic control.

Based on this converging evidence across neuroimaging, neuropsychology and brain stimulation methods, we and others have proposed that pMTG is involved in semantic control. Co-activation of LIFG and pMTG may help to maintain *currently relevant* aspects of knowledge, shaping activation within the semantic system such that dominant but irrelevant features and associations do not inappropriately dominate ongoing processing. In addition, ventral occipital-temporal cortex (pITG) has been implicated in the multiple-demand executive network (Duncan, 2010). This site shows an increased response together with IFS and IPS when non-semantic executively-demanding decisions are made, however it might form a part of the wider semantic network as we observed peak activation for hard semantic decisions in pITG (Chapter 4; Davey et al., 2015). The aim of this study was therefore to determine whether there are two distinct neural networks supporting context-driven and goal-driven aspects of flexible semantic retrieval, and whether these networks have dissociable components within both LIFG and posterior temporal cortex.

Method

Participants: 21 right-handed, native English speaking participants were recruited from the University of York, UK. All participants had normal or normal to corrected vision. Two participants were removed due to movement artefacts during fMRI data acquisition, leaving a final data set of 19 participants.

Study design: Knowledge of two semantic categories (animals and tools) was probed using three tasks. (1) The first task manipulated global semantic associations; participants matched probe and target words based on the strength of their global semantic association (e.g., selecting HONEYCOMB for the probe BEE, as opposed to an unrelated distracter). This task did not require participants to apply a specific goal or instruction to constrain semantic retrieval; instead participants were able to uncover a linking context from the items themselves. (2) The second task manipulated relative size judgements between items; participants were asked to identify a target which had similar dimensions to the probe concept (e.g. selecting FLANNEL for the probe SANDPAPER, as these items are a similar size, even though they are not globally related). (3) The final tasks required participants to match items based on specific features of both semantic categories; participants matched animals and tools on the basis of specific features that could only be probed for these categories. For tool items, participants matched items on the basis of action features (e.g. selecting SCREWDRIVER for the probe KEY, as these tools involve similar turning actions). For animals, participants matched items on the basis of colour similarity (e.g., selecting BASKETBALL for the probe TIGER, as both are orange and black).

The experiment was organised into a total of 36 mini-blocks divided equally among the 6 experimental conditions (i.e., the 3 tasks probed using 2 categories). There were 5 trials per block.

Before each block commenced, an instruction slide was presented stating the task to be performed (global, size, action, or colour matching) for 1000ms. A reminder of the instructions was also present on each trial in parentheses under the probe word. A two-alternative forced choice paradigm was used; participants were instructed to match the centrally presented probe word to one of two potential targets. Probe words were presented for 1000ms, followed by the response options which remained on screen till a response was recorded via button press, with maximum trial duration set to 4.5 seconds. The inter-trial interval was 4000-6000ms, with 10 seconds of rest between each experimental block. One null event was present in each experimental block; the screen was blank for 4500ms plus jitter (4000-6000ms) with the location of the null event randomised in each experimental block. Before the fMRI experiment participants were given a practice session consisting of two blocks for each condition.

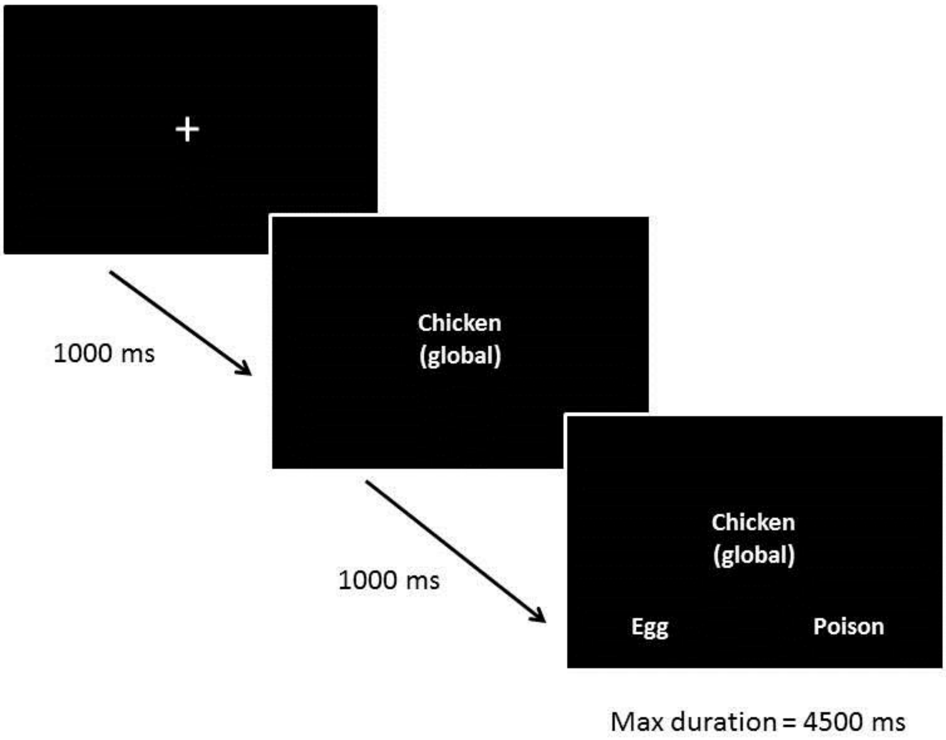


Figure 5.1 - Example of a trial. For a null event the screen was blank for 4.5 seconds, followed by a fixation cross to signal the start of the next trial.

Stimuli: All words used in the experiment were concrete nouns denoting manipulable objects or animals. Ratings of manipulability, familiarity and imageability were collected from 11 participants on a seven point scale (1 – low, 7 – high) who did not take part in the final fMRI experiment, alongside statistics on number of letters and words. Table 5.1 contains the psycholinguistic variables for all conditions, ANOVA results can be seen in Table 5.2. For manipulability the ANOVA revealed a significant main effect of category, revealing that the tool targets had significantly higher manipulability ratings than targets used in the animal judgements. For familiarity the ANOVA revealed a significant main effect of category and feature; overall animal targets had higher ratings of familiarity than tool targets. A marginally significant effect was observed between the different features, revealing that the targets in the size condition (irrespective of semantic category) had higher familiarity ratings than targets in the global or specific feature matching conditions. For imagability there were significant main effects of category, feature, and a significant interaction. Further examination revealed that the animal targets were rated as being significantly more imagable compared to the tool targets, and that the size condition (irrespective of category) significantly had the highest imagability ratings. A significant interaction was observed for imagability, driven by the imagability ratings for the animal size targets (*t*(29) = 8.13, p <.001). The implications of the differences between animals and tools for all word measures will contribute to the differences between categories, but will not affect the results of the conjunctions.

We also collected ratings from 13 participants about how useful retrieving the shared spatiotemporal context between items aided them in the specific feature matching conditions (colour and action judgements), on a seven point scale (1 – not very useful, 7 – retrieving the context was very helpful). When looking at the trials across both judgements (a judgement was repeated but mirrored in the tool conditions [SCREWDRIVER and KEY, KEY and SCREWDRIVER] resulting in 29 unique trials in this analysis). The data showed that across categories retrieving the spatiotemporal context was significantly more helpful for action trials than colour trials *t*(28) = 1.64, p <.001).

Each condition had 30 targets (180 targets in total: for 3 tasks x 2 categories, see Appendix 5.1). In the global semantic condition 60 semantically unrelated objects were used as distracters, combined with 180 semantically and feature unrelated distracter items in the harder feature matching conditions. Distracter items were generated through the recycling of target items, controlling for any potential feature overlap with the target. No restrictions were placed on the number of times a word (mean number of repetitions = 2, s.d = 1.4, range = 6) could be used throughout the experiment; however the number of repetitions was matched across conditions.

Table 5.1 - *Manipulability, familiarity and imagability statistics for all each experimental condition*

Judgement	**Category**	**Manipulability**		**Familiarity**		**Imagability**	
		Mean	S.D.	Mean	S.D.	Mean	S.D.
Global	Animal	4.62	.777	5.91	.733	6.18	.417
	Tool	4.97	.449	5.86	.660	5.82	.345
Size	Animal	4.72	.578	6.26	.757	6.38	.359
	Tool	4.96	.628	6.00	.638	6.04	.493
Colour	Animal	4.66	.792	6.31	.821	6.04	.403
Action	Tool	5.27	.586	5.85	.749	5.65	.564

Table 5.2 - *Word statistics ANOVA results*

Word statistics	Category			Feature			Interaction		
	F	Sig.	effect size (eta²)	F	Sig.	effect size (eta²)	F	Sig.	effect size (eta²)
Manipulability	**27.35**	**<.001**	**.485**	1.91	.157	.062	2.11	.130	.068
Familiarity	**13.87**	**.001**	**.324**	2.96	.060	.093	2.16	.124	.069
Imagability	**132.12**	**<.001**	**.820**	**5.40**	**.007**	**.157**	**5.33**	**.007**	**.155**

Data acquisition: Images were acquired using a 3T GE HDx Excite MRI scanner utilising an 8 channel head coil. High-resolution structural images (3D FSPGR) were acquired for all participants. Functional data was recorded from the whole brain using a gradient-echo EPI sequence (FOV: 192x192, matrix: 64x64, slice thickness: 4.5mm, voxel size; 3x3x4.5mm, flip angle: 90^{o}, TR = 2000ms, TE: 30ms) with bottom up sequential data acquisition. The experiment was split into two 20 minute runs collecting a total of 600 volumes. The first 2 volumes were rejected as dummy volumes. An intermediary scan (T1 FLAIR) with the same parameters as the functional scan was collected at the end of data acquisition to improve the co-registration between individual structural and functional scans. NBS presentation version 16 (Neurobehavioral Systems inc., 2013) was used to present the experiment and record participants' responses (reaction time and accuracy) during the fMRI scan. Stimuli were projected using a Epson EB-G5900 projector with a long throw lens onto an in-bore screen acrylic screen (45x30 visual degree angle) viewed by participants via a front silvered mirror. Participants responded using a Lumina Response Pad (Cedrus Corporation), placed in their left hand.

Data processing/analysis: fMRI data analysis was conducted using FSL version 4.1.9. First and higher level analyses were conducted using FEAT (fMRI Expert Analysis Tool). Pre-processing of the data for both experimental runs included McFLIRT motion correction (Jenkinson et al., 2002), skull-brain segmentation (Smith, 2002), slice timing corrections, spatial smoothing using a Gaussian kernel of full-width-half-maximum of 5mm, and high-pass temporal filtering. Time series data were modelled using a general linear model (FILM; FMRIB Improved Linear Model) correcting for local autocorrelation (Woolrich et al., 2001).

A block design was used for the analysis to maximise statistical power. The GLM included the six experimental conditions modelling for block start time and duration. Both experimental runs were analysed independently at the lower level then combined using a fixed-effects higher level analysis. Six contrasts were defined; individual conditions > rest (animal/tool global, animal/tool size, tool action, animal colour).

Results

Behavioural results: Descriptive statistics (RT, accuracy, and response efficiency) are provided in Table 5.3, response efficiency was calculated by dividing RT by accuracy in order to characterise overall performance. Repeated measures ANOVAs for response efficiency revealed significant main effects of semantic category and semantic feature (category; F(1,18) = 5.72, p =.028 , eta^2 = .241, semantic feature; F(1,18) =68.52, p <.001 , eta^2 = .792), demonstrating poorer performance for tool judgements, and poorer performance decreased response efficiency as trial difficulty improves. A significant interaction was observed (F(1,18) = 4.33, p =.021 , eta^2 = .194); further examination revealed significantly reduced performance for tool size trials compared to animal size trials (Bonferonni *t*(19) = -4.84, p <.001). The observed differences in behavioural performance might explain some of the differences observed between categories and semantic judgements, but will not influence the results of the conjunctions which will allow for the observation of common activation across semantic categories and judgements.

Paired samples t-tests were conducted to examine the differences in response efficiency irrespective of semantic category. Response efficiency for specific feature selection (action and colour judgements combined) trials was significantly reduced compared to the global trials (Bonferonni *t*(38) = 11.252, p <.001), and when compared to the size trials (Bonferonni *t*(38) = 3.21, p =.003). Paired t-tests further revealed significantly reduced response efficiency for size trials when contrasted against global trials (Bonferonni *t*(38) = 9.66, p <.001).

Table 5.3 - *Behavioural results (RT, accuracy and response efficiency)*

Condition	Response efficiency		RT		Accuracy	
	Mean	Stdev.	Mean (milliseconds)	Stdev.	Mean (% correct)	Stdev.
Animal global	1662.56	400.58	1582.54	335.31	.96	.06
Tool global	1647.67	341.05	1593.25	335.96	.97	.03
Animal size	1942.64	366.73	1819.13	351.81	.94	.05
Tool size	2171.37	454.19	1937.75	419.25	.89	.05
Animal colour	2192.37	493.55	1879.66	401.85	.86	.07
Tool action	2250.06	434.88	2021.32	374.51	.90	.07

Footnote: Stdev – standard deviation

Whole brain analysis – Category effects: All category effects were investigated using a mixed effects higher level analysis (after combining individual runs using a fixed-effects higher level analysis) by contrasting each experiment condition against baseline/rest. To control for multiple comparisons, cluster-based thresholding was applied to all analyses. Voxel inclusion was set at z = 1.96 with a cluster significance threshold at FWE *p* < .05 (Appendix 5.2, 5.3, 5.4, and 5.5 contains the global associations and specific feature matching conditions against rest). Figure 5.3 shows the significant effects of category within each task (the opposite contrasts revealed no significant clusters).

Global associations; the global tool > animal effect could be a consequence of uncontrolled differences, particularly for manipulability between the properties of items in these categories. Tools elicited more activity in brain areas linked to actions, tools and object knowledge, compared with global associations for animals: i.e., a right frontal response that extended from MFG/IFG to precentral gyrus, with a separate left hemispheric cluster in lateral occipital (LO) cortex extending into the supramarginal gyrus (SMG). The activation of these regions is consistent with previous investigations into tool knowledge (Noppeney et al., 2006; Liljeström et al., 2008; Wadsworth and Kana, 2011). For *size judgements*, there was more activation for animals bilaterally in the frontal pole spreading into superior frontal gyrus and right IFG (pars opercularis). Further activation was observed in both anterior and posterior aspects of the cingulate gyrus, alongside activation in the precuneus. Left hemispheric activation was observed in the left temporal pole, anterior MTG and left precentral gyrus. Previous work has linked these areas to animacy – i.e., they are recruited when participants think about mental states (Lombardo et al., 2009; Spunt et al., 2011). However, similar to the effects observed for global tools > animals this effect could be a consequence of the greater familiarity and imagability differences between these categories. Finally, when looking at *specific feature matching,* action vs. colour decisions activated posterior and anterior regions of LIFG, IFS, precentral gyrus, IPS, and posterior inferior occipital-temporal regions. These regions have been implicated in tool action knowledge/selection (Johnson-Frey et al., 2005; Liljeström et al., 2008; Yee et al., 2010), and in semantic control (Badre et al., 2005; Noonan et al., 2013).

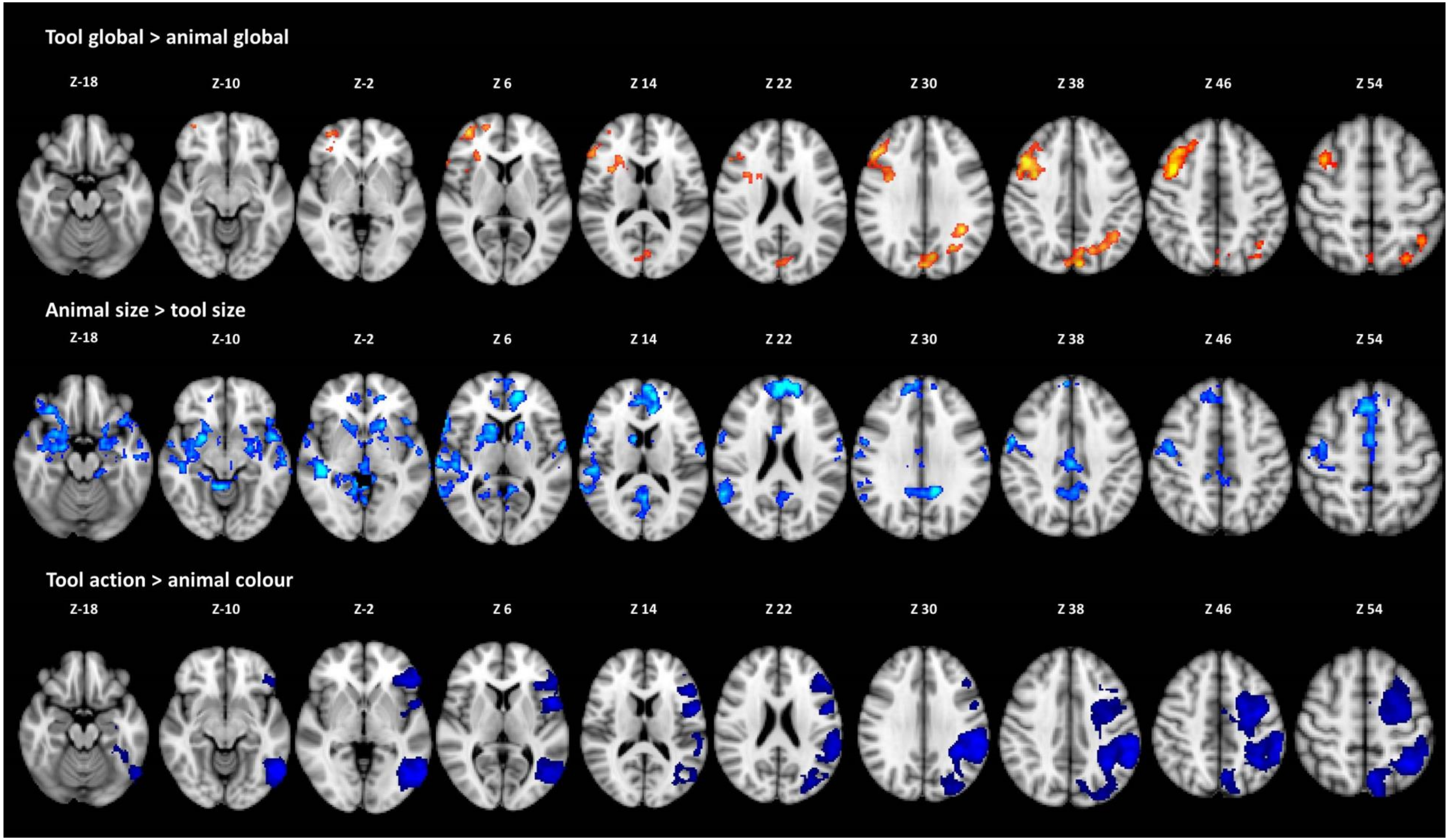


Figure 5.2 Activation for significant category effects. All contrasts presented are cluster corrected for multiple comparisons (z inclusion = 1.96, cluster significance p <.05). Images are presented in radiological convention (e.g., left hemisphere is on right side of image).

Easy global semantic association matching vs. goal driven selection: Here we look at tasks which maximise goal-driven semantic selection (i.e., the most difficult, executively-demanding specific feature-matching trials) relative to easier judgements about global associations. The analysis pathway used here was the same as the analysis used to investigate category effects; all feature selection trials and global trials were contrasted in a mixed effects higher level analysis. Figure 5.2 displays the regions that responded more strongly in the easy task (global > specific features) and in the hardest goal-driven feature selection trials (i.e., the reverse contrast), alongside the interaction between semantic category vs. task. An interaction was computed by determining whether the difference between the two categories differed across the different features used in this experiment, establishing whether the same regions are recruited for difficult semantic judgements across categories, or if executive demands depend on the category of concepts that are driving the retrieval.

