Deficits of semantic cognition in stroke aphasia: Underlying causes and ameliorating factors

A thesis submitted to the University of York for the degree of
Doctor of Philosophy

December 2012

Hannah Elizabeth Thompson

Department of Psychology

Table of Contents

Number of words: 98108

List of tables

List of figures

Abstract

Research suggests that semantic memory deficits can occur in at least three ways. Patients can (1) show amodal degradation of concepts within the semantic store itself, such as in semantic dementia (SD), (2) have an impairment of semantic control, leading to difficulty accessing appropriate knowledge in line with current goals or context, as in semantic aphasia (SA), and (3) experience a semantic deficit in only one modality following degraded input from sensory cortex. Patients with SA show damage to prefrontal cortex which extends posteriorly (PF+), or damage restricted to temporoparietal regions (TP-only), and have deficits of semantic control and 'access' across word and picture tasks, consistent with the view that their problems arise from impaired multimodal control processes. This thesis aims to explore the nature of these deficits, in four themes. (1) "Refractory effects" in SA patients are explored across modalities – i.e., these patients are shown to experience declining accuracy in cyclical matching tasks when semantically-related sets are presented rapidly and repeatedly. (2) We studied one case study with 'verbal-only' refractory effects, to investigate an apparent anomaly in the literature – the existence of patients who have 'access' deficits which are restricted to a single modality. These patients challenge the notion that semantic control processes are modality-general. We assessed the hypothesis that multimodal semantic control/ access impairments can follow a modality-specific pattern if paired with an input deficit of a single modality. (3) We explore the effect of lesion location on behavioural performance of semantic aphasia (SA) patients, who have PF+ or TP-only lesions by bringing together data published previously in different papers, together with some new SA cases. Past research suggests SA patients with these two lesions may show similar deficits of semantic control, yet the functional neuroimaging literature proposes a unique role for the prefrontal cortex. PF+ patients were less fluent, showed more associative picture naming errors, and overall somewhat stronger SA characteristics (e.g., they were more inconsistent, and less affected by frequency). (4) Semantic control recruits a wide cortical network, in both the left hemisphere (LH) and right hemisphere (RH). Semantic representations in the RH are partially distinct from the LH, including specialised knowledge of faces and metaphors. Our aim was to test whether damage to RH control regions would negatively affect performance on semantic control tasks which use items stored in the RH, in a similar way to our SA patients in the LH. Overall, the results suggest that semantic control operates in an amodal fashion, with deficits found across modalities. There was evidence to suggest a wide network involved in semantic

control beyond the prefrontal cortex – including left posterior cortex and right hemisphere regions. However, these regions are subtly distinct in their role in semantic control.

Declaration

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning. This work has been completed by the candidate under the supervision of Dr. Beth Jefferies. The research was supported by an Age UK studentship.

Part of the work in this thesis has been presented as a poster at the following conferences:

Chapter 2: '*Multimodal refractory effects in semantic aphasia'*. Hannah Gardner, Beth Jefferies, Naomi Dodds, Theresa Jones, Sheeba Eshan and Matthew Lambon Ralph. Age UK, Nottingham, September 2010; 5th International Conference on Memory, York, August 2011.

Chapter 3: '*Understanding the causes of verbal-only comprehension problems'*. Hannah Thompson and Beth Jefferies, 'Ageing: Moving Beyond Boundaries', Lancaster, September 2012; British Neuropsychological Society, London, November 2012.

Chapter 4: '*Does posterior temporoparietal cortex support semantic control? A comparison of temporoparietal, prefrontal and bilateral anterior temporal lobe lesions'*. Hannah Thompson, Krist Noonan, Paul Hoffman, Matthew Lambon Ralph, and Beth Jefferies, Neurobiology of Language, San Sebastian, October 2012.

Chapter 2 is a published paper: Gardner, H. E., Lambon Ralph, M. A., Dodds, N., Jones, T., Ehsan, S., & Jefferies, E. (2012) The differential contributions of pFC and temporo-parietal cortex to multimodal semantic control: exploring refractory effects in semantic aphasia. Journal of Cognitive Neuroscience, 24(4), 778-793.

Part of this thesis was conducted in collaboration with others. Acknowledgements for help with stimuli and data collection are at the beginning of each chapter.

Acknowledgements

I would like to thank **Paul Hoffman**, for his unfaltering help with many aspects of this thesis, **Krist Noonan**, for several chats about Chapter 4, **Katya Krieger-Redwood**, for always having the time to help out, and **Matt Lambon Ralph** and other collaborators in Manchester for energetic discussions and being a friendly face at conferences.

I would also like to thank all my wonderful friends who supported me at my wedding this year. Particularly, I'd like to mention **Richard Harris**, because he failed to acknowledge me in his acknowledgements section, and I would like to make him feel guilty about this. I would like to thank my **mum and dad**, who could not have been more supportive or thoughtful, and always helped me pursue my ambitions. I would like to thank my husband, **Neil**, "who's provided insight, wit, and a new perspective" (Neil Thompson, 2012).

Finally, and most importantly, I would like to thank my supervisor **Beth Jefferies**. She has never failed to be interested in my new ideas, be thorough in her feedback, to be giving in her acknowledgement of my input, and to be incredibly kind in her whole approach to me both personally and academically.

The Author

I graduated from University College London with a BSc (1st class hons) in Psychology in 2008. This degree gave me an interest in many aspects of psychology, particularly executive control. I became interested in how control interacted with long term semantic memory, and moved to York in 2009 to start work on the current thesis.

1. CHAPTER ONE

Overview of thesis

This thesis is presented so that each chapter is prepared as a self-contained paper, in the style of a journal article. Within each chapter, the motivation behind each study is outlined along with a summary of the most relevant aspects of the literature. This introductory chapter will: (1) identify the key aims of the thesis and its corresponding research questions; (2) place the work in a broader context by discussing a wider background literature; and (3) outline the structure of the thesis.

Thesis aims and research questions

Semantic cognition involves retrieval of generic and specific knowledge which puts meaning to our world and helps guide our interactions with it (Binney, Embleton, Jefferies, Parker, & Lambon Ralph, 2010; Jefferies & Lambon Ralph, 2006; Whitney, Kirk, O'Sullivan, Lambon Ralph, & Jefferies, 2012). Although retrieval occurs in a normal brain almost instantly, it involves at least three aspects: (i) conversion and combination of sensory properties into meaning (e.g., Andrews, Vigliocco, & Vinson, 2009), (ii) a storage system linking items together according to meaning, across modalities and perceptually different objects (e.g., Binney, Embleton, Jefferies, Parker, & Lambon Ralph, 2010; Mion et al., 2010; Patterson, Nestor, & Rogers, 2007), and (iii) control mechanisms which allow flexibility and specificity of retrieval from the store in a context appropriate way (e.g., Jefferies & Lambon Ralph, 2006; Rogers & McClelland, 2004). Neuropsychological data shows that patients can be impaired at each stage of semantic retrieval. (i) Damage to connections between the sensory input and semantic store cause modality specific recognition impairments, such as visual agnosia (Catani & Ffytche, 2005). (ii) The progressive degradation of grey matter in the anterior temporal lobes correlates with progressive loss of amodal semantic knowledge, seen in semantic dementia (SD; Hodges, Patterson, Oxbury, & Funnell, 1992b; Warrington, 1975). (iii) Some patients with stroke aphasia show control impairments on tasks in which semantic processing must be directed according to the demands and context of the task. These patients have semantic aphasia (SA; Jefferies & Lambon Ralph, 2006).

This thesis will focus on both the nature of the deficits in SA, what these can tell us about the cognitive and neural organisation of semantic control; and how these deficits related to semantic impairments in other patients – including those with right hemisphere (RH) lesions and deficits more restricted to a particular modality. (1) Previous work suggests multimodal deficits arising from domain-general executive deficits (Corbett, Jefferies, Ehsan, & Lambon Ralph, 2009; Corbett, Jefferies, & Lambon Ralph, 2009, 2011; Jefferies & Lambon Ralph, 2006). We tested this idea using parallel word, picture and environmental sound tasks, to see if these deficits existed across modalities. (2) An individual case study will be presented, exploring the underlying deficits in a patient who showed a discrepancy between executive control of verbal and non-verbal items. Such a case appears to present problems for the account of SA, in which modality-free control mechanisms interact with amodal semantic representations (Jefferies & Lambon Ralph, 2006). Our findings suggest this pattern can be explained in terms of a dual deficit, to both multimodal semantic control and auditory input processing. (3) The neural basis of semantic control will be explored, following evidence from the first study (Chapter 2) that suggests SA cases with prefrontal damage and those with damage only to temporoparietal regions behave in different ways on a control-demanding semantic task. We examine different aspects of semantic control, and compare SA subgroups (with different lesions) across a range of tasks. (4) While many studies have considered the role of left hemisphere regions in semantic control (Fridriksson, Bonilha, Baker, Moser, & Rorden, 2010), the contribution of the RH remains largely unstudied. We explore semantic control tasks designed to be parallel to those in which we have found impairment in SA patients with LH lesions, but this time focussing on domains of knowledge linked to the RH, to explore the RH's contribution to the semantic control network.

This opening chapter will first describe the amodal semantic store, and semantic dementia patients with deficits of this store. It will then describe 'access' patients, who have difficulties retrieving semantic knowledge, although their semantic store remains intact. Then SA patients will be described in detail, both in terms of lesion sites and behavioural characteristics.

These patients have ‘access’ deficits, but have additional difficulties which correlate with executive control demands. Areas implicated in semantic control will then be reviewed, using neuroimaging data to complement this patient work. Finally, the four research themes will be outlined in detail: (1) multimodal refractory effects, (2) ‘verbal-only’ refractory effects, (3) anterior compared with posterior patients, and (4) the role of the RH in semantic control.

Bilateral multimodal semantic store

There is a consensus emerging that the representation of amodal semantic knowledge is in the ventral anterior region of the temporal lobes (ATL), with a focal point in the basal fusiform gyrus (Binney, et al., 2010; Binney, Parker, & Lambon Ralph, 2012; Lambon Ralph, Sage, Jones, & Mayberry, 2010; Mion et al., 2010; Visser, Jefferies, Embleton, & Lambon Ralph, 2012; Visser & Lambon Ralph, 2011). Binney et al. have found that a model of white-matter connectivity of this region is limited to other temporal regions, and suggests that this reduced connectivity would remove it from the influence of control or context-coding systems; allowing it to extract modality and context invariant semantic representations (Binney, et al., 2012). Anatomically, there is evidence for a caudal-to-rostral convergence of information in the temporal lobe, where regions which are near modality-specific areas show specialisation (e.g., the posterior superior temporal gyrus for auditory processing), and regions which are more distant to modality-specific areas are impartial to modality (e.g., ATL), and processing becomes amodal (Damasio, 1989b; Plaut, 2002; Visser, Embleton, & Lambon Ralph, 2012).

Severe semantic impairment to semantic representations is invariably associated with bilateral damage in SD and herpes simplex encephalitis patients (Mion, et al., 2010; Nestor, Fryer, & Hodges, 2006). Patients with greater damage to the RH over the left show the same pattern of comprehension impairments, whilst lacking the severe anomia associated with a left hemisphere lesion (Lambon Ralph, McClelland, Patterson, Galton, & Hodges, 2001). As noted above, bilateral ATL activation has been found in semantic processing, albeit with the RH showing slightly reduced peak activations than the LH across studies of semantic comprehension (Visser, Embleton, Jefferies, Parker, & Lambon Ralph, 2010; Visser, Jefferies, & Lambon Ralph, 2010). Most conclusively, rTMS studies have found that stimulation to either hemisphere disrupts semantic processing. For example, a significantly increased reaction time for a synonym judgement is found after rTMS of either left or right temporal pole (Lambon Ralph, Pobric, & Jefferies, 2009a). Patients with unilateral lesions – through temporal lobectomies or temporal lobe epilepsy – show subtle and much less dramatic semantic impairments (Lambon Ralph, Cipolotti, Manes, & Patterson, 2010; Lambon Ralph, Ehsan, Baker, & Rogers, 2012), with deficits in comprehension only on the most demanding tasks (Lambon Ralph & Patterson, 2008). In these patients, normal interaction with the contralateral hub can occur, and compensate for the damage. If the damage is bilateral or the connectivity is lost, this cannot occur.

Damage to posterior ITG results in visual agnosia (James, Culham, Humphrey, Milner, & Goodale, 2003; Karnath, Ruter, Mandler, & Himmelbach, 2009), and damage to posterior STG causes auditory agnosia (Griffiths, 2002). However, semantic dementia (SD) patients with degeneration of the ATL show parallel progressive deterioration of semantic knowledge across the modalities (Bozeat et al., 2003; Bozeat, Lambon Ralph, Patterson, Garrard, & Hodges, 2000; Bozeat, Lambon Ralph, Patterson, & Hodges, 2002; Coccia, Bartolini, Luzzi, Provinciali, & Lambon Ralph, 2004; Garrard & Carroll, 2006; Lambon Ralph, Graham, Patterson, & Hodges, 1999; Lambon Ralph & Patterson, 2008; McClelland & Rogers, 2003; Patterson, Nestor, & Rogers, 2007). This multimodal semantic 'hub' is thought to be necessary to form semantic relationships for items which may share few sensory properties, as well as connecting multimodal properties of each item to allow matching of objects with words, sounds, smells etc. (Nestor, et al., 2006; Patterson, et al., 2007; Williams, Nestor, & Hodges, 2005).

Until recently, the notion of a semantic 'hub' in the ATL was highly controversial. Instead, the 'distributed-only' theory suggests that the conjoined action of modality-specific association cortices, without a hub, is sufficient for multimodal semantic representations to exist (Martin, 2007). These two theoretical frameworks are displayed in Figure 1.1.

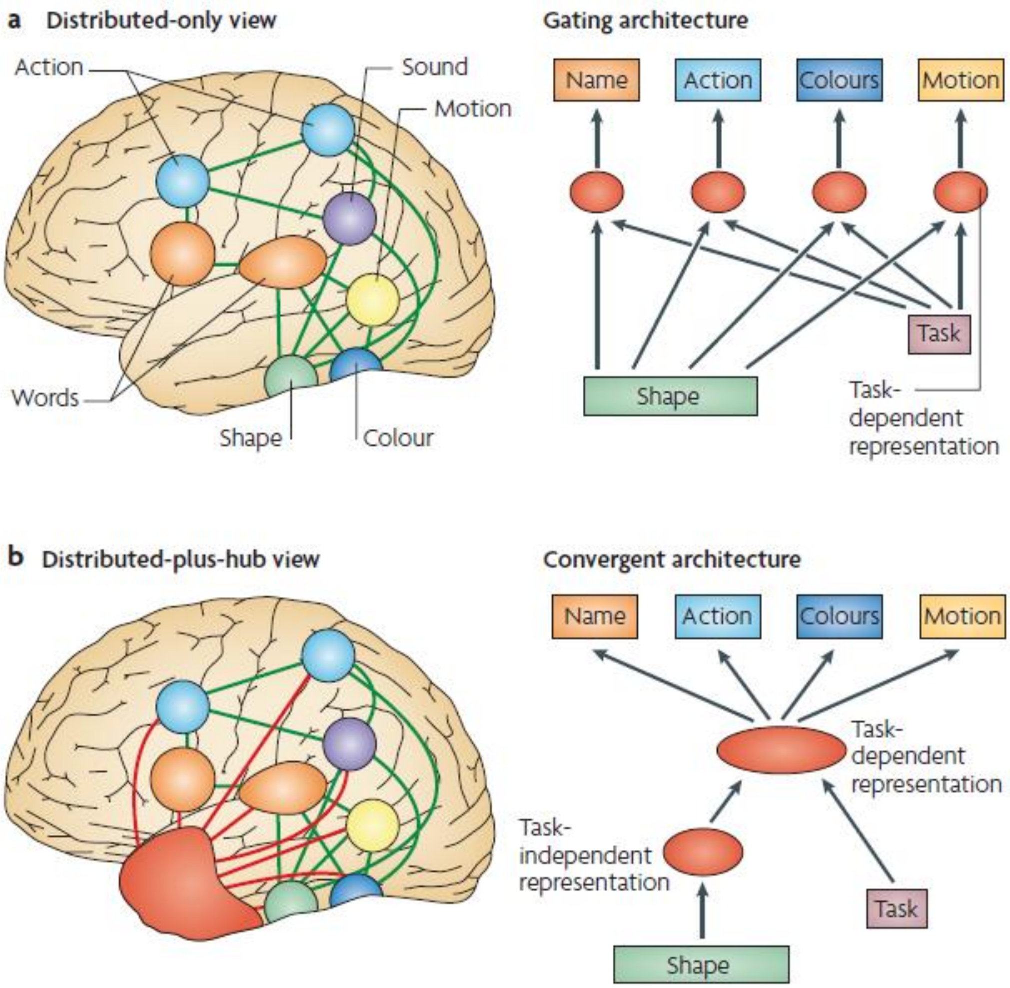


Figure 1.1: Two theoretical positions regarding the neuroanatomical distribution of the cortical network, reproduced from Patterson et al. (2007).

Nonetheless, proponents of the ‘distributed-plus-hub’, or ‘hub-and-spokes’ model argue that both modality-specific cortices and the ATL are crucial for semantic representation. The existence of patients with modality or category specific deficits in semantic representation is predicted by both theories, after damage to a ‘spoke’ (Caramazza & Mahon, 2003; Gainotti, 2000). Pobric et al. (2010b) found that rTMS to the ‘hub’ (left ATL) disrupted response across domains, and stimulation of a ‘spoke’ (the left IPL) slowed responses only to a single domain (nonliving items). TMS studies like this have shown the importance of the ATL over a range of verbal and non-verbal semantic tasks (Binney, et al., 2010; Lambon Ralph, et al., 2009a; Pobric, Jefferies, & Lambon Ralph, 2007; Pobric, et al., 2010b).

It is also possible that category effects emerge from nonselective damage to a unitary semantic system (in ATL). Concepts can be represented as patterns of activation distributed over multiple units, which correspond to different features (Tyler, Moss, Durrant-Peatfield, & Levy, 2000). Therefore, similar representations have similar patterns of activation, to allow generalisations to be made about new items. Patients with ‘modality-specific’ deficits usually show varying degrees of impairment, rather than an all-or-nothing deficit (Devlin, Gonnerman, Andersen, & Seidenberg, 1998). It seems unlikely to have category-specific deficits, as category membership is often unclear (e.g., is a tomato a fruit or vegetable), multiple (e.g., a horse is a vehicle and animal) or unnatural (e.g., which category do railway platforms or traffic lights belong to). Garrard and colleagues (2001) suggest that categories may emerge from similarity in features amongst a group of concepts – without the need for a separate coding mechanism. If this were the case, a semantic control mechanism as envisaged by Jefferies and Lambon Ralph (2006) would impact different categories equally.

Martin and colleagues doubt the evidence for the role of the ATL for two reasons. Firstly, Simmons and Martin (2009) argue that rTMS studies may not be evidence to support the role of ATL, as rTMS disrupts activity in regions remote from the stimulation site, so that rTMS to ATL also affects activity more posteriorly (Rounis et al., 2006; Simmons & Martin, 2009; Whitney, Hymers, Gouws, & Jefferies, submitted). SD patients are also not good evidence for a ‘hub’, as they often show damage not restricted to the ATL along the temporal lobe (Bambati et al., 2009; Gorno-Tempini et al., 2004; Noppeney et al., 2007; Williams, et al., 2005). fMRI evidence is sparse, as it is insensitive to signal in ATL due to their proximity to air-filled sinuses.

Nonetheless, this ATL region is has been shown to be core to semantic representations not only through SD patients (Desgranges et al., 2007; Galton, Patterson, Graham, & Lambon Ralph, 2001), but distortion corrected fMRI (Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996; Visser, Embleton, et al., 2010; Visser, Embleton, et al., 2012; Visser, Jefferies, et al., 2012; Visser, Jefferies, et al., 2010; Visser & Lambon Ralph, 2011), adding to evidence from PET (Bright, Moss, & Tyler, 2004; Noppeney & Price, 2002; Price, Devlin, Moore, Morton, & Laird, 2005; Rogers et al., 2006; Sharp, Scott, & Wise, 2004; Spitsyna, Warren, Scott, Turkheimer, & Wise, 2006; Vandenberghe, et al., 1996) and MEG and EEG (Halgren et al., 2006; Marinkovic et al., 2003). This evidence has led to increased popularity for the idea of ATL involvement in semantic representation across categories and modalities, and has added support to the ‘hub-and-spoke’ model.

‘Access’ versus ‘storage’

There is clearly a distinction between regions of the brain implicated in SA and SD, and it is now commonly accepted that there is a behavioural distinction between permanent loss of semantic knowledge and an inability to retrieve the appropriate semantic information at certain times (Warrington & Cipolotti, 1996; Jefferies & Lambon Ralph, 2006). Rapp and Caramazza (1993) argued that patients who were assumed to have a ‘storage’ deficit were not tested on the characteristics of ‘access’ patients, and vice versa. This point has been addressed by Warrington and colleagues (Warrington & Cipolotti, 1996), and later Jefferies and colleagues (Jefferies & Lambon Ralph, 2006). Rapp and Caramazza also argued that patients exist who do not show all the characteristics of an ‘access’ or ‘storage’ patient. This has been accounted for in a model by Gotts and Plaut, who suggest that storage deficits come from damage to neurons that encode semantic information, and access deficits result from damage to neuromodulatory mechanisms which enhance neural signals that are otherwise attenuated by synaptic depression (Gotts & Plaut, 2002). It is therefore possible that some patients will show elements of both deficits (see also Crutch & Warrington, 2011a; Warrington, 1981). It is also addressed by Jefferies and Lambon Ralph (2006), who suggest that different areas of the brain are involved in representation and control, and so it is possible to have damage to both a ‘spoke’ and also a semantic control region.

In the section below, we consider contrasting theoretical accounts of semantic ‘access’ deficits. According to one view, there are separable verbal and visual semantic processes, and a semantic access impairment arises when the processing of verbal or visual semantics enters an abnormal refractory state, making the participant less able to process new verbal or visual input (Warrington & Crutch, 2004). By an alternative account, executive dysfunction can give rise to semantic ‘access’ deficits, including refractory effects (Jefferies, Baker, Doran, & Lambon Ralph, 2007). If a domain-general executive control mechanism interacts with amodal semantic representations, as anticipated by Jefferies and Lambon Ralph (2006), ‘access’/refractory effects should not be specific to a particular sensory modality.