Easy global semantic association matching (global > features) decisions activated a network implicated in automatic semantic retrieval, and included many core elements of the 'default mode network' which is implicated in spontaneous thought and tends to deactivate in a task context (especially for non-semantic tasks; Duncan, 2010; Wirth et al., 2011; Yeo et al., 2011). These regions included bilateral ATL and AG which have been implicated in the automatic retrieval of semantic concepts (Binder et al., 2009; Whitney et al., 2011a; Lau et al., 2013). Activation was also observed bilaterally across the middle and superior frontal gyrus, spreading into ventral aspects of the paracingulate gyrus. It is noticeable that the activation extends across the right MTG and temporoparietal cortex. Two of the key regions implicated in semantic control (LIFG and pMTG) were not activated for easy over hard semantic judgements (i.e. richness of semantic retrieval), but that the right pMTG exhibits a greater response for easy semantic retrieval, thus it is possible that this part of the semantic control network is lateralised.

A small yet significant task by category interaction was observed in left inferior LO and left SMG. Further examination was conducted by placing a 5mm sphere around the peak coordinate in each interaction cluster. The FEAT query tool in FSL was used to extract the mean percentage signal change within each ROI; this data was subjected to the same ANOVA used in the analysis of the behavioural data. Table 5.4 contains the mean percentage signal change for 5mm spheres placed around the significant task by category interaction peak in LO and SMG. The ROI analysis revealed that difficult feature selection elicits more activation in the SMG for action trials, and greater activation in the LO for colour trials, supporting previous findings of SMG activation in response to tool action judgements (Liljeström et al., 2008; Yoon et al., 2012), and the role of the LO in animal judgements (Chouinard and Goodale, 2010). These findings suggest there might be some additional recruitment of visual areas for difficult tasks involving visual feature selection, and some additional recruitment of praxis areas for difficult tasks involving action feature selection. However, the overwhelming message is that very few voxels show an interaction between type of task and semantic category, suggesting that, for the most part, the same brain regions support goal-driven semantic selection irrespective of the features that need to be retrieved.

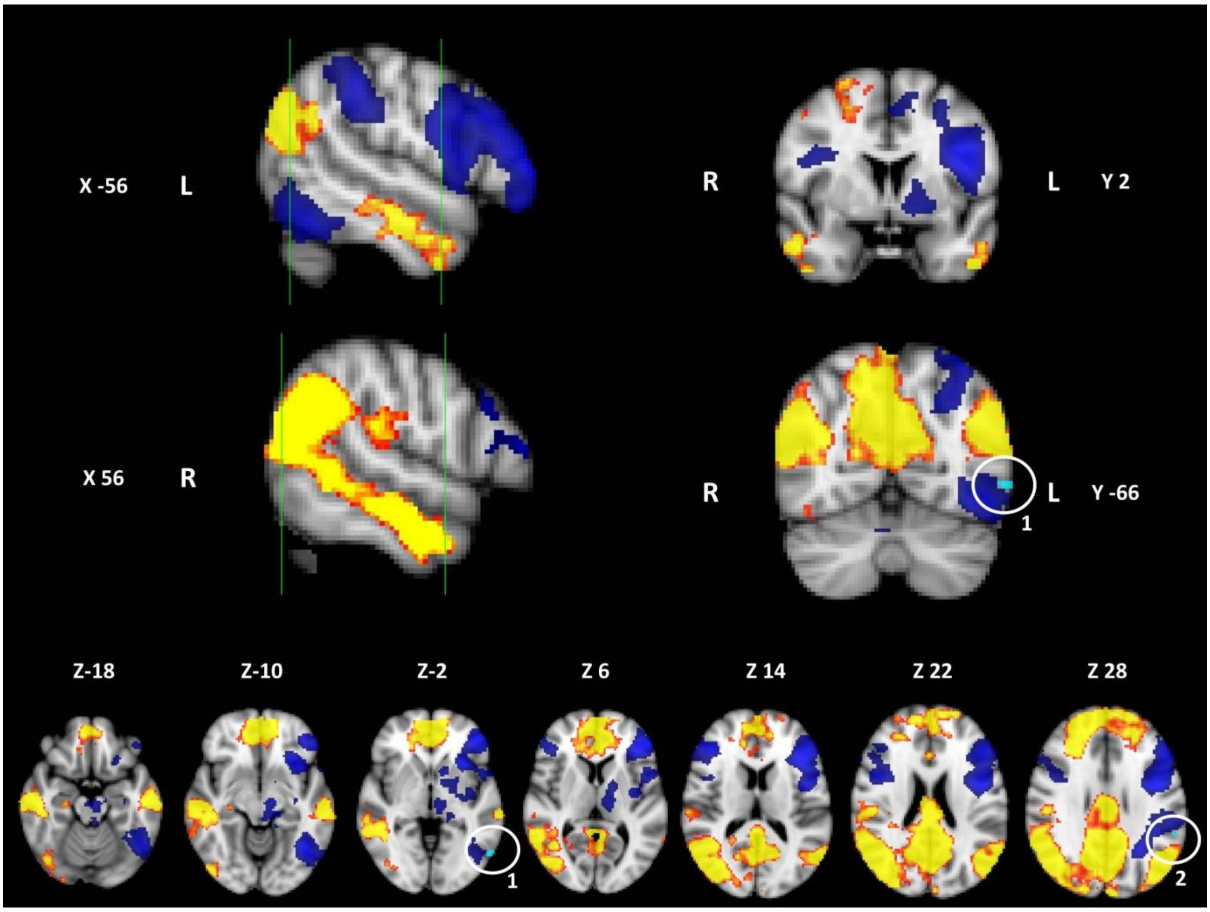


Figure 5.3- Activation for all feature selection (actions & colour) contrasted against their relative global conditions (global tool & global animal) in blue, with activation for global judgements over feature selection in yellow/red, with the interaction term in cyan. The interaction has been circled; 1 = LO, 2 = SMG. All contrasts presented are cluster corrected for multiple comparisons (z inclusion = 1.96, cluster significance p <.05).

Table 5.4 - *Mean percentage signal change and standard error for the interaction term in LO and SMG, extracted using 5mm spheres around the peak co-ordinate.*

Judgement	**Category**	**Mean % signal change**	**standard error**
Lateral occipital cortex (-56-68 -2)			
Global	Animal	.015	.040
	Tool	.016	.048
Size	Animal	.040	.046
	Tool	.005	.056
Colour	Animal	.373	.075
Action	Tool	-.162	.044
Supramarginal gyrus (-58 -42 28)			
Global	Animal	-.002	.026
	Tool	-.002	.025
Size	Animal	-.016	.024
	Tool	-.092	.038
Colour	Animal	-.126	.043
Action	Tool	.229	.063

Whole brain analysis – goal-driven semantic selection demands

To investigate the networks involved in goal-driven semantic selection we contrasted the specific feature for each category against their global selection condition (e.g. action > global tool judgements).These contrasts were defined as goal-driven due to the need to retrieve specific features in contrast to global semantic associations. We investigated these effects further through the use of conjunctions to identify shared areas of activation, computed using the easythresh tools in FSL. While matching items based on their size is another example of goal-driven semantic selection no differences were observed between size judgements and global semantic associations, motivating the use of the specific feature matching conditions only. The conjunctions were conducted on the uncorrected z-stat maps for action > tool global and colour > animal global, both maps were thresholded at $z = 1.96$, revealing shared voxels between these contrasts at the provided Z-stat threshold. The following conjunction was then cluster corrected (z inclusion = 1.96, cluster significance $p <.05$) to control for multiple comparisons). Conjunctions were conducted both across the whole brain and within regions previously implicated in controlled retrieval using small-volume correction (SVC) to examine LIFG and posterior inferior temporal cortex (see Appendix 5.6). In this study the conjunctions refer to the testing of the null conjunction hypothesis (Nichols et al., 2005); under this method a voxel should be significantly activated by both tasks, activation should not be modulated by an interaction, and the relationship between each voxel and task should not be significantly different. This analysis will reveal if an overlap is present between these different types of feature matching conditions. The contrasts and the conjunction between them can be seen in Figure 5.4, cluster index can be found in Appendix 5.7, with the cluster index for the conjunctions in Appendix 5.8.

The conjunction revealed significant shared activation in the LIFG, IFS, precentral gyrus, and the posterior inferior occipital-temporal lobe. This pattern is consistent with previous results implicating the LIFG in semantic selection (Thompson-Schill et al., 1997; Badre et al., 2005; Whitney et al., 2012; Noonan et al., 2013), and also for the role of the IFS and precentral gyrus in domain general cognitive control (Fedorenko et al., 2013). Badre et al. (2005) characterised goal-driven selection in posterior IFG (as opposed to the controlled retrieval in anterior LIFG), however the distinction actually appears to be dorsal IFG/IFS for goal driven selection, and this response stretches from pars opercularis to orbitalis. Activation for goal-driven semantic selection was also observed in ITG which has been previously implicated in cognitive control using functional connectivity (Yeo et al., 2011) and in incorporating object change (Hindy et al., 2013). This suggests that regions of the posterior temporal lobe are implicated in goal-driven semantic selection alongside LIFG, however activation in pMTG is not observed; a site previously implicated in semantic control (Whitney et al., 2011b; Whitney et al., 2012; Noonan et al., 2013), suggesting that dissociations between different types of selection can be observed in the posterior temporal lobe, like those observed in LIFG.

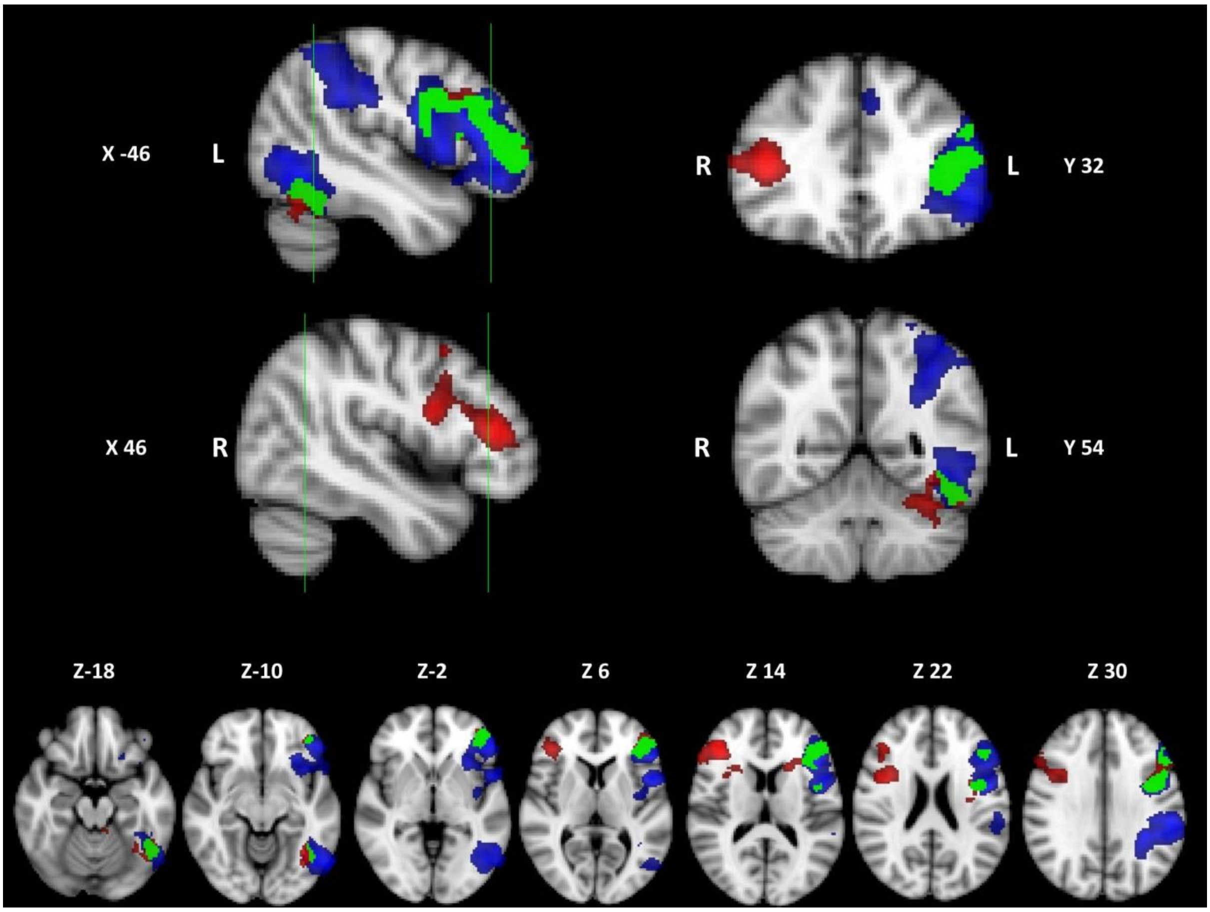


Figure 5.4- Activation for specific feature selection contrasts > selection of global semantic features. All contrasts presented are cluster corrected for multiple comparisons (z inclusion = 1.96, cluster significance p <.05). Action > tool global = blue, colour > animal global = red. The conjunction is presented in green and is a composite of the whole brain and SVC conjunctions projected onto the same volume.

Whole brain analysis – context-driven semantic selection demands

Badre et al. (2005) linked controlled semantic retrieval to the successful retrieval of relatively weak global semantic associations. The key semantic control regions (much of LIFG and pMTG) were not seen for the goal-driven semantic selection, and this could be because they are involved in "controlled retrieval" not selection using Badre's (2005) terminology (subsequently we will refer to this as context-driven semantic selection). To look at the control idea, we want to reduce the difficulty manipulation by contrasting between global associations and (easy) feature selection based on shape/size dimension. Global associations are labelled as requiring controlled retrieval as in a similar manner to the action feature selection judgements, the nature of the semantic association between items is dependent on the stimuli themselves, which requires participants to engage in controlled contextual retrieval irrespective of difficulty. See Figure 5.5 for the contrasts of action > colour, global > size and the conjunction between these contrasts, cluster index can be found in Appendix 5.7, with the cluster index for the conjunctions in Appendix 5.8.

. Activation for global decisions relative to size feature selection was observed bilaterally along the temporal lobe including anterior temporal regions (ATL), left pMTG, AG, and a cluster in ventral LIFG. This network of regions has been implicated in multimodal semantic processing, which might be activated by the contrast of global > size because global semantic associations involve richer semantic retrieval. The pattern of activation includes regions implicated in the default mode network (DMN; Duncan, 2010; Spreng et al., 2010; Yeo et al., 2011) and the frontoparietal control system regions (FPCS; Vincent et al., 2008; Spreng et al., 2010). To work out which are contributing to controlled retrieval of global associations, we look at a conjunction with another contrast which also involves retrieval that is driven by a spatiotemporal context, but this time the context task is harder than the non-context task (actions > colour). The conjunction was created using the same method documented in the section for goal-driven selection. Similar to the previous section on category differences, the contrasts which form the basis of the conjunctions contain confounds of imagability, familiarity, and manipulability, with animals having significantly higher imagabiltiy and familiarity ratings, whereas tools have higher ratings of manipulability. While these confound(s) make differences between conditions and contrasts troublesome, they will have no effect on the conjunctions which are the main aim of this analysis.

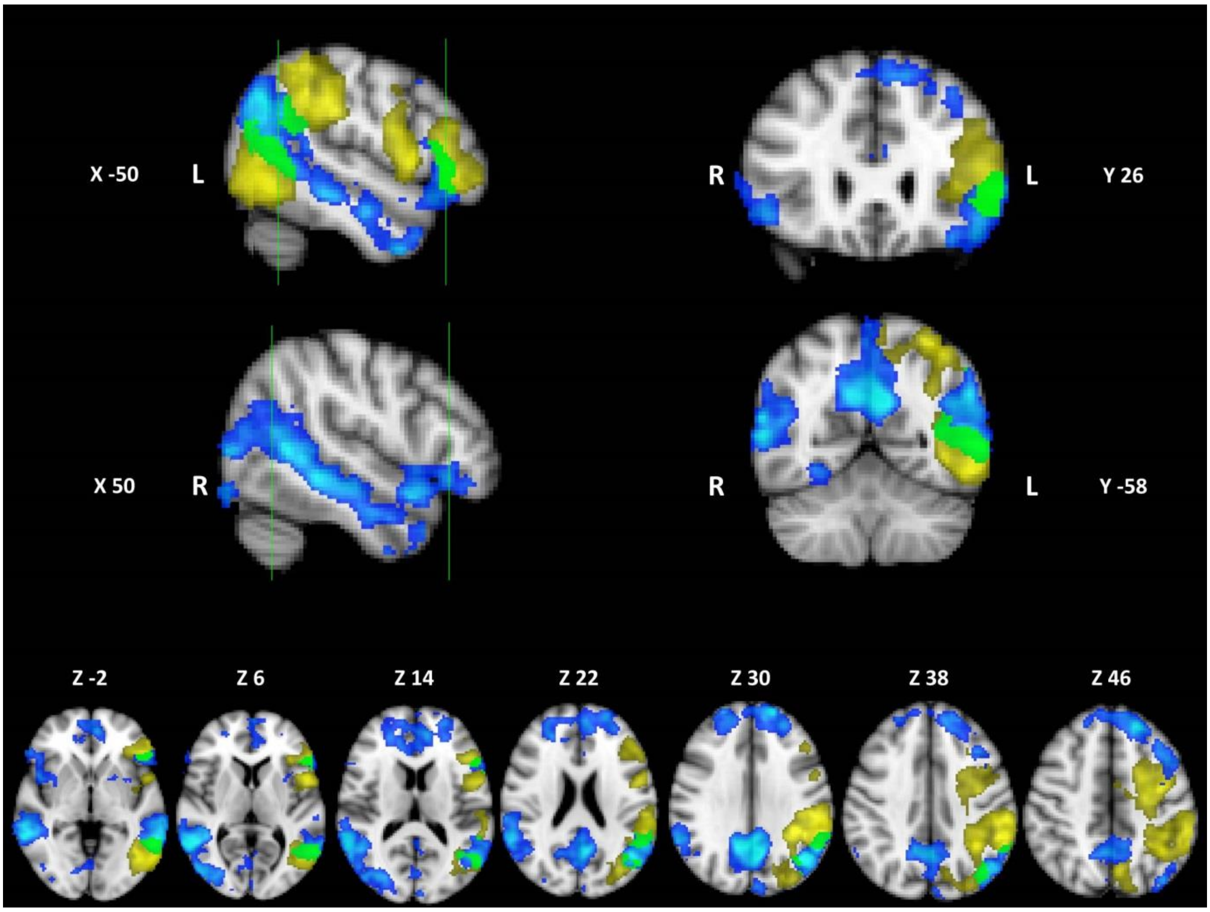


Figure 5.5 - Activation for conditions requiring context-driven selection > of context invariant feature selection. All contrasts presented are cluster corrected for multiple comparisons (z inclusion = 1.96, cluster significance p <.05). Action > colour =yellow, global all > size all = blue/light blue. The conjunction is presented in green and is a composite of the whole brain and SVC conjunctions projected onto the same volume.

A conjunction between action > colour and global all > size all was computed to reveal shared activation for the contrasts implicated in context-driven semantic feature selection.. This conjunction revealed shared activation in medial pMTG and AG, with a second cluster centring on anterior IFG. There is evidence to suggest that medial pMTG and AG are contributing to different things (i.e. they are implicated separately in the DMN and FPCS) but both come into play when context is used to drive retrieval. This pattern expands on the results of Badre et al. (2005), who observed anterior LIFG responses for context-driven selection; here we observe activation in ventral aspects of LIFG, alongside activation within the temporoparietal cortex which co-activates with ventral LIFG to support context-driven aspects of semantic retrieval.