‘Access’ patients

In contrast to Jefferies and colleagues, who envisage that an amodal store of knowledge interacts with modality-free control mechanisms, a parallel area of research focused on a small number of single cases, suggests that deficits in semantic access (as opposed to storage) can selectively affect verbal comprehension. Warrington and colleagues have described several stroke cases with a large left hemisphere lesion who show four key behavioural characteristics (Warrington & Cipolotti, 1996). (1) Firstly, and most importantly, performance on one trial does not correlate with performance on another trial with the same item (Crutch & Warrington, 2005b). This suggests that the item is not “degraded”, as in SD patients, but items are inaccessible at certain times. This is particularly noticeable in a subset of patients with a ‘refractory’ access disorder, where inconsistent performance is related to temporal factors and multiple presentations of the target and distractors (Crutch, Ridha, & Warrington, 2006; Warrington & Crutch, 2004), with the semantic distance of the target and distractors being of particular importance (Crutch & Warrington, 2003a, 2004, 2007, 2010b). Not all ‘access’ patients, however, show refractory effects (Warrington & Leff, 2000; Warrington & Shallice, 1979). (2) Secondly, these patients are not influenced by item frequency (Crutch & Warrington, 2010a; Warrington & Cipolotti, 1996), while SD patients are worse at low frequency items. For example, Crutch and Warrington (2005b) found ‘access’ patient AZ showed worse performance on a refractory task using close compared to distant items, across all frequencies. However, in SD patients, frequency had a much stronger effect than cycle or distance. With these patients, only ‘middle’ frequency items showed an effect of semantic distance (with patients showing higher performance for distant relations in this condition), which the authors suggest reflects preserved high frequency items, impaired low frequency items, and utilisation of superordinate information for ‘middle’ frequency items – which is only useful in distant arrays. (3) Thirdly, ‘access’ patients can match subordinate and superordinate items equally well, where SD patients show reduced accuracy for subordinate categorization (Warrington, 1975). If anything, ‘access’ patients can show an increased performance with basic level descriptors, rather that superordinate category names (Crutch & Warrington, 2008a; Humphreys & Forde, 2005). This may reflect higher control requirements for superordinate items which have more associated items, and so require executive processing to match the word to the appropriate picture. Tyler et al. (2004) reported fMRI data that showed that superordinate naming activated the anterior temporal cortex (paired with posterior temporal regions), while basic naming activated prefrontal regions (again, with posterior temporal regions). Raposo et al. (2012) suggest that superordinate concepts have less shared features among category members, and therefore might require control to coordinate information. In their study, a true-false decision was made about sentences that were either on a basic or superordinate level. These either shared many features with other members of that concept (e.g., the car has a steering wheel, or the plant needs water – both these statements are true for all exemplars of the concepts ‘car’ and ‘plant’), or had less shared features with other members of the concept (e.g., the piano is an antique, or the clothes are made from wool). They found LIFG activation for sentences with less shared concepts – to the same extent in superordinate and basic level items. There was also higher activation in LIFG and pMTG for superordinate concepts with more shared features in relation to basic level concepts. (4) Finally, ‘access’ cases show strong priming or cueing effects, which are not predicted in those with permanent damage to semantic representations (Warrington & Shallice, 1979; Warrington & Weiskrantz, 1982). There is evidence of priming in a number of aphasic patients (Blumstein, Milberg, & Shrier, 1982; Hagoort, 1997). Semantic cueing effects have been shown to help picture naming. For example, Wambaugh (2003) studied two 6-week picture naming treatments, either semantic (e.g., giving a feature of the item, such as ‘a farm animal that gives milk’ for a cow, or a sentence, such as ‘the farmer fed the...’), or a phonological cue (e.g., for pig, giving the initial letter, /p/, or a rhyming non-word “chig”). Both cues led to dramatic improvements in aphasic patients, but this was particularly noticeable with semantic cues.

Elizabeth Warrington and colleagues, who described semantic ‘access’ deficits also emphasised that access impairments were specific to a particular sensory modality. This led to the theory of ‘multiple’ semantic systems (Warrington, 1975), with “partially independent meaning systems” for different modalities (Warrington & Shallice, 1979). However, ‘access’ patients who do show a difference between modalities may not be at ceiling on visual tasks (Warrington & McCarthy, 1987; Warrington & Shallice, 1984). Indeed, the initial case study VER showed performance of just 68% on one visual object matching task (Warrington & McCarthy, 1983). This suggests that there is little evidence for distinct modality systems.

Single-modality deficits have been well documented – but there is divergent opinion about whether single-modality deficits reflect an 'access' deficit, or a simple input deficit. For example, Warrington and McCarthy (1994) describe DRS, who had visual agnosia. His performance on non-semantic visual tasks was unimpaired, or 'credible', but he showed visual semantic impairments. His ability to pantomime actions or name objects was impaired when using visual, but not spoken probes. This is thought to reflect disconnection between sensory processing and semantic meaning (Geschwind, 1965). Warrington further argues that semantic representations of words and pictures are separate, given their different time course in development, and 'synonymy and equivalence relationships are different for language and vision' (Warrington & McCarthy, 1994). However, factors which signify 'access' deficits, such as consistency, presentation rate and the semantic distance of distractors and the target, have been either not tested at all, or rarely tested in the same way across modalities (Riddoch & Humphreys, 1987a, 1987b; Riddoch, Humphreys, Coltheart, & Funnell, 1988; Shallice, 1988, 1993; Warrington, 1975; Warrington & McCarthy, 1983; Warrington & Shallice, 1984).

The theory of 'multiple semantics' also suggests categories are stored and accessed separately. Capitani et al. (2003) note that modality and category independent systems are not independent – and that identifying living things largely depends on the visual system (as living things are visually similar), whereas manipulable objects require the knowledge of how to use them (Borgo & Shallice, 2001; Humphreys & Forde, 2001; Humphreys & Riddoch, 2003; Humphreys, Riddoch, & Quinlan, 1988; Martin, Ungerleider, & Haxby, 2000; McCarthy & Warrington, 1985; Saffran & Schwartz, 1994). These distinctions have largely been tested in patients with *comprehension* impairments, rather than *access* impairments (Caramazza & Shelton, 1998; Crutch & Warrington, 2003b; de Renzi & Lucchelli, 1994; Farah, McMullen, & Meyer, 1991; Hart & Gordon, 1992; Hillis & Caramazza, 1991; Moss, Tyler, & Jennings, 1997; Sacchett & Humphreys, 1992; Saffran & Schwartz, 1994; Satori & Job, 1988; Warrington & McCarthy, 1983, 1987; Warrington & Shallice, 1984), with the majority of representational impairments found in the domain of living things. This can be accounted for in the 'hub-and-spoke' model of semantic representations, explained above.

Refractory effects

One way in which the independent semantic systems hypothesis has been explored in the same way across modalities is the ‘refractory’ task. Refractory effects occur when an item has been activated, it becomes temporarily unavailable for a period of time (Warrington & McCarthy, 1983). Cyclical tasks are used to probe this, which typically use picture-matching, where the target and semantically related distractors are repeatedly presented over multiple cycles (Forde & Humphreys, 1995). While access patients initial performance is only marginally impaired, their error rates increase over cycles as a consequence of the task (Warrington & Cipolotti, 1996). This task typically uses a spoken word probe to be matched with a visual target (Crutch & Warrington, 2003c, 2004, 2005a, 2005b, 2007, 2008a, 2010b, 2011b; Forde & Humphreys, 1995; Hamilton & Coslett, 2008; Jefferies, et al., 2007; McNeil, Cipolotti, & Warrington, 1994; Warrington & McCarthy, 1983, 1987). However, efforts have been made to compare performance on visual and verbal versions of the task in access patients. The existence of individual cases who show refractory effects on verbal but not visual tasks might suggest a cognitive and neural dissociation between verbal and visual semantic systems (Crutch & Warrington, 2008b; Warrington & Crutch, 2004). For example, Crutch and Warrington (2011a) describe two patients with a ‘verbal-only’ deficit, showing increased error rates across cycles in spoken-word to picture and written-word to picture matching tasks (although this was only significant in the spoken domain). Of particular importance, in a picture or spoken-word to written-word task presented in 8 semantically related arrays, their patient showed a large increase in error rate for spoken-word to written-word, but not picture to written-word.

Forde and Humphreys (1997) carried out several tasks comparing visual and verbal refractory effects on single stroke aphasia case JM. They found that when using unusual views item-matching, there was a decrease in performance only for the word-picture matching, and not picture-picture matching (possibly due to presemantic perceptual access). They then assessed associative matching performance, with a task involving matching an item (e.g., EGG) with another item (e.g., HEN). Here, JM did show refractory effects in both picture and verbal tasks. A similar 5-item task was run, matching category associates (e.g., a training shoe with a walking shoe), when presented among related distractors (e.g., WATCH, UMBRELLA, TIE, SHOE). This again found refractory effects across modalities. Cross-modal refractory effects were tested with auditory-written word matching or auditory-picture matching, including switching the modalities. They found words presented for the first time on the forth trial, following repetition of the same items as pictures, were significantly impaired. Similarly a colour test involved matching either an auditory word to a written word or auditory word to a colour patch. Finally, they tested colour association via written-word to written-word (e.g., FIRE ENGINE to RED), or colour patches to line drawings. There was a significant decline in performance, whether in the word or picture modality, or interleaved modalities.

However, Warrington and Crutch found a different pattern (Crutch & Warrington, 2008b; Warrington & Crutch, 2004). They compared a visual-visual with verbal-visual matching. The visual-visual matching task used two visually dissimilar examples of the same item (e.g., two types of kettle). When assessing different semantic categories (e.g., animate and inanimate), they found case study AZ showed no serial effects in the visual domain, but there was an increased number of errors across cycles in the verbal domain. In their later paper, they presented two patients, AZ and BBB, who both showed refractory effects in the verbal but not visual domain. Both patients also showed evidence of refractory effects with environmental sounds stimuli. They suggest this reflects a close relationship between nonverbal sounds and language (Saygin, Dick, Wilson, Dronkers, & Bates, 2003), and suggest refractoriness is not lexical, but rather an auditory-semantic process which reflects neuromodulatory processes (Gotts & Plaut, 2002).

SA patients' behavioural characteristics

Although there is evidence that 'access' patients are influenced by modality, the relationship between executive impairment and access deficits has not been considered (e.g., Warrington & Crutch, 2004), although in some cases, it seems there may be some association between digit span length and refractory effects (Crutch & Warrington, 2011a). The SA patients which Jefferies and Lambon Ralph (2006) have tested show two distinct patterns of semantic performance which differ from those originally reported by Crutch and Warrington. Firstly, SA patients are not influenced by modality, and show deficits across visual and verbal domains to the same extent (Corbett, Jefferies, Ehsan, et al., 2009; Corbett, Jefferies, & Lambon Ralph, 2009; Corbett, et al., 2011; Jefferies & Lambon Ralph, 2006). Secondly, SA patients are affected by executive control demands of the task, showing reduced accuracy on tasks which have high control demands in relation to tasks with low control demands (Jefferies, in press; Jefferies, et al., 2007; Jefferies & Lambon Ralph, 2006; Noonan, Jefferies, Corbett, & Lambon Ralph, 2010). Given the refractory impairment and effects on cyclical tasks might be explicable in terms of executive deficits, Jefferies and colleagues investigated the performance of SA patients, who are defined in terms of multimodal semantic impairment, in relation to access impairments and other impairments which are distinct from 'access' patients.

Correlations across semantic tasks

SA patients have strong correlations across the same task in different modalities (e.g., picture and word version of the Camel and Cactus task, and sound-picture and word-picture matching tasks; Jefferies & Lambon Ralph, 2006). They suggested that tasks which are similar in nature (requiring a certain level of semantic control), are highly correlated, whilst tasks which have different control demands (e.g., the picture version of the Camel and Cactus task, and word-picture matching), have no significant correlation, even though the same 64 items are used in both tasks. In comparison to SA patients, correlations and item-by-item consistency for high and low demand tasks (e.g., matching and association tasks) remained strong for SD patients.

Manipulations of semantic control within task

SA patients have been shown to vary their response to the same item when semantic control manipulations are varied within a task. Noonan et al. (2010) used several experiments to explore this. (1) First, they tested patients' ability to match items which had the same category, whether they were close or distant in semantic space (e.g., a close relation such as HAT and CAP, and a distant relation such as HAT and STOCKING). Although the probe and distractors were the same, the distance of the target from the probe was varied. Control participants were not affected by semantic distance, whereas patients were more impaired when matching semantically distant items. This is because when probes and targets are closely related, they share a large amount of semantic structure/features, but when they are more distant, they require additional semantic control to work out the relevant semantic link (Noonan, et al., 2010). (2) In a second task, participants were required to match items with varying distractor strength. In a synonym task, they either matched synonyms with weakly associated antonym distractors (e.g., NEAT with TIDY, MESSY or LUCKY), or a strongly associated antonym distractor (e.g., HAPPY with CHEERFUL, SAD or CONSCIOUS). SA patients were less accurate at making synonym judgements with a strong distractor. When two concepts are strongly related, their relationship becomes hard to ignore even when this is irrelevant to the task (Samson, Connolly, & Humphreys, 2007). (3) Finally, the authors assessed patients' ability to process dominant and non-dominant meanings of homonyms in a semantic judgement task (e.g., in the dominant condition, PEN with PENCIL, or the subordinate condition, PEN with PIG). Competition between alternative meanings of an item is determined (in part) by frequency, and so less frequent meanings have a processing disadvantage (Noonan, et al., 2010). They found SA patients had significantly more difficulty retrieving non-dominant meanings than dominant meanings of the same word.

Cued picture naming

Jefferies and Lambon Ralph (2006) found that, like 'access' patients, SA performance was greatly affected phonemic cues in picture naming paradigms (Conroy, Sage, & Lambon Ralph, 2009; Howard & Gatehouse, 2006; Jefferies, Patterson, & Lambon Ralph, 2008; Lambon Ralph, Sage, & Roberts, 2000; Noonan, et al., 2010; Soni et al., 2009; Soni, Lambon Ralph, & Woollams, 2011). The positive effect of cueing correlates significantly with overall accuracy and performance on measures of executive functioning (Soni et al., 2009). It is hypothesised that cues boost activation of the target word relative to semantically related competitors, to narrow the field of competing responses dramatically. Dell and colleagues (Dell & O'Seaghdha, 1992; Dell, Schwartz, Martin, Saffran, & Gagnon, 1997; Schwartz, Dell, Martin, Gahl, & Sobel, 2006) argue that there is strong connectivity between semantics and lexical and phonological nodes, such that phonemic cues will boost semantic activation for the target, and dampen down semantic competitors. Jefferies and colleagues (2008) tested picture naming in SA and SD patients using cumulative phonemic cues, starting with the first phoneme. SA patients showed a larger cueing effect than SD patients, with large improvements after phonemic cues in comparison to spontaneous naming. The partial benefit of SD patients to cues is thought to reflect the graded nature of deterioration. There was also a difference in the type of errors produced – with SA patients producing more associative errors (e.g., SQUIRREL – NUT) and SD patients producing more superordinate errors (e.g., SQUIRREL – ANIMAL; Jefferies et al., 2008). This suggests SA patients activate semantically relevant items and are unable to correctly select the appropriate name. Soni et al. (2011) also suggested that associative relationships are integral to semantic representations of concrete items, reflected in the high level of associative naming errors in SA patients (Jefferies and Lambon Ralph, 2006). However, SD patients have degraded concepts of individual features of a category, although they still retain the knowledge of the correct superordinate category.

Soni et al. (2009) argued that if semantic activation of a group of category nodes was activated, then cueing a semantically related competitor (e.g., providing /l/ for TIGER) should boost activation of the competitor lion and reduce the patients' ability to produce the correct label. They found that miscueing SA patients led to lower accuracy and more semantic errors (see also Noonan, et al., 2010; Soni, et al., 2011). This suggests that these patients have intact semantic representations which are not utilised in a task appropriate way. They found a significantly higher performance with a cue in relation to an associative miscue (e.g., /w/ for BATH), with correlations between the effect of miscue and executive control. Cueing also aids performance on non-verbal semantic tasks. For example, Corbett et al. (2011) found that SA patients were better able to mime an action for an object when shown a picture cue of the recipient of the action, e.g. NAIL for HAMMER.

Correlations of executive control and semantic memory

SA patients have been shown to exhibit deficits beyond the semantic domain – in executive control functioning (Baldo et al., 2005; Jefferies & Lambon Ralph, 2006; Stuss & Alexander, 2000; Weiner, Connor, & Obler, 2004). Frontal lesions are often associated with impaired problem solving or executive control (Badre, Hoffman, Cooney, & D'Esposito, 2009; Roca et al., 2010; Stuss, 2007; Stuss et al., 2000; Turken et al., 2008). Baldo et al. (2005) tested the correlation between language and problem solving (see also Dronkers, Ludy, & Redfern, 1998; Hamsher, 1991; Hermer-Vazquez, Spelke, & Katsnelson, 1999; Nelson, Reuter-Lorenz, Persson, Sylvester, & Jonides, 2009; Weiner, et al., 2004). Baldo et al. found that performance on the Wisconsin Card Sorting Task correlated with comprehension and picture naming. They suggested that covert language may be required for complex problem solving. They also found that perservation errors correlated with language abilities, and suggested that in particular, flexibility and cognitive switching may depend on language. Baldo et al. (2010) found aphasic patients to be disproportionately impaired on relational reasoning, in relation to pattern matching, and that performance on Raven's Progressive Matrices correlated with language scores. Jefferies and Lambon Ralph (2006) found strong correlations between executive control measures and semantic performance, including non-verbal tasks such as picture association matching ($r > .61$).

This correlation was not found for SD patients (*r* < .29). However, despite a significant correlation, this does not prove causality, so it may be that either semantic deficits impair reasoning, or that executive deficits underpin semantic deficits.

Frequency/familiarity

Jefferies and Lambon Ralph (2006) found that over several tasks, such as synonym matching or semantic association tasks, SD patients showed strong effects of frequency/ familiarity (see also Bird, Lambon Ralph, Patterson, & Hodges, 2000; Bozeat, et al., 2000; Corbett, Jefferies, Ehsan, et al., 2009; Funnell, 1995; Jefferies, Patterson, Jones, & Lambon Ralph, 2009; Lambon Ralph, Graham, Ellis, & Hodges, 1998; Noonan, et al., 2010). Items that are used frequently develop more robust semantic representations (Hoffman, Rogers, & Lambon Ralph, 2011), and so lower performance on low frequency items is associated with degradation of conceptual knowledge itself. In SA patients, there was no advantage for high frequency items – which is also true of 'access' patients (see also Almaghyuli, Thompson, Lambon Ralph, & Jefferies, 2012; Crutch & Warrington, 2005a; Hoffman, Jefferies, & Lambon Ralph, 2011; Marshall, Pring, Chiat, & Robson, 2001; Nickels & Howard, 1995; Warrington & Cipolotti, 1996; Warrington & Shallice, 1979). Hoffman and colleagues (2011) argue that high frequency words have a natural advantage, being more often encountered and therefore benefitting from higher resting levels. Nonetheless, high frequency items also have higher semantic control demands, because of automatic activation of a high number of lexical associates, contexts and meanings. For example, a high frequency word such as 'dog' can be used to mean a number of different things, such as 'he's really gone to the dogs', and 'the detective will dog your footsteps', and so on. This range of uses for a high-frequency word has been described as 'semantic diversity' (see Hoffman, Rogers and Lambon Ralph, 2011), as the word appears in a large number of linguistic contexts (Adelman, Brown, & Quesada, 2006).

Imageability

SA patients are often cited to show strong imageability effects (Almaghyuli, et al., 2012; Forde & Humphreys, 1995; Jefferies, Hoffman, Jones, & Lambon Ralph, 2008), which match those found in 'access' patients (Crutch, et al., 2006). Hoffman et al. (2011) show a strong negative correlation between imageability and semantic diversity – with abstract words occurring in more semantic contexts. However, the positive effect of imageability in SA patients was robust beyond semantic diversity (Degroot, 1989; Katz & Goodglass, 1990). High imageability words have lower control demands because these representations are better constrained by their sensory features. Low imageability concepts are not pinned down in the same way, and so might require more internally-generated constraints on semantic processing (Plaut & Shallice, 1993).

Refractory effects

SA patients', like 'access' patients, show refractory effects, or a decline in accuracy over cycles. Jefferies et al. (2007) studied three variables with regards the refractory pattern: speed of presentation, item repetition (cycles) and semantic blocking (relatedness of distractors). They found that when targets were presented with other semantically related distractors, performance was significantly worse than when items were presented with unrelated distractors. There was also an effect found for speed of presentation (with SA patients showing worse performance with an RSI of 0 compared to 5 seconds), and cycle (with performance lower on cycle 4 in relation to cycle 1). Deficits of semantic control should produce stronger refractory effects in more demanding conditions (e.g., with related distractors and quicker presentation time), because semantic activation spreads between items and does not decay fully between trials. This increased activation leads to stronger competition between the target and distractors. This effect occurs across modalities (see Chapter 2).

Multimodal control deficits

Several studies have found that SA patients show semantic control deficits in non-verbal tasks (Corbett, Jefferies, Ehsan, et al., 2009; Corbett, Jefferies, & Lambon Ralph, 2008, 2009; Corbett, et al., 2011; Jefferies & Lambon Ralph, 2006). In all modalities that have been tested, patients have most difficultly on trials which require a flexible application of knowledge, such that items must be matched even when they do not share a strong association. Corbett et al. (2011) used a picture task of tools to be matched target objects (e.g., HAMMER-NAIL), and found a significant difference in SA performance between tools which were canonical and non-canonical alternatives (e.g., an item not usually used to perform an everyday action, but nonetheless a plausible alternative). For example, a 'fly-swat' is most commonly used to kill a fly, but if this option is not available, controls but not SA patients readily select a 'magazine' as a plausible alternative. As with word tasks involving non-dominant semantic associations, the patient has to inhibit the most familiar meaning of the item (Noonan, et al., 2010).

There are also equivalent verbal and non-verbal cueing effects in production tasks (Corbett et al., 2011). This suggests SA patients have difficulty controlling their own semantically-driven behaviour, and thus benefit from external constraints. Under these circumstances, SA patients reveal that they retain knowledge that they previously failed to demonstrate.

As with verbal tasks, Corbett et al. (2009) found evidence for a lack of consistency across a variety of non-verbal (action and tool) tasks for SA but not SD patients. They found that in some less demanding tasks (e.g., word-picture matching), SA patients were better than SD patients. In other tasks (e.g., picture-picture semantic attribution matching, involving matching an item with its recipient, which was another tool with the same function or action) led to similar performance in SA and SD patients. Finally, SA patients were poorer at solving mechanical puzzles than SD patients, which was the task which required the most semantic control.

Corbett, Jefferies and Lambon Ralph (2009) tested non-verbal semantic control within a single task. They found that performance on a naturalistic object use task varied according to the task demands. When performing actions which have multiple substages, which involve dual-task situations, or which have a semantically related distracting object present, patients' performance was reduced.

Deficits have been found to the same extent with the same semantic items using either verbal or visual stimuli, such as a refractory word- and picture-picture matching task (Chapter 2, Gardner et al., 2012), and the camel and cactus semantic association task in picture and word modalities (Jefferies & Lambon Ralph, 2006). There is also evidence from action and tool tasks described above which suggest SA patients have similar semantic control deficits across modalities. This data fits with Jefferies and Lambon Ralph's (2006) theory that SA patients have damage to an amodal semantic control network.

SA patients' brain lesions

As the ATL has been causally implicated in the representation of semantic knowledge within a long-term store, it is important to note that, in comparison to SD patients, SA patients almost always have no damage to the fusiform region of the ATLs which is thought to be the crucial amodal ‘hub’ for semantic representations (Jefferies, in press; Jefferies & Lambon Ralph, 2006; Noonan, Jefferies, Visser, & Lambon Ralph, submitted). This suggests that SA patients’ deficits may arise from a different underlying impairment. SA occurs after stroke, and the inferior ATLs are well protected from blood clots, which is the main cause of stroke. Firstly, they have a blood supply from two arteries: (i) the anterior temporal cortical artery, which branches off the middle cerebral artery, and (ii) the anterior temporal branch of the distal posterior cerebral artery. It is unusual for both of these blood supplies to be affected by stroke simultaneously (Conn, 2003). Although the superior ATL is more vulnerable to stroke, basal areas within ATL which are associated with representation of knowledge are watershed regions. Secondly, the artery branch supplying the anterior temporal lobe subdivides below the main trifurcation of the artery: this might make it less vulnerable to emboli, which can pass beyond this point (Borden, 2006). Thirdly, the ATL stores semantic knowledge bilaterally, and it is unusual to have a bilateral stroke (Visser, Jefferies, et al., 2010). This accords well with previous findings suggesting SA patients’ semantic store is intact, but the retrieval mechanisms are faulty (Jefferies & Lambon Ralph, 2006; Warrington & Cipolotti, 1996). The regions implicated in semantic control in SA patients include the prefrontal and temporoparietal regions. Damage can occur at any site within this network, with apparently similar consequences – degraded semantic control (see Chapter 4).

Deficits across semantic tasks have been reported in stroke aphasia patients. In particular, evidence has focused on verbal impairments, as these are perhaps the most obvious form of impairment in stroke aphasia patients. For example, sentence-to-picture matching performance is associated with the middle temporal gyrus (MTG), angular gyrus (BA39), and prefrontal regions, particularly BA 47 and 46 (Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004). Berthier (2001) also found both anterior and posterior regions to be implicated in picture naming, digit span and sentence completion. Schwartz et al. (2009) tested naming and comprehension in stroke patients (using both pictures and word associations). They found semantic errors during picture naming were associated with lesions to pMTG and the prefrontal cortex (BA 45 and 46; see also Mirman, 2011). Picture naming abilities were significantly correlated with other tests of verbal and non-verbal comprehension. Cacciari et al. (2006) found that stroke patients who performed poorest on an figurative meaning task had damage to lateral prefrontal and/or temporoparietal regions, producing semantic association errors (see also Schwartz et al., 2011). Those with focal damage to medial prefrontal, temporal or motor regions did not show deficits on this task. While this work has focussed on verbal impairments, which are perhaps the most obvious difficulties in stroke aphasia, evidence suggests that there may be parallel comprehension deficits for both verbal and non-verbal items in these patients. For example, Chertkow et al. (1997) studied a group of patients with posterior damage after a left hemisphere middle cerebral artery infarction. They found all patients with posterior temporal lobe damage showed impairment on a non-verbal, picture-picture association task (e.g., matching a LEMON with either a TEA CUP or COFFEE CUP), which was also reflected in low performance on a non-verbal, non-semantic task (Raven's Coloured Progressive Matrices, RCPM; Raven, 1962). Those who did not show impairment on these tasks had damage which was more focal and posterior to the semantic control network, centring at the parietal-occipital sulcus. Saygin et al. (2003) found deficits in a word-picture or sound-picture matching task with a strongly related distractor (in comparison to an unrelated distractor). Deficits were found to correlate across the word and sound modalities. Low performance was associated with damage to posterior temporal regions – particularly posterior superior gyrus (pSTG) and posterior middle gyrus (pMTG).

Anterior vs. posterior lesions

SA patients have damage to left hemisphere prefrontal and/or temporoparietal areas. Damage to either brain region appears to produce similar neuropsychological profiles, although many studies have put these two subgroups together in statistical analyses, and lesion comparisons have included relatively few patients to date (Corbett, Jefferies, Ehsan, et al., 2009; Corbett, et al., 2011; Jefferies & Lambon Ralph, 2006; Jefferies, Patterson, et al., 2008; Noonan, et al., 2010). Chapters 2 and 4 add to this evidence. Other groups, however, have found that patients with transcortical sensory aphasia (like some of our SA cases) can have anterior or posterior lesions, and again reported similar comprehension impairments in these two groups (Berthier, 2001).

Although central to this theme is the role of individual semantic control regions and distinctions between stroke patients, there is ongoing debate about whether the pMTG is involved in control at all. This is because semantic knowledge is thought to be stored throughout the cortex, in a distributed architecture of knowledge (Martin, 2007). This is discussed later, in the section on pMTG. Nonetheless, it is currently unclear whether posterior patients show effects of semantic storage variables which are comparable to that seen in SD patients, particularly of a certain category e.g., tools and actions; *as well as* impairments on semantic control tasks (see Chapter 4). Therefore, the role of the pMTG in semantic cognition remains controversial.

The semantic control network

Although SA patients often have large lesions, neuroimaging studies have isolated specific regions of this frontoparietal network which are implicated in semantic control, rather than language or semantic tasks per se, adding support to the idea that SA patients have disrupted retrieval/ selection mechanisms which are predictably related to control demands. One left prefrontal region, the inferior frontal gyrus (LIFG) and two left posterior regions, the posterior middle temporal gyrus (pMTG) and dorsal angular gyrus (dAG) overlapping with IPS, are particularly associated with controlled retrieval in fMRI studies, which maps directly onto areas of damage in SA patients (Noonan, et al., submitted). There are also other regions implicated in semantic control in Noonan et al.'s meta-analysis, including RIFG, more medial prefrontal regions (pre-SMA/anterior cingulate) and mid angular gyrus (mid-AG). Several of these sites are implicated in domain-general control (medial PFC, posterior LIFG, and IPS), and other appear specific to semantic control (pMTG, anterior LIFG and mid-AG).

Left inferior frontal gyrus (LIFG)

The more demanding a semantic task, the more activation in the BA 44, 45, and 47 of LIFG (Desai, Conant, Waldron, & Binder, 2006; Roskies, Fiez, Balota, Raichle, & Petersen, 2001; Sabsevitz, Medler, Seidenberg, & Binder, 2005; Ullsperger & von Cramon, 2001). Less demanding semantic tasks (e.g., verifying word associations) show little or no LIFG activation (Martin, Wiggs, Ungerleider, & Haxby, 1996; Wise et al., 1991). Task demands can be increased in two fundamental ways: (1) by increasing the retrieval demands, for example, recovering weakly associated relationships, and (2) by increasing the selection demands, through manipulating the element of semantic knowledge which is required to be used in a particular task, for example, matching the colour of previously activated items, such as BEETROOT with BLOOD. Badre et al. (2005) describe a two-step model of semantic control: (i) initial controlled retrieval, and (ii) post-retrieval selection. They suggest that anterior prefrontal cortex (BA 47) and posterior middle temporal gyrus (BA 21) are critical for initial retrieval, whilst the posterior prefrontal cortex alone (BA 44/45) is involved in post-retrieval selection. Several studies have aimed to distinguish selection from retrieval, in order to discover the precise role of the LIFG.

LIFG is widely believed to play a role in selection between competing alternatives (Badre, et al., 2005; Bedny, Hulbert, & Thompson-Schill, 2007; Nagel, Schumacher, Goebel, & D'Esposito, 2008; Robinson, Shallice, Bozzali, & Cipolotti, 2010; Robinson, Shallice, & Cipolotti, 2010; Wagner, Maril, Bjork, & Schacter, 2001). For example, Thompson-Schill et al. (1997; 1999) showed that the BOLD response increased with higher selection demands, when retrieval demands were purportedly held constant or reduced (but see Snyder et al., 2010). This was found in a feature selection task, where selection of task-relevant information is required. Participants were required to select an associated item by matching its colour (e.g., BEETROOT with BLOOD), which involves initial retrieval of the meaning of the probe, target and distractors, before selecting the feature ‘colour’ (Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997). In contrast, when comparing items on their global properties (e.g., RAISIN and PRUNE), no post-retrieval selection is necessary. In the same experiment, when shown a word (e.g., APPLE), participants were asked to generate an associated colour or action in response to that word. They were then presented with the same item again and asked to select a different feature (reducing retrieval demands but increasing selection demands). LIFG activated increased even though the concept had already been retrieved, which supports the evidence for a selection role of LIFG. Repetition without the selection component increases the dominance of the target response over distractors, and also decreases LIFG activation (Demb et al., 1995; Raichle et al., 1994). Moss et al. (2005) used what they considered to be an automatic retrieval task (picture naming), and found that competitor priming - which should increase selection demands - also increased IFG activation. However, LIFG also shows activation on tasks which have low selection demands, such as generating a verb from a concrete noun (Martin & Cheng, 2006), suggesting the LIFG has a role to play in both aspects of semantic control (Raichle, et al., 1994; Wise, et al., 1991).

SA patients show deficits on both semantic and executive tasks that are correlated, suggesting that there are shared properties of semantic and executive control tasks. Difficult semantic tasks will recruit domain-general control regions, including posterior/dorsal parts of LIFG. Indeed, fMRI studies have shown overlap between regions of the LIFG involved in semantic and non-semantic tasks (Dosenbach, Fair, Cohen, Schlagger, & Petersen, 2008; Duncan, 2006, 2010; Duncan & Owen, 2000; Nagel, et al., 2008; Wager, 2004; Wagner, Paré-

Blagoev, Clark, & Poldrack, 2001). For example, Devlin et al. (2003) found common areas of activation in a task involving a semantic decision (e.g., ‘is it manmade?’) and a phonological decision (e.g., ‘are there two syllables?’). The LIFG is associated with language production, particularly in demanding contexts with lexical or semantic competitors (Schnur, Lee, Coslett, Schwartz, & Thompson-Schill, 2005); but it is involved beyond language production (Hagoort, 2005; Thompson-Schill, 2003), in particular during semantic memory retrieval (Badre, et al., 2005; Thompson-Schill, et al., 1997). Broca’s area also shows activation during visual target search (Fink et al., 2006), action recognition (Hamzei et al., 2003) and face recognition tasks (Rajah, Ames, & D'Esposito, 2008).

Nonetheless, there are thought to be regions of the LIFG, particularly the anterior region, which are specialized for semantics. Gold and Buckner (2002) used both a non-semantic task, involving deciding whether words/pseudowords were short or long vowel items, and a semantic task, which required decisions about whether a word was abstract or concrete. Findings suggest similar regions of activation for phonological and semantic decisions, with stronger activation during controlled semantic decisions. Additionally, certain regions are dissociable, with anterior portions activating during semantic decisions, and posterior LIFG specialised for phonological control (see also Poldrack et al., 1999).

Research has found converging evidence for a role of the LIFG in control from both patient and neuroscientific experiments. Hoffman et al. (2010) showed impaired comprehension of abstract words without a contextual cue, in both SA patients and those with rTMS to LIFG (see also Robinson, Shallice, Bozzali, et al., 2010). Campanella et al. (2012) studied a single patient following the resection of a left frontal glioma, and showed more errors with distantly related items (compared to closely related items), inconsistency of concept retrieval, but no effect of frequency. This difficulty extends to homonyms which are words with multiple meanings according to context (Bedny, et al., 2007). Thompson-Schill et al. (1998) have shown that focal inferior prefrontal damage can affect the ability to generate verbs for nouns, but only in ‘high selection’ conditions. They found patients with LIFG damage were impaired at word generation tasks which are executively demanding, generating a verb for the noun CAT (high demand) compared to the noun SCISSORS (low demand; but see Martin & Cheng, 2006). Generating sentences when the stimulus has multiple conceptual propositions that compete for selection are impaired in frontal patients (Robinson, Shallice, & Cipolotti, 2005). Martin and others have argued that impairment on high “selection” tasks may in fact reflect weak association strength between cues and targets (Martin & Cheng, 2006; Wagner, Paré-Blagoev, et al., 2001). Martin and Cheng (2006) manipulated both selection and retrieval, by having a ratio of first to second verb frequency greater than 4 (low selection), or less than 2 (high selection); and having and association strength of < .2 (high selection, low association), and association strength of > .28 (high selection, high association). They found no difference between the two selection conditions, but a strong effect of association strength. They suggest that strategic retrieval is required for low association conditions, but automatic for high association conditions (Badre & Wagner, 2002; Martin & Byrne, 2006; Snyder & Munakata, 2008). Although patients often have a lesion encompassing much of the inferior prefrontal region making subtle distinctions within this region challenging, it seems clear from this data that the LIFG plays a crucial role in controlled retrieval and/or selection (potentially in combination with dorsolateral and medial PFC).

Right inferior frontal gyrus (RIFG)

As well as the LIFG, the right IFG has shown to be consistently activated by semantic tasks (Noonan, et al., submitted; Vigneau et al., 2011), including many neuroimaging studies employing contrasts tapping semantic control (Badre, et al., 2005; Snyder, Banich, & Munakata, 2011; Thompson-Schill, et al., 1997; Wagner, Paré-Blagoev, et al., 2001). However, little research has explored the role of the right hemisphere in semantic control (see Chapter 5). Nonetheless, in terms of domain-general executive control, the right prefrontal cortex plays a key role. A bilateral domain general control network has been described in detail, highlighting the bilateral fronto-parietal loop as crucial for a number of executively demanding tasks (Dumontheil, Thompson, & Duncan, 2011; Duncan, 2006, 2010; Duncan & Owen, 2000; Woolgar, Hampshire, Thompson, & Duncan, 2011).

The RIFG has also been linked to a particular aspect of executive control – inhibition (Aron, Robbins, & Poldrack, 2004; Chikazoe, Konishi, Asari, Jimura, & Miyashita, 2007; Lenartowicz, Verbruggen, Logan, & Poldrack, 2011). Inhibition is required for task eligible but incorrect items. Milham et al. (2001) devised a Stroop task which involved the traditional conflict of ink colour and written colour, with participants having to name the ink colour and ignore the written colour word. Additionally, they studied the effect of adding written colours which were never ink colours ("ineligible"). This condition did not activate RH regions of the prefrontal cortex, although homologue LH regions showed similar activation for both "eligible" and "ineligible" conditions. This suggests that the RH is recruited in response to "higher-level" or relevant conflicts, when an automatic behaviour in the context needs to be overridden. Similarly in a "go no-go" task, where participants have to press a button when presented with one stimulus, but withhold this behaviour after presentation of another stimulus, the RIFG is crucial in the "no-go" inhibition trials. Recruitment of this area is seen in more complex versions of the task, such as when the subject has to remember a sequence presentation of the stimulus (e.g. "X-Y-X-Y"), and inhibit responding to previously relevant items (e.g. "X-Y-Y-X") which requires a high degree of inhibitory control (Garavan, Ross, & Stein, 1999). Importantly, the regions of the RH associated with the go no-go task (the inferior frontal gyrus, middle frontal gyrus, insula and inferior parietal lobe), are also activated for other "inhibitory" tasks, such as the Wisconsin Card Sorting Test, WCST(Stuss, et al., 2000), which requires sorting cards according to one criteria (e.g. colour of the card), and shifting this sorting according to another criteria (e.g. number of items on the card) without being explicitly told the sorting rule (Konishi et al., 1999).

An alternative view to either the bilateral control network, or the role of the RH in inhibition, is that the RIFG is recruited when LIFG is insufficient. According to this view, there is no strong functional division - at least for manipulations of semantic control demands - since selection and inhibition are two sides of the same coin (Simmonds & Mostofsky, 2008), and inhibition requires selecting the appropriate item, and correct selection requires inhibiting inappropriate items. Indeed, the role of RIFG has been further investigated to clarify whether this region is involved in motor response inhibition per se, or whether it is involved in responding to cues, which requires some aspects of inhibition/ selection (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010; Hampshire, Thompson, Duncan, & Owen, 2009). Hampshire et al. (2010) presented multiple arrows, most of which were left or right. Occasionally, an up arrow appeared, which formed a cue for an additional behaviour. During the COUNT condition, participants counted the total number of up arrows; the RESPOND condition required responding with the preceding arrow (either left or right); in the INHIBIT condition, participants were required to respond to all left and right arrows, but withhold responding whenever an up arrow occurred. The researchers found activation in the bilateral frontoparietal network to all conditions. Additionally, it was the right *parietal* cortex which showed the greatest activation to the INHIBIT condition; while the RIFG, like the LIFG, was recruited most during the RESPOND condition, but also showed activation to the INHIBIT condition, and some activation to the COUNT condition. Authors suggest that inhibition tasks are confounded with the detection of the cue to stop responding (target detection). It may be target detection in general, rather than inhibition, which is related to activity within RIFG (which is why it activated during the RESPOND condition). However, it is involved in switching attention between objects which are more dissimilar (Hampshire, Thompson, Duncan, & Owen, 2008), and these results could be interpreted as requiring ‘inhibition’, as the RESPOND condition required inhibiting the current arrow direction (up) and reporting the previous arrow direction, like an n-back task.

If the RH is involved in task switching, be that through oriented attention or inhibition of a previous response (which may be related), one would expect patients with damage to this brain region to show impairments of both semantic and non-semantic executive tasks that involve task switching. Evidence from patient data has supported the fMRI claims that the right hemisphere is related to tasks involving inhibition and switching. Aron et al. (2003) studied reaction times in go no-go tasks, in particular how long it took a participant to stop after a signal. They found that volume of lesion damage to the right inferior frontal cortex directly correlated with time taken to stop after a signal ($r = .83$). Additionally, “switching” tasks such as the WCST also showed correlation with RIFC damage (Aron, et al., 2004). Therefore, the RIFG does appear to have a different role to LIFG in executive control.

Posterior middle temporal gyrus (pMTG)

Semantic control studies showing the LIFG involvement in semantic control have commonly found a second peak of activation in the pMTG (Badre & Wagner, 2007; Noonan, et al., submitted; Thompson-Schill, et al., 1997). This activation follows the same pattern as the LIFG, and is influenced by association strength and number of targets (Badre, et al., 2005; Thompson-Schill, et al., 1997; Wagner, Maril, et al., 2001), plus ambiguity (Bedny, McGill, & Thompson-Schill, 2008; Gennari, MacDonald, Postle, & Seidenberg, 2007; Rodd, Davis, & Johnsrude, 2005; Snijders et al., 2009; Whitney, Grossman, & Kircher, 2009). Both pMTG and LIFG show a smaller response when the dominant meaning of a homonym is probed, compared with a less frequent alternative (Copland, de Zubicaray, McMahon, & Eastburn, 2007; Copland et al., 2003; Grindrod, Bilenko, Myers, & Blumstein, 2008; Zempleni, Renken, Hoeks, Hoogduin, & Stowe, 2007). pMTG is also influenced by depth of meaning processing – activating more with meaning processing of words in relation to syllable judgements (Price, Moore, Humphreys, & Wise, 1997). A TMS study (Whitney, et al., 2012) found that selective TMS to the pMTG had a negative effect on reaction time to a semantic task involving weak semantic association pairing. This effect was indistinguishable from TMS over LIFG, and did not have any effect on decisions which were not executively demanding (pairing words which had a strong association).

Although much of LIFG is domain general, the anterior LIFG (BA 47; aLIFG) has been shown to activate during semantic tasks (Devlin, et al., 2003; Gold & Buckner, 2002). The pMTG shows the same pattern as aLIFG. These regions do not activate during non-semantic tasks, suggesting a circumscribed role in semantic processing and semantic control (Noonan, et al., submitted). Whitney et al. (2011) used rTMS to pMTG and aLIFG, and found disruption only for semantic control tasks. A non-semantic control task involved matching a local letter (embedded within a different global letter shape) with a probe letter (the Navon task). This was not impaired after rTMS to pMTG. The pMTG seems to play a role in semantic control which does not translate to other domains (Dosenbach, et al., 2008; Duncan, 2006, 2010; Nagel, et al., 2008).

As mentioned previously, Badre et al.’s (2005) two-step model of semantic control involves (i) initial controlled retrieval, and (ii) post-retrieval selection. These authors suggest the pMTG is only involved in retrieval, rather than selection. In agreement with Badre et al.’s model, the temporoparietal (TP) region is sensitive to repetition of stimuli, suggesting a role in initial retrieval of previously learnt items which is reduced after retrieval has already occurred. Jiang and colleagues (2000) examined the effect of repetition in a neuroimaging study, for both targets and distractors. Participants were given a target face to remember, and then viewed many different faces rapidly and in succession. Their task was to press a button when they saw the target. Both the target and distractors repeated. They found that RIFG and insular regions were activated with the presentation of a target face, regardless of how many times it had been presented. In contrast, extrastriate regions extending to temporoparietal cortex were associated with stimulus repetition, with activation decreasing over repetitions regardless of whether the stimulus was a target or distractor.

It would be expected that areas associated with initial retrieval activate more for ambiguous words, because both/all meanings of the word are retrieved. Whitney et al. (2011) used relatedness judgement task on the last word of a triplet, participants were asked whether the last word related to any of the preceding items. This was either related to a single meaning of the item (e.g., LION-STRIPE-TIGER), or in an ambiguous condition, related to two different concepts of a homonym (e.g., GAME-DANCE-BALL). There were either two primes, or a single prime (being the dominant or subordinate meaning of the homonym) presented with an unrelated word. When two meanings of a homonym were activated (e.g., GAME-BALL-DANCE) in comparison to a single prime (e.g., BREAD-DANCE-BALL), only left mid-ITG (BA 20) showed activation. This was also true in the non-ambiguous double prime condition (e.g., LION-STRIPE-TIGER). A subordinate, in relation to dominant meaning of a single prime increased activation in prefrontal (BA 44, 45, 47) and pMTG regions. This suggests that pMTG activation is related to the semantic control demands of the task, rather than retrieval demands per se.

As well as literature on semantic control, both advocates of the ‘hub and spoke’ theory, and the ‘distributed only’ view suggest the pMTG is involved in semantic representations of tools and actions, as a ‘spoke’ (Patterson, et al., 2007). For example, distortion-corrected fMRI has shown paired pMTG and ATL activation during amodal semantic processing, suggesting they are strongly connected, and may reflect shared representational processing (de Zubicaray, Rose, & McMahon, 2011; Visser, Embleton, et al., 2012). Although the motor representations for tools actions are thought to be stored in a more dorsal region, largely centering on the parietal cortex (Johnson-Frey, 2004), ‘action semantics’ is thought to focus on the pMTG (Chao, Haxby, & Martin, 1999; Kellenbach, Brett, & Patterson, 2003; Martin, Haxby, Lalonde, Wiggs, & Ungerleider, 1995; Martin, et al., 1996). For example, using voxel-based lesion-symptom mapping of 43 stroke patients, damage to pMTG and not LIFG was predictive of performance on a recognition task, matching a written word (e.g., HAMMERING), to a video corresponding to that word (Kalenine, Buxbaum, & Coslett, 2010). However, this study, and many others, did not use a non-tool control task, so activation may simply reflect semantic retrieval which may also be evident for demanding non-tool items.

fMRI activity has been found pMTG activation to be greater for pictures of actions (a person sawing) compared to the object alone (SAW), as well as being more active for noun-verb homonyms like HAMMER and COMB compared to pure object words (Chao, et al., 1999; Gennari, et al., 2007; Kable, Kan, Wilson, Thompson-Schill, & Chatterjee, 2005; Tranel, Martin, Damasio, Grabowski, & Hichwa, 2005). However, although the area is dwarfed by studies of retrieval of tools, animal retrieval has also been found to activate the pMTG (Martin & Chao, 2001). Additionally, it is not always the temporal lobe which appears necessary to functional knowledge (Goldberg & Spatt, 2009; Pelgrims, Olivier, & Andres, 2011), and a wide range of cortical regions have been implicated in tool knowledge, particularly inferior frontal regions and superior parietal lobe (Lewis, 2006). Thus, it remains unclear whether activation of the pMTG is associated with representation of tools, or whether it is simply because 'tool' tasks tend to be more semantically demanding – e.g., involving videos or pantomiming gestures.

A number of studies have detected semantic comprehension deficits resulting from posterior cortical damage. Hart & Gordon (1990) found comprehension problems were connected with damage to specific temporal and parietal areas (see also Bates et al., 2003; Binder, Desai, Graves, & Conant, 2009; Chertkow, et al., 1997; Dronkers, et al., 2004; Hickok & Poeppel, 2004, 2007). However, this pMTG region which has been labelled a 'spoke' appears to be similar to that suggested to be involved in semantic control (Hoffman, Pobric, Drakesmith, & Lambon Ralph, 2011; Whitney, Kirk, O'Sullivan, Lambon Ralph, & Jefferies, 2011).