Whole brain analysis – comparisons between the networks identified for goal-driven and context-driven semantic selection

Figure 5.6 projects the conjunctions (whole brain and small volume corrected) revealing shared activation between the contrasts which involve goal-driven semantic selection (actions and colour > tool/animal global) in green, with the conjunction for context-driven semantic selection (actions > colour and global all > size all) in orange. Within LIFG a dorsal/ventral difference is observed with a cluster in dorsal LIFG for contrasts which require goal-driven semantic retrieval, in contrast to a cluster in ventral LIFG for contrasts requiring contextual retrieval of semantic knowledge. A similar dissociation is observed in posterior temporal cortex revealing shared activation in pMTG, stretching into AG for context-driven semantic retrieval, whereas goal-driven semantic retrieval activates a small cluster of shared voxels in ITG. Comparison of the two sets of conjunctions reveals that the shared voxels for different types of semantic retrieval are dissociable in both the LIFG and in the temporoparietal cortex. These differences will be investigated further in the next section through the use of ROIs focused on peaks taken from studies which have investigated the LIFG (Badre et al., 2005) and temporoparietal cortex (Noonan et al., 2013) in semantic cognition.

Interim summary

The whole brain analyses demonstrate that left ventral prefrontal cortex is involved in both goal-driven and context-driven selection; however these processes are spatially distinct, with context-driven retrieval recruiting ventral and anterior aspects of LIFG, and goal-driven feature selection recruiting dorsal IFG/IFS (Figure 5.6). Different areas beyond LIFG are also recruited during these two types of semantic retrieval, with inferior temporal regions recruited when features are selected according to a specific goal, and pMTG and AG recruited when retrieval is driven by a context (Figure 5.6). This demonstrates that goal-driven and context-driven selection effects activate spatially distinct regions in the temporoparietal cortex, coordinating with different regions of LIFG based on task demand.

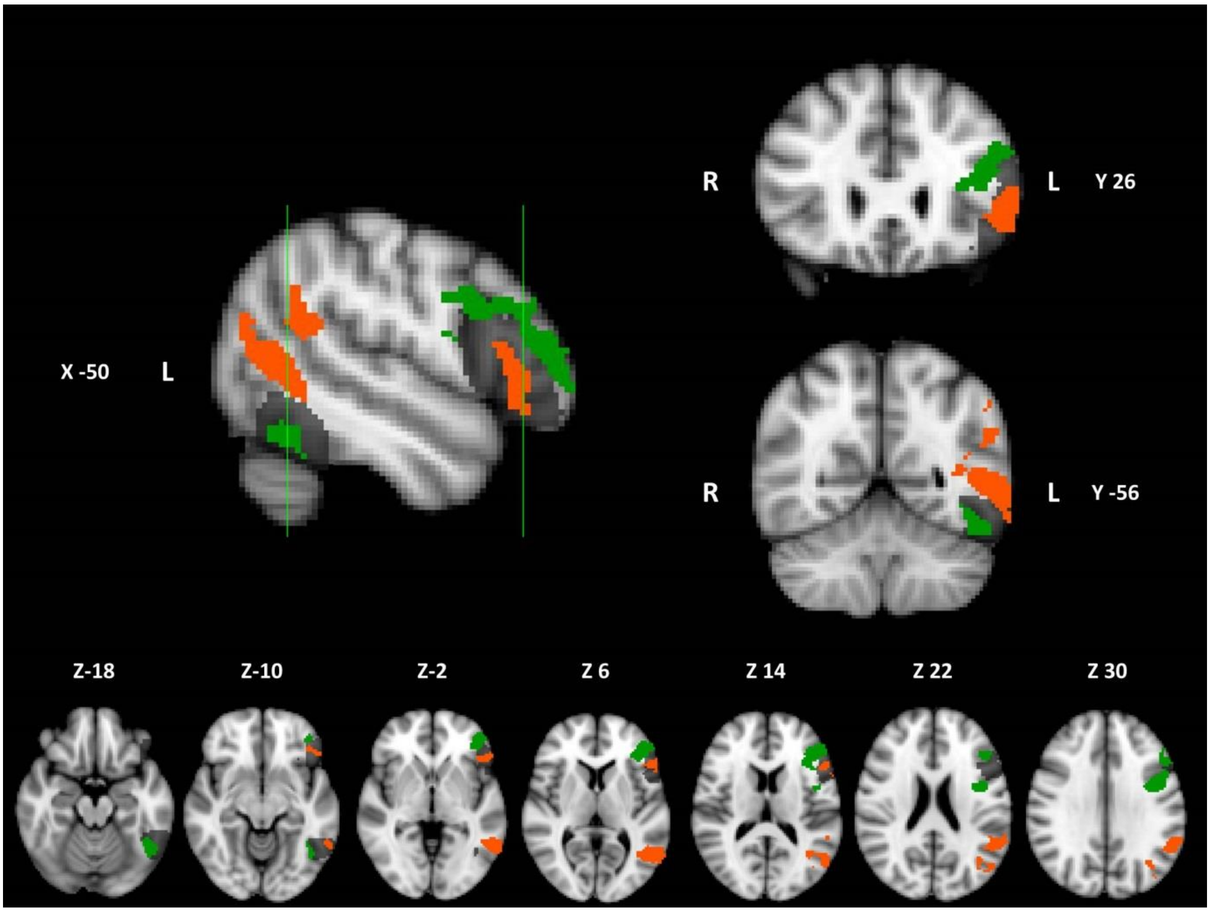


Figure 5.6 - Composite image combining whole-brain and small volume corrected (SVC) analyses for the conjunctions for goal-driven selection (conjunction of action > tool global and colour > animal global = dark green) and context-driven selection (conjunction of action > colour and global all > size all = orange) demands. Masks used for the SVC are presented in dark grey, activation for the orange cluster in LIFG and the green cluster in ITG were only observed in the SVC analyses. Conjunctions are cluster corrected for multiple comparisons z inclusion = 1.96, cluster significance p <.05).

ROI analysis

8mm spherical ROIs were placed within LIFG using peak coordinates linked to “selection” and “controlled retrieval” by Badre et al. (2005) (Figure 5.7). The peaks corresponded to dorsal posterior and anterior LIFG, with a third peak in ventral anterior LIFG. Both dorsal peaks were implicated in aspects of semantic selection (which corresponded with goal-driven semantic selection), with ventral anterior LIFG responding to aspects of semantic retrieval which corresponded with context-driven semantic selection). We used these peaks to investigate how the areas implicated in selection and controlled retrieval in Badre et al. (2005) responded to goal-driven and context-driven semantic retrieval demands in this experiment. These ROIs were supplemented with temporoparietal peaks (pMTG, dorsal AG/IPS, and ventral AG) taken from a recent meta-analysis of neuroimaging studies of semantic control (Noonan et al., 2013). Two of these sites (pMTG and dAG/IPS) are implicated in the controlled selection of semantic information, and lay either side of the ventral AG (vAG), which has been implicated in automatic retrieval/attention to semantic representations. Similar to the selection of ROI's in the LIFG these sites were selected to investigate temporoparietal contributions to goal-driven and context-driven semantic selection demands in areas previously implicated in controlled selection and automatic retrieval. The FEATquery tool in FSL was used to extract unthresholded percentage signal change in each ROI for all six conditions for each participant. Average responses for all voxels within the ROI were computed and ANOVA was used to examine the effects of item category, task, and their interaction for each ROI.

A 2 semantic category: animals vs. tools) x 3 (task: specific feature selection; size/shape judgements; global semantic similarity) omnibus ANOVA was conducted for each ROI. To further investigate the effects of feature selection and contextual retrieval, paired comparisons between pairs of semantic judgements were conducted to examine the responses observed at the whole brain level and to observe the contributions of key semantic control regions to goal-driven and context-driven effects. Goal-driven effects will manifest as greater activation for feature selection contrasts (actions and colours) compared to global judgements, whereas context-driven effects are driven by significantly greater activation for actions when compared to colour judgements and global judgements when compared to size judgements irrespective of semantic category (i.e. there should be no significant difference between categories, only between features). Figure 5.7 shows the spheres represented on a glass MNI-152 brain alongside the conjunctions for both feature selection and contextual retrieval. Paired contrast effects looking at goal-driven demands are presented in Table 5.5 with context-driven effects in Table 5.6, with omnibus ANOVA results presented in table 5.7. In this section particular focus will be placed on paired-contrasts between conditions and judgements as these will reveal whether the differences observed in the conjunctions and omnibus ANOVA are statistically significant

In LIFG, based on the findings from (Badre et al., 2005) we would expect to see an anterior-posterior distinction in LIFG; signal change in posterior sites will be greatest for conditions that require goal-driven semantic selection, whereas anterior sites should display significant signal change for context-driven semantic selection demands. However based on our own whole brain analysis we would predict that dorsal LIFG would significantly responded to goal-driven semantic selection, with ventral LIFG responding to context-driven effects.

Paired contrasts revealed that across all LIFG ROIs revealed robust differences for actions compared to global tool decisions with significantly greater signal change for actions. Activation in all LIFG sites was also significantly greater for action selection when contrasted against animal colour. Ventral anterior LIFG also displayed significantly greater signal change global conditions when contrasted to size judgements, with no significant difference between global and size trials observed in dorsal posterior and anterior LIFG. This pattern reveals dissociation within LIFG with dorsal posterior LIFG and dorsal anterior LIFG demonstrating response profiles consistent with a specific involvement in goal-driven selection demands, whereas the response in ventral anterior LIFG suggests it is involved in context-driven aspects of semantic retrieval, which suggests specifically that the controlled retrieval response identified by Badre et al. (2005) is seen not only in association judgements but also for feature selection trials which involve the retrieval of a spatiotemporal context (action trials).

In the temporoparietal cortex, paired contrasts, revealed that in dorsal AG/IPS there were no significant differences between action or colour decisions relative to global decisions, supporting the conjunction analysis which revealed no goal driven effects in this region. For context effects significantly greater activation for actions > colour was observed, but there was no significant difference between global and size trials. Looking at the omnibus ANOVA revealed no significant effects of features but revealed a significant category effect, suggesting that the difference between this actions > colour can be explained by category effects.

The response profile of pMTG demonstrates significantly greater activation for global decisions compared to size judgements and also exhibited strong effects of action selection compared to colour selection, displaying a similar response profile to ventral anterior LIFG, consistent with involvement in the controlled retrieval of contextual features rather than the selection of features based on current goals. Similar to the pattern in Dorsal AG/IPS no significant difference was observed between action and colour judgements and their global counterparts supporting the role of the pMTG in context-driven selection but not goal-driven selection.

vAG demonstrated significantly greater deactivation for both animal colour and size judgements compared to animal global judgements and significantly greater deactivation for tool size judgements compared to tool global judgements with no significant difference observed between the degree of deactivation between action and tool global. This pattern of deactivation is consistent with an increased focus of internal attention required for feature selection judgements compared to global judgements which require a greater degree of controlled retrieval. vAG on the other hand only demonstrates a significant effect between global judgements and size judgements, with significantly less deactivation for global judgements, consistent with the findings of the previous set of paired contrasts, demonstrating an increased focus of internal attention for context based judgements that require a greater degree of controlled retrieval.

ROI analyses – global association difficulty effects

The global association judgements cover a large degree of different associations; for example some judgements are based on spatiotemporal context (ICECUBE TRAY – FREEZER), whereas others are based on global semantic relations (BEE – HONEYCOMB). We investigated whether there as any difference between easy and more difficult semantic associations (based on participant responses) by splitting the global associations into high and low association strength based on global median RT (20 trials in each split, equal numbers across the two categories).

Both dorsal posterior and anterior LIFG demonstrated significant category effects with greater activation for the difficult global association trials (dorsal posterior; *t* (39) = -2.85, p =.007, dorsal anterior; *t* (39) = -2.86, p =.007), however no significant difference was observed in ventral anterior LIFG (*t* (39) = -.41, p =.686). This pattern is consistent with results from the conjunction analysis demonstrating difficulty effects in areas implicated in goal-driven semantic selection but not in context-driven selection as both easy and hard global semantic judgements require contextual manipulation.

Responses in pMTG are consistent with the pattern in ventral anterior LIFG demonstrating no significant difference between easy and difficult global trials (*t* (39) = -1.33, p =.191), with dAG demonstrating significantly greater activation for global easy trials (*t* (39) = -2.40, p =.021), and vAG displaying significant deactivation for hard global judgements compared to easy global judgements (*t* (39) = -2.48, p =.017). The results of posterior temporoparietal ROI's reveal consistent results to the previous ROI analysis and whole-brain analysis, demonstrating the role of pMTG in the contextual selection of semantic information and are consistent with the reduction in signal/task-related deactivation for harder semantic decisions in AG.

Table 5.5 - *Goal-driven paired contrast results*

Site	Description	Contrast	T-value	Sig.
Dorsal anterior LIFG	Goal-driven selection of action not colour	Colour > animal global	1.58	.131
		Action > tool global	**4.65**	**<.001**
Ventral anterior LIFG	Goal-driven selection of action not colour	Colour > animal global	-1.01	.327
		Action > tool global	**2.66**	**.016**
Dorsal posterior LIFG	Goal-driven selection across feature types	Colour > animal global	**3.05**	**.007**
		Action > tool global	**5.47**	**<.001**
Left pMTG	No goal driven retrieval effect	Colour > animal global	-1.77	.092
		Action > tool global	0.72	.479
Dorsal AG/IPS	No goal driven retrieval effect	Colour > animal global	1.09	.289
		Action > tool global	1.09	.286
Ventral AG	No goal driven retrieval effect (negative t-stat indicates greater response to animal global trials)	Colour > animal global	**-4.28**	**<.001**
		Action > tool global	-1.04	.311

Table 5.6 - *Context-driven paired contrast results*

Site	Description	Contrast	T-value	Sig.
Dorsal anterior LIFG	Action feature retrieval only	Action > colour	**2.85**	**.010**
		Global (all) > size (all)	1.20	.239
Ventral anterior LIFG	Context-driven retrieval of features and associations	Action > colour	**2.90**	**.009**
		Global (all) > size (all)	**3.68**	**.001**
Dorsal posterior LIFG	Action feature retrieval only	Action > colour	**3.16**	**.005**
		Global (all) > size (all)	-1.45	.156
Left pMTG	Context-driven retrieval of features and associations	Action > colour	**3.22**	**.005**
		Global (all) > size (all)	**3.29**	**.002**
Dorsal AG/IPS	Action feature retrieval only	Action > colour	**2.37**	**.028**
		Global (all) > size (all)	0.27	.792
Ventral AG	Associations only	Action > colour	1.88	.076
		Global (all) > size (all)	**4.08**	**<.001**

Table 5.7 - *Omnibus ANOVA results for all experimental ROI's*

ROI Location	Category			Feature			Interaction		
	F	Sig.	effect size (*r*)	F	Sig.	effect size (*r*)	F	Sig.	effect size (*r*)
LIFG sites from Badre et al. (2005)									
Dorsal posterior LIFG	3.40	.081	.152	**12.986**	**<.001**	**.406**	2.344	.110	.110
Ventral anterior LIFG	0.07	.799	.004	**4.964**	**.012**	**.207**	**8.006**	**.001**	**.296**
Dorsal anterior LIFG	**7.96**	**.011**	**.295**	**18.209**	**<.001**	**.489**	1.568	.222	.076
pMTG and AG sites from Noonan et al. (2013)									
Left pMTG	3.41	.081	.152	**7.08**	**.002**	**.271**	2.43	.102	.113
Dorsal AG/IPS	**4.96**	**.038**	**.207**	1.88	.166	.090	1.34	.273	.066
Ventral AG	0.05	.827	.003	**11.47**	**<.001**	**.376**	**3.70**	**.034**	**.163**

Results for the 2 (category) x 3 (task) omnibus ANOVA, significant results(p<.05) are highlighted in bold

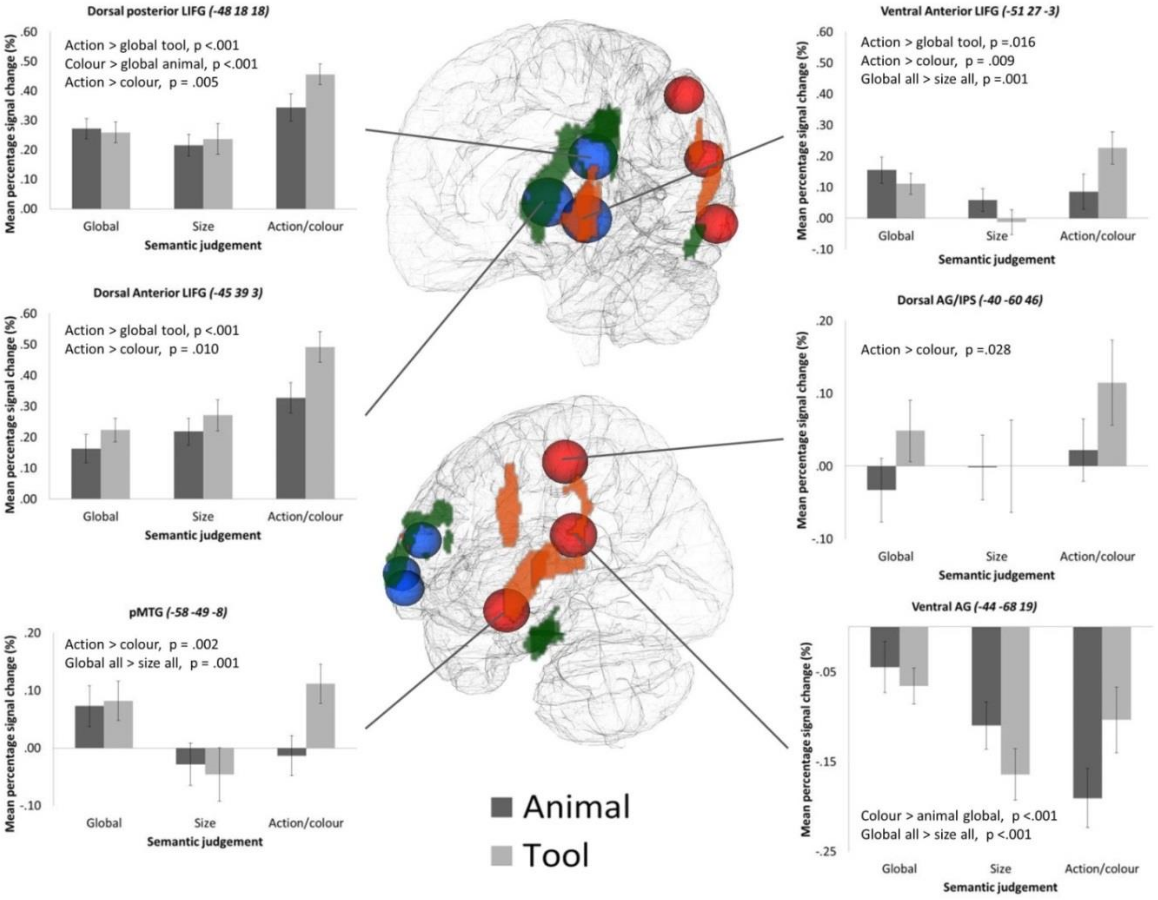


Figure 5.7 – Graphs displaying the mean percentage signal change (%) for each condition at each ROI; error bars represent the standard error of the mean. ROI coordinates are given in MNI space, peaks taken from Badre et al. (2005) are presented in blue, with peaks from Noonan et al. (2013) presented in red. Glass brains display the relative location of these ROIs against sagittal slices of the conjunction results (goal-driven selection, green, context-driven selection orange) which are tilted to provide views of the LIFG and posterior temporal cortex. Brain images were generated using the DV3D software (Gouws et al., 2009).

Discussion

This study provides support for two distinct neural networks supporting context-driven and goal-driven semantic retrieval. Previous research has suggested that different regions of LIFG are recruited when making decisions about weak global semantic associations (ventral anterior IFG) and about specific semantic features according to the task instructions (dorsal IFG; Badre et al., 2005). We replicated and extended this distinction by (1) showing that dorsal IFG is involved in goal-driven semantic retrieval irrespective of the type of feature to be retrieved; and (2) that ventral, anterior IFG is involved in two rather different types of context-driven semantic retrieval: it is activated both when a global (yet somewhat unpredictable) *association* between two items must be uncovered and when action *features* must be compared (which involves the generation of a spatiotemporal context to constrain action retrieval). Secondly, while previous research has implicated the pMTG in controlled semantic retrieval (Whitney et al., 2012; Noonan et al., 2013) and in response to tool/action processing (Watson et al., 2013), we showed that this distinction between goal-driven and context-driven retrieval extends to posterior temporal cortex, with pMTG specifically implicated in context-driven retrieval irrespective of semantic category and pITG involved in goal-driven executively-demanding forms of semantic retrieval. Thus, IFS, dorsal IFG and inferior temporal-occipital cortex are implicated in goal-driven flexible semantic retrieval (i.e., selection of specific features according to task instructions) and these structures overlap with the multi-demand network (Duncan, 2010). In contrast, ventral anterior IFG, IPS and pMTG are recruited when semantic retrieval is driven by the context – e.g., when a linking context must be used to establish a connection between two words. Although these structures are involved in "controlled retrieval" (e.g., they are involved in retrieving relatively *weak* or non-dominant semantic associations and are thus crucial for more flexible forms of semantic cognition; Badre et al., 2005), context-driven retrieval does not appear to be executively-demanding in the same way. ROI analyses supported these conclusions; areas of LIFG involved in selection by Badre et al. (2005) demonstrated stronger responses for goal-driven selection demands (dorsal posterior and dorsal anterior LIFG) and greater activity in more difficult trials (increased response with longer

RT). Ventral anterior LIFG and pMTG demonstrated stronger responses for context-driven retrieval and no effect of overall difficulty/RT.

Previous models of LIFG function have suggested that; (i) there is anterior ventral engagement for semantics and posterior dorsal engagement in semantics and phonology (Poldrack et al., 1999; Gold et al., 2005; Gough et al., 2005; Snyder et al., 2007), (ii) that there is a distinction within LIFG due to differences in controlled retrieval vs. selection (Badre et al., 2005), and (iii) that anterior areas of LIFG are involved in abstract forms of control beyond simple response selection (Badre and D'Esposito, 2007). The data we obtained is compatible with all three of these models of LIFG function; we observed a dorsal-ventral distinction between different forms of flexible semantic retrieval, whereby the contrasts that required retrieval driven by a context – i.e. global associations irrespective of semantic category and action judgements which are made within a spatiotemporal context activated ventral LIFG irrespective of difficulty, with goal-driven selection demands (matching on the basis of specific features specified by the task instructions) driving activation in dorsal LIFG. We propose that these differences reflect an engagement of ventral IFG when semantic retrieval is modulated by context – since the semantic associations that are relevant at any given moment vary depending on task context (Saffran, 2000; Corbett et al., 2011), whereas matching items based on features which do not require a spatiotemporal context (animal colour and animal/tool size judgements) activate dorsal LIFG, which has been implicated in the multi-demand system (Duncan, 2010) and responds to goal-driven selection demands beyond the semantic domain.

Our findings regarding posterior temporal cortex are consistent with previous accounts of a distributed cortical network underpinning semantic control working alongside LIFG (Whitney et al., 2011a; Whitney et al., 2012; Jefferies, 2013; Noonan et al., 2013). However, we extend this work by showing separate responses within posterior temporal cortex for goal-driven and context-driven retrieval. Goal-driven feature selection elicits recruitment of posterior inferior temporal gyrus (pITG) alongside dorsal LIFG, with context-driven effects observed in pMTG. This distinction is comparable with early selection effects in inferior visual cortex (Hindy et al., 2013), and increasing recruitment of pMTG in response to difficulty manipulations in semantic retrieval tasks (Whitney et al., 2011a; Whitney et al., 2011b; Hindy et al., 2012).

Posterior MTG has been linked to tool action representation (Liljeström et al., 2008; Chouinard and Goodale, 2010; Spunt and Lieberman, 2012) and event knowledge, specifically in the encoding of new events (Kim, 2011; Romagno et al., 2012). Semantic control and action/event understanding seem to recruit the same network in the meta-analyses on these same topics (see Kim, 2011 for a meta-analysis of event knowledge; Noonan et al., 2013 for a meta-analysis into semanic control; Watson et al., 2013 for a meta-analysis into action understanding). This puzzle is potentially explained by the data here. We propose that this overlap can be explained through the role of this region in context-driven retrieval, since actions and events, like global semantic associations require flexible semantic retrieval that is appropriate to the current context. We tentatively suggest that pMTG may retrieve and maintain aspects of knowledge that are *currently* relevant, and that this is especially important when these are not dominant features and associations for a given input. In contrast, the anterior temporal lobe (ATL) is implicated in more automatic aspects of semantic processing and shows strong coupling with other nodes within the DMN (see Chapter 3, Figure 3.1). Since unguided spreading activation in ATL is expected to recover strong associations and features, even when these are irrelevant, pMTG may play a crucial role in maintaining a context-specific set of features which can *shape* ongoing spreading activation. We propose that pMTG in concert with LIFG allows for flexibility in how semantic information is used and selected. This proposal helps to explain the deficits in semantic aphasia (SA) patients who demonstrate a specific impairment in the selection of weakly associated information and rely on irrelevant automatic strong associations following damage to pMTG and LIFG. This response pattern is not isolated to tools, but also for other semantic categories (e.g. animals) for which their relationships vary as a factor of context (for example a different set of behaviours are associated for a *Tiger*, depending on whether the context is a *Zoo* or *Jungle)* suggesting that pMTG is driven by sensitivity for context-based flexibility. This has the potential to explain why pMTG responds more to events and actions, but without the response being specifically restricted to these aspects of knowledge.

Both pMTG and AG demonstrate sensitivity to sentence context-type effects (Smirnov et al., 2014) alongside knowledge of thematic associations (de Zubicaray et al., 2013; de Zubicaray et al., 2014) and action knowledge (Liljeström et al., 2008), as demonstrated by the conjunction in this study, however they have different responses to aspects of controlled versus automatic aspects of semantic cognition respectively. The AG forms part of the default mode network (Spreng et al., 2010; Uddin et al., 2010; Power et al., 2011; Wirth et al., 2011) and demonstrates task-related deactivation in this study and others (Wirth et al., 2011; Humphreys and Lambon Ralph, 2014). The pMTG on the other hand has been implicated in the frontoparietal control system (Vincent et al., 2008; Spreng et al., 2010) and demonstrates task related activation (Noonan et al., 2013). In this study, they both fell within the conjunction for context-driven retrieval, showing that they were recruited during the retrieval of both action features (over colour features) and global associations (over the easier size feature retrieval). Despite this similarity ventral AG exhibited task-related deactivation, whereas pMTG demonstrated task-related activity. This pattern suggests that ventral AG demonstrates reverse difficulty effects fitting with the findings from resting networks, i.e. more deactivation for difficult judgements consistent with previous observations (Binder et al., 2008). Deactivation in the ventral AG has been associated to its involvement in the default mode network (DMN), a set of regions which demonstrate deactivation under task conditions (Anticevic et al., 2010; Mayer et al., 2010; Power et al., 2011). However the ventral AG demonstrates greater deactivation for non-semantic tasks than semantic tasks when difficulty is matched across different experiments (Binder et al., 2009; Wirth et al., 2011). While the AG is implicated in more automatic aspects of semantics, it is also implicated in other types of tasks while demonstrating activation for sentence-level tasks and in memory retrieval tasks (Humphreys and Lambon Ralph, 2014), suggesting that the AG might play a role in allocating attention (Woolgar et al., 2011); this possible explanation is consistent with the data presented here (but is not the only interpretation). Both sites are involved in context driven retrieval for different reasons we propose that pMTG is involved in shaping semantic space bringing together distant semantic associations together, whereas AG is involved in the reflexive orientation to concepts and memories, as context is important in directing attention, this is an extension of the idea discussed in Chapter 3.

Previous work has implicated the AG/pMTG as a separate hub for the storage of thematic associations between concepts (Schwartz et al., 2011; de Zubicaray et al., 2013), with other research suggesting that these areas specifically represent action/event knowledge (Martin, 2007; Liljeström et al., 2008; Binder et al., 2009). The findings here contradict the notion that the AG and pMTG capture thematic associations specifically or represent actions because these sites also respond to (1) feature selection tasks for actions and (2) global associations which fail to strongly tap action/event knowledge (global associations in the context of the current study are not based on actions but on determining the correct link between items as participants were required for each global judgement to work out what the relevant relationship was for each case). If these theories were correct we would predict AG/pMTG responses to global semantic decisions only or specific involvement for action trials only. However, the activation of temporoparietal cortex to both these contrasts is broadly compatible with its previously reported role in event semantics (since global associations and actions are both ‘event like’).

In conclusion the current study has demonstrated dissociations for goal-driven and context-driven flexibility in the wider semantic control network. Dorsal IFG/IFS and ITC form part of the goal-driven selection network (overlapping extensively with the multi-demand network; Duncan, 2010) while anterior IFG and pMTG form part of the context-driven flexibility network which is more specifically implicated in semantics. The evidence suggests that both these networks have a key role to play in semantic control but that their responses are dissociable, forming a wider semantic control network beyond LIFG.

Chapter 6 - Thesis discussion

Summary of empirical findings

This thesis sought to understand the cognitive and neural architecture of semantic cognition. Previous research has identified the networks involved in semantic cognition; this thesis used fMRI, TMS, and data from patients with semantic aphasia (SA) to explore controversial issues in the literature. The key objectives were; (i) to distinguish the roles of the AG and pMTG in semantic cognition; these sites display co-activation in semantic tasks (Binder et al., 2009; Noonan et al., 2013) and are often damaged together in SA; however their individual contributions to semantic cognition are unclear. (ii) To investigate the networks required for automatic and different aspects of controlled semantic retrieval; previous fMRI studies have demonstrated that these aspects of semantic selection are dissociable in the LIFG (Badre et al., 2005), however it is unclear whether this distinction spreads into the wider semantic network. (iii) The final objective was to explore the overlap between event semantics and semantic control; examination of the brain areas implicated in the selection of event/action knowledge (Kellenbach et al., 2003; Liljeström et al., 2008; Kim, 2011) and semantic control (Noonan et al., 2013) reveal activation in similar brain regions however it is unclear about the degree of overlap due to previous investigations manipulating only event/action knowledge and semantic control. We investigated these issues by manipulating aspects of semantic control and representation within a single paradigm.

In Chapter 2 we contrasted easy and difficult word-picture matching judgements requiring either associative knowledge (strong vs. weak thematic links; e.g. 'Racing car' – HELMET vs. 'Racing car' – CHAMPAGNE) or identity knowledge (superordinate vs. specific name matching; e.g. 'Labrador' – ANIMAL, vs. 'Labrador' – LABRADOR). In this Chapter we investigated these two different judgments in both SA patients and in healthy participants under dual-task conditions in order to dissociate two theories describing the nature of impairment in this patient population. Both these theories agree that some aspect of semantic knowledge is stored in a hub in the ATL outside of the area of damage observed in SA; the two-hubs hypothesis suggests that the ATL hub stores identity knowledge, with a second hub in the temporoparietal cortex which stores associative knowledge explaining why SA patients are particularly impaired in associative judgements (Schwartz et al., 2011). The second hypothesis suggests that there is only one hub for semantic knowledge and impairments are the result of impaired control mechanisms (Jefferies and Lambon Ralph, 2006; Jefferies et al., 2010; Jefferies, 2013). In both participant groups we discovered that the harder associative judgements were disproportionately affected in comparison to the other judgements, and that the harder associative judgements were the most affected under dual-task conditions in healthy young participants (and in some SA cases superordinate category judgements were also impaired, as these items have greater control demands due to increased contextual diversity; Hoffman and Lambon Ralph, 2011). This pattern suggests that the impairments in SA are the result of impaired control mechanisms rather than damage to a second associative hub in the temporoparietal lobe.

Chapter 3 built on the findings of Chapter 2 utilising TMS to stimulate two regions in the temporoparietal cortex (AG and pMTG) which are often damaged together in SA and co-activated in semantic contrasts (Binder et al., 2009; Noonan et al., 2013), making it difficult to pull apart their individual contributions to semantic cognition. Using the same tasks in as Chapter 2 we demonstrated that TMS to AG disrupted the automatic aspects of semantic cognition; disruption was observed for all associative judgements.. We also observed disruption for specific identity judgements, which required more precise semantic retrieval following AG stimulation. We hypothesise that the AG is involved in the reflexive attentional orientation to activated aspects of semantic space; TMS to AG affects the attentional focus, disrupting associative judgements irrespective of association strength and impairs the ability to focus accurately on a restricted aspect of semantic space preventing fine-grained differentiation of similar concepts. Stimulation to pMTG disrupted judgements which required controlled semantic retrieval; disruption was observed for judgements between weakly associated items and for superordinate and basic level identity matching judgements. Judgements between weakly associated items require increased amounts of controlled retrieval due to the need to shape/guide retrieval towards aspects which are currently relevant, whereas high-frequency words (superordinate and basic level terms) occur in a wide range of contexts which increases their control demands (Hoffman et al., 2010). Whereas AG is involved in the orientation of attention to aspects of semantic space, we hypothesise that the role of pMTG is in the re-representation of task-relevant aspects of semantic knowledge, brining concepts together that are only normally weakly associated into a context where they are strongly linked. This pattern supports the conclusions of Chapter 2 and expands on the role of the temporoparietal region in semantic cognition.

The results of Chapter 3 suggest that there is an overlap between semantic control and thematic knowledge and event retrieval. Chapter 4 takes this further by examining specific action feature retrieval whilst simultaneously manipulating semantic control. In Chapter 4 we used fMRI to investigate the potential overlap between semantic control and event/action semantics as both sets of literature report overlapping brain regions (LIFG, pMTG, AG/IPS) but without manipulating both aspects within a single study it is uncertain to what degree these aspects of cognition overlap in individuals due to the low spatial resolution of meta-analyses. We manipulated both semantic control and feature decisions for tool words; semantic control was manipulated through the use of targets from the same semantic category (easy decisions), contrasted against non-semantic category targets in the presence of semantically associated distracter items (hard decisions). The requirement for action/event semantics was manipulated by contrasting decisions where both the probe and target had to share a similar action against decisions where the probe and target did not share an action feature but had to be matched based on their visual similarity. We observed overlapping activation between the areas activated for the hard vs. easy contrast (irrespective of feature) and the areas activated for action decisions vs. visual decisions (irrespective of difficulty) in LIFG and pMTG/ITG. This was further investigated using ROIs which revealed activation across LIFG for all difficult decisions irrespective of category, whereas pMTG specifically responded for difficult tool action decisions. The pattern observed suggests that the network involved in action/event semantics partially overlaps with the semantic control network in LIFG and pMTG, but that both sites exhibit dissociable contributions to semantic control depending on what aspects of semantic cognition are being manipulated.

The final empirical Chapter (Chapter 5) expanded on the work in Chapter 4; in the previous fMRI experiment we only used one semantic category (tools) and only used one feature which required event/action knowledge. In this Chapter we used two different semantic categories of objects (animals and tools), and contrasted semantic decisions with different selection demands; we used conditions which required features to be selected based on a prior set goal (goal-driven selection), contrasted against context-driven retrieval which required participants to generate a shared spatiotemporal context to determine which probe matched the target. Previous work has implicated posterior LIFG with goal-driven feature selection and anterior LIFG with controlled retrieval of global associations (Badre et al., 2005). We were interested in how pMTG would respond to goal and context driven retrieval and whether we could observe a dissociation between these components in the wider semantic control network. Both types of flexible retrieval activated LIFG, with dorsal LIFG responding to goal-driven selection and ventral AG responding to context-driven retrieval. Beyond the LIFG we observed context-driven effects in pMTG/AG irrespective of semantic category, with goal-driven effects activating posterior aspects of the ITG. This Chapter builds on the results of the previous Chapter demonstrating that activation in pMTG is dependent on a task requiring the manipulation of spatiotemporal context irrespective of semantic category, and not just for associations but also for features retrieved within a spatiotemporal context. Thus, the overlap between semantic control and actions/event knowledge maybe driven by the importance of context in both of these types of tasks.

Research Themes

The research in this thesis can be discussed within two main research themes;

1 – Networks for automatic and controlled aspects of semantic retrieval

a) The network supporting semantic retrieval is not unitary - there are multiple networks that come together. The ATL has been heavily implicated in automatic semantic retrieval (Binney et al., 2010; Visser et al., 2010d; Lau et al., 2013) enabling the retrieval of semantic information and is implicated in the formation of cross-modal links between material (Rogers et al., 2006; Patterson et al., 2007; Pobric et al., 2010). The LIFG has been implicated as a site involved in the controlled selection of semantic information, specifically when automatic spreading activation is not sufficient and can cause unwanted competition between potentially related items (Thompson-Schill et al., 1997; Jefferies et al., 2010; Whitney et al., 2011b; Whitney et al., 2012). While the roles of these regions in semantic cognition are relatively well accepted, activation in these sites is not isolated. The thesis focuses on large-scale networks that include both anterior and posterior components.

b) The roles of the pMTG vs. AG - semantic contrasts activate regions in the temporoparietal lobe, namely AG and pMTG (Binder et al., 2009; Noonan et al., 2013). Sometimes AG and pMTG appear to have similar functions – both respond to contrasts examining event semantics, yet they show clear differences between automatic and controlled retrieval. It has been some have hypothesised that pMTG is involved in the controlled aspects of retrieval like LIFG (Whitney et al., 2011a; Whitney et al., 2011b; Whitney et al., 2012; Noonan et al., 2013), and that AG is involved in automatic aspects of semantics (Binder et al., 2009) the role of these regions is still controversial.

c) How does semantic control overlap with domain-general executive control. The retrieval of semantic information can be flexibly shaped depending on the current context. In some circumstances items have to be retrieved/selected in line with a predetermined goal (for example matching items based on their size). In other situations, associations or relationships between items can only be uncovered when they are considered within a spatiotemporal context which allows for these links to form (for example to determine the link between DEER and RIFLE, the linking context of hunting needs to be activated and maintained). The LIFG has been strongly linked to semantic retrieval (Thompson-Schill et al., 1997; Wagner et al., 2001a), and anatomical distinctions have been observed within LIFG for the different types of semantic retrieval; posterior LIFG has been implicated in goal-driven selection with anterior regions of LIFG implicated in context-based retrieval (Badre et al., 2005). It is unclear whether there are different networks beyond LIFG for these different aspects of semantic retrieval, and this is investigated in this thesis.

2 – Overlap between event semantics and control

Previous fMRI studies have implied that there is a potential overlap between the areas implicated in event semantics and semantic control, but have not directly contrasted these aspects of semantic cognition in the same paradigm. Event semantics are linked to thematic associations as they are based on objects participating in the same event (de Zubicaray et al., 2014), activating the same brain regions implicated in semantic control (LIFG, pMTG, IPS/AG; Kim, 2011), which are also implicated in tool action understanding (Kellenbach et al., 2003; Noppeney et al., 2006; Liljeström et al., 2008; Noppeney, 2008). Tools and actions are intrinsically linked to events as they are used to describe what has happened to an object (Kable et al., 2002), with research into object change suggesting that multiple representations of an object compete with each other based on an event (Hindy et al., 2012), thus actions and event knowledge are explicitly linked and potentially processed by overlapping regions which are implicated in semantic control. This overlap is potentially explained in terms of the variability of retrieval in different contexts for actions/events/associations. However this overlap is impossible to determine based on the findings of past studies as previous work has manipulated only one aspect (event/action semantics or semantic control). One of the aims of this thesis was to manipulate both aspects simultaneously and observe the consequences on the wider semantic network and whether an overlap exists within these networks.