However, other authors have suggested a different role for this region in semantic processing. Some authors (Hickok & Poeppel, 2004, 2007; Indefrey & Levelt, 2004; Turken & Dronkers, 2011) suggest that the pMTG provides a lexical interface between words and meanings, mapping between phonological forms of words which are processed in Wernicke's area, and semantic knowledge which is distributed in the temporal lobe. However, it is important to note that pMTG involvement has been found for entirely non-verbal picture tasks (Hoffman, Pobric, et al., 2011; Kable, Lease-Spellmeyer, & Chatterjee, 2002; Kellenbach, et al., 2003), and many (e.g., Saygin, et al., 2003) have found overlapping areas involved in verbal and non-verbal comprehension in temporal and parietal regions (see also Lewis et al., 2004; Martin, 2007). pMTG is involved in semantic judgements for non-verbal items, such as actions relating to pictured objects (Kellenbach, et al., 2003), and in word and picture semantic association tasks (Hoffman, Pobric, et al., 2011; Visser, Jefferies, et al., 2012).

Turken and Dronkers (2011) suggest that the pMTG's interaction with LIFG allows sustained short-term memory representations, to integrate contextual meaning (see also Lerner, Honey, Silbert, & Hasson, 2011). This may be why the pMTG region is vital for both tool representations and semantic control, given tool use is context dependent and requires an online interaction between the tool, the subject, and motor responses (Jefferies, in press). Evidence suggests this region has rich connections with other temporal, frontal, parietal and occipital regions (Turken & Dronkers, 2011). BA 47 is engaged only when successful performance depends on the ability to keep track of several pieces of information and to resolve between the alternative interpretations of sentence components. This could be achieved by reciprocal interactions between BA 47 and the MTG, so that the appropriate lexical-semantic representations can be selected, sustained in short-term memory throughout sentence processing, and integrated into the overall context.

Dorsal angular gyrus (dAG)/IPS boundary

Another small site of activation found during semantic control tasks is the dorsal angular gyrus (dAG), bordering and potentially extending into the IPS (Binder, et al., 2009; Devlin, et al., 2003; Mummery, Patterson, Hodges, & Price, 1998; Seghier, Fagan, & Price, 2010). This activation encompasses many elements of semantic processing, including plausibility processing (Mashal, Faust, Hendler, & Jung-Beeman, 2009), sentence processing (Obleser & Kotz, 2009), and word triad tasks (Simmons, Miller, Feinstein, Goldberg, & Paulus, 2005). Additionally, areas of the parietal lobe, including the dAG, also show activation on a broad range of executive control tasks, such as go/no-go response inhibition (Menon, Adleman, White, Glover, & Reiss, 2001), Stroop tasks (Marek et al., 2010) and flanker tasks (Hazeltine, Bunge, Scanlon, & Gabrieli, 2003; see also Seghier, et al., 2010; Whitney, et al., 2012; Woolgar, et al., 2011). This is unlike other areas of the semantic control network, which show specificity to semantics. This has led to the conclusion that a network encompassing the fronto-parietal regions are involved in executive control (Collette, Hogge, Salmon, & Van der Linden, 2006; Duncan, 2010; Gold & Buckner, 2002). Evidence comes from rTMS, which shows disruption to IPS leads to a different pattern of behaviour to disruption to pMTG or aLIFG – rTMS reduces performance on a non-semantic Navon task, as well as semantic control of a specific task which requires orienting to a semantic feature (Whitney, et al., 2012). Evidence suggests that this brain region is critical for tasks involving *feature selection* (e.g., colour – matching BLOOD with BEETROOT), and not necessary for global semantic associations (Whitney, et al., 2012), which may not require orientation of attention to a specific semantic feature to the same degree. Both of these tasks have a common feature - that of orienting attention to the task appropriate aspect of an item. Indeed, orienting attention to a semantic category activates the same region which is involved in attention to particular semantic features or spatial locations (Cristescu, Devlin, & Nobre, 2006; Cristescu & Nobre, 2008; Woolgar, et al., 2011). This suggests the dAG is involved in allocating attention to internal and external representations beyond the semantic domain.

Research themes

Theme 1: The multimodal nature of semantic aphasia

‘Access’ and SA patients seem to show similar patterns of behaviour on a number of semantic tasks, but because they have been studied by different groups of researchers, it is useful to consider to what extent ‘access’ and SA patients overlap. This is because it may be the case that one theory can describe both patients’ behavioural characteristics. A defining feature of ‘access’ patients is that they show refractory effects in the verbal modality. Jefferies et al. (2007) showed that SA patients show refractory effects in verbal tasks (like ‘access’ patients, Warrington & McCarthy, 1983). However, ‘access’ patients do not show multimodal deficits – a defining feature of SA. According to the amodal hub theory, an amodal semantic store is interacting with an amodal executive control network (Jefferies & Lambon Ralph, 2006), with there being no reason why one modality would be more affected than another with regards semantic control.

The hypothesis tested in this thesis is that SA patients have an intact semantic store, but impaired semantic control processes and mechanisms associated with task-specific retrieval and selection. The cyclical matching task was tested across spoken-verbal, visual and non-verbal auditory domains to see if SA cases would show parallel refractory effects across these different input modalities.

Theme 2: An input processing deficit leading to reduced semantic control in a single modality

'Access' patients show refractory deficits only for verbal materials (Crutch & Warrington, 2008b; Warrington & Crutch, 2004), and this appears to pose a problem for Jefferies and Lambon Ralph's (2006) theory of a multimodal control network, and in particular, the way this theory was extended to explain refractory effects in SA. If refractory effects are linked to domain-general executive dysfunction (and/or disruption of amodal semantic control processes), as in SA, these effects would not be expected to be specific to verbal information.

How might we account for refractory effects restricted to the spoken word domain, as in the classic 'access' pattern? The possibility described in Chapter 3 is one of an amodal semantic control deficit which is paired with an input processing deficit. If this was the case, we would expect deficits in all modalities when the task is demanding enough. Additionally, performance on all auditory tasks (semantic and non-semantic) would be severely impaired in relation to other modalities. 'Noisy' auditory input could lead to error-prone activation of amodal concepts in ATL, not associated with executive control deficits, but restricted to the auditory domain. It is not disputed that it is possible to have damage limited to the input of speech (e.g., pure word deafness), with isolated impairment of speech discrimination despite good hearing ability and preserved functioning in other domains of language, usually occurring from bilateral superior temporal lobe damage (Badecker, 2005; Slevc, Martin, Hamilton, & Joanisse, 2011; Stefanatos, Gershkoff, & Madigan, 2005). This is supported by neuroimaging studies, which have shown activation in superior temporal cortex when subjects are presented with speech sounds in contrast to no sounds (Binder et al., 1994; Howard et al., 1992; Price et al., 1996; Wise, et al., 1991). Additionally, STS regions activate for non-word conditions - such as pseudo-words, syllables or reversed speech (Benson et al., 2001; Binder et al., 1999; Binder et al., 2000; Demonet et al., 1992; Demonet, Price, Wise, & Frackowiak, 1994; Hirano et al., 1997; Wise, et al., 1991). It may be that poor input to STS can usually be compensated for by executive control, so the effects of mild damage to both (input and control) would be multiplicative. This would lead to deficits in semantic control across domains, with an accentuated semantic control deficit in the verbal domain. The distributed semantic control network is thought to include the LIFG, pMTG and dAG. The pMTG is adjacent to the auditory association cortex, and so if patients have a lesion involving pMTG, it is likely that this will have also affected auditory cortex, leading to deficits which are more pronounced in the auditory domain (Howard, et al., 1992; Knight, Scabini, Woods, & Clayworth, 1989; Scott, Blank, Rosen, & Wise, 2000).

We analysed an individual patient, DNe, who showed refractory effects in the spoken-verbal but not in non-verbal domains – either picture-picture matching, sound-picture matching or written words-picture matching (Experiment 2). He showed the same pattern as ‘access’ patient AZ (Warrington & Crutch, 2004). Therefore, we were interested in testing whether he showed any impairment on executive control tasks, or difficulties in ‘high’ in relation to ‘low’ control demanding tasks. We tested the hypothesis that DNe had a mild semantic control impairment across modalities, paired with an input processing deficit for the auditory domain by assessing his semantic control performance on a range of tasks across modalities.

Theme 3: Multimodal control deficits in patients with anterior or posterior lesions

SA patients can have damage to prefrontal regions which often also extend posteriorly (PF+) or temporoparietal regions (TP-only). However, patients with these two lesion types have for the large part been studied in a group together, for two reasons. Firstly, neuronal damage after stroke is often broad and affects both prefrontal and temporoparietal regions, as these regions are both supplied by the middle cerebral artery, and either a clot or haemorrhage which alters normal blood flow in the temporoparietal region often also affects flow to prefrontal regions. Secondly, when patients are recruited on the basis of detailed neuropsychological testing, sample sizes are typically low (voxel-based lesion-symptom mapping studies can account for a single behaviour/ group of behaviours with large samples sizes, such as in Baldo, Schwartz, Wilkins, & Dronkers, 2006; Robinson, Shallice, Bozzali, et al., 2010; Schwartz, et al., 2009). Stroke patients with PF+ or TP-only lesions show no notable differences on a range of semantic tasks (Berthier, 2001). For example, there is equal impairment on semantic tasks such as the Pyramids and Palms test (PPT), item naming or word-picture matching, Camel and Cactus tasks (CCT) in word and picture modalities, and category fluency (see background assessments in Jefferies, et al., 2007; Jefferies & Lambon Ralph, 2006; Jefferies, Patterson, et al., 2008). Tasks which manipulate semantic control, for example by using distantly related words, also show similar control deficits for PF+ and TP-only patients (Corbett, Jefferies, & Lambon Ralph, 2009; Noonan, et al., 2010). Additionally, both lesion locations also show equal improvement to external constraints, such as cues (Jefferies, Patterson, et al., 2008).

However, despite many similarities, some differences have emerged. Prefrontal patients are nearly always less fluent than TP-only patients (Berthier, 2001). Additionally, several different authors (Campanella, Mondani, Skrap, & Shallice, 2009; Gardner et al., 2012; Jefferies, et al., 2007; Schnur et al., 2009) have found refractory effects correlating with lesion of the LIFG, but reduced or non-existent refractory effects in TP-only patients. That is to say, although TP-only patients showed reduced accuracy to the same degree as PF+ patients on the first cycle, they are unaffected by the repetition of stimuli, and do not worsen over time. This suggests that the temporoparietal region is less involved in the re-selection of targets, following their inhibition as distractors, as required for this required for this refractory task.

Chapter 4 will describe the similarities and differences between patients, and pull apart three main hypotheses which explain the differences in patient performance. (1) Firstly, *the temporoparietal region may be involved to a lesser extent in all aspects of semantic control* – with an equivalent function. This is a plausible hypothesis given fMRI data, which shows higher peaks and broader spread of activation in the LIFG compared to the temporoparietal region, across studies which publish whole brain analyses (see Noonan, et al., submitted). It is possible, however, that this may be caused by a reporting bias, with many researchers focusing on prefrontal regions in relation to control – for example, through the use of region of interest analyses that target LIFG but not pMTG (Badre & D'Esposito, 2007; Thompson-Schill, et al., 1997). (2) A second hypothesis is that the *temporoparietal region is specifically important for certain types of semantic items*. In particular, research focusing on “tools” has suggested the pMTG as a region involved in action semantics, mediating between primary visual motion regions and temporal semantic stores (see above). Often, categories are grouped together in reported patient performance, so it is impossible to tell TP-only patients have particular problems with certain items. However, while there are category effects within posterior temporal cortex in neuroimaging studies (Martin, et al., 2000; Martin, et al., 1996; Phillips, Humphreys, Noppeney, & Price, 2002; Wagner, Paré-Blagoev, et al., 2001), this theory does not anticipate sensitivity to semantic control demands in both prefrontal and TP-only cases. (3) The final theory, with the most evidence to support it, suggests that *the semantic network regions each play a different role in semantic control.* This would agree with Badre et al.’s (2005) two-step model of semantic control: initial retrieval of previously learnt items, with more retrieval demands on items with multiple meanings, followed by selection among activated and competing items is required to make task and context dependent decisions (see also Thompson-Schill, et al., 1997; Wagner, Maril, et al., 2001). The temporoparietal region is not thought crucial for "selection".

We will test these hypotheses by comparing TP-only, PF+ and SD patients' performance on range of semantic tasks, assessing item consistency, effects of increased semantic control demands, cross modal task performance, and picture naming errors. This will add to the comparison in Chapter 2 of refractory effects in PF+ and TP-only patients.

Theme 4: The semantic control network involving right hemisphere regions: a multimodal control deficit

Both domain-general executive control (Duncan, 2010) and semantic representations (Lambon Ralph & Patterson, 2008) occur bilaterally and amodally. However, semantic representations are thought to be more prominently stored in left ATL (Lambon Ralph, et al., 2001; Mummery et al., 2000; Visser, Jefferies, et al., 2010), and neuroimaging data on semantic control has found much greater activation in left compared to right control regions (Noonan, et al., submitted; Thompson-Schill, et al., 1997; Thompson-Schill, D'Esposito, & Kan, 1999; Wagner, Paré-Blagoev, et al., 2001). There are certain specialisations between the hemispheres (Snowden, Thompson, & Neary, 2004). Both hemispheres seem to show some degree of specialisation in both the nature of the semantic representations and what is being processed, and also the nature of the control processes (as mentioned above; Aron et al., 2004). Because of this, it is unclear whether: (1) a semantic control deficit like that seen in SA would occur with RH stroke to the same extent, (2) or whether a control deficit would occur with only certain stimuli which is stored in the right ATL, (3) or if no semantic control deficit would be found at all, given the LH is intact.

Processing differences

Despite the bilateral nature of semantic cognition, there are functional specialisations at all levels of processing. In terms of initial interpretation of sensory input, there is evidence that the RH is specialised for configural processing, that individual aspects of an item are not explicitly represented and are coded only to contribute to the overall picture (Farah, Wilson, Drain, & Tanaka, 1998; Murray, Yong, & Rhodes, 2000; Rossion & Gauthier, 2002; Wilkinson et al., 2009). Conversely, but to much less of an extent (Martinez et al., 1997), the LH is thought to be more analytical (Levy-Agresti & Sperry, 1968), with serial (Sergent, 1982) and local processing (Hubner & Studer, 2009; Robertson & Lamb, 1991; Schlosser, Hubner, & Studer, 2009; Van Kleeck, 1989). The visual-word form area (VWFA) is located in the left mid-fusiform (Cohen & Dehaene, 2004), and the fusiform face area (FFA) is in a virtually identical region in the RH – although this is marginally anterior to the VWFA (Gauthier, Skudlarski, Gore, & Anderson, 2000). Because of this processing specialisation, each hemisphere dominates processing of different stimuli (language or vision), though there is debate about whether these regions are specialised solely for words (Cohen & Dehaene, 2004; Price & Devlin, 2003) and faces (Bukach, Gauthier, & Tarr, 2006; Gauthier & Palmeri, 2002; Palmeri & Gauthier, 2004; Tarr & Gauthier, 2000), or instead relate to the type of processing required (Dien, 2009).

Prefrontal and temporoparietal regions are vulnerable to stroke in the RH as well as the left. This evidence suggests that there will be differences between LH and RH stroke cases in presemantic processing deficits. There may also be semantic control impairments which emerge differently between LH and RH stroke patients due to access impairments of semantic representations in the left and right ATL respectively.

Representational differences

Following from these processing specialisations, there is evidence for representational specialisations too, for: (1) pictures, and most notably, emotions (Haxby, Hoffman, & Gobbini, 2000; Kanwisher, McDermott, & Chun, 1997; Pitcher, Walsh, Yovel, & Duchaine, 2007); and (2) higher-level language processing, such as metaphors (Bottini et al., 1994; Jung-Beeman, 2005). Certain semantic tasks, such as the Camel and Cactus task in picture form (CCTp), are correlated with damage to the RH basal fusiform region within the ATL (Mion, et al., 2010). Snowden, Thompson and Neary (Snowden, et al., 2004) found that SD patients with greater RH atrophy were more impaired at recognising faces than names (see also Kriegeskorte, Formisano, Sorger, & Goebel, 2007; Lambon Ralph, et al., 2001). Different inputs to ATL might result in graded specialisation for the LH and RH (Damasio, 1989a).

Besides from literature on faces, a line of research explores the role of the RH in language. There is evidence that there is bilateral prefrontal activation for normal language processing (Vigneau, et al., 2011), with areas of the RIFG involved in semantic control (Noonan, et al., submitted) The RH clearly has capacity for language processing, as it has been shown to aid language recovery after LH damage (Cambier, Elghozi, Signoret, & Henin, 1983; Finger, Buckner, & Buckingham, 2003; Heiss, Kessler, Karbe, Fink, & Pawlik, 1993), and rTMS to both LIFG and RIFG disrupted verb-generation in LH tumour patients, but rTMS only affected controls on LIFG (Thiel et al., 2005; Winhuisen et al., 2005). This suggests that reorganisation of the language function is possible in slowly progressing conditions. Indeed, increased RH activation in the chronic phase of stroke suggests its involvement in functional reorganisation of language functions (Thulborn, Carpenter, & Just, 1999; van Oers et al., 2010; Weiller et al., 1995), with early activation thought to correspond to reduction of normal LH transcallosal inhibition (Price & Crinion, 2005), which may explain the limited role of the RH in healthy subjects. However, the phase of stroke recovery affects how successful the RH is in reorganisation. Saur et al. (2006) repeated fMRI language tasks with stroke patients, and found that in the acute phase (2 days post stroke), there was little activation of the normal language regions (or RH), while the sub-acute phase (12 days post stroke) showed swathes of activation in both LH and right Broca-homologue. There was also a strong correlation between improved language function and increased RH activation. In the chronic phase (a year post stroke), normalized activation occurred, with a shift back to LH regions, also correlated with language improvement. This change in function of the RH may reflect inconsistencies in the literature of the usefulness of this region post stroke (Naeser et al., 2005; Perani et al., 2003; Rosen et al., 2000). This also suggests that the RH is not well-optimised for language processing.

Indeed, in split-brain patients, the RH shows little functions of syntax and phonology (Bogen, 1997; Gazzaniga, 1983, 2000; Gazzaniga, Smylie, & Baynes, 1984; Sperry, 1982). fMRI shows the RH plays little role in simple access from words to meaning (Vigneau, et al., 2011), but bilateral activation is common for more demanding tasks, such as making semantic associations (Booth et al., 2002; Vingerhoets et al., 2003), categorization (Bright, et al., 2004), word generation (Kircher, Brammer, Tous, Williams, & McGuire, 2001) or selection (Wagner, Paré-Blagoev, et al., 2001), and sentence comprehension (Crinion, Lambon Ralph, Warburton, Howard, & Wise, 2003; Meyer, Steinhauer, Alter, Friederici, & Von Cramon, 2004). Peaks of activation in the RH are much weak are less frequently reported than in the LH (Vigneau, et al., 2011). This has led to a strong body of evidence which claims that the LH plays a more prominent role in language processing.

However, RH patients' problems can be thought of in two ways: (1) RH patients have a loss of knowledge about more distant semantic representations, and so have an impaired ability to comprehend metaphors, or (2) metaphors are distant, less literal, and more abstract – and metaphorical interpretations require more control. It is hard to separate these possibilities experimentally, but since, as noted above, neuroimaging studies have found *bilateral* activation (e.g., in IFG) for contrasts focussing on semantic control, RH cases could conceivably have damage to *executive* semantic processing, similar to that seen in SA cases with LH stroke. SA patients are highly sensitive to the degree to which conceptual processing is constrained by the task: they can access semantic information in circumstances that minimise the executive requirements, but not in more open-ended tasks. Therefore, in Chapter 5, we tested the hypothesis that RH patients might show a similar pattern: i.e., can understand metaphors when the executive demands of processing metaphorical interpretations are reduced. Indeed, patients with RH lesions have been shown to be inconsistent and highly sensitive to task demands: they performed more poorly than LH aphasics on a picture metaphor task, giving more literal responses (Winner & Gardner, 1977), but they were within the normal range for metaphor sentence comprehension, leading to the suggestion that patients are unable to identify the appropriate situation in which a specific expression is suitable (Brownell, Simpson, Bihrle, Potter, & Gardner, 1990; Foldi, Cicone, & Gardner, 1983; Myers, 1983; Rehak, Kaplan, & Gardner, 1992; Rinaldi, Marangolo, & Baldassarri, 2004; Zaidel, Kasher, Soroker, & Batori, 2002). Of course, it may be the case that there are different control demands for pictures and sentences with regards metaphors, as picture distractors are highly attractive as a very concrete way to capture some of the metaphoric expression, not found in word versions of the task.

The idea that the RH is involved in higher-order language comprehension is well documented (Beeman, 1998; Fersti, Neumann, Bogler, & Yves von Cramon, 2008; Tompkins, Fassbinder, Scharp, & Meigh, 2008; Vanhalle et al., 2000). Many studies, for example, have found presenting metaphors for comprehension in the right visual field (RVF, 'left hemisphere') compared with the left visual field (LVF, 'right hemisphere'), leads to an increased reaction time in comprehension (Anaki, Faust, & Kravetz, 1998; Faust & Mashal, 2007; Faust & Weisper, 2000; Schmidt, DeBuse, & Seger, 2007). RH involvement has also has been found in lexical ambiguity tasks, including comprehension of homonyms (Klepousniotou, 2002; Klepousniotou & Baum, 2005a, 2005b). Jung-Beeman (2005) proposed a 'coarse-coding' model of the RH, which suggests that all stages of semantic cognition (which he describes as activation, integration and selection) involve both hemispheres, but that "the hemispheres compute information differently, such that the RH performs relatively coarser semantic coding...The two hemispheres probably store similar representations, but differ in the way they dynamically access information." (p.513). The premise of the model is that the RH stores weak but diffuse representations of all semantic items, so that it is unnecessary for many tasks, but important for more unusual connections, for example, in metaphors. If it is the case that the RH stores these representations, then damage to RH 'control' mechanisms could produce deficits in language tasks (or non-verbal tasks) which require comprehension of distant or weakly related items, but only in high demand conditions.

Coarse coding occurs early (Gernsbacher, 1990; Kintsch, 1998), with irrelevant activation dampened down in a later phase of comprehension. For example, those with RH lesions and controls show the same degree of priming for close features e.g., APPLE with CRUNCHY, but not subordinate features e.g., APPLE with ROTTEN (Tompkins, et al., 2008). This has also been explained by a similar theory, the graded salience hypothesis (Giora, 1999, 2009), which suggests that the LH has privileged access to meanings stored in the lexicon of highly salient items. Salience is determined by "conventionality, frequency, familiarity, and prototypicality" rather than literality or context (Giora, Zaidel, Soroker, Batori, & Kasher, 2000). The RH is thought, therefore, to be involved in non-salient (or novel) meaning retrieval (Giora, 2007). Both the 'coarse coding' and 'graded salience' hypothesis suggest it is not necessarily the type of language process (such as metaphor comprehension), but the salience, or coarseness, of a meaning relating to a word or phrase.

fMRI evidence for the RH involvement in metaphors is a little less convincing than patient work. For example, Stringaris et al. demonstrated that metaphoric sentences (in comparison to literal sentences) show more LIFG activation – not RIFG (Stringaris et al., 2006), and often studies which find involvement of the RH in metaphor comprehension find either equivalent activation in both hemispheres (Lee & Dapretto, 2006; Rapp, Leube, Erb, Grodd, & Kircher, 2004), or the majority of activation in the LH for language tasks – even for non-literal language processing (Rapp, Erb, Grodd, Bartels, & Markert, 2011; Rapp, Leube, Erb, Grodd, &

Kircher, 2007; Rapp, Mutschler, & Erb, 2012). Few, however, find no activation located in the RH (Chen, Widick, & Chatterjee, 2008; Mashal & Faust, 2010). Many maintain that the RH is primarily an 'overflow' hemisphere, used only on particularly demanding tasks (Rapp, et al., 2004; Yang, Edens, Simpson, & Krawczyk, 2009). For example, a recent meta-analysis found only 3 of 16 clusters to be in the RH for comparisons of literal and non-literal stimuli (Rapp, et al., 2012), and novel metaphors compared to literal sentences revealed 9 clusters, 1 of which was RH. Both this, and a meta-analysis of semantic processing, revealed overall that around 1/3 of semantic activation is RH (Binder, et al., 2009).

Given the mixed evidence, it seems the RH may not be involved in conventional metaphors per se, but instead making new or unusual connections between words, such as in novel metaphors (Gold & Faust, 2010; Mashal & Faust, 2008; Pobric, Mashal, Faust, & Lavidor, 2008; Schmidt, et al., 2007), unexpected punch lines (Marinkovic et al., 2011) or making remote associations more generally (Gold, Faust, & Ben-Artzi, 2011). This may be due to familiar metaphors being stored in a similar way to familiar literal phrases, in the LH. We attempt to test the hypothesis that RH patients have deficits to semantic control mechanisms which interact with the RH store by adapting semantic control paradigms from SA patients.

In summary, there seems to be some evidence that the RH is involved in storing some aspects of higher-level language processing, particularly for non-salient items. Additionally, it has strong links to face and emotion processing and representation. Fronto-parietal networks within the RH, along with those in the LH, play a part in executive control. Therefore, it is plausible that RH damage will generate similar patterns of semantic control seen after LH damage. Damage to semantic 'control' regions in the RH will not damage the stored knowledge of faces or metaphors, but disrupt access to it in demanding conditions. In Chapter 5, we test the hypothesis that RH patients have a deficit of semantic control for items which are processed and stored in the RH. This means that face or metaphor tasks which are highly demanding (e.g., presenting target items with a prepotent distractors) are more difficult to retrieve and select, and so will result in lower performance than targets presented in a way which is less demanding (e.g., with unrelated distractors).

Thesis structure

Chapter 2 explores semantic aphasia (SA) patients on a task sensitive to poor semantic control, as opposed to a loss of semantic knowledge per se. SA patients show “refractory effects” – i.e., declining accuracy in cyclical word-picture matching tasks when semantically-related sets are presented rapidly and repeatedly. This is argued to follow from a build up of competition between targets and distractors. However, the link between poor semantic control and refractory effects is still controversial for two reasons. (1) Some theories propose that refractory effects are specific to verbal or auditory tasks, yet SA patients show poor control over semantic processing in both word and picture semantic tasks. (2) SA can result from lesions to either left prefrontal or temporoparietal cortex, yet previous work suggests that refractory effects are specifically linked to left inferior frontal cortex. Verbal, visual and non-verbal auditory refractory effects were explored in nine SA patients who had prefrontal (PF+) or temporoparietal (TP-only) lesions. We hypothesised that patients would have reduced control over *multimodal* semantic retrieval, leading to similar refractory effects in all modalities. Additionally, we hypothesised that those with prefrontal damage may have greater refractory effects, suggesting a functional specialisation within the posterior vs. prefrontal elements of the semantic control network.

Chapter 3 explores reports in the literature of patients with semantic ‘access’ problems restricted to verbal materials. These challenge the notion that semantic control processes are modality-general and suggest instead a separation of ‘access’ to verbal and non-verbal semantic systems. We had the rare opportunity to study a single case who showed refractory effects restricted to the verbal domain. We examined the effect of manipulations of control demands in verbal semantic, non-verbal semantic and non-semantic tasks, allowing us to assess the hypothesis that deficit semantic control/ ‘access’ impairment can follow a modality-specific pattern. We hypothesised that our patient had a mild domain general semantic impairment, paired with disrupted connectivity from auditory input, giving rise to ‘access’ semantic deficits seemingly affecting only the auditory domain.

Chapter 4 explores the neural underpinnings of executive control. SA patients have damage to prefrontal and/or temporoparietal regions. Contemporary accounts of semantic cognition frequently acknowledge a division in labour between semantic representations and higher level semantic control processes. However, many believe semantic representations are stored in the posterior areas, while semantic control is underpinned by prefrontal regions. Evidence from SA patients contradicts this claim, by suggesting that both prefrontal and temporoparietal regions make contributions to semantic control. Nonetheless, there is recent evidence to suggest the contributions these regions make to semantic control are different. Our aim was to compare for the first time SA patients with prefrontal damage (PF+) and those with temporoparietal damage (TP-only), in relation to semantic dementia (SD) patients. We hypothesised that PF+ and TP-only patients (in relation to SD patients) would show semantic control deficits in the following ways: (1) reduced item consistency when the task demands changed; (2) influence of task selective semantic retrieval and inhibitory processing; (3) attenuated effects of lexical frequency; and (4) evidence of poor semantic regulation in verbal output. We expected, however, that PF+ patients would show a greater effect of semantic control, given evidence that the prefrontal cortex is involved in more aspects of control than posterior regions (Badre et al., 2005).

Chapter 5 investigates the relationship between semantic control and the RH. The semantic control network involves three main regions of the LH (LIFG, pMTG, IPS/dAG), but a recent meta-analysis revealed strong activation in the RIFG in a number of semantic control studies. Research suggests a subtle specialisation between the hemispheres, with the RH showing more involvement in (i) higher-order language processing, particularly of non-salient or distant meanings; and (ii) face processing, particularly of emotions. We will explore the possibility that SA (LH cases) and RH cases have similar deficits of internal constraint. If this is found, this would be evidence that RH semantic control processes are impaired and the knowledge that these processes operate on is largely intact.

Chapter 6 will discuss the findings of this thesis.

2. CHAPTER TWO

The differential contributions of prefrontal and temporoparietal cortices to multimodal semantic control: Exploring refractory effects in semantic aphasia

Acknowledgements: Data collection was by Naomi Dodds, Theresa Jones and Sheeba Eshan. Stimuli in Experiment 1 were developed by Warrington and Crutch (2004), and those in Experiments 2 &3 by Naomi Dodds, Theresa Jones and Beth Jefferies.

Abstract

Aphasic patients with multimodal semantic impairment following prefrontal or temporoparietal damage (semantic aphasia – SA) have deficits characterized by poor control of semantic activation/retrieval, as opposed to loss of semantic knowledge per se. In line with this, SA patients show “refractory effects” – i.e., declining accuracy in cyclical word-picture matching tasks when semantically-related sets are presented rapidly and repeatedly. This is argued to follow a build up of competition between targets and distractors. However, some theories propose that refractory effects are specific to verbal or auditory tasks, yet SA patients show poor control over semantic processing in both word and picture semantic tasks. Secondly, SA can result from lesions to either left prefrontal or temporoparietal cortex, yet previous work suggests that refractory effects are specifically linked to left inferior frontal cortex. For the first time, verbal, visual and non-verbal auditory refractory effects were explored in nine SA patients who had prefrontal (PF+) or temporoparietal (TP-only) lesions. In all modalities, patient accuracy declined significantly over repetitions. This refractory effect at the group level was driven by the PF+ patients and was not shown by individuals with TP-only lesions. These findings support the theory that SA patients have reduced control over *multimodal* semantic retrieval and, additionally, suggest there may be functional specialisation within the posterior vs. prefrontal elements of the semantic control network.

Introduction

Semantic cognition involves the retrieval of information about the meanings of words, pictures, sounds and objects, and the application of this knowledge to a specific task or context. Evidence from patients suggests that semantic cognition can be impaired in at least three ways. First, patients may have degeneration of information within the semantic store itself, as in semantic dementia (SD; Hodges, et al., 1992b; Warrington, 1975). Secondly, patients may be unable to recognise an object in a specific modality (as in visual agnosia), due to damaged connectivity between the sensory input and the semantic store (Catani & Ffytche, 2005). Finally, patients may be unable to control activation within the semantic system such that it becomes harder for task-relevant aspects to be brought to the fore, as in semantic aphasia (SA; Jefferies & Lambon Ralph, 2006).

Both SD patients (Binney, et al., 2010; Bozeat, et al., 2000; Coccia, et al., 2004), and SA patients (Corbett, Jefferies, Ehsan, et al., 2009; Corbett, Jefferies, & Lambon Ralph, 2009; Jefferies & Lambon Ralph, 2006), show deficits across modalities, but in qualitatively different ways. SA patients do not appear to have damage to core semantic representations, unlike those with SD. In particular, this has been shown in a 'refractory' effect – their accuracy in word-picture matching declines when a small set of semantically-related items is presented repeatedly and rapidly over a number of cycles (Jefferies, et al., 2007). Refractory tasks are likely to produce a build-up of competition across cycles because the items in the set are both targets and distractors on different trials, and so the participant has to choose the target among highly activated and related distractors (see also Schnur, Schwartz, Brecher, & Hodgson, 2006).

Research by several other groups has suggested that the semantic storage deficit in SD can be contrasted with a 'semantic access' disorder observed in some stroke/tumour cases (Forde & Humphreys, 1995; Warrington & Cipolotti, 1996; Warrington & McCarthy, 1983; Warrington & Shallice, 1979). Unlike SD cases (but similar to SA patients), 'access' patients show inconsistent performance when semantic tests are repeated and they exhibit refractory effects. This refractory pattern is typically accompanied by strong cueing effects and insensitivity to item frequency – symptoms which again differentiate access patients from SD. Jefferies et al. (2007) examined the possibility that 'semantic access' disorder overlaps with the semantic control deficit in patients with SA. SA patients were found to display all the classic symptoms of access disorder, including effects of item repetition and speed of presentation, and this refractory pattern was linked to poor executive control over semantic activation. However, SA patients with left temporoparietal lesions were less sensitive to refractory variables than those with prefrontal damage in this study. This is in clear contrast to other manipulations of semantic control, which affected both lesion subgroups equally (e.g., Noonan, et al., 2010).

Several questions remain from this research. First, refractory effects have largely been explored in the verbal domain, both in the study conducted by Jefferies and colleagues (2007) and in other research (Schnur, et al., 2006; Warrington & Cipolotti, 1996; Warrington & McCarthy, 1983). However, the semantic control impairment in SA affects all modalities equally (Corbett, Jefferies, Ehsan, et al., 2009; Corbett, Jefferies, & Lambon Ralph, 2009; Jefferies & Lambon Ralph, 2006). Therefore, we would expect *multimodal* refractory effects in these patients. In contrast, as noted below, several theories of 'access' semantic disorder predict this impairment will be restricted to verbal/auditory tasks. Secondly, it is important to confirm whether patients with left prefrontal and temporoparietal lesions differ in terms of the influence of refractory variables – and to consider how such a difference could be reconciled with the semantic control deficits which appear to characterise both subgroups of SA patients.

Verbal-only vs. multimodal refractory effects: There are at least two distinct theories of "access" semantic disorders which predict different refractory effects according to modality. The first, proposed by Warrington and Crutch (2004), is one of "multiple semantics". This idea is again motivated by the comparison of patients with SD vs. 'refractory access' impairment, who typically have stroke aphasia. In contrast to patients with SD, assessment of the refractory patients has most commonly focussed on comprehension within the verbal modality (McNeil, et al., 1994; Warrington & Cipolotti, 1996; Warrington & McCarthy, 1983, 1987). Moreover, the existence of individual cases who show refractory effects on verbal but not visual tasks has been taken as evidence for a cognitive and neural dissociation between verbal and visual semantic systems (Crutch & Warrington, 2008b; Warrington & Crutch, 2004). However, testing for visual refractory effects is relatively rare, and where it has been done, there is some debate as to whether tasks in different modalities are equally difficult and whether they control for the intrinsic differences in the nature of mapping from words or pictures to a concept (see Forde & Humphreys, 1997; Lambon Ralph & Patterson, 2003; Shallice, 1987). Therefore, it is still very much open to question whether SA patients have a purely verbal, or a multimodal, refractory deficit.

Another modality-specific theory suggests that refractory deficits result from impairment of verbal selection, with increases in lexical competition across cycles (Belke, Meyer, & Damian, 2005; Damian, Vigliocco, & Levelt, 2001; Schnur, et al., 2006). According to this theory, activation of word nodes spreads to semantic associates, generating competition at the stage of lexical production in picture naming. When sets of semantically-related items are presented repeatedly for naming, competition becomes stronger. Therefore, the framework predicts refractory effects in verbal but not non-verbal tasks, and much stronger refractory effects in picture naming compared to word-picture matching tasks. Jefferies et al. (2007) directly compared naming and matching tasks, and found SA patients showed refractory impairments in both tasks.

In contrast with these two proposals, several theories predict multimodal refractory effects in SA. As discussed above, we have suggested that SA patients have semantic control deficits which produce multimodal impairment (Corbett, Jefferies, Ehsan, et al., 2009; Jefferies & Lambon Ralph, 2006). The control network is required to activate the specific subset of information within the semantic store, in order to generate time- and task-appropriate behaviour. This is particularly demanding when there is strong competition or in more open-ended situations, and has been associated with regions in both left prefrontal and temporoparietal cortex (Badre, et al., 2005; Thompson-Schill, et al., 1997; Wagner, Paré-Blagoev, et al., 2001; Whitney, et al., 2009; Whitney, Jefferies, et al., 2011; Whitney, Kirk, et al., 2011). This kind of controlled processing is necessary in both verbal and nonverbal activities (Corbett, Jefferies, Ehsan, et al., 2009; Jefferies & Lambon Ralph, 2006) and so this theory would predict that the SA patients should exhibit refractory effects in all domains, given the correct assessment materials (see below).

Finally, using an implemented model of semantic processing, Gotts and Plaut (2002) demonstrated that refractory effects can result from neuromodulatory deficits which generate increased synaptic depression, thus reducing the efficiency with which new stimuli can override current processing during the refractory period. Although this theory does not explicitly consider the issue of modality, if extended to an amodal semantic system, it would predict refractory effects for both verbal and non-verbal tasks, with the effect for both arising from the same general neuromodulatory deficit.

Cortical regions associated with refractory semantic deficits: Brain regions damaged in SA patients include left prefrontal and/or left temporoparietal cortex (Jefferies & Lambon Ralph, 2006; Noonan, et al., submitted). Neuropsychological, rTMS and neuroimaging evidence suggests these two regions work together to underpin semantic control. Lesions of left prefrontal and temporoparietal cortex produce highly similar patterns of semantic impairment (Berthier, 2001; Jefferies & Lambon Ralph, 2006; Noonan, et al., 2010) plus common deficits in attention (Peers et al., 2005). For example, Noonan and colleagues (2010) found no significant differences between left prefrontal and temporoparietal cases on a range of tasks that manipulated semantic control by varying (i) semantic distance between probes and targets in category matching, (ii) associative strength between probes and distractors in synonym judgement, (iii) the presence of semantic cues and miscues on picture naming and (iv) semantic ambiguity of the target word. Equally, a recent TMS study (Whitney, Kirk, et al., 2011) found that selective TMS to the pMTG specifically increased response times on a task requiring greater control over semantic retrieval that required participants to retrieve weak associations between probe and target words (e.g., SALT with either RADIO, GRAIN or ADULT). This effect was indistinguishable from TMS over IFG, and did not have any effect on a task involving more automatic semantic retrieval of strong associations (e.g., SALT with PEPPER, MACHINE or LAND). Moreover, functional neuroimaging studies of healthy participants reveal that both regions show activation modulated by the executive demands of semantic tasks (Noonan, et al., submitted; Whitney, Jefferies, et al., 2011). The same findings have been obtained across a wide range of semantic control manipulations, tapping selection between competing responses (Thompson-Schill, et al., 1997), controlled semantic retrieval (Badre, et al., 2005) and semantic judgements to ambiguous words (Rodd, et al., 2005; Wagner, Paré-Blagoev, et al., 2001; Whitney, et al., 2009).

Despite these similarities, previous studies have suggested that in refractory tasks, patients with left prefrontal lesions show stronger effects of stimulus set repetition than those with temporoparietal damage, implying a subtle specialisation within this control network. In a cyclical picture naming, Schnur et al. (2006) found increased error rates in Broca's aphasics, but not non-Broca patients. Refractory effects were associated with the degree of damage to left inferior frontal cortex – but not with damage to either posterior temporal or inferior parietal regions (Schnur, et al., 2009). Researchers argue that spreading activation causes lexical competition within Broca's area (Schnur, et al., 2006), By this view, refractory effects should only occur in verbal production tasks, and in patients with left inferior frontal lesions. Similarly, Campanella et al. (2009) studied 20 tumour patients with posterior damage and found that effects of word-picture matching set repetition and speed of presentation were very weak. They suggest that posterior damage causes pre-semantic lexical "noise". Finally, Jefferies et al. (2007) found only weak refractory effects (i.e., in response times and not accuracy) in naming and word-picture matching in SA patients with temporoparietal damage, compared with patients whose lesions included left prefrontal cortex. Differential performance of these subgroups of SA patients are at odds with the hypothesis that both left prefrontal and temporoparietal regions contribute to domain-general semantic control (Jefferies & Lambon Ralph, 2006; Noonan et al., 2010) and that refractory deficits can be understood in terms of semantic selection/competition demands that increase over time (e.g., Jefferies et al., 2007).

In summary, previous work on this topic highlights two controversial issues which are the focus of the current study: (1) comparison of refractory effects across different modalities, and (2) lesion location. The current study subdivides SA patients according to the location of their brain injury and directly compares them using refractory tasks that probe the same items in different modalities across three experiments. In Experiment 1, we contrast word-picture matching (WPM) and picture-picture matching (PPM; requiring participants to match visually-dissimilar exemplars of the same object, e.g., vintage-style dial telephone with modern cordless button telephone). In Experiment 2, we compare spoken WPM with environmental sound-picture matching (SPM; requiring the sound of 'barking' to be matched with a picture of a dog). In Experiment 3, we compare word and picture matching tasks that tap associative relationships (e.g., the word "train" or a picture of this item, matched to train tracks).

Subjects and Methods

Patients: Nine aphasic stroke patients (seven male, two female) were recruited from stroke clubs and speech and language therapy services in Manchester and York, UK. Following previous studies on SA, patients were selected who showed semantic comprehension deficits affecting both words and pictures. They were not chosen to show refractory effects. All patients had chronic impairment after a CVA at least one year prior to testing. Three patients had transcortical sensory aphasia, with fluent speech but poor comprehension. The remaining six patients had less fluent speech and/or poor repetition. Patients were aged between 36 and 83, with a mean age of 66 years, as shown in Table 2.1.

Patient lesion analysis: CT/MRI scans were available for eight patients (see Figure 2.1). Five cases (NY, BB, DB, KA and LS) had damage to both left prefrontal and temporoparietal areas (PF+) and three (HN, SC and ME) displayed infarcts confined to left temporoparietal cortex (TP-only). A scan was not available for PG due to contraindications for MRI; however, a radiological report indicated a left frontal lesion, so in subsequent analyses he is included in the PF+ group. Further details of the patients' lesions are shown in Table 2.2. The TP-only subgroup all show some damage extending anterior along the temporal cortex, but crucially these patients do not have damage to regions in the anterior temporal lobe which have been found to store semantic representations (Binney, et al., 2010; Mion, et al., 2010). Additionally, the damage is more dorsal than studies which show involvement to category specific items, namely the inferior parietal lobe (Pobric, et al., 2010b).

Table 2.1: Aphasia profiles and demographic information

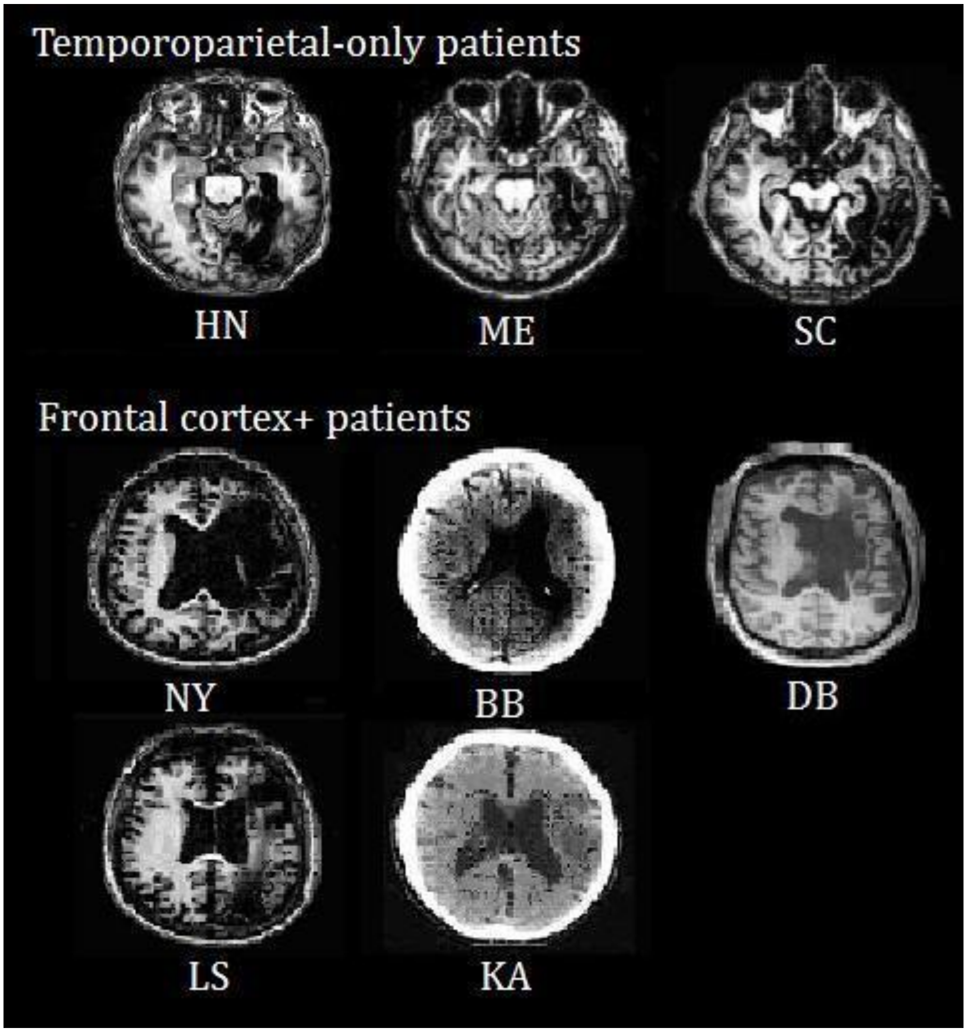
Case	Age	Sex	Full-time education (leaving age)	Aphasia classification	BDAE comprehension percentile	BDAE fluency percentile	BDAE repetition percentile	Nonword repetition (% correct)	Word repetition (% correct)
HN	80	M	15	Anomic/TSA	NA	NA	NA	56	86
SC	76	M	16	Anomic/TSA	37*	90	60	87	98
ME	36	F	16	TSA	33*	100	100	93	100
PG	59	M	18	TSA	20**	40*	80	73	91
NY	63	M	15	Mixed transcortical	47*	37*	40*	40	81
BB	55	F	16	Mixed transcortical	10**	17**	55*	83	96
DB	83	M	16	TSA/ Wernicke’s	13**	90	30*	70	85
KA	74	M	14	Global	0**	23**	0**	0	0
LS	71	M	15	TSA	13**	90	90	90	96

NA = information not available. BDAE = Boston Diagnostic Aphasia Examination (Goodglass & Kaplan, 1983). Comprehension percentile is derived from three subtests (word discrimination, commands, complex ideational material). Fluency percentile is derived from phrase length, melodic line and grammatical form ratings. Repetition percentile is an average of word and sentence repetition subtests. Percentile scores from 0 to 30 were considered “severely impaired” (** denotes severely impaired performance), 31 to 59 as “intermediate” (* denotes intermediate performance), and 60 to 100 as good. Word/nonword repetition = Tests 8 and 9 from Psycholinguistic Assessments of Language Processing in Aphasia: PALPA (Kay, Lesser, & Coltheart, 1992). Aphasia classifications were based on the BDAE and word/non-word repetition scores. TSA (transcortical sensory aphasia) was defined as good or intermediate fluency/repetition and poorer comprehension.