Linking the themes to the empirical findings

In this section the findings from the four empirical Chapters will be discussed in relation to the research themes described above.

Chapter 2**;** we observed a pattern of deficits in our sample of SA patients suggesting that their semantic deficits are the result of impaired control mechanisms rather than damage to a second hub specifically for thematic/associative knowledge. These patients have damage to the LIFG which has been specifically implicated in the controlled retrieval of semantic information (Thompson-Schill et al., 1997; Wagner et al., 2001a; Badre et al., 2005; Whitney et al., 2011b; Whitney et al., 2012; Noonan et al., 2013). Damage in our subset of patients often extends into the pMTG, which has been implicated in the wider semantic control network (Whitney et al., 2011a; Whitney et al., 2011b; Whitney et al., 2012; Noonan et al., 2013). The damage in these patients does not extend into the ATL a site implicated in controlled automatic semantic retrieval and thought to form an amodal conceptual hub (Rogers et al., 2006; Patterson et al., 2007; Pobric et al., 2010), but does extend into the AG (in at least seven out of the nine cases) which has been linked to aspects of automatic semantic retrieval (Binder et al., 2009). Even with this damage to AG, overall the pattern of impairment suggests that in these patients the damage is limited to areas involved in controlled aspects of retrieval, with the automatic network relatively intact.

We also observed reverse specificity effects in a number of patients, whereby they showed a selective impairment for matching items to their superordinate label, whilst being able to match items to their specific level names. Superordinate level terms might place greater demands on control processes due to their increased contextual diversity (Hoffman et al., 2010): they can be applied to a far wider range of contexts and objects in comparison to their specific level counterparts. The pattern observed in our patients suggests that different networks are responsible for controlled vs. automatic aspects of semantic retrieval and that there might be possible differences between AG and pMTG in semantic cognition. However due to the large in our patients with semantic aphasia it is impossible to distinguish between individual areas and networks thus motivating the use of TMS in Chapter 3, and the use of fMRI in Chapters 4 and 5 to further investigate networks for automatic and controlled semantic retrieval.

The findings from our healthy participants under hard dual task conditions also support the findings observed in the SA patients; the harder associative judgements were significantly more impaired whilst participants were performing the 1-back task when compared to all other tasks. This suggests that there is overlap between semantic control and domain-general executive control, as the harder secondary task interfered with semantic judgements which required the greatest degree of semantic control, and performance on the 1-back task was significantly reduced when participants were performing associative judgements. We also found evidence suggesting that the processes involved in identity judgements do not overlap executive semantic processes due to the lack of an interaction between the level of identity judgements and the secondary task demands, supporting the distinction observed in the patients. Areas damaged in SA and in our patient sample have been linked to controlled semantic retrieval in healthy populations (Thompson-Schill et al., 1997; Wagner et al., 2001a; Badre et al., 2005; Whitney et al., 2011b; Whitney et al., 2012; Noonan et al., 2013), whereas the areas implicated in category/identity knowledge (ATL; Schwartz et al., 2011; Coutanche and Thompson-Schill, 2014) are undamaged in this patient sample. Patients with damage to this area are more likely than those with LIFG/temporoparietal damage to make associative errors (e.g. saying ‘animal’ when presented with a picture of a Dog; Jefferies and Lambon Ralph, 2006; Jefferies et al., 2010; Schwartz et al., 2011), similarly basic naming performance is disrupted when using TMS to stimulate the ATL (Pobric et al., 2010).

The results of Chapter 2 help to demonstrate the overlap between event semantics and semantic control. Some research has specifically implicated the temporoparietal cortex in the storage of thematic associative knowledge (Schwartz et al., 2011; de Zubicaray et al., 2013) suggesting that the deficits in SA are due to damage to this store, whereas others have suggested the deficits are the result of impaired control mechanisms (Jefferies and Lambon Ralph, 2006; Jefferies et al., 2010; Jefferies, 2013). In this study, in both participant groups (SA patients and healthy participants under dual-task conditions, specifically for the harder secondary task), we observed a greater disruption for weakly associated items. This suggests that the deficits observed in this patient population are the result of impairments to the semantic control mechanisms required to uncover distant associations between objects, demonstrated by the impairment to weak thematic relationships only, and are not the result of damage to a thematic/associative store in temporoparietal cortex. The results also suggest that retrieving distant thematic relationships places greater demands on the executive-semantic control systems potentially indicating that they rely on the same neural architecture.

Overall the findings from this Chapter demonstrate the potential overlap between event semantics and semantic control. It also suggests that the impairment in SA is best categorised by an impairment to control mechanisms rather than damage to a second thematic/associative hub in temporoparietal cortex.

Chapter 3**;** in this Chapter we used inhibitory TMS, delivered to both AG and pMTG and observed the consequences of TMS stimulation on tasks which tax either identity or associative knowledge, using the same tasks employed in Chapter 2. Stimulation of pMTG disrupted decisions which required the controlled selection of semantic information; disruption was observed to judgements between weakly associated items, and for superordinate/basic level label matching. We observed a different pattern following stimulation to AG; stimulation to this site disrupted all associative judgements apart from judgements on highly related items (we collected association ratings on a 7 point scale, items with an association rating greater than 6 were unaffected by TMS), alongside disruption for specific identity judgements.

Using TMS we observed dissociations between the contributions of pMTG and AG to semantic cognition; we found supporting evidence for the role of the pMTG in the wider semantic control network working alongside LIFG in the selection and maintenance of currently relevant semantic information, consistent with previous TMS (Whitney et al., 2011b; Whitney et al., 2012) and fMRI evidence (Noonan et al., 2013). Regarding AG we observed deficits to automatic aspects of semantic retrieval in the presence of an unstimulated ATL which has been implicated in the storage of semantic information (Jefferies and Lambon Ralph, 2006; Binney et al., 2010; Jefferies et al., 2010; Visser et al., 2010d; Visser et al., 2010a; Visser et al., 2012b). We propose that the role of the AG in semantic cognition is in reflective attention towards the relevant aspects of semantic space required for fine-grained distinctions between highly similar concepts and in retrieving associations between concepts, analogous to how AG directs attention to stimuli in the external visual world (Corbetta and Shulman, 2002; Anderson et al., 2010), but in this case AG decouples attention away from irrelevant external inputs to allow for accurate internal representational capture (Schooler et al., 2011; Smallwood et al., 2013). Based on the findings of our study we build on the results of Chapter 2 and previous work observing AG/pMTG co-activation demonstrating that AG and pMTG make dissociable contributions to semantic cognition.

As well as providing evidence for dissociation between AG and pMTG, the findings in Chapter 3 also expand on the roles of these areas in the knowledge of thematic associations and semantic control. Previous work has implicated the temporoparietal cortex in the storage to thematic concepts (Schwartz et al., 2011) supported by fMRI activation in this region for thematic decisions (de Zubicaray et al., 2013). This model suggests that thematic and identity decisions can be independently manipulated and that TMS to either AG or pMTG should only affect association decisions. Our TMS data does not support this conclusion; following AG stimulation we observe disruption for both semantic and identity decisions, whereas pMTG exhibits selective disruption for harder semantic associations and for identity selection amongst superordinate labels, which can be applicable to a range of items depending on context. This pattern of results allows for a rejection of the notion of a thematic hub in the temporoparietal cortex based on the pattern in AG and pMTG supporting aspects of automatic and controlled semantic retrieval. The results also suggest that there is an overlap between semantic control and thematic knowledge/event retrieval, as we demonstrate that weak thematic association require substantial semantic control and flexible semantic retrieval which is shared by tasks which tap event/action knowledge, since actions and events have different meanings depending on context. Chapter 4 takes this further by examining specific action feature retrieval using fMRI.

Overall the findings of this Chapter suggest that AG and pMTG are making dissociable contributions to semantic cognition, and that their contributions are in the allocation of attention and shaping of semantic space, rather than the storage of thematic information.

Chapter 4**;** In this Chapter we used fMRI to investigate the potential overlap between semantic control and event/action semantics as both sets of literature report overlapping brain regions (Noonan et al., 2013; Watson et al., 2013), but have failed to manipulate both within a single paradigm. Here we used a task which manipulates both semantic control and tool action knowledge contrasted against a non-action tool feature (visual feature matching), ensuring that we manipulated both semantic control and event/action semantics. We observed activation in both pMTG and LIFG in response to increased semantic control demands similar to previous studies (Noonan et al., 2013), whereas task related deactivation was observed in AG, specifically for harder judgements, again consistent with previous work (Wirth et al., 2011; Humphreys and Lambon Ralph, 2014) which observed deactivation in AG. These results support the distinction between AG and pMTG observed in Chapter 3, that pMTG co-activates with LIFG for controlled semantic retrieval, with AG directing attention away from irrelevant external inputs resulting in deactivation, suggesting AG is involved in the orientation of attention during automatic aspects of semantic retrieval.

We specifically investigated the overlap between event semantics (specifically for tool action knowledge) and semantic control in Chapter 4. We used a task which contrasted action matching against visual matching on semantically associated (easy/low semantic control) and un-associated (hard/high semantic control) for visually presented tool words. We hypothesised that the overlap between event semantics and semantic control will be greater for the action trials compared to the visual trials, due to the fact that matching items based on actions requires greater spatiotemporal manipulations of contexts which are intrinsically linked to events. This is due to the requirement for retrieving action contexts for tools, in order to determine whether two tools share similar action features. Whole brain analyses revealed significant overlap between the areas responding to task difficulty (semantic control) and when actions are contrasted against visual decisions in LIFG and pMTG, with no overlap between the regions implicated in semantic control and those activated for visual decisions. While overlapping activation was observed in LIFG and pMTG ROI analyses revealed that they might make dissociable contributions; LIFG responded to both feature manipulation conditions (action and visual judgements) irrespective of difficulty, whereas pMTG selectively responded to action decisions relative to visual decisions. We argue that this is due to the shared requirement for semantic cognition and action/event understanding which require activation to be shaped by current context.

While this pattern of results suggests that event semantics and semantic control activate overlapping regions, differences were observed; ROI analyses revealed that pMTG specifically responded to context-driven action features while all aspects of semantic selection activated LIFG. This pattern suggests that pMTG is only activated when contextual information is required as dictated by task context, whereas LIFG is involved in all aspects of semantic selection and retrieval. This was hinted at through our individual level analyses which revealed overlapping peaks in LIFG for both actions and semantic control, but spatially distinct peaks in the posterior temporal regions, with actions in pMTG and control in ITG. We can conclude that while these sites are activated together in decisions that require the controlled manipulation of semantic information, that the LIFG might interact with different areas of posterior temporal cortex depending on current task demand, which is investigated in greater detail in Chapter 5.

***Chapter 5*;** In Chapter 5 we used fMRI to contrast semantic decisions which require participants to match items based on a pre-determined goal (goal-driven selection) with decisions which require a spatiotemporal context to be generated and maintained in order to determine the matching feature between concepts (context-driven selection). We also expanded on the stimuli used in Chapter 4 by using items from the category of animals as well as tool items. While pMTG has previously demonstrated tool specific responses (Liljeström et al., 2008; Chouinard and Goodale, 2010), we wanted to determine whether non-tool selection decisions activate pMTG, as well as determine what types of semantic selection activate pMTG. If pMTG is specifically involved in goal-driven semantic selection we should observe activation irrespective of category for decisions which require goal-driven selection, however if it is involved in context-driven retrieval we would expect responses to conditions requiring a spatiotemporal context irrespective of category. We replicated the previous findings of Badre et al. (2005) demonstrating different recruitment within the LIFG in response to the different types of selection. However instead of an anterior-posterior distinction, we observed a dorsal-ventral distinction with dorsal LIFG responding to goal-driven selection demands, and ventral anterior LIFG responding to context-driven effects. Beyond LIFG we observed different recruitment of the wider semantic control network depending on whether goal-driven or context-driven selection was required. Goal-driven selection demands activated an additional cluster in ITG implicated in the multi-demand executive network (Duncan, 2010), whereas context-driven selection demands activated additional clusters in pMTG and AG, irrespective of semantic category. This pattern of activation supports the findings of the individual level analysis in Chapter 4, which suggested that the posterior temporal regions make dissociable contributions to difficulty and action understanding (ITG in selection irrespective of category, with pMTG involved in tasks which require spatiotemporal manipulations).

In addition, of pMTG and AG for context driven retrieval, there were clear differences between pMTG and AG revealed through ROI analyses; pMTG exhibited task related activation irrespective of semantic category for conditions which require the manipulation of a spatiotemporal context, dorsal AG which fell within the context-driven semantic cluster exhibited greater responses to difficult feature matching conditions (specifically for actions), with ventral AG exhibiting increasing deactivation as a function of difficulty (closely resembling the opposite pattern observed in dorsal posterior and anterior LIFG, two sites which formed part of the goal-driven selection network). These findings suggest that there are separable components of semantic control; goal-driven selection demands activate a network consisting of dorsal LIFG and

ITG, with the context-driven network found in ventral LIFG and pMTG. Here we expand on previous studies implicating pMTG in semantic control (Whitney et al., 2011a; Whitney et al., 2011b; Whitney et al., 2012; Noonan et al., 2013) and demonstrate that the strongest responses in pMTG are when the decision requires the manipulation of spatiotemporal context in order to identify or retrieve the association between items. This explanation captures why pMTG fails to activate for difficulty matched phonological decisions, which activate dorsal regions of LIFG (which overlap with the goal-driven semantic selection network) as the understanding and selecting of phonological information requires no integration of spatiotemporal context (Poldrack et al., 1999; Gold et al., 2005; Snyder et al., 2007).

One interesting difference between Chapter 4 and 5 was observed in dorsal AG/IPS; in Chapter 4 we observed deactivation specifically for harder action decisions consistent with previous work indicating deactivation in AG in response to semantic contrasts (Seghier et al., 2010; Wirth et al., 2011; Humphreys and Lambon Ralph, 2014). However in Chapter 5 we observed a context-driven effect in the same site, with ROI analyses revealing strong activation for tool action decisions. It is possible that differences in the experimental task are behind the differences between these two Chapters. In Chapter 4 we used a challenging four alternative-forced choice (4AFC) paradigm, where features were selected in the presence of globally-associated distracter items, whereas in Chapter 5 we used an easier 2AFC paradigm without global distracters. In the easier judgements in Chapter 4, where participants were required to select the global association, no deactivation was observed for tool action trials, similar to the activation in AG observed in Chapter 5 which used an easier feature selection task. The wider literature shows that deactivation is typically observed in mid-AG for harder tasks when contrasted against baseline (Binder et al., 2008). It is therefore possible that the deactivation observed in AG in Chapter 4 is a reflection of difficulty even after controlling for RT and accuracy differences (reaction times were used in the development of the GLM, thus accounting for reaction time differences between conditions; Grinband et al., 2008). Future experiments utilising similar stimuli and comparisons between two and four AFC tasks are needed to further examine the activation differences between these two studies.

In summary we can conclude that the network involved in event semantics only overlaps with the regions implicated in context-driven semantic selection, aiding in the selection of aspects of semantic representations that vary by context, and in manipulating and processing event knowledge. While other areas of the semantic control network are activated in response to other non-semantic decisions (e.g. phonology), only when a decision requires the flexible use of existing semantic knowledge is the overlap with event semantics revealed.

Future directions

In Chapters 4 and 5 the posterior ITG was activated in response to harder semantic tasks in Chapter 4, and as part of the goal-driven selection network in Chapter 5. While the ITG has been implicated in event knowledge specifically when participants are engaged in tasks where an object is changed by an event (Hindy et al., 2013) little is known about the role of the posterior ITG in semantic control. ITG activation has been associated with amodal semantic knowledge (Binder et al., 2008; Fairhall and Caramazza, 2013), similar to conclusions made about pMTG (Martin, 2007; Binder et al., 2008; Fairhall and Caramazza, 2013; Martin et al., 2014). However our data would suggest that ITG forms part of the semantic control network, alongside pMTG and LIFG. To evaluate these claims one future direction would be to extend the work in Chapter 3, but to add a stimulation site in ITG and observe the consequences on semantic cognition. However delivering precise TMS to the ITG would be challenging due to the location of ITG and the difficulty of stimulating inferior regions of the brain with TMS. Another possibility to investigate ITG contributions to semantic cognition would be to use functional connectivity. In this thesis we have used functional connectivity to demonstrate the connectivity patterns of our TMS sites, demonstrating that pMTG is strongly connected to LIFG, with AG connected with ATL, which supports our conclusion about the role of this region in semantic cognition. In a similar vein we could use functional connectivity to investigate which sites are strongly connected to ITG. If ITG is implicated in semantic control (as indicated by our fMRI data), we would expect to see strong connectivity with dorsal LIFG as it has been specifically implicated in goal-driven selection (Chapter 5), and was only implicated in hard semantic decisions in Chapter 4 (it did not share any overlap with action contrasts).

In Chapter 5 we investigated the networks involved in goal-driven and context-driven semantic retrieval through the use of conjunctions, to identify significant shared activation between contrasts which manipulated features which loaded heavily on one of these components. This method of investigating these different aspects of semantic retrieval is an indirect way of assessing these components of semantic cognition; our results could be improved by utilising tasks which are specifically designed to achieve this. For example participants would be tasked with selecting a matching location for two visually presented items (e.g. KETTLE & MUG; KITCHEN, BATHROOM, GARAGE); this would require participants to identify the matching spatiotemporal context, i.e. context-driven selection for both these items. The goal-driven selection component could be manipulated by recycling the size condition from Chapter 5 but redesigning it whereby the task would be to identify which of these three items is the closest in size to the item pair presented at the top (e.g. GLASS TUMBLER & MUG; JAM JAR, KETTLE, MICROWAVE). This paradigm would allow us to look at these different networks directly, instead of having to rely on conjunctions between contrasts.

One future avenue of research would be to combine fMRI and TMS, which would allow for observation of the consequences of TMS stimulation to a region in the semantic cognition network, and its effect on other areas implicated in semantic cognition. TMS in this case would be combined with functional connectivity measures allowing us to investigate the functional relationships between brain regions (Ruff et al., 2009). For example, stimulating dorsal LIFG should alter functional connectivity with posterior ITG, while TMS to ventral IFG might change connectivity with pMTG. Using combined fMRI and TMS would better allow us to interpret the results of TMS stimulation as different patterns of stimulation might produce different functional changes in the network, and would provide more detailed picture of how the semantic cognition network interacts and how it performs following virtual lesions.

Multi-voxel pattern analysis (MVPA) would be a useful tool in investigating the differences between the networks discussed in this thesis. MVPA has a number of advantages over conventional fMRI analyses; it allows for greater sensitivity to examine differences in cognitive states, how they are represented in the brain, and it can be used to relate brain activity to behaviour on a trial-by-trial basis (Norman et al., 2006). MVPA is a widely used technique; for example Mahon and Caramazza (2010) used MVPA to identify areas which carry information when participants were thinking about auditory presented object names. This revealed activation in the inferior portions of the frontal lobes alongside clusters in IPS, implicating these regions in the carrying the conceptual information between stimulus pairs. Other work using MVPA has revealed that activation in left ATL is predicted by the temporal convergence of shape and colour information in early visual regions (Coutanche and Thompson-Schill, 2014). In the context of the work contained in this thesis MVPA could be used to investigate the neural representations occurring during encoding and retrieval, this would allow us to examine regions of the semantic network implicated in feature selection and those implicated in semantic retrieval. For example we could observe different MVPA profiles in dorsal and ventral LIFG representing the different networks identified in Chapter 5 depending on the features needing to be retrieved and/or matched. MVPA could also be used to further dissociate AG and pMTG by looking at the correlation matrix between the different judgements in Chapter 3, due to the ability of MVPA to look at behaviour on a trial-by trial basis. It could be hypothesised for example that MVPA measures in AG would categorise trials according association strength, for both strong and weak associations, whereas significant correlations in pMTG would only be observed for weakly associated items. The same pattern would be expected for the specificity trials with differing response profiles in pMTG and AG depending on the judgement requiring superordinate, basic, or specific level matching.