Table 2.2: Details of patients' lesions

Patient	Lesion size (% of template damaged)[a]	Aetiology of CVA	Years since CVA	Left prefrontal lesion	Left temporal-parietal lesion	DLPFC		orbIFC	trIFG	opIFG	STG	MTG	ITG	FG	POT	AG	SMG	TP
						BA9	BA 46	BA 47	BA 45	BA 44	BA 22	BA 21	BA 20	BA 36	BA 37	BA 39	BA 40	BA 38
HN	6	Ischemia	2	×	✓	-	-	-	-	-	-	2	1	-	2	w	-	-
SC	8	Haemorrhage	5.5	×	✓	-	-	-	-	-	-	-	2	-	2	2	w	-
ME	5	Subarachnoid haemorrhage	6.5	×	✓	-	-	-	-	-	-	2	2	2	2	w	w	-
PG[c]	NA	Subarachnoid haemorrhage	5	✓	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
NY	14	Not known	4.5	✓	✓	1	1	2	2	2	1	-	-	-	-	-	2	2
BB [b]	3	Subarachnoid haemorrhage	2.5	✓	✓	-	-	2	2	2	2	-	-	-	-	-	-	-
DB	12	Haemorrhage	24	✓	✓	1	1	1	2	2	2	1	-	-	-	-	1	-
KA	6	Thomoboembolic/ partial haemorrhage	1	✓	✓	-	-	-	-	-	-	2	2	2	2	w	w	-
LS	17	Not known	3	✓	✓	2	1	1	2	2	-	2	2	-	2	2	1	-
					% Patients with grey matter damage	33	33	50	50	67	50	50	50	17	67	50	50	0
					% Patients with grey or white matter damage	33	33	50	50	67	50	50	50	17	67	67	83	0

Quantification of lesion: 2 = complete destruction/serious damage to cortical grey matter; 1 = partial destruction/mild damage to cortical grey matter; w = damage confined to white matter immediately underlying cortex. 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; TP = temporal pole; STG = superior temporal gyrus; MTG = middle temporal gyrus; ITG = inferior temporal gyrus; FG = fusiform gyrus; POT = posterior occipitotemporal area; SMG = supramarginal gyrus; AG = angular gyrus. [a] Lesion size was estimated by overlaying a standardised grid of squares onto each patient's template and working out the percentage of squares damaged relative to the complete undamaged template. [b] BB showed additional signs of ventricular enlargement in the left hemisphere. A scan for PG was unavailable, a radiographer's report identified frontal damage.



MR images are shown for HN, ME, SC, NY, DB and LS. CT scans are shown for BB and KA. PG's scan was unavailable.

Figure 2.1: Neuroimaging for the SA patients

Table 2.2 breaks down patient damage to regions of interest described by previous researchers (see Noonan, et al., 2010). Lesion size did not significantly correlate with background semantic scores ($r = -.65$, $p > .05$) or refractory effects in the current task ($r = -.14$ – $-.69$, $p > .05$).

Neuropsychological and semantic assessment: The patients were examined on a range of general neuropsychological tests to assess cognitive ability. These were: forward and backward digit span (Wechsler, 1987), Visual Object and Space Perception battery, VOSP (Warrington & James, 1991), Elevator Counting with and without distraction from the Test of Everyday Attention, TEA (Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994), Brixton Spatial Rule

Attainment task (BSRA, Burgess & Shallice, 1997), and the Ravens Coloured Progressive Matrices test of non-verbal reasoning (RCPM, Raven, 1962). Factor analysis was used to compute a composite executive/attentional score from tasks for which data was available for each patient (digit span, TEA, RCPM and BSRA).

Semantic assessments included three components of the 64-item semantic test battery (Bozeat, et al., 2000): word-picture matching (WPM) with ten semantically-related distractors and picture and word versions the Camel and Cactus Test (CCT). This test of semantic association involves deciding which of four semantically-related items has an association to a probe (e.g., does CAMEL go with CACTUS, TREE, SUNFLOWER, or ROSE?). Additionally, there was a 96-item synonym judgment task, which involves matching a probe to a target word with the same meaning, presented with two unrelated distractors (Jefferies, et al., 2009). Factor analysis of these four semantic tests was used to compute a composite semantic score, with larger values representing better performance. Table 2.3 provides this background assessment, plus the semantic and executive composite scores.

Table 2.3: Semantic and executive performance for each patient

			TP-only			**PF+**					
	Max score	**Cut-off**	**HN**	**SC**	**ME**	**PG**	**NY**	**BB**	**DB**	**KA**	**LS**
WPM	64	62	50*	59*	50*	58*	60*	54*	46*	26*	37*
CCT pictures	64	51	54*	46*	13*	44*	36*	38*	39*	46*	16*
CCT words	64	56	54*	56	34*	40*	39*	30*	33*	36*	16*
Synonym Judgement	96	89	89	71*	80*	69*	69*	63*	54*	60*	47*
Composite Semantic score			1.47	1.1	-0.24	0.48	0.33	-0.2	-0.5	-0.56	-1.9
Digit Span Forward	-	5	4*	6	6	6	3*	5	4*	0*	4*
Digit Span Backward	-	2	3	2	3	2	2	0*	1*	0*	1*
VOSP screening	20	15	NT	20	19	20	19	20	NT	20	18
TEA elevator counting (no distraction)	7	6	7	7	7	3*	3*	4*	3*	5*	3*
TEA elevator counting (with distraction)	10	3	9	1*	9	0*	2*	0*	1*	5	2*
RCPM	36	36	20	22	13	23	26	24	31	12	16
BSRA	55	28	28	25*	11*	26*	34	23*	24*	6*	14*
Composite Executive score			0.94	.01	1.69	-0.78	-0.88	-082	-1.12	0.97	-0.00

*impaired performance. NT = not tested. WPM = word-picture matching. CCT = Camel and Cactus Task (both from Bozeat, et al., 2000). RCPM = Raven's Coloured Progressive Matrices (Raven, 1962). BSRA = Brixton Spatial Rule Attainment Task (Burgess & Shallice, 1997). TP-only = patients with temporoparietal lesions. PF+ = patients with frontal lesions (often also encompassing posterior regions). NT = not tested, TA = test abandoned. Composite scores in factor analysis derived from task scores. Semantic composite includes WPM, CCT words and pictures, and synonym judgement. Executive score includes digit span, TEA, RCPM and BSRA.

Controls: Twelve age-matched control participants (six male, six female) were selected from a participant database at the University of York. Participants had no prior history of brain injury, and showed unimpaired cognitive functioning on the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975). Participants were aged between 35 and 90, with a mean age of 69 years. Independent *t*-tests showed that the age of the controls did not differ from the patients: $t(19) < 1$.

Design: This study consisted of three experiments, each involving a within-subjects manipulation of modality: (1) identity matching of spoken words and pictures to pictures, (2) identity matching of spoken words to pictures and environmental sounds to pictures, and (3) matching a probe item to its associated location, using spoken word to picture and picture to picture matching.

Procedure: The experiments were run using E-prime 1.1. An array of four semantically-related pictures was displayed. Following all past studies of refractory effects, items were presented repeatedly such that the target on one trial became the distractor on another, until all items within a semantic category had been the target. This completed one cycle. There were a total of four cycles for each set of items, which probed the items in the semantic array in a pseudorandom order[1]. After each set of four cycles, participants have a short break.

The probe item was presented together with the four-item array, either through speakers or as a picture at the top of the screen. SA patients indicated their response by pointing to one of the pictures and the experimenter pressed a key which advanced the task onto the next trial (this method was used as aphasic participants had difficulty using a stylus with a touch-sensitive screen in a pilot study). The experimenter recorded accuracy (our primary dependent variable) while response time (RT) was recorded by the computer. As soon as a response was given, the next trial was presented. Each participant had ten seconds to respond, and if they did not respond within this time, the next trial was presented and an error was recorded. There were four practice items before the start of each block. Each experiment was carried out in four blocks using an ABBA design to control for order effects across the verbal and non-verbal tasks.

---

[1] Presenting items in according to set, each running from cycle one to four ensures no overall fatigue of the task, as cycle four of block one is presented before cycle one of block two.

Experiment 1: Categorical matching in the verbal and visual modality

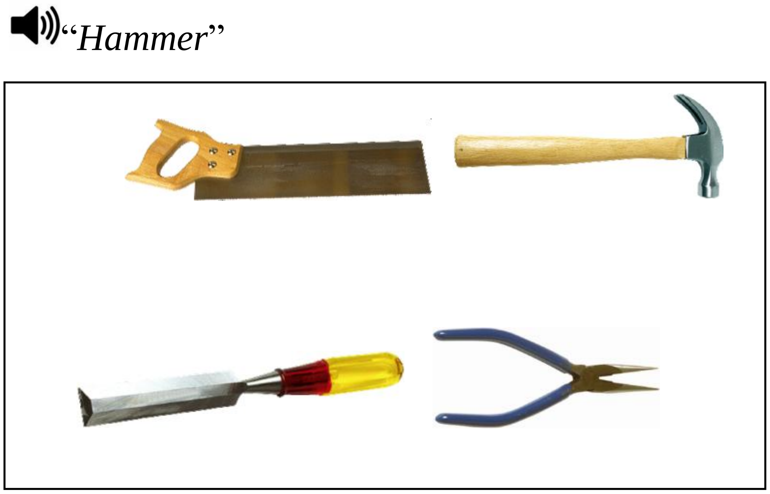
This experiment combined Experiments 5 and 6 from Warrington and Crutch (2004). There were two presentation conditions: visual (picture-picture matching: PPM) and verbal (word-picture matching: WPM). The stimuli consisted of forty inanimate objects. These were grouped into ten semantic sets (TOOLS, ELECTRICAL ITEMS, DRINK CONTAINERS, CLOTHES, HOUSEHOLD APPLIANCES, KITCHEN TOOLS × 2, FURNITURE × 2 and VEHICLES). WPM and PPM from this experiment are show in Figure 2.2. In WPM, a spoken voice recording of the object name was used as the probe. In PPM, two dissimilar pictures of the same item were selected to be the probe and target, in an attempt to prevent simple visual matching.

Experiment 2: Categorical matching in the verbal and non-verbal auditory modality

This experiment had two presentation conditions: verbal (WPM) and non-verbal auditory (sound-picture matching: SPM). The stimuli in this experiment consisted of 32 inanimate and animate objects. These were grouped into eight sets (FARM ANIMALS, OTHER ANIMALS, BIRDS, TOOLS, VEHICLES, HOUSEHOLD OBJECTS, HUMANS and MUSICAL INSTRUMENTS). The WPM and SPM from this experiment are shown in Figure 2.3. In the SPM task, a recording of an environmental sound produced by the object was presented as the probe, while in WPM a spoken voice recording of the object name was used.

Experiment 3: Associative matching in the verbal and visual modality

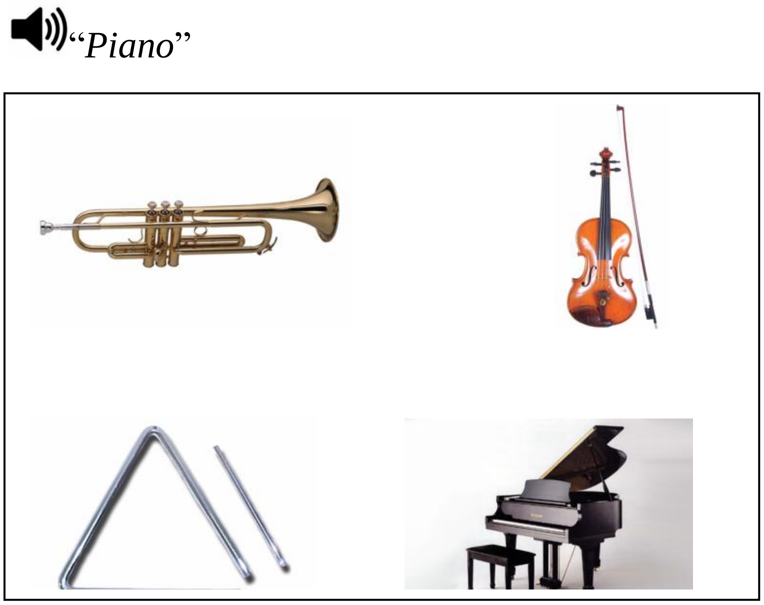
This experiment had two presentation conditions: visual (PPM) and verbal (WPM). The stimuli in this experiment consisted of forty inanimate and animate objects and forty associated locations. These were grouped into ten sets (FARM ANIMALS, PETS, EXOTIC ANIMALS, CLOTHES, PLANTS, LARGE HOUSEHOLD OBJECTS, SMALL HOUSEHOLD OBJECTS, PEOPLE, VEHICLES and FOOD). On every trial, participants selected the typical location of the probe object from an array of four locations within the set. The WPM and PPM from this experiment are shown in Figure 2.4.



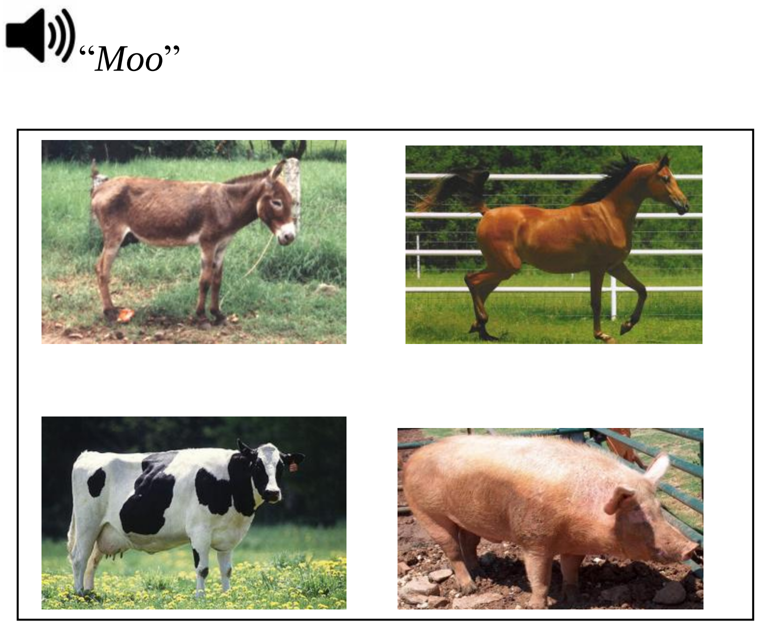
Verbal condition (WPM)

Visual condition (PPM)

Figure 2.2: Examples of trials used in Experiment 1 (category identity matching)



Verbal condition (WPM)



Non-verbal auditory condition (SPM)

Figure 2.3: Examples of trials used in Experiment 2 (category identity matching)

Verbal condition (WPM)

Visual condition (PPM)

Figure 2.4: Examples of trials used in Experiment 3 (association matching)

Results

Across all experiments, control participants' accuracy was close to ceiling levels (the control mean ranged from 92% to 100%, and there were no refractory effects). Repeated measures ANOVAs of control RT indicated facilitation from repetition; in contrast there were no significant effects in RT for the patients across cycles (see Table 2.4 for RT data and analysis). The following analysis, therefore, focuses on response accuracy.

Table 2.4: Mean reaction time for patients and controls across all experiments

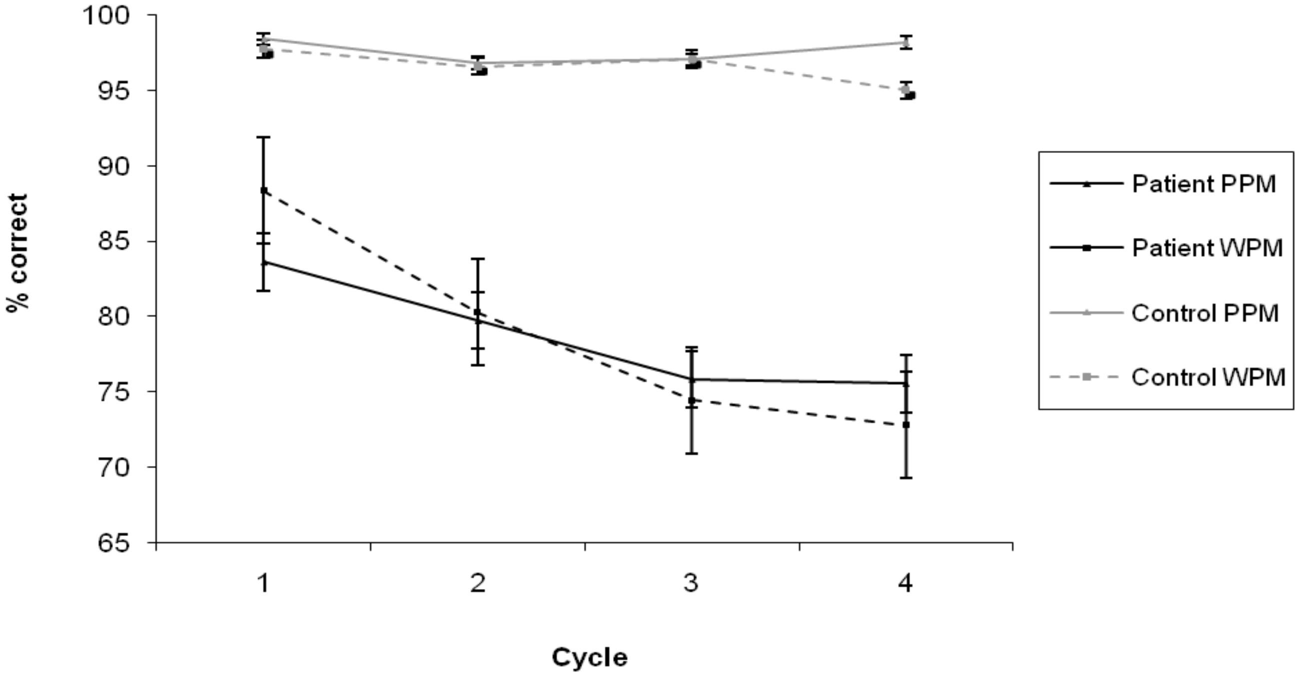
	Experiment 1		Experiment 2		Experiment 3	
	PPM	WPM	SPM	WPM	PPM	WPM
Patients						
Cycle 1	4627 *(753)*	2882 *(526)*	3289 *(402)*	3034 *(520)*	4950 *(770)*	4092 *(591)*
Cycle 2	4498 *(657)*	2928 *(314)*	3263 *(481)*	3205 *(599)*	4684 *(641)*	3957 *(524)*
Cycle 3	4221 *(707)*	2833 *(250)*	3120 *(438)*	3020 *(436)*	4573 *(762)*	3521 *(363)*
Cycle 4	4237 *(886)*	3082 *(308)*	3180 *(365)*	3130 *(556)*	4336 *(659)*	3423 *(388)*
F value	1.48	6.92	2.10	1.81	3.70	3.00
p	.348	.073	.219	.262	.156	.196
Controls						
Cycle 1	1696 *(405)*	1607 *(331)*	2050 *(468)*	1373 *(211)*	2249 *(515)*	1834 *(295)*
Cycle 2	1505 *(322)*	1503 *(354)*	1880 *(414)*	1300 *(183)*	1819 *(396)*	1613 *(254)*
Cycle 3	1453 *(262)*	1402 *(306)*	1780 *(321)*	1265 *(172)*	1694 *(348)*	1487 *(222)*
Cycle 4	1468 *(259)*	1426 *(310)*	1807 *(379)*	1281 *(193)*	1676 *(370)*	1525 *(228)*
F value	5.02	9.22	5.74	6.56	10.06	38.41
p	.026	.004	.018	.012	.003	<.001

Mean RT in milliseconds (*standard deviation*). Patient data includes cases who scored 65% or higher in accuracy (HN, SC, ME, PG, NY, BB). Tasks were picture-picture matching (PPM), word-picture matching (WPM) and sound-picture matching (SPM).

Category (living or manmade) was mixed in Experiments 2 and 3. A paired t-test for each experiment was used to confirm that patients show no difference in accuracy according to category: $t(8) < 1$. Additionally, an ANOVA assessing the interaction between the effect of category and subgroup (TP-only compared with PF+ patients) revealed no significant interaction: *F*(7) < 1.

Experiment 1: Categorical matching in the verbal and visual modality

The accuracy data were analysed using a three-way mixed factor ANOVA, including group (patients vs. controls), and two within-subjects factors – cycle (repetition 1-4) and modality (words vs. pictures). There was a significant main effect of group: *F*(1, 19) = 20.77, *p* < .001. There was also an interaction between cycle and group: *F*(3,54) = 3.65, *p* = .034, indicating that the patients showed greater refractory effects than controls. This is shown in Figure 2.5. No significant effect of modality was found: *F*(1,19) < 1, and there was no group by modality interaction: *F*(1,19) < 1, or cycle by modality interaction: *F*(3,24) = 2.40, n.s., indicating that refractory effects were equivalent for both tasks. Similarly, the three-way task-by-cycle-by-group interaction was not significant: *F*(3,54) = 2.67, n.s.



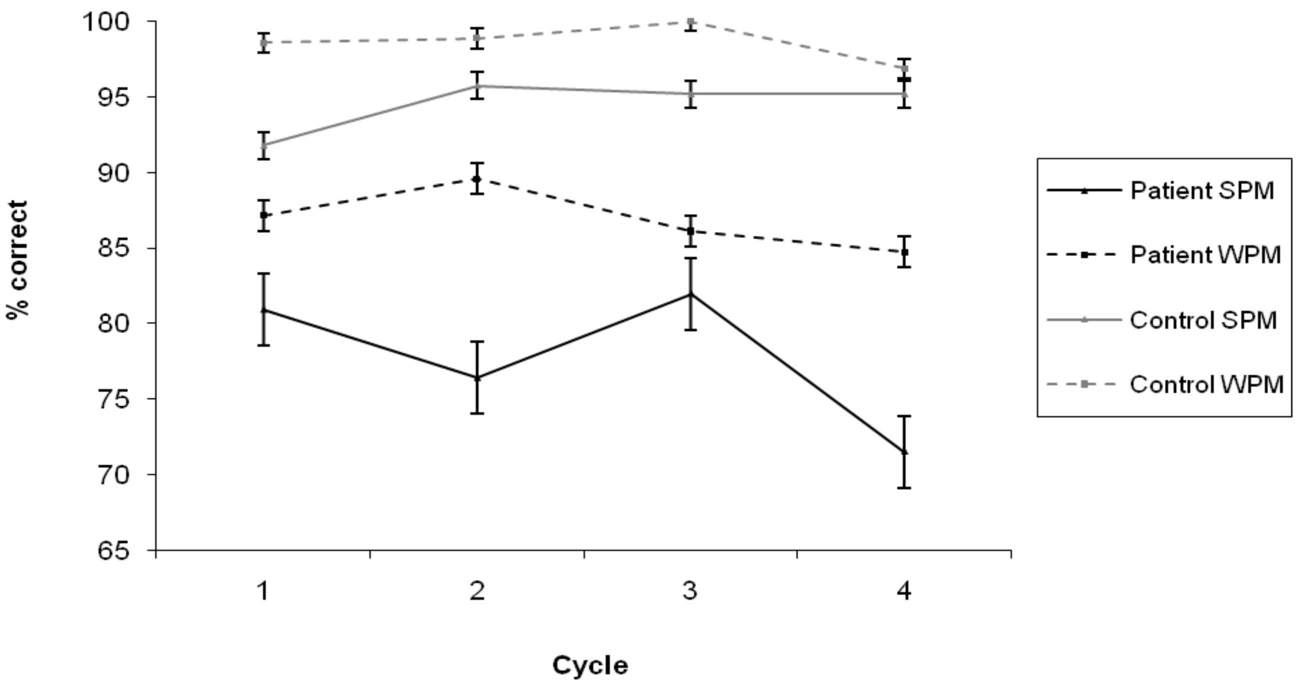
PPM = picture-picture matching. WPM = word-picture matching. Error bars show standard error of the mean.
Figure 2.5: Mean response accuracy across cycles in Experiment 1.

The effects of cycle and modality were examined further in the patient group using a two-way, within-subjects ANOVA. The main effect of cycle was significant: *F*(3,24) = 8.18, *p* = .011, but there was no influence of modality: *F*(1,8) < .1. Again, the interaction between cycle and modality was not significant: *F*(3,24) = 1.94, n.s., confirming equal refractory effects for WPM and PPM.

Experiment 2: Categorical matching in the verbal and non-verbal auditory modality

A three-way mixed-factor ANOVA revealed a main effect of group: *F*(1,19) = 15.85, *p* = .001, and an interaction between cycle and group: *F*(3,54) = 7.18, *p* = .003, indicating that refractory effects were stronger in patients than controls. In this experiment, however, the effect of modality was significant: *F*(1,19) = 17.58, p < .001. Accuracy was higher in WPM than SPM, as shown in Figure 2.6. There was no modality-by-group interaction: *F*(1,19) = 1.93, n.s., or modality-by-cycle interaction: *F*(1,19) = 1.53, n.s., but the three-way interaction between task, group and cycle was significant: *F*(3,54) = 7.06, *p* = .003.

These findings were explored further in the patient group using a two-way, within-subjects ANOVA. The main effect of cycle was significant: *F*(3,24) = 8.75, *p* < .001, and the influence of modality approached significance: *F*(1,8) = 4.83, *p* = .06. However, the interaction between modality and cycle was not significant: *F*(3,24)=1.66, n.s., indicating that the patients showed equal refractory effects for WPM and SPM. The three-way interaction reported above is therefore likely to reflect the fact that, in contrast to patients, the control participants showed some improvement in SPM but not WPM over cycles. In may also reflect that the data in the SPM is particularly noisy, as seen in Figure 2.6.

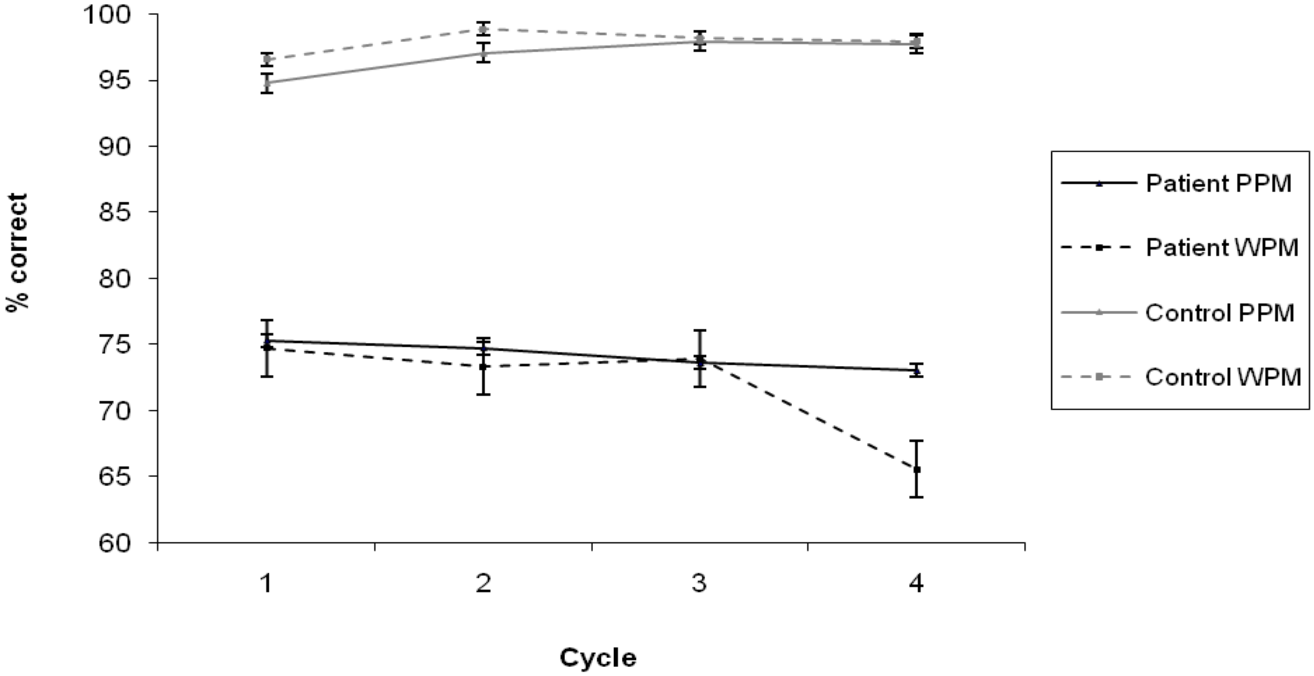


SPM = sound-picture matching. WPM = word-picture matching. Error bars show standard error of the mean.
Figure 2.6: Mean response accuracy across cycles in Experiment 2.

Experiment 3: Associative matching in the verbal and visual modality

A three-way mixed factor ANOVA revealed a main effect of group, with controls performing at a higher level than patients: *F*(1,19) = 29.31, *p* < .001. There were no significant effects of modality: *F*(1,19) < 1, or cycle: *F*(3,54) = 2.60, n.s. There was also no significant interaction between cycle and group: *F*(3,54) = 1.98, n.s., or between modality and group: *F*(1,19) = 2.33, n.s. However, there was a significant interaction between modality and cycle: *F*(3,54) = 5.35, *p* = .009, and the three-way interaction was significant: *F*(3,54) = 4.89, *p* = .012. These data are shown in Figure 2.7.

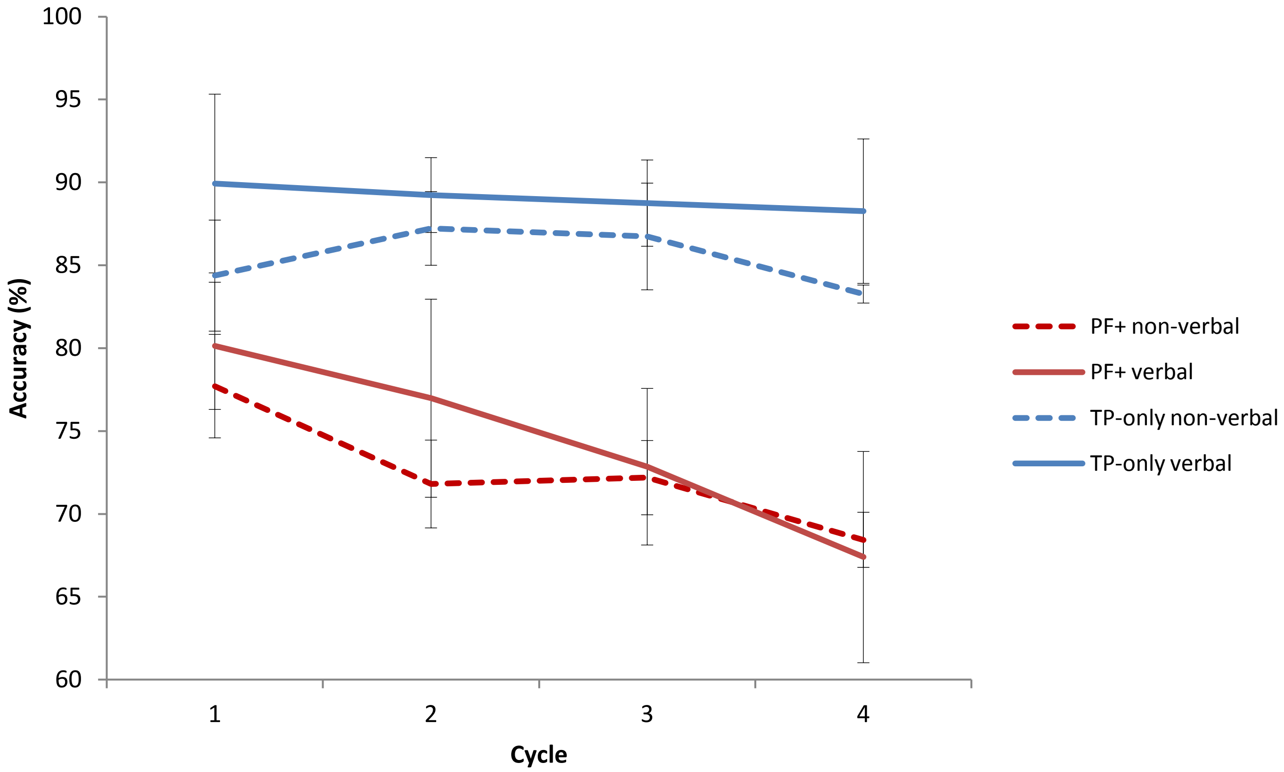
The possibility that refractory effects were found in only one task was explored using separate two-way mixed factor ANOVAs for each modality. In WPM, there was a significant main effect of cycle: *F*(3,54) = 4.79, *p* = .013, and group: *F*(1,19) = 23.30, *p* < .001. Additionally, there was an interaction between cycle and group: *F*(3,54) = 3.24, *p* = .048, as the patients showed stronger refractory effects than controls. In the PPM task, there was a main effect of group: *F*(1,19) = 25.27, *p* < .001, but no effect of cycle: *F* <1, and no interaction between cycle and group: *F*(3,54) = 1.13, n.s. Bonferroni-corrected paired-samples t-tests were used to compare the patients' performance on WPM and PPM at each cycle. There was a difference between the two modalities only on the fourth cycle: *t*(8) = 5.13, *p* = .004, with no differences between modalities on cycles one, two, or three: *t*(8) < 1.



PPM = picture-picture matching. WPM = word-picture matching. Error bars show standard error of the mean.
Figure 2.7: Mean response accuracy across cycles in Experiment 3.

<u>Anterior/posterior patient differences</u>

It was predicted that for TP-only patients, accuracy would not decline over cycles: therefore, significant refractory effects would be shown in the PF+ group but not the TP-only group. Logistic regression was used to establish whether the effect of cycle interacted with lesion location. Overall, lesion subgroup alone explained 14.6% of the variance in the data. Accuracy was higher in the TP-only than PF+ group, as shown in Figure 2.8. A model which included experiment, distinguishing all six tasks (Wald = 3.24), cycle (Wald = 40.28), individual patient identifiers (Wald = 305.69) and lesion subgroup (Wald = 10.66) found a significant predictive value for each variable ($p \leq .001$), except experiment.



Accuracy across all three experiments, grouped according to modality: non-verbal (picture-picture matching, PPM; or sound-picture matching, SPM) and verbal (word-picture matching, WPM), and lesion location: PF+ (frontal and temporoparietal lesion) and TP-only (temporoparietal lesion). Error bars show standard error of the mean.

Figure 2.8: Overall accuracy of PF+ and TP-only patients across cycles

A model adding two interactive terms found a significant effect of cycle-by-subgroup, but not experiment-by-subgroup (inclusion of this interaction also led to the main effects of subgroup and cycle becoming non-significant; see Table 2.5). PF+ patients showed significantly greater effects of cycle than TP-only patients but there were no significant differences across the subgroups in the effects of experiment. The cycle-by-subgroup interaction remained significant (p = .007) with the addition of cycle-by-patient ID in the equation.

Table 2.5: Logistic regression analysis showing the significant influence of each variable on the model

Predictor	**B**	**Waldχ^2**	**p**	**Exp(B)**
Cycle	.125	1.330	.249	1.133
Patient ID	-.229	306.084	<.001	.796
Subgroup	.095	.174	.677	1.1
Experiment	-.148	.799	.371	.862
Cycle by subgroup	-.160	7.246	.007	.852
Experiment by subgroup	.049	.239	.625	1.046

Variables entered: subgroup, experiment, cycle, patient ID, cycle x subgroup, experiment x subgroup

Separate logistic regression analysis of each cycle, using the predictor variables modality, subgroup and patient ID, revealed that there was no difference in accuracy between subgroups at cycle 1, but this difference became increasingly significant as the number of cycles increased. These four analyses are shown in Table 2.6.

Table 2.6: Four logistic regression analyses showing the effect of subgroup at each cycle

Subgroup at each level of cycle	**B**	**Waldχ^2**	**p**	**Exp(B)**
Subgroup at Cycle 1	.121	.595	.441	1.128
Subgroup at Cycle 2	-.284	3.414	.065	.752
Subgroup at Cycle 3	-.347	5.290	.021	.707
Subgroup at Cycle 4	-.413	152.453	<.001	.661

Variables entered: experiment, patient ID and subgroup. Data comes from four separate analyses examining each cycle.

Further logistic regression separating modality compared (1) picture and verbal modalities from Experiment 1 and 3, and (2) sound and verbal modalities from Experiment 2. The model included modality, cycle, patient identifier, subgroup and cycle by subgroup. The first model found a significant predictive value of patient identifier (Wald = 286.16, p <.001), subgroup (Wald = 5.99, p = .014) and cycle by subgroup (Wald = 10.30, p = .001). There was no significant predictive value of modality (Wald = .375, p = .54) or cycle (Wald = 2.87, p = .09).

In the second comparison, including sound and word picture matching scores from Task 2, the model found a predictive value of modality (Wald = 35.90, p <.001), patient identifier

(Wald = 32.37, p = <.001) and subgroup (Wald = 4.84, p = .028), but not cycle (Wald = .48, p = .49), or cycle by subgroup (Wald = .05, p = .83). The significant predictive value of modality is driven by a higher performance in the WPM on this task, as shown in Figure 2.6.

To explore this further, a model was applied separately to the verbal and sound tasks of Experiment 2, using cycle, subgroup and patient identifier as the variables. The verbal modality found no significant effect of cycle (Wald = 1.40, *p* = .236), or subgroup (Wald = 1.57, *p* = .210), and only a significant main effect of patient identifier (Wald = 49.49, *p* = <.001). Conversely, the sound modality found an effect of cycle (Wald = 4.40, p = .036), and subgroup (Wald = 25.43, *p* <.001). The patient identifier was not significant (Wald = 1.98, *p* = .160).

<u>Individual patients</u>

McNemar tests were carried out on the data from each patient to determine which individuals showed significant refractory effects. The results are provided in Table 2.7. All of the PF+ patients showed some degree of refractory impairment, while none of the TP-only patients did. There were also substantial individual differences in the refractory effects shown by PF+ patients. Some patients showed refractory effects at the beginning of the task, between the first two cycles (e.g., KA). In contrast, some showed refractory effects between the last two cycles (e.g., LS), while others showed subtle but consistent refractory effects, which became significant across the whole task (e.g., DB).

Table 2.7: McNemar tests showing refractory effects between different cycles for each patient

Patient	Lesion	Cycles 1-2	Cycles 2-3	Cycles 3-4	Cycles 1-3	Cycles 2-4	Cycles 1-4
HN	TP only	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
SC	TP only	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
ME	TP only	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
PG	PF+	n.s.	n.s.	WPM3: p = .021	n.s.	WPM3: p = .001	WPM3: p = .002
NY	PF+	n.s.	n.s.	n.s.	WPM3: p = .039	n.s.	WPM3: p = .021
BB	PF+	n.s.	n.s.	n.s.	n.s.	PPM3: p = .031	n.s.
DB	PF+	WPM1: p = .031	n.s.	n.s.	WPM1: p = .002	WPM3: p = .031	PPM1: p = .021; WPM1: p <.001; WPM3: p = .019
KA	PF+	PPM3 = p = .035	PPM1: p = .008; WPM3: p = .041	n.s.	PPM1: p = .022; WPM1: p = .027	WPM3: p = .031	WPM1: p = .021
LS	PF+	n.s.	n.s.	SPM2: p = .016	n.s.	WPM1: p = .025	WPM1: p = .007

Word-picture matching task in Experiment 1 (WPM1), picture-picture matching task in Experiment 1 (PPM1), sound-picture matching task in Experiment 2 (SPM2), WPM in Experiment 3 (WPM3), PPM in Experiment 3 (PPM3). Only significant statistics at p<.05 are shown.

Discussion

This study assessed the multimodal nature of refractory effects in semantic aphasia (SA) using, for the first time, a case-series approach as opposed to analysis of individual cases. Additionally, it explored the effect of lesion location on refractory semantic access. Refractory deficits were found in all modalities - in word, picture and sound-matching tasks. Secondly, patients with left prefrontal lesions always showed deterioration in performance across cycles, whereas none of the temporoparietal patients did.

Our finding of equivalent refractory effects in verbal and non-verbal modalities is compatible with the view that, in SA, the store of semantic representations remains intact (shown by good performance on the first cycle), while executive control over semantic activation is impaired (shown in the reduction of accuracy over cycles). This pattern of impairment might be expected from the brain injury in SA: the anterior temporal lobes – which are thought to form a key hub for semantic knowledge (Lambon Ralph, Sage, et al., 2010; Patterson, et al., 2007; Pobric, et al., 2010b) – are intact, while there is significant damage to left prefrontal and temporoparietal regions. These brain areas are associated with semantic control functions in neuropsychological research (Jefferies & Lambon Ralph, 2006; Noonan, et al., 2010), functional neuroimaging studies of healthy volunteers (for a review, see Noonan et al., submitted) and TMS work (Whitney, Kirk, et al., 2011). In refractory tasks, the same set of semantically-related items is presented repeatedly such that targets become distractors and vice versa. This should produce significant competition between targets and distractors in later cycles irrespective of input modality – and consequently SA patients with semantic control impairment show refractory effects across words, pictures and environmental sounds.

Our findings pose significant challenges to theoretical frameworks that only predict refractory effects in verbal tasks. For example, Warrington and Crutch (2004) argue that there are separate semantic systems, with their patient only showing refractory effects in the verbal modality. Given later evidence that this same patient showed non-verbal refractory effects for environmental sounds, this proposal was modified to suggest that the visual system is qualitatively distinct from the auditory system (Crutch & Warrington, 2008b). The current study confirms that refractory effects can emerge in parallel in verbal, picture and sound tasks. Moreover, some of our patients (e.g., LS, DB) resembled Warrington and Crutch's patient AZ in Experiment 1 (which used Warrington & Crutch's materials) in that they showed refractory effects in the verbal modality that did not extend to the visual task. However, in further experiments, these patients showed the opposite pattern (e.g., stronger refractory effects in non-verbal than verbal judgements). Therefore, it is helpful to consider performance across different tasks that may vary in their sensitivity to refractory effects. In picture-picture identity matching tasks (used in Experiment 1 and by Crutch & Warrington), it is difficult to avoid probe and targets looking somewhat alike (given they are examples of the same object) and even partial visual similarity may be enough to weaken the refractory effect. In contrast, there is no surface similarity issue to consider when matching sounds or words to target pictures.

Our findings are also at odds with another theoretical perspective that accounts for refractory effects in picture naming in terms of lexical competition (Belke, et al., 2005; Damian, et al., 2001; Schnur, et al., 2006). In this theory, co-activation of a word (e.g., 'dog') and its category node (e.g., 'animal') results in activation spreading back to semantically-related word nodes (e.g., 'cat', Levelt, 2001) and this gives rise to strong competition within the lexical network when sets of semantically-related items are presented. This framework only predicts refractory effects in picture naming tasks - nevertheless, if similar competition is envisaged in the semantic system, effects of cycle might be expected in semantic judgement tasks (i.e., decisions not requiring spoken output) and across verbal and non-verbal input modalities.

The current study also confirms that lesion location affects the likelihood of refractory deficits, with PF+ patients showing deterioration in accuracy, whilst TP-only patients maintain performance across cycles. A difference between these patient groups has been predicted by previous research (Campanella, et al., 2009; Schnur, et al., 2009), although the explanation given for refractoriness is not compatible with the current findings of multimodal refractory effects in PF+ patients. Indeed, the difference between PF+ and TP-only patients is perhaps surprising as several lines of research indicate that both left prefrontal and posterior temporal/inferior parietal regions make a critical contribution to multimodal semantic control. First, in several investigations of verbal and non-verbal semantic control, SA patients with lesions in these two locations have shown highly similar deficits, characterised by strong sensitivity to manipulations of semantic control demands (Corbett, Jefferies, Ehsan, et al., 2009; Corbett, Jefferies, & Lambon Ralph, 2009; Jefferies & Lambon Ralph, 2006; Noonan, et al., 2010). Secondly, neuroimaging studies frequently reveal activation of both left prefrontal and posterior temporal/inferior parietal regions in tasks that load semantic control (Badre, et al., 2005; Noonan, et al., submitted; Whitney, Jefferies, et al., 2011). Thirdly, a recent TMS study found that a 'virtual lesion' in either LIFG or pMTG disrupted executively-demanding semantic judgements to an equal degree (Whitney, Kirk, et al., 2011). Consequently, if refractory effects in SA occur simply because the patients have poor control over activation within the semantic system, then we would expect both lesion sub-groups to show parallel deficits.

One possible explanation for this difference between the lesion subgroups is that TP-only patients have a *milder* deficit of semantic control. A recent meta-analysis of neuroimaging studies revealed the left prefrontal cortex is strongly and consistently activated in executive-semantic tasks, while the TP-region shows a somewhat smaller peak of activation which is only significant in some studies/tasks (Noonan, et al., submitted). However, in the current study, while two of the TP-only patients had relatively mild semantic impairment, another (patient ME) showed much more substantial deficits.

A second possibility is that both left prefrontal and temporoparietal regions contribute to semantic control, but their exact roles vary. If so, the temporoparietal region may be necessary for aspects of semantic control that do not interact with cycle in refractory tasks. For example, left inferior frontal gyrus (LIFG) may be crucially involved in inhibition, especially when activation of *previously-relevant* semantic information must be dampened down (leading to more perseverative errors as well as strong refractory effects in patients with left prefrontal lesions; see (Corbett, et al., 2008). In contrast, temporoparietal areas, alongside LIFG, may help to retrieve non-dominant semantic associations and/or bring task-relevant information to the fore in a flexible way. Based on findings from fMRI, Badre and colleagues (2005) proposed a two-step semantic retrieval model involving 'controlled retrieval' and 'post-retrieval selection'. They found that activation in posterior temporal cortex was sensitive to controlled retrieval demands, as measured by the associative strength between a cue and a target or the number of response alternatives, but not manipulations of post-retrieval selection demands, such as whether the judgement related to global semantic similarity or a specific attribute. In contrast, regions within LIFG responded to both of these elements of semantic control (although Badre et al. focussed on divisions within LIFG that were not testable in our patient sample).