Finally it is also unclear about whether the two networks identified for goal-driven and context driven semantic selection are typically anti-correlated or whether they could be brought together in the service of a specific task. It is possible that the activation in these networks was differentiated by our contrasts in Chapter 5 but in other task contexts these networks might be brought together. Functional connectivity measures could be used to investigate the connectivity between the regions implicated in these two networks whilst participants performed goal-driven and context-driven selection tasks and at rest.

Conclusion

This thesis sought to examine the cognitive and neural network responsible for semantic cognition, using experimental psychology, neuropsychology, fMRI, and TMS. For the first time this thesis manipulated both semantic control and aspects of representation in the same paradigm to investigate the semantic network as a whole. We revealed that the AG and pMTG make dissociable contributions to semantic cognition; AG is involved in automatic semantic retrieval guiding attention towards the relevant aspects of semantic space, whereas pMTG is implicated in controlled aspects of semantic retrieval, reshaping semantic space to bring together weakly associated items and concepts. This thesis also demonstrated that the network involved in event semantics heavily overlaps with that involved in semantic control (LIFG and pMTG), but that dorsal LIFG/ITC and ventral LIFG/pMTG make dissociable contributions to semantic control, as shaped by current task context and goals.

Appendices

Appendix 4.1

Stimuli list and psycholinguistic variables

Probe	Easy action target	Hard action target	Easy visual target	Hard visual target
Axe	***Sledgehammer***	***Fishing Rod***	***Spade***	***Shotgun***
Chair	Stool	Saddle	Throne	Box
Dart	Javelin	Paper Aeroplane	Arrow	Cocktail Umbrella
Drill	Glue Gun	Skewer	Nail Gun	Hair Dryer
Drinking Straw	Sports Bottle	Inhaler	Cocktail Stirrer	Allen Key
French Horn	Whistle	Balloon	Trumpet	Funnel
Hammer	Mallet	Drumstick	Pick Axe	Handle Bars
Highlighter	Felt Tip	Match	Paint Brush	Stanley Knife
Kettle	Jug	Hour Glass	Blender	Petrol Container
Lego	Duplo	Dominos	Toy Block	Stock Cube
Needle	***Safety Pin***	***Scoop***	***Sewing Pin***	***Prong***
Pen	Quill	Eyeliner	Felt Tip	Drinking Straw
Pencil	***Pen***	***Pin***	***Crayon***	***Chopstick***
Piano	Organ	Typewriter	Xylophone	Work Bench
Pin	Tack	Thermometer	Needle	Toothpick
Pliers	Shears	Bike Brake	Scissors	Nutcracker
Rake	Broom	Mini-Vac	Pitch Fork	Comb
Sandpaper	Wire Wool	Dust Cloth	Scourer	Velcro
Screwdriver	Key	Volume Dial	Soldering Iron	Syringe
Sieve	***Tea Strainer***	***Tambourine***	***Colander***	***Fencing Mask***
Spoon	Ladle	Trowel	Fork	Frying Pan
Torch	TV Remote	Hose	Microphone	Rolling Pin
Toy Car	Model Train	Clothes Iron	Skateboard	Roller Skate
TV Remote	Laser Pointer	Bubble Wrap	Mobile Phone	Soap Bar
Water Pistol	Spray Bottle	Petrol Pump	Toy Gun	Blow Torch

Analysis of the behavioural data from the scanner revealed a small but significant difference in accuracy between the action and visual form conditions, contrary to the results of pilot testing. Therefore, contrasts of action and visual feature selection were conducted on a set of 21 items matched for accuracy and RT; i.e., all of the trials related to four specific probe words (shown in bold italics) were removed from all conditions when computing this contrast, for every participant.

Appendix 4.2

Word frequency, length and imageability for the target words used in the contrast of action and visual feature selection

Condition	Celex frequency (Log transformed)		Word length		Imageability	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Easy action	1.15	0.86	6.71	2.67	4.55	0.47
Hard action	1.10	0.80	8.33	2.37	4.57	0.40
Easy visual	0.93	0.61	8.19	2.64	4.63	0.27
Hard visual	0.86	0.88	8.66	3.32	4.69	0.23

Table provides psycholinguistic properties for the 84 targets (presented with the same 21 probe words across conditions) used in the analysis of action and visual feature selection. Celex frequency in counts per million were taken from the program N-watch (Davis, 2005). Word length = no. of letters. Imageability ratings were collected from a set of 16 participants (each participant completed half of the experimental stimuli, providing eight ratings for each item). Participants were asked to rate the stimuli using a 5-point scale on how easy it was to generate a mental image of the item (1 representing very difficult and 5 being very easy).

Appendix 4.3

ANOVA results demonstrating matching of psycholinguistic variables for the target words used in the contrast of action and visual feature selection

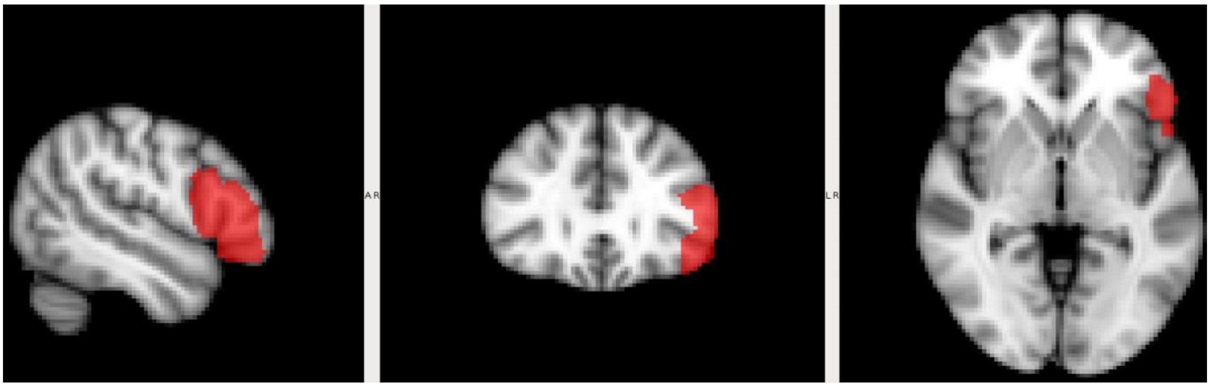
	Effects	F	*p*
Celex frequency	Action vs. visual	1.29	.28
	Easy vs. Hard	<1	.80
	Task by difficulty	<1	.95
Word length	Action vs. visual	2.23	.15
	Easy vs. Hard	2.02	.17
	Task by difficulty	1.05	.32
Imageability	Action vs. visual	2.23	.15
	Easy vs. Hard	<1	.63
	Task by difficulty	<1	.76

Table provides ANOVA results demonstrating that psycholinguistic properties were matched for the targets used in the analysis of action and visual feature selection (i.e., 84 targets presented with the same 21 probe words across conditions). These properties were also matched for the complete set of 100 trials (i.e., including all 25 probe words); all main effects and interactions were non-significant, *p* > .09.

Appendix 4.4

Masks used in the small volume correction for the individual level analysis

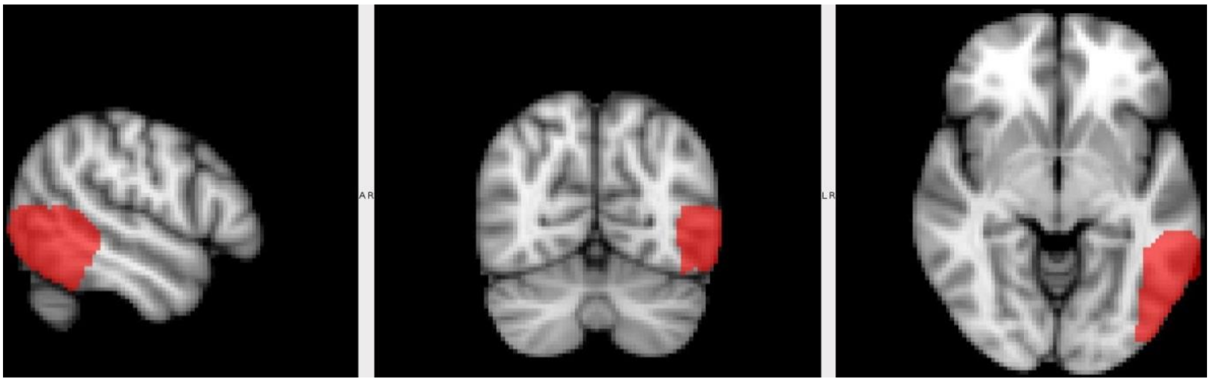
Left inferior frontal gyrus and precentral gyrus mask used for individual subject analysis.



Mask was created using Harvard-Oxford cortical structural atlas in FSLview to extract the three subdivisions of the LIFG (BA44, 45, and 47) at a 25% threshold. The three masks were combined into one mask using FSLmaths and were binarised.

Appendix 4.5

Posterior middle/inferior temporal cortex mask used for individual subject analysis.



Mask was created using Harvard-Oxford cortical structural atlas in FSLview to locate the middle/inferior temporal gyrus, temporooccipital part at a 10% threshold. Both these masked were created using the create mask tool in FSLview and binarised using FSLmaths.

Appendix 4.6

Behavioural results

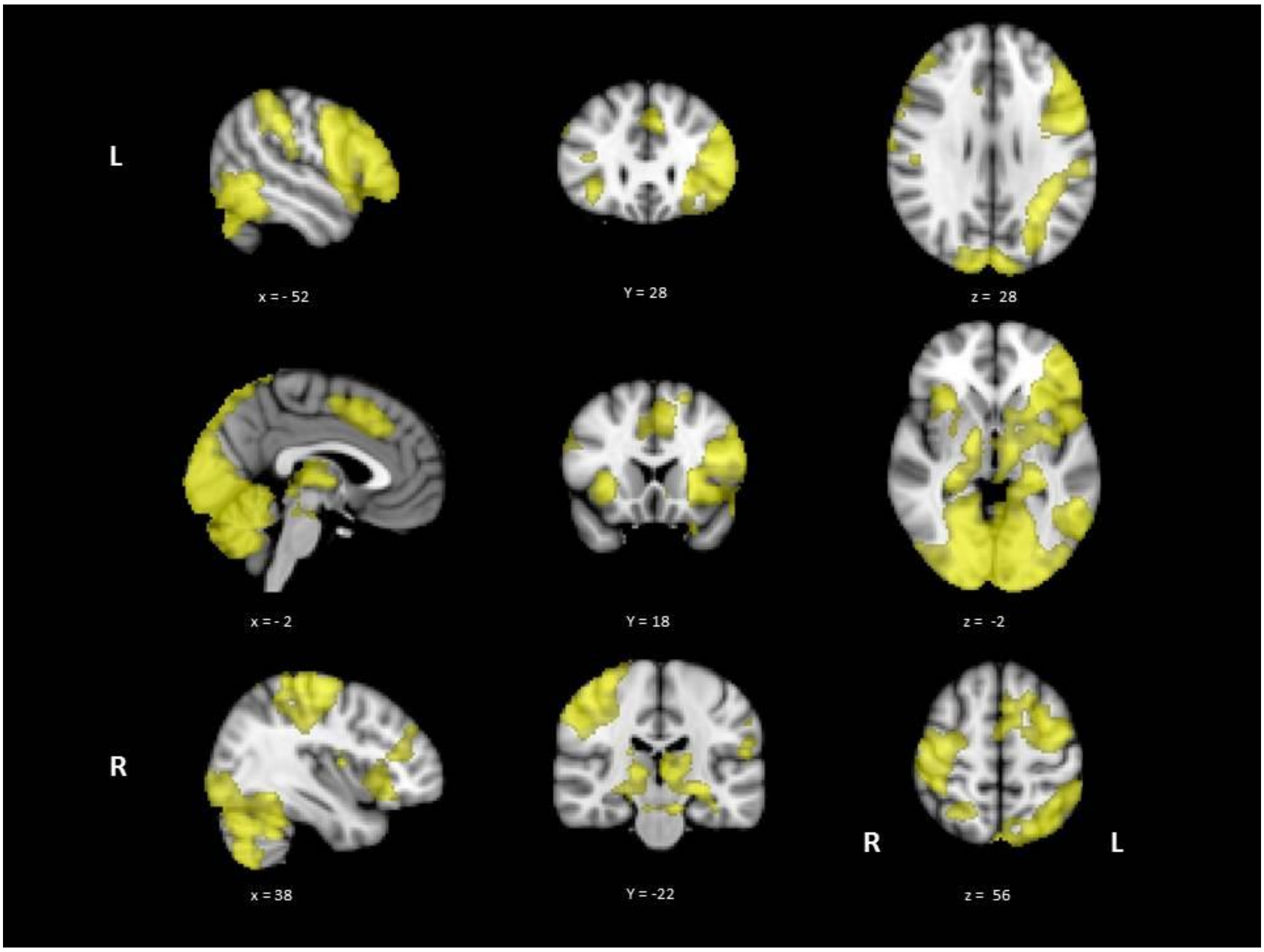
Condition	Response time (ms)		Accuracy (% trials correct)	
	Mean	S.D.	Mean	S.D.
Easy action	2916.25	540.18	0.91	0.06
Hard action	3464.80	378.80	0.81	0.10
Easy vision	3042.73	419.20	0.93	0.06
Hard vision	3509.41	533.51	0.83	0.09

Table shows response times and accuracy for the trials used in the contrast of action and visual feature selection. Response times were recorded from the presentation of the four response options. Analysis of the behavioural performance is provided in Section 3.1: there was an effect of difficulty but not task, and no interaction.

Appendix 4.7

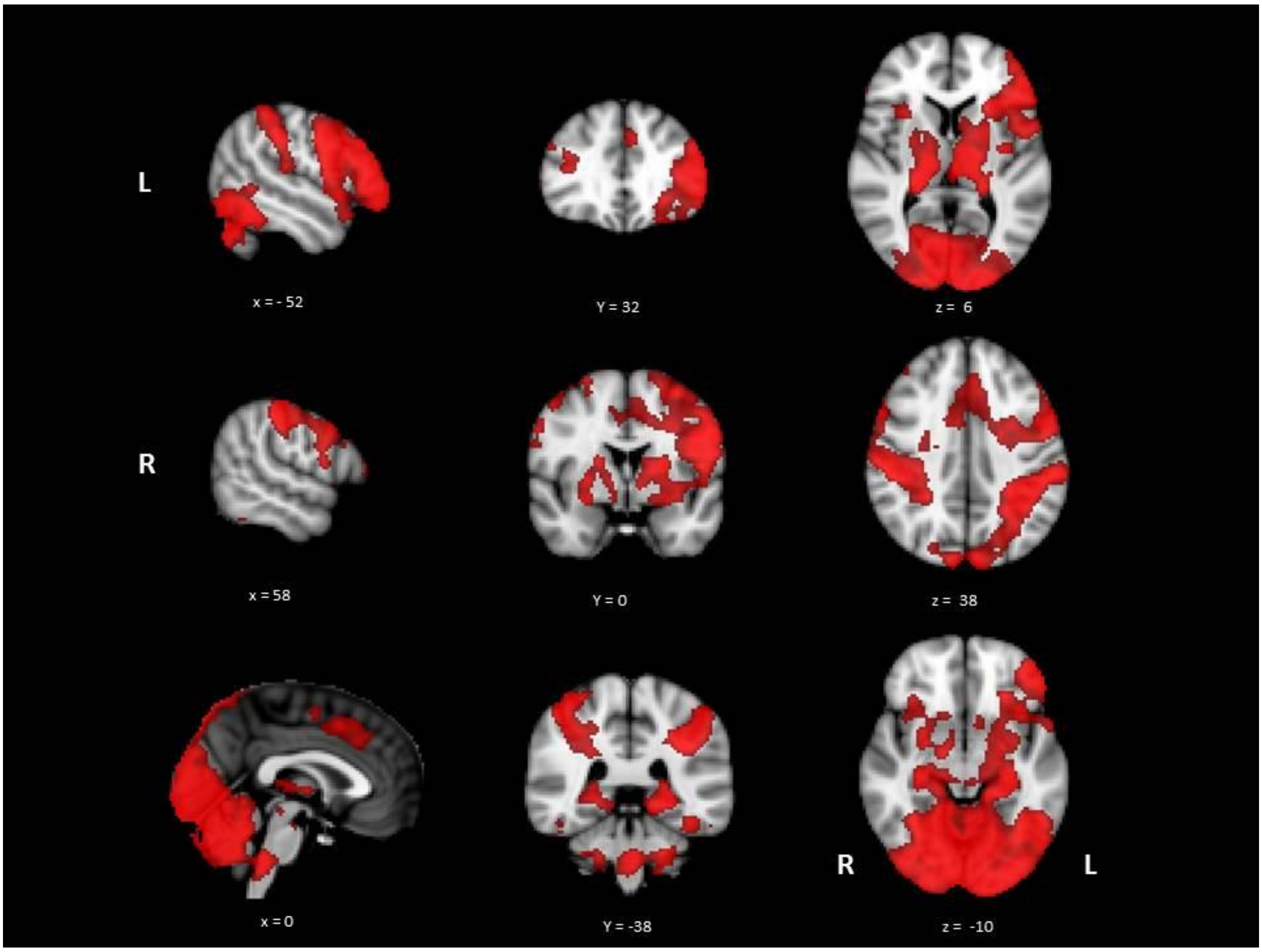
Category specific activation contrasted against rest (baseline)

Contrast of all action feature conditions contrasted against rest.



Appendix 4.8

Contrast of all visual feature conditions contrasted against rest.



Appendix 4.9

Cluster index and peak locations within clusters revealed by contrasts of action > visual decisions, visual > action decisions, corrected for multiple comparisons (voxel inclusion threshold: z = 2.3; cluster significance threshold = p < .05).

	Cluster size (voxels)	Z	MNI coordinates			Location
			X	Y	Z	
Action > visual						
Cluster 1 (COG -51 -58 20)	3901	5.91	-56	-60	2	L Middle temporal gyrus temporooccipital region/inferior lateral occipital cortex
		5.54	-62	-56	-2	L Middle temporal gyrus temporooccipital region/inferior lateral occipital cortex
		5.19	-56	-48	44	L Supramarginal gyrus/angular gyrus
		5.08	-58	-46	32	L Supramarginal gyrus/angular gyrus
		4.88	-48	-62	18	L Superior lateral occipital cortex/angular gyrus
		4.45	-52	-68	16	L Superior lateral occipital cortex/inferior lateral occipital cortex
Cluster 2 (COG -35 17 32)	3752	5.12	-42	14	44	L Middle frontal gyrus
		5.1	-52	12	2	L Inferior frontal gyrus (pars opercularis)/Precentral gyrus
		5.04	-36	20	44	L Middle frontal gyrus
		4.99	-38	4	52	L Middle frontal gyrus/Precentral gyrus/superior frontal gyrus
		4.87	-48	26	-4	L Frontal operculum cortex/frontal orbital cortex/inferior frontal gyrus (pars triangularis)
		4.84	-50	26	0	L Inferior frontal gyrus (pars triangularis)/frontal operculum cortex/frontal orbital cortex

Visual > action

Cluster 1 (COG 35 -47 44)	2918	4.7	54	-32	42	R Posterior supramarginal gyrus/angular gyrus
		4.47	52	-38	42	R Posterior supramarginal gyrus
		4.45	34	-42	34	R Posterior supramarginal gyrus
		4.24	56	-24	42	R Anterior supramarginal gyrus/postcentral gyrus
		3.97	18	-64	56	R Superior lateral occipital cortex
		3.93	30	-48	42	R Superior parietal lobule/angular gyrus
Cluster 2 (COG -27 -89 8)	798	4.07	-26	-84	12	L Superior lateral occipital cortex
		3.85	-28	-88	12	L Superior lateral occipital cortex/occipital pole
		3.73	-20	-94	12	L Occipital pole
		3.58	-32	-82	2	L Superior lateral occipital cortex
		3.49	-36	-90	8	L Occipital pole/superior lateral occipital cortex
		3.43	-24	-96	6	L Occipital pole

Table provides data for all significant clusters and sub-peaks within each cluster, with the first sub-peak being the cluster maxima. Location was determined using the Harvard-Oxford cortical structural atlas built into FSL. COG = centre of gravity.

Appendix 4.10

Cluster index and peak locations within clusters revealed by contrast of hard > easy decisions, corrected for multiple comparisons (voxel inclusion threshold: z = 2.3; cluster significance threshold = p < .05).

	Cluster size (voxels)	Z	MNI coordinates			Location
			X	Y	Z	
Cluster 1 (COG -42 16 9)	3898	5.64	-30	22	-8	L Frontal orbital cortex/insular cortex
		4.97	-44	22	16	L Inferior frontal gyrus (pars opercularis/pars triangularis)
		4.92	-38	2	22	L Precentral gyrus/inferior frontal gyrus (pars opercularis)
		4.91	-34	14	-8	L Insular cortex
		4.81	-48	6	22	L Precentral gyrus/inferior frontal gyrus (pars opercularis)
		4.46	-36	16	14	L Frontal operculum cortex
Cluster 2 (COG -4 18 42)	2917	5.33	0	16	42	Paracingulate gyrus/anterior cingulate
		5.29	0	12	46	Paracingulate gyrus/anterior cingulate
		5.29	4	16	44	R Paracingulate gyrus/anterior cingulate
		4.84	2	18	50	R Paracingulate gyrus/superior frontal gyrus
		4.75	-6	24	32	L Paracingulate gyrus/anterior cingulate
		3.7	6	26	36	R Paracingulate gyrus/anterior cingulate
Cluster 3 (-4 41 -1)	1376	5.05	32	26	-4	R Frontal orbital cortex/insular cortex
		4.52	42	18	-12	R Frontal orbital cortex/insular cortex
		4.38	40	22	-4	R Frontal orbital cortex/insular cortex/frontal

						operculum cortex
		3.31	46	28	22	R Middle frontal gyrus/inferior frontal gyrus (pars triangularis)
		3.27	48	20	6	R Inferior frontal gyrus (pars opercularis/pars triangularis)/frontal operculum cortex
		3.17	40	18	22	R Inferior frontal gyrus (pars opercularis)
Cluster 4 (COG -4 -17 -0)	1078	3.91	-8	-18	8	L Thalamus
		3.88	-8	-14	-2	L Thalamus
		3.73	-4	-26	-4	Brain stem/L thalamus
		3.65	-6	-22	-2	L Thalamus
		3.62	8	-32	-4	Brain stem
		2.93	-12	0	6	L Thalamus
Cluster 5 (COG -46 -61 -15)	869	3.98	-44	-50	-22	L Temporal occipital fusiform cortex/inferior temporal gyrus
		3.92	-46	-60	-22	L Temporal occipital fusiform cortex/inferior temporal gyrus
		3.8	-54	-72	-8	L Inferior lateral occipital cortex
		2.99	-52	-64	2	L Inferior lateral occipital cortex/middle temporal gyrus
		2.94	-50	-64	-8	L Inferior lateral occipital cortex/inferior temporal gyrus
		2.87	-52	-60	6	L Middle temporal gyrus/inferior lateral occipital cortex

Table provides data for all significant clusters and sub-peaks within each cluster, with the first sub-peak being the cluster maxima. Location was determined using the Harvard-Oxford cortical structural atlas built into FSL. COG = centre of gravity. The reverse contrast of easy > hard decisions revealed no significant effects.

Appendix 4.11

Results of individual analyses within LIFG and posterior temporal cortex examining the responses of each voxel

		Difficulty effect: YES	*Difficulty effect: NO*
LIFG mask	*Action > form: YES*	Mean = 35; S.D. = 74.4 Total count = 525 Expected count = 467 Standardised residual = **2.7**	Mean = 233; S.D. = 297.1 Total count = 3501 Expected count = 3559 Standardised residual = -1.0
	Action > form: NO	Mean = 203; S.D. = 249.2 Total count = 3051 Expected count = 3109 Standardised residual = 1.0	Mean = 1583; S.D. = 348.6 Total count = 23748 Expected count = 23690 Standardised residual = 0.4
Posterior temporal mask	*Action > form: YES*	Mean = 27; S.D. = 63.6 Total count = 424	Mean = 274, S.D. = 348.0 Total count = 4383

	Expected count = 223 Standardised residual = **13.4**	Expected count = 4584 Standardised residual = -3.0
Action > form: NO	Mean = 113.3, S.D. = 130.0 Total count = 1812 Expected count = 2013 Standardised residual = -4.5	Mean = 2597, S.D. = 419.8 Total count = 41555 Expected count = 41354 Standardised residual = 1.0

Table shows number of voxels within each mask which fell into the following categories: (i) response to both difficulty and feature type; (ii) difficulty only; (iii) feature type only; (iv) neither contrast. Data are voxel counts across 15/17 participants for LIFG and 16/17 participants for posterior temporal areas who responded to both contrasts at some point within the mask (p = .05 uncorrected). S.D. = standard deviation. Standardised residuals are derived from chi-square analysis on total (observed) and expected counts within each cell.

Appendix 4.12

Results of individual analyses within LIFG and posterior temporal cortex examining the location of peak responses

	x	**y**	**z**
LIFG: Difficulty	-49(4)	18(9)	16(12)
LIFG Action > visual	-50(4)	21(8)	4(10)
Posterior temporal: Difficulty	-50(5)	-59(6)	-7(12)
Posterior temporal Action > visual	-56(5)	-58(7)	1(9)

Table shows mean location of peak responses to the two contrasts across individuals in MNI space, plus the standard deviation in parentheses.

Appendix 5.1

Stimuli used in Chapter 5

Animal global		Tool global	
Probe	**Target**	**Probe**	**Target**
Lion	Binoculars	Remote Control	Television
Racehorse	Reins	Cafetiere	Kettle
Garden Snail	Shell	Tap	Plug
Earthworm	Garden fork	Spanner	Wrench
Tamworth Pig	Sausages	Bottle Opener	Corkscrew
Indian Elephant	Tusk	Bread Bin	Cookie jar
Shark	Knife	Skewer	BBQ
Crab	Claw	Knife	Fork
Slug	Pellet	Roller	Paint tray
Rabbit	Hutch	Colander	Sieve
Jellyfish	Bucket	Shovel	Spade
Chicken	Egg	Manual Juicer	Orange
Pigeon	Crumbs	Steering Wheel	Hand brake
Tabby Cat	Wool ball	Syringe	Cotton wool
Maggot	Apple	Icecube Tray	Freezer
Rat	Poison	Grater	Plate
Koala	Leaves	Spoon	Egg cup
Duckling	Bread	Electric Drill	Screw
Humpback Whale	Boat	Stretcher	Neck brace
Goat	Cheese	Mower	Strimmer
Mute Swan	Feather	Glasses Case	Spectacles
Hamster	Wheel	Axe	Sword
Grey Squirrel	Nuts	Sandpaper	Wood
Bee	Honeycomb	Screwdriver	Hammer
Lizard	Branch	Frying Pan	Wok
Red Deer	Rifle	Stopwatch	Water bottle
Pheasant	Shotgun	Chisel	Hammer
Dove	Olive branch	Pin	Tack
Tortoise	Lettuce	Nut Cracker	Can opener
Frog	Water lily	Paint Brush	Roller

Animal size		Tool size	
Probe	**Target**	**Probe**	**Target**
Earthworm	Nail	Glasses Case	Mobile phone
Crocodile	Surfboard	Spanner	Torch
Goldfish	Key	Grater	Metronome
Lizard	Stapler	Toilet Brush	Hammer
Tamworth Pig	Coffee table	Icecube Tray	Notebook
Emperor Penguin	Basin	Spade	Desk lamp
Duckling	Sellotape	Sandpaper	Flannel
Hamster	Tea spoon	Frying Pan	Frisbee
Rat	Paperweight	Clamp	Mug
Racehorse	Industrial bin	Shovel	Floor lamp

Maggot	Stock cube	Pin	Match
Mute Swan	Cello	Bread Bin	Document file
Red Deer	Arm chair	Colander	Helmet
Garden Snail	Rubber	Chisel	Ruler
Slug	Cigarette	Paint Brush	Torch
Crab	Plate	Light Switch	Ipod
Bee	Earring	Manual Juicer	Saucer
Seahorse	Doorstop	Mower	Wheelchair
Lobster	Shoe	Tap	Egg cup
Indian Elephant	Van	Screwdriver	Pencil
Bengal Tiger	Bike	Stretcher	Desk
Jellyfish	Hat	Skewer	Ruler
Shrimp	Coin	Stopwatch	Bracelet
Octopus	Football	Cafetiere	Torch
Koala	Toaster	Knife	Stapler
Kangaroo	Postbox	Bottle Opener	Pine cone
Newt	Toothbrush	Mallet	Shoe
Oyster	Pebble	Hammer	Hairdryer
Tortoise	Helmet	Microphone	Torch
Rabbit	Shoe box	Rolling Pin	Spanner

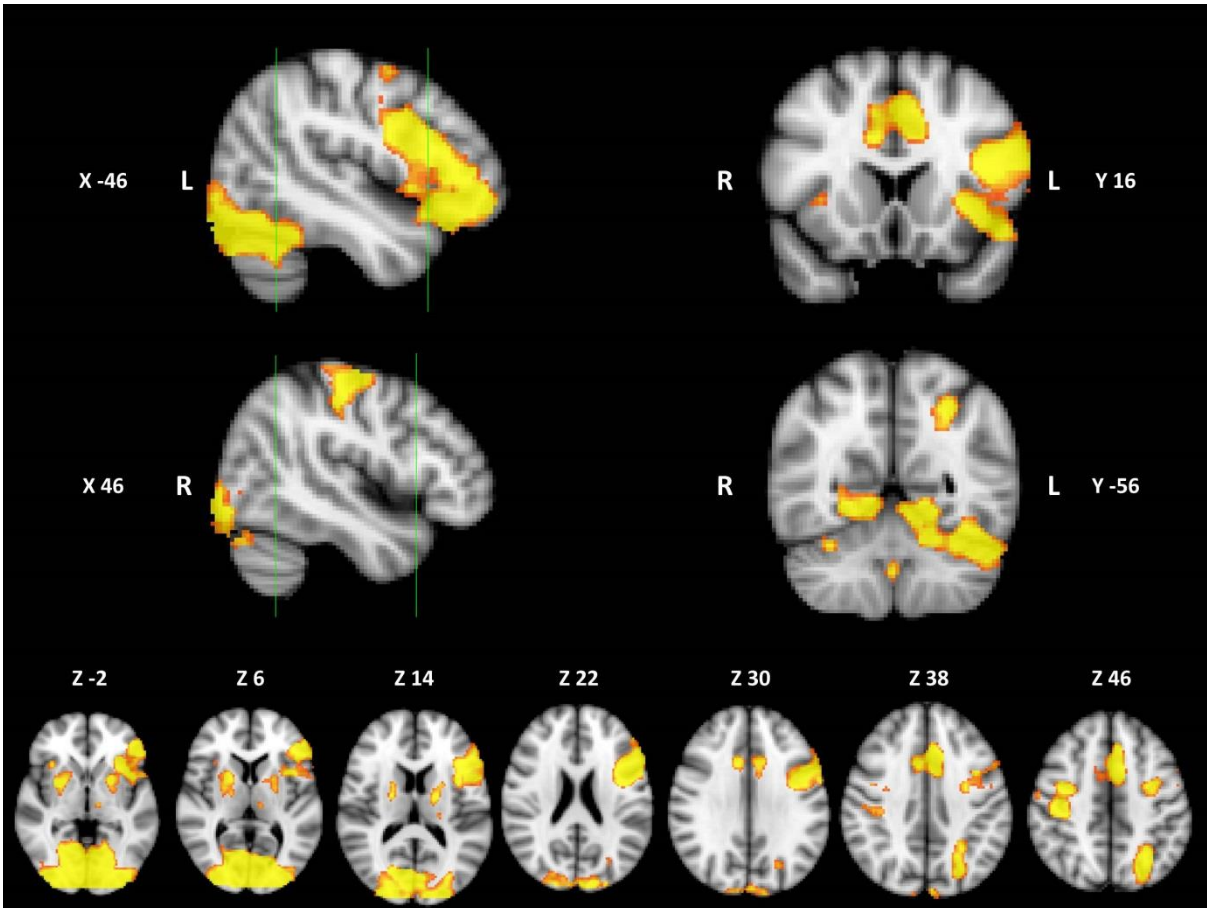
Animal colour		**Tool action**	
Probe	**Target**	**Probe**	**Target**
Indian Elephant	Pebble	Skewer	Plunger
Kangaroo	Violin	Tin opener	Tap
Lion	Peanuts	Stopwatch	Mechanical pencil
Mute Swan	China cup	Spanner	Door handle
Dove	Lily	Chisel	Dagger
Cow	Dice	Scoop	Spade
Rat	Fossil	Sandpaper	Cloth
Shrimp	Blossom	Saw	Lever
Pet mouse	Paper	Mower	Zimmer frame
Emperor Penguin	Keyboard	Mallet	Racket
Chicken	Peanuts	Key	Screwdriver
Bee	Sunflower	Remote Control	Calculator
Bengal Tiger	Basket ball	Frying pan	Vaccum
Lizard	Brocolli	Pin	Dart
Crab	Pumpkin	Glasses case	Jewelry box
Koala	Gravel	Spade	Mop
Jellyfish	Glass	Screwdriver	Key
Camel	Banana	Clamp	Fishing reel
Racehorse	Doormat	Axe	Fishing rod
Fox	Basketball	Paint brush	Wand
Dog	Paper bag	Tap	Screw top
Budgie	Kiwi fruit	Toilet brush	Plunger
Tortoise	Army Jeep	Nut cracker	Stress ball
Tabby Cat	Fur coat	Grater	Match
Frog	Garden hose	Shovel	Mop
Slug	Fig	Steering wheel	Winch
Duckling	Builders hat	Microphone	Toothbrush

Octopus	Pumpkin	Stretcher	Wheelbarrow
Tamworth Pig	Candy floss	Bottle opener	Lever
Goldfish	Carrot	Hammer	Drumstick

Appendix 5.2

Feature specific activation contrasted against rest

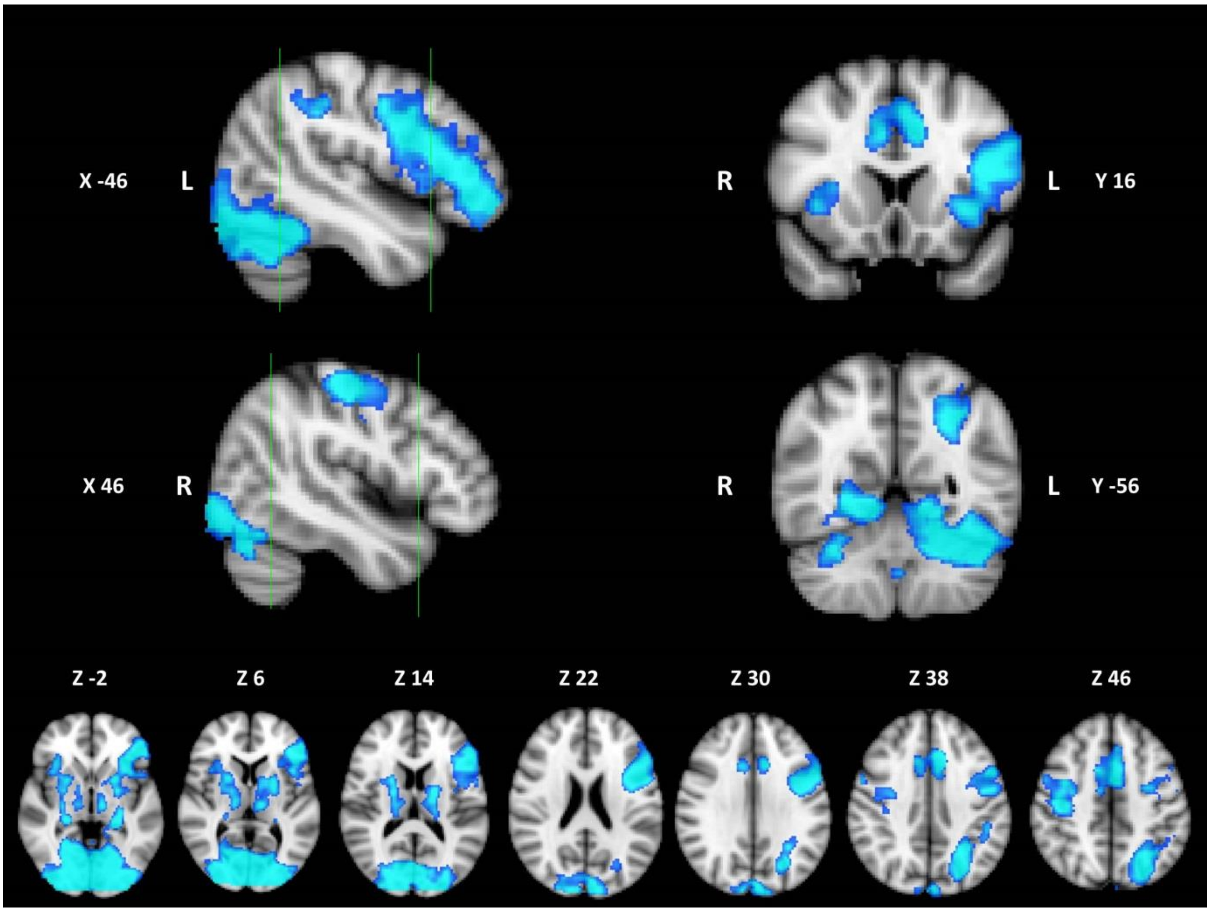
Contrast of global animal > rest



Activation for global animal > rest. The contrast presented is cluster corrected for multiple comparisons (z inclusion = 1.96, cluster significance p <.05). One individual subject had signal loss from the occipital lobe due to head size, resulting in a sharp cutoff line in the occipital lobe.

Appendix 5.3

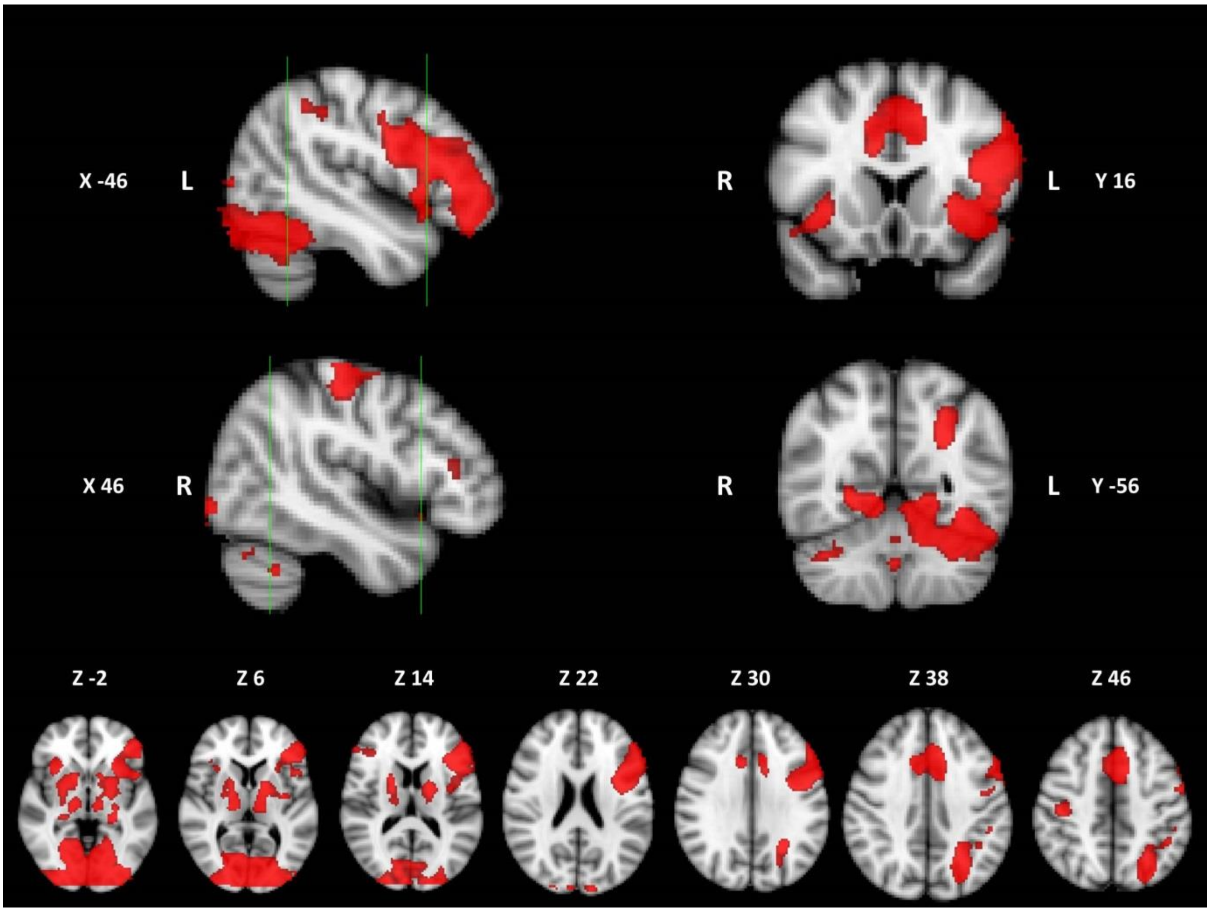
Contrast of global tool > rest



Activation for global tool > rest. The contrast presented is cluster corrected for multiple comparisons (z inclusion = 1.96, cluster significance p <.05). One individual subject had signal loss from the occipital lobe due to head size, resulting in a sharp cutoff line in the occipital lobe.

Appendix 5.4

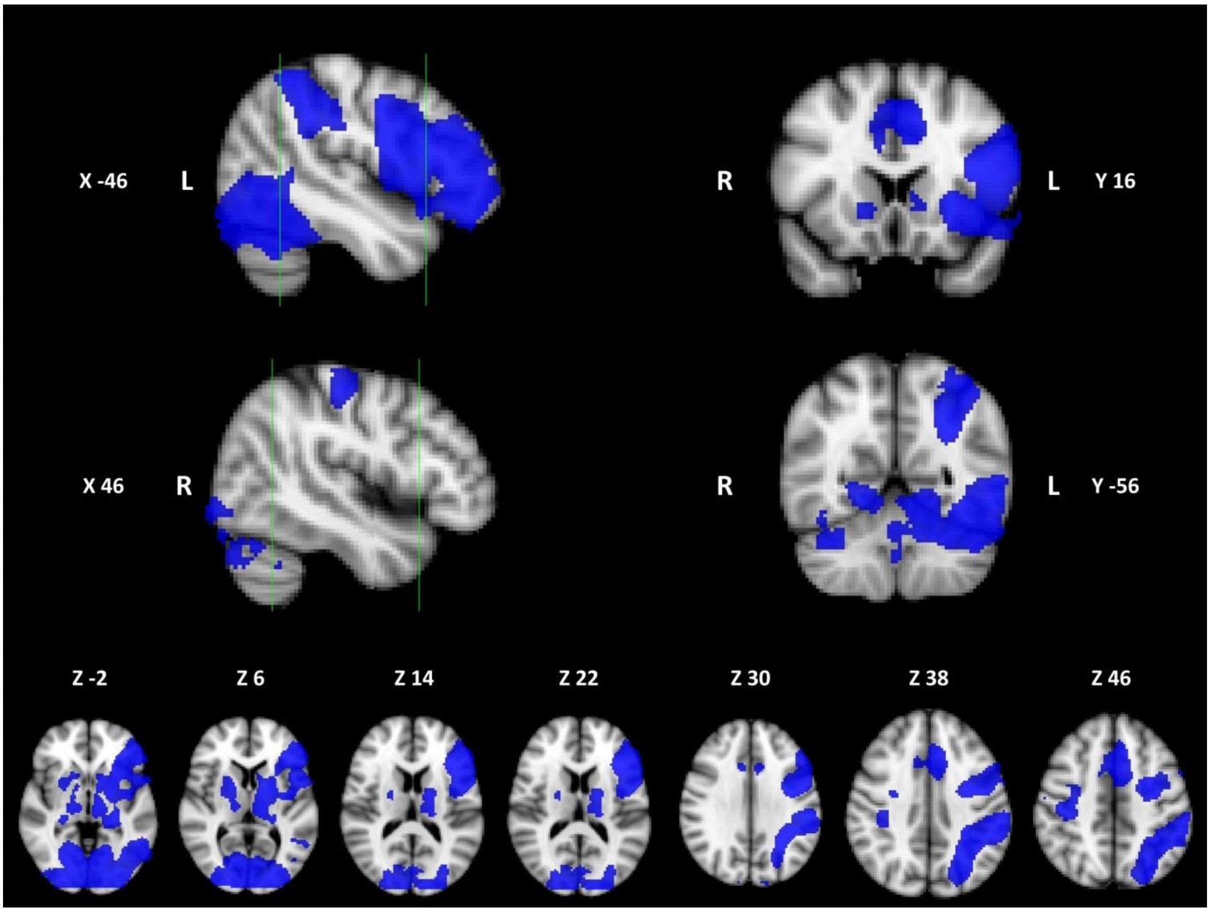
Contrast of colour animal > rest



Activation for colour animal > rest. The contrast presented is cluster corrected for multiple comparisons (z inclusion = 1.96, cluster significance p <.05). One individual subject had signal loss from the occipital lobe due to head size, resulting in a sharp cutoff line in the occipital lobe.

Appendix 5.5

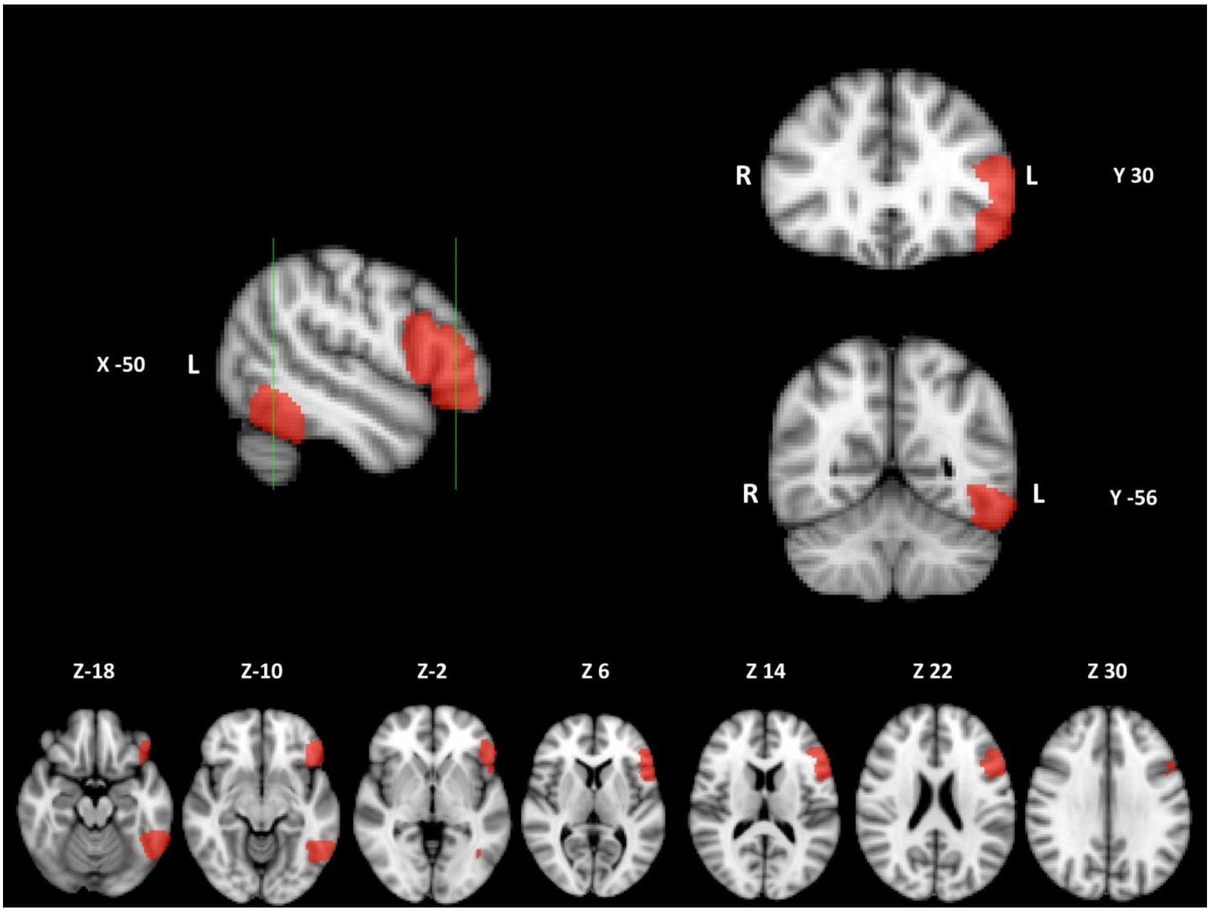
Contrast of action tool > rest



Activation for action tool > rest. The contrast presented is cluster corrected for multiple comparisons (z inclusion = 1.96, cluster significance p <.05). One individual subject had signal loss from the occipital lobe due to head size, resulting in a sharp cutoff line in the occipital lobe.

Appendix 5.6

LIFG and ITG masks used for the small volume correction



Both masks were created using the Harvard-Oxford Cortical structural atlas in FSLview. For the LIFG the subdivisions of the LIFG (BA 44, 45, and 47) at a 25% threshold. The ITG mask was created by extracting the temporooccpital inferior temporal gyrus at a 15% threshold. The LIFG subdivisions were combined into one mask using FSLmaths, all masks used were binarised prior to use.

Appendix 5.7

Cluster index and peak locations within clusters revealed by the contrasts entered into the conjunctions (actions > colour, actions > tool global, colour > animal global, global all > size all), corrected for multiple comparisons (voxel inclusion threshold z = 1.96, cluster significance threshold p <.05)

	Cluster size (Voxels)		MNI coordinates				
		Z	X	Y	Z	Hemisphere	Location
Action > colour							
Cluster 1 COG (-43 -53 26)	10128	5.25	-58	-66	-6	LH	Inferior Lateral Occipital cortex
		5.22	-58	-68	-12	LH	Inferior Lateral Occipital cortex
		5.17	-52	-44	36	LH	Posterior Supramarginal gyrus
		5.12	-60	-34	30	LH	Anterior Supramarginal gyrus
		5.08	-54	-32	44	LH	Anterior Supramarginal gyrus
		5.04	-38	-54	52	LH	Superior Parietal Lobule
Cluster 2 COG (-37 7 31)	5922	5.27	-52	10	6	LH	Inferior Frontal gyrus, pars opercularis
		4.62	-36	-6	46	LH	Precentral gyrus
		4.27	-48	32	-4	LH	Inferior Frontal gyrus, pars opercularis
		4.19	-42	30	-2	LH	Frontal Orbital cortex
		4.08	-52	4	20	LH	Precentral gyrus
		4.05	-50	24	12	LH	Inferior Frontal gyrus, pars triangularis
Action > tool global							
Cluster 1 COG (-38 15 20)	7480	5.3	-52	10	6	LH	Inferior Frontal gyrus, pars opercularis
		5.23	-52	8	2	LH	Precentral gyrus
		4.83	-42	24	18	LH	Inferior Frontal gyrus, pars triangularis
		4.7	-50	42	0	LH	Frontal Pole
		4.62	-48	-2	20	LH	Precentral gyrus
		4.51	-48	32	-2	LH	Inferior Frontal gyrus, pars triangularis
Cluster 2 COG (-45 -42 39)	3422	4.98	-58	-34	30	LH	Anterior Supramarginal gyrus
		4.9	-36	-50	38	LH	Posterior Supramarginal gyrus
		4.82	-36	-44	36	LH	Posterior Supramarginal gyrus
		4.76	-58	-38	34	LH	Anterior Supramarginal gyrus
		4.35	-52	-34	42	LH	Anterior Supramarginal gyrus
		4.29	-50	-30	36	LH	Anterior Supramarginal gyrus
Cluster 3 COG (-49 -62 -8)	1933	5.36	-56	-68	-6	LH	Inferior Lateral Occipital cortex
		4.81	-48	-62	-8	LH	Inferior Lateral Occipital cortex
		4.16	-46	-66	0	LH	Inferior Lateral Occipital cortex
		4.14	-58	-58	-2	LH	Temporooccipital Middle Temporal gyrus
		4.05	-46	-70	2	LH	Inferior Lateral Occipital cortex
		3.38	-36	-62	-4	LH	Occipital Fusiform gyrus
Colour > animal global							
Cluster 1 COG (-41 24 16)	1832	3.92	-42	36	10	LH	Inferior Frontal Gyrus, pars opercularis
		3.88	-40	0	28	LH	Precentral gyrus
		3.88	-44	46	0	LH	Frontal pole
		3.62	-42	30	16	LH	Inferior Frontal gyrus, pars opercularis
		3.49	-38	32	6	LH	Inferior Frontal gyrus, pars triangularis
		3.26	-48	28	26	LH	Middle Frontal gyrus
Cluster 2 COG (42 22 21)	1660	4.43	42	34	12	RH	Frontal pole
		3.54	40	6	24	RH	Precentral gyrus
		3.07	56	26	16	RH	Inferior Frontal gyrus, pars triangularis
		2.94	40	12	54	RH	Middle Frontal gyrus
		2.92	48	12	50	RH	Middle Frontal gyrus
		2.92	54	34	12	RH	Inferior Frontal gyrus, pars triangularis

Cluster 3 COG (-36 -61 -29)	1415	3.52	-34	-48	-26	LH	Temporal Occipital Fusiform Cortex
		3.46	-42	-60	-12	LH	Temporal Occipital Fusiform Cortex
		3.43	-50	-58	-18	LH	Temporooccipital Inferior Temporal gyrus
		3.21	-38	-68	-36	LH	Cerebellum
		3.02	-44	-74	-46	LH	Cerebellum
		2.99	-34	-68	-50	LH	Cerebellum
Global all > size all							
Cluster 1 COG (-50 -30-2)	7863	5.01	-58	-32	-8	LH	Posterior Middle Temporal gyrus
		5.01	-44	-62	26	LH	Superior Lateral occipital cortex
		4.99	-42	-68	32	LH	Superior Lateral occipital cortex
		4.88	-68	-44	-8	LH	Posterior Middle Temporal gyrus
		4.84	-60	-56	2	LH	Temporooccipital Middle Temporal gyrus
		4.76	-54	-56	30	LH	Angular gyrus
Cluster 2 COG (5 -69 8)	7544	5.28	-6	-60	28	LH	Precuneous cortex
		4.83	8	-54	30	RH	Precuneous cortex
		4.62	-2	-50	28	LH	Cingulate gyrus
		4.49	16	-86	-36	RH	Cerebellum
		4.3	32	-80	-42	RH	Cerebellum
		4.26	18	-86	-42	RH	Cerebellum
Cluster 3 COG (-7 39 31)	7471	4.71	-16	38	44	LH	Superior Frontal gyrus
		4.65	-16	56	30	LH	Frontal pole
		4.22	-42	10	52	LH	Middle Frontal gyrus
		4.06	-42	6	52	LH	Middle Frontal gyrus
		4.06	-40	2	52	LH	Middle Frontal gyrus
		3.94	-8	50	-6	LH	Paracingulate gyrus
Cluster 4 COG (51 -33 1)	7415	5.15	58	-52	4	RH	Temporooccipital Middle Temporal gyrus
		5.04	60	-54	16	RH	Angular gyrus
		5.01	58	-44	0	RH	Temporooccipital Middle Temporal gyrus
		5.01	60	-48	2	RH	Temporooccipital Middle Temporal gyrus
		4.49	46	-82	10	RH	Inferior Lateral Occipital cortex
		4.42	54	-10	-22	RH	Posterior Middle Temporal gyrus

Table provides data for all significant clusters and sub-peaks within each cluster, with the first sub-peak being the cluster maxima. Location was determined using the Harvard-Oxford cortical structural atlas built into FSL. COG = centre of gravity.

Appendix 5.8

Cluster index and peak locations within clusters revealed for the conjunctions at the whole brain and within small volume corrections which yielded significant results, corrected for multiple comparisons (voxel inclusion threshold z = 1.96, cluster significance threshold p <.05)

			MNI coordinates				
	Cluster size (Voxels)	**Z**	**X**	**Y**	**Z**	**Hemisphere**	**Location**
Action > global tool & Colour > global animal - Whole brain							
Cluster 1 COG (-44 24 16)	1487	3.72	-46	44	0	LH	Frontal pole
		3.62	-42	30	16	LH	Inferior Frontal gyrus, pars triangularis
		3.62	-42	30	12	LH	Inferior Frontal gyrus, pars triangularis
		3.54	-44	36	10	LH	Inferior Frontal gyrus, pars triangularis
		3.43	-44	-2	28	LH	Precentral gyrus
		3.37	-38	-2	28	LH	Precentral gyrus
Action > global tool & Colour > global animal - ITG small volume correction							
Cluster 1 COG (-46 -56 -16)	209	3.22	-44	-60	-12	LH	Temporooccipital Inferior Temporal gyrus
		2.42	-48	-50	-26	LH	Temporooccipital Inferior Temporal gyrus
Action > colour & global all > size all - Whole brain							
Cluster 1 COG (-50-60 14)	1567	4.45	-58	-56	0	LH	Temporooccipital Middle Temporal gyrus
		4.21	-56	-54	-4	LH	Temporooccipital Middle Temporal gyrus
		3.62	-54	-52	28	LH	Angular gyrus
		3.62	-50	-62	6	LH	Temporooccipital Middle Temporal gyrus
		3.50	-56	-48	30	LH	Posterior Supramarginal gyrus
		3.43	-56	-52	22	LH	Angular gyrus
Action > colour & global all > size all - LIFG small volume correction							
Cluster 1 COG (-50 24 2)	301	3.73	-52	28	2	LH	Inferior Frontal gyrus, pars triangularis
		3.11	-50	26	-6	LH	Frontal orbital cortex
		3.11	-54	22	12	LH	Inferior Frontal gyrus, pars triangularis
		2.85	-40	32	-8	LH	Frontal orbital cortex
		2.31	-60	12	16	LH	Inferior Frontal gyrus, pars opercularis
		2.06	-56	18	4	LH	Inferior Frontal gyrus, pars opercularis

Table provides data for all significant clusters and sub-peaks within each cluster, with the first sub-peak being the cluster maxima. Location was determined using the Harvard-Oxford cortical structural atlas built into FSL. COG = centre of gravity.

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