This distinction between controlled retrieval and post-retrieval selection could prove to be crucial in understanding refractory performance. The first block in cyclical tasks always demands controlled retrieval, but with stimulus repetition, the items have already been retrieved and post-retrieval selection is required. If the temporoparietal region plays a key role in controlled retrieval, patients with temporoparietal lesions but intact prefrontal selection processes would not find the last trial any more difficult than the first. In line with this theory, damage to the LIFG has been linked to heightened difficulty in processing words with multiple propositions which tax semantic selection (often, counterintuitively, high frequency words, Hoffman, Jefferies, et al., 2011; Hoffman, Rogers, et al., 2011). For example, a recent study of 72 brain-injured patients found focal damage to LIFG caused impaired performance on a sentence generation task when the probe word referred to multiple conceptual propositions (Robinson, Shallice, Bozzali, et al., 2010). These findings suggest that LIFG may be specifically involved in selection between competing items which have been retrieved (see also Robinson, Blair, & Cipolotti, 1998; Robinson, et al., 2005).

While the current data are consistent with the view that anterior and posterior sites within the semantic control network have varying roles, further research is required to fully specify the control processes that they underpin. Given the differences between Badre et al.'s (2005) semantic selection task and the refractory paradigm, it is not currently known whether IFG makes a greater contribution to all forms of semantic selection, or only when previously-relevant information must be inhibited. The current data advance knowledge in two ways: (1) they show that refractory impairments resulting from poor semantic control generalise from verbal to non-verbal modalities, and (2) they provide evidence that lesion location is important in determining deficits in the refractory paradigm. This lends further support to the theory that deregulated semantic control results in an amodal "access" impairment (Jefferies & Lambon Ralph, 2006). Additionally, it sparks new interest into the function of the temporoparietal and prefrontal cortex in semantic cognition and executive control.

3. CHAPTER THREE

Semantic aphasia and modality: An input processing deficit leading to reduced semantic control in a single modality

Acknowledgements: The Semantic Association task was developed by Katya Krieger-Redwood. In the tasks which use words embedded in white noise, the stimuli were produced with the help of Katya, and Carina Tudor-Sfetea collected age-matched control data for this task.

Abstract

Research suggests that semantic memory deficits can occur in at least three ways. Patients can (1) show amodal degradation of concepts within the semantic store itself, such as in semantic dementia (SD), (2) have difficulty in controlling activation within the semantic system, and accessing appropriate knowledge in line with current goals or context as in semantic aphasia (SA), and (3) experience a semantic deficit in only one modality following degraded input from sensory cortex. Patients with SA show deficits of semantic control and access across word and picture tasks, consistent with the view that their problems arise from impaired domain-general control processes. However, there are a few reports in the literature of patients with semantic access problems restricted to verbal materials, who show decreasing ability to retrieve concepts from words when they are presented repeatedly with closely related distractors. These patients challenge the notion that semantic control processes are modality-general and suggest instead a separation of ‘access’ to verbal and non-verbal semantic systems. We had the rare opportunity to study such a case in detail. Our aims were to examine the effect of manipulations of control demands in verbal semantic, non-verbal semantic and non-semantic tasks, allowing us to assess the hypothesis that semantic control/ access impairments can follow a modality-specific pattern. Our findings revealed: (1) deficits on executive tasks, unrelated to semantic demands, which was more evident in the auditory domain than the visual domain; (2) deficits in executively-demanding semantic tasks which were accentuated in the verbal domain compared with the visual domain, but still present on non-verbal tasks, and (3) a coupling between comprehension and executive control requirements, in that mild impairment on single word comprehension was greatly increased on more demanding, associative judgements across modalities. This pattern of results suggests that mild executive/ semantic impairment, paired with disrupted connectivity from auditory input, may give rise to semantic ‘access’ deficits seemingly affecting only the auditory domain.

Introduction

Chapter 2 found evidence for multimodal refractory effects in Semantic Aphasia (SA) patients. However, patients have been described who do not show this pattern (Crutch & Warrington, 2008b; Warrington & Crutch, 2004). Under the 'hub-and-spoke' model, it is entirely possible to have a deficit circumscribed to the auditory domain, but this deficit does not interact with task demands. Semantic knowledge is thought to be stored across a wide range of cortical regions relating to motor and perceptual features (Barsalou, 1999; Goldberg, Perfetti, & Schneider, 2006; Martin, 2007; Pulvermuller, 2005). For example, those with pure word deafness have bilateral damage to STG leading to deficits understanding spoken words – in both simple tasks, such as word-picture matching, and more complex control-demanding contexts, such as forming verbal associations in the presence of strong distractors (Tanaka, Yamadori, & Mori, 1987). fMRI evidence suggests this region is largely insensitive to the difficulty of the task, and plays a major role in spectro-temporal analysis of speech sounds (Scott & Johnsrude, 2003; Wise et al., 2001). For example, Blumstein et al. (2005) assessed fMRI signal for both phonetic categorization and tone categorization tasks. Although reaction times were longer for the phonetic categorization task, signal change in STG did not correlate with these changes in task demands.

In addition, semantic cognition also requires controlled activation of knowledge, such that task-relevant meanings can be brought to the fore. Patients with SA have multimodal semantic control deficits which reflect difficulty in retrieving task-relevant meanings. SA patients with semantic control deficits will have deficits on executively demanding semantic tasks irrespective of whether they are presented verbally, through pictures, sounds or actions. Indeed, SA patients show parallel deficits in verbal and non-verbal action tasks (Corbett, Jefferies, Ehsan, et al., 2009; Corbett, et al., 2008; Corbett, Jefferies, & Lambon Ralph, 2009; Jefferies & Lambon Ralph, 2006). (1) In all modalities that have been tested, patients have most difficultly on trials which require a flexible application of knowledge, such that items must be matched even when they do not share a strong association. For example, in a picture task representing tools and target objects, a significant difference was found between tools which were canonical and non-canonical alternatives (e.g., an item not usually used to perform an everyday action, but nonetheless a plausible alternative). A 'fly-swat' is most commonly used to kill a fly, but if this option is not available, controls, but not SA patients, can readily select a 'magazine' as a plausible alternative (Corbett, et al., 2011). As with word tasks involving non-dominant semantic associations, successful performance requires inhibition of the most familiar use of the item (Noonan, et al., 2010). (2) There are also equivalent verbal and non-verbal cueing effects in production tasks. Performance on picture naming improves dramatically when patients are given a phonetic cue (Jefferies, Patterson, et al., 2008). Similarly, when asked to mime an action for an object, SA patients perform poorly. Their abilities improve significantly, however, when shown a picture cue of the recipient of the action, e.g., 'nail' for 'hammer' (Corbett, et al., 2011). The effects of cueing on both picture naming and object use suggest SA patients have difficulty constraining their semantically-driven behaviour and thus benefit from external constraints. Under these circumstances, SA patients reveal that they retain knowledge that they previously failed to demonstrate.

Although a distinction between a permanent loss of semantic knowledge and a temporary inability to retrieve appropriate semantic information is not disputed (Jefferies & Lambon Ralph, 2006; Warrington & Cipolotti, 1996), the nature of this distinction is. In contrast to Jefferies and colleagues, who envisage that an amodal store of knowledge interacts with modality-free control mechanisms, a parallel literature focused on a small number of single cases suggests that deficits in semantic access (as opposed to storage) can selectively affect verbal comprehension. This distinction between access and storage deficits has been shown most clearly through refractory effects in cyclical semantic tasks (Warrington & Cipolotti, 1996). These occur when a small group of semantically related items are repeatedly presented, with the participant required to select a target among closely-related distractors. The target and distractors are presented repeatedly across several cycles, so that competition with the target increases. In those who have 'access' impairments, there is a decline in performance over cycles, due to "a reduction in the ability to utilize the system efficiently for a period of time following activation" (Warrington & McCarthy, 1983). Impairments of this nature suggest there are modality-specific semantic systems which are independent (Warrington & Cipolotti, 1996; Warrington & Crutch, 2004; Warrington & McCarthy, 1983; Warrington & Shallice, 1979), since access to the visual domain is completely intact, while refractory effects occur only in the verbal domain (Warrington & Crutch, 2004; Warrington & McCarthy, 1983). In a more recent version of this account, investigating a wider range of modalities, the key distinction has been between the auditory and visual domains – with both spoken word and environmental sound tasks showing refractory effects (Crutch & Warrington, 2008b).

SA patients can show the same pattern of refractory effects, but across modalities, and not restricted to the verbal domain . These are suggested to result from a multimodal control impairment (Gardner, et al., 2012; Jefferies, et al., 2007), since executive control requirements should increase on later cycles which are characterised by stronger activation of competitors. Although SA patients and 'access' patients show a difference in performance relating to modality, other key characteristics of 'access' patients are also shared with SA patients. Both SA and 'access' patients show strong cueing effects, inconsistent performance when the same items are retested, an absence of word frequency effects, sensitivity to semantic relatedness of distractors and to both speed of presentation as well as cycle (Gardner, et al., 2012; Jefferies, et al., 2007; Warrington & Crutch, 2004; Warrington & McCarthy, 1983). The decline in performance over cycles is a central feature in both groups of patients, revealing that knowledge is retained but retrieval can fail in certain circumstances (in contrast to SD patients).

While there are few verbal only access patients in the literature, with much of the work done in a single individual, AZ (Crutch & Warrington, 2003c, 2004, 2005a, 2005b, 2007; Warrington & Crutch, 2004), plus one or two additional cases (Crutch & Warrington, 2008a, 2008b), such patients appear to pose a problem for our account of semantic cognition, in which domain-general semantic control mechanisms interact with amodal representations, resulting in refractory deficits which occur regardless of modality – in both word and picture tasks in SA. Moreover, it is unclear if verbal-only access patients show (i) a strong influence of the control demands of semantic tasks, like SA cases (this time restricted to verbal stimuli), and (ii) an association between their verbal comprehension problems and executive deficits (which would also be restricted to verbal inputs). We had an unusual opportunity to study a patient with a verbal-only semantic access deficit in detail.

We test the following accounts to explain this pattern: (1) A semantic 'access' deficit, as envisaged by Warrington and Crutch (2004), where accuracy is inconsistent and refractory in the verbal domain, but at ceiling in the visual domain, implying separate access mechanisms for verbal and non-verbal semantic systems, which can be independently damaged. (2) A semantic control deficit, revealed by strong effects of control demands on semantic tasks like those seen in SA, but this time restricted to the verbal domain. This pattern might be suggestive of parallel semantic control systems organised according to modality. (3) An input processing deficit, where performance in all auditory tasks (semantic and non-semantic) is severely impaired in relation to other modalities. ‘Noisy’ auditory input could lead to error-prone activation of amodal concepts within the ATL, and since auditory cortex is responsive to both speech and non-speech sounds (Benson, et al., 2001), such a deficit might affect semantic judgments for environmental sounds as well as speech. (4) A combination of damage to the auditory input paired with damage to semantic control regions might lead to deficits in semantic control across domains, with an accentuated deficit in the verbal domain, if auditory input deficits can normally be compensated for by executive control mechanisms.

In the case study that follows, we assess (i) whether the patient shows sensitivity to control manipulations only in the verbal domain, (ii) if he shows association between executive and comprehension impairments along modality specific lines, and (iii) if any of the accounts above might be able to explain his impairment.

Case report

Our male participant, DNe, was 68 years old, with a secondary school education until the age of 15. He had had several jobs prior to his stroke, including being a bus driver and draftsman. He had a large left hemisphere lesion resulting from haemorrhage 22 years previously, which was characterised via lesion tracing using the Damasio templates (Damasio & Damasio, 1989). His MRI showed damage to the angular gyrus (BA 39, 40) spreading anteriorly to include large sections of the temporal lobe (particularly the superior temporal gyrus), and prefrontal regions including BA 6, 9, 44, 47, and the majority of BA 45 (see Figure 3.1). He had right-sided hemiplegia.

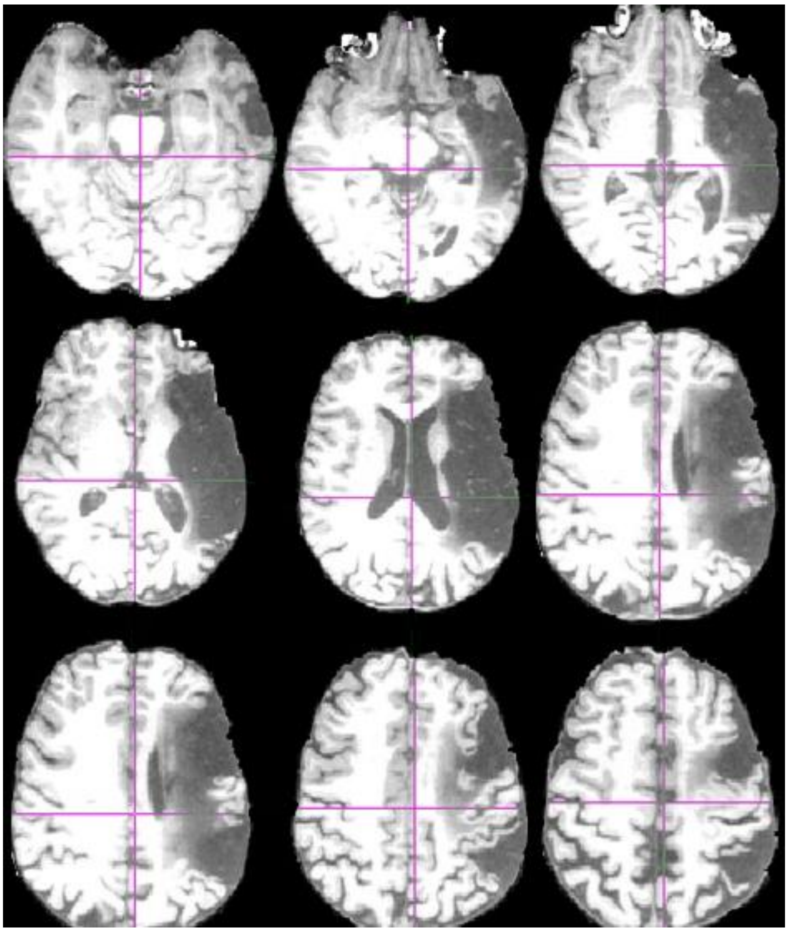


Figure 3.1: MRI images of DNe's lesion

DNe was severely dysphasic: over the course of the study he said only, 'yes', 'no' and 'why', with some evidence of counting up to three (when self initiated). He showed verbal comprehension impairments, and severe speech processing impairment on auditory discrimination and rhyme judgment tasks (background neuropsychological assessments are detailed in Table 3.1). Nonetheless, a pure tone audiogram reveals he had normal, or higher than the average age-matched norms for tones between 500Hz and 4000Hz (Davis, 1995). His hearing level was marginally impaired at a very low (250Hz) and very high tones (8000Hz). Impairments in this range are not expected to impact on the perception of speech, given the spectral properties of speech (Charpentier, 1986).

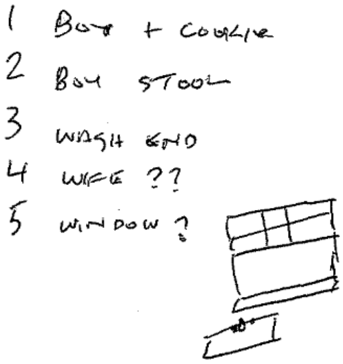
Table 3.1: Background neuropsychological test scores

	Test	Max	Normal cut-off	DNe
Picture naming	From Cambridge semantic battery	64	59.1	0*
Auditory discrimination	Minimal pairs (PALPA 2)	72	63.7	46*
Rhyme judgment	Spoken words (PALPA 15)	60	NA	29
	Written words (PALPA 15)	60	NA	37
	Pictures (PALPA 14)	40	NA	22
Comprehension	Cambridge word-picture matching	64	62.7	56*
	Word-picture matching (PALPA 4)	40	35.6	34*
	Spoken sentence-to-picture matching (CAT) – a subset of items	10		7
	Written sentence-to-picture matching (CAT) – a subset of items	10		7
Executive	Raven's Colored Progressive Matrices sets A, AB & B	36	13.0[a]	29
	Trail making A	24		24
	Trail making B	23		23
	Brixton Spatial Rule Attainment	55	28.0	34
Visual/spatial (VOSP)	Dot counting	10	8.0	8
	Position discrimination	20	18.0	20
	Number location	10	7.0	8
	Cube analysis	10	6.0	9
Attention (TEA)	Map search	80	38.4	43
	Visual elevator count	10	1.3	10
	Telephone search (time per target)		2.0	3.9
	Auditory elevator count	7	4.2	5
	Auditory elevator count with distraction	10	2.6	1*

Working memory	Auditory digit span (forwards)	-	5	0*
	Auditory digit span (backwards)	-	2	0*
	Auditory digit matching span (PALPA 13) with ‘yes’ or ‘no’ response	7		6
	Written digit matching span (using PALPA 13 materials) with ‘yes’ or ‘no’ response	7	NA	4
	Corsi block-tapping task	7	3.6	3*

* Denotes impaired performance. Control performance and normal cut-offs taken from published texts except where stated. NA = not available. [a] = norms standardised on children. PALPA (Psycholinguistic Assessments of Language Processing in Aphasia, Kay, Lesser & Coltheart, 1992), Cambridge Semantic Memory Battery (Adlam, Patterson, Bozeat & Hodges, 2010; Bozeat, Lambon Ralph, Patterson, Garrard & Hodges, 2000), CAT (Comprehensive Aphasia Test; Swinburn, Porter & Howard, 2004), Raven’s Colored Progressive Matrices (Raven, 1962), Trail Making test (Reitan, 1958), Brixton Spatial Rule Attainment Task (Burgess & Shallice, 1997), VOSP (Visual Object and Space Perception battery, Warrington & James, 1991), TEA (Test of Everyday Attention, Robertson, Ward, Ridgeway & Nimmo-Smith, 1994), Corsi block-tapping task (Kessels, van Zandvoort, Postma, Kappelle & de Haan, 2000).

DNe was notably expressive in his mannerisms, and was able to communicate to some extent through writing and drawing, for example, describing the ‘cookie theft’ cartoon (see Figure 3.2). In contrast, his spoken description comprised only repetition of the word ‘yeah’ with hand gestures pointing to different aspects of the picture. It was noted in preliminary testing that he showed refractory effects only in the verbal domain. Impairments on executive control/attention tasks were largely restricted to the auditory domain, for example the elevator counting task, TEA (Robertson, et al., 1994). In contrast, non-verbal executive tasks, such as the trail making and Brixton Spatial Rule task were performed within the normal range (see Table 3.1).



1 BOY + COOKIE
2 BOY STOOL
3 WASH END
4 WIFE ??
5 WINDOW ?

Figure 3.2: DNe’s written description of the Cookie Theft picture (Goodglass & Kaplan, 1983).

Experimental tasks

In the following section we investigate (1) a go-no go task involving auditory and written words for semantic and phonological judgements, (2) semantic processing across picture, written and spoken word and environmental sound tasks, (3) the effect of semantic variables on comprehension; e.g., imageability and frequency, (4) semantic control manipulations across modalities, (5) cyclical matching across modalities and (6) effect of degraded speech input on controls’ performance on our experimental tasks.

1. Go-no go task involving auditory and written words for semantic and phonological judgements

In order to compare performance across modalities, a go-no go task was devised in a 2x2 design, comparing two modalities (written and spoken), and two conditions, semantic or phonological. The semantic condition involved deciding if words were animals or man-made objects. The phonological condition involved distinguishing words beginning with a /b/ and those beginning with other phonemes (/n/, /p/, /m/).

Procedure

75% of 200 trials involved a ‘go’ response (a button press), and 25% involved inhibiting a response, or button press (‘no go’). In the written conditions, a word appeared on the screen for the length of the trial (1500ms), and for the auditory conditions, a green dot was displayed whilst the sound file played (mean 474ms, 241ms) with the trial length fixed at 1500ms. In the perceptual task, nonwords of one syllable which began with /b/ required a ‘no go’ response (e.g., ‘bip’, ‘bem’), whilst all other non-words, which had as their initial phoneme /n/, /p/ and /m/ required the spacebar to be pressed (e.g., ‘nup’, ‘pag’, ‘mip’). In the semantic task, animals required a ‘no go’ response (e.g., ‘sheep’), whilst manmade items required a ‘go’ response (e.g., ‘chair’). All items were monosyllabic. To explore the effect of time of presentation, the auditory semantic task was presented for both 1500ms and 650ms (in separate testing sessions). E-prime was used to present the stimuli and collect the responses. Both accuracy and RT were recorded. RT analysis is for correct responses only.

Results

Reaction time data (RT, shown in Table 3.2) revealed no significant differences ($p > .1$), so accuracy effects are reported. In both the written semantic and perceptual task, DNe scored near ceiling (193/200 and 196/200 respectively). In the auditory perceptual task, DNe’s performance fell to chance. He scored 99/200, with the majority of errors (68%) reflecting failures to respond on ‘go’ trials. In the auditory semantic task, DNe scored 156/200. Again, the majority of errors (77%) were no responses on ‘go’ trials. A McNemar test revealed higher accuracy on the semantic task ($p < .001$). Reducing the trial length to 650ms in the auditory semantic task reduced DNe’s accuracy to 90/200, with 87% of errors from not responding to ‘go’ trials. A McNemar test showed a significant effect of presentation time on accuracy: $p < .001$.

Table 3.2: DNe's reaction time in the go-no go task

		Mean (ms)	SD
Written	Semantic 1500ms	778	230
	Perceptual 1500ms	745	201
Spoken	Semantic 1500ms	712	159
	Semantic 650ms	526	116
	Perceptual 1500ms	1145	220

Written/spoken refers to presentation modality. Semantic/perceptual refers to the type of decision. 1500ms/650ms refers to the trial duration. Trials where the reaction time was greater than 2 SD from the mean were not included in analysis.

Summary

These results suggest an auditory processing deficit, or a input processing deficit paired with a semantic control deficit. DNe showed impairment in his ability to activate semantic representations, although this impairment was not specifically semantic. There was no evidence of an inhibitory deficit on no-go trials, but instead failure to activate phonological/semantic representations from spoken words on go trials. This pattern would be expected to occur with an input processing deficit. In the next section, we explore how this deficit affects semantic tasks across modalities.

2. Semantic processing across picture, written, spoken word and environmental sounds tasks

We investigated DNe's performance across modalities in a range of tasks which assess semantic comprehension.

Procedure

We used two tests from the Cambridge Semantic Battery (Adlam, Patterson, Bozeat, & Hodges, 2010; Bozeat, et al., 2000), (1) The Camel and Cactus task (CCT, Bozeat et al., 2000) contained 64 trials, and involved matching a probe with one of four related items (e.g., does CAMEL go with CACTUS, TREE, SUNFLOWER, or ROSE?). There were three versions of the test, (i) a picture-picture matching task, matching a probe picture (e.g., CAMEL) with a target picture (e.g., CACTUS); (ii) a written word-written word matching task, matching a written probe word with a written target word; and (iii) a spoken word-written word matching task, matching a spoken probe with a written target word. All 3 conditions used the same items, and were presented on different testing sessions. In both tasks in which written words were used, the target and distractors were read out aloud by the researcher. (2) A 48-item environmental sounds matching task (Bozeat et al., 2000) involved matching a sound or word to one of ten pictures. The distractors were semantically related to the target. The probe was given as a sound (e.g., ‘woof’), spoken word (e.g., ‘dog’) or written word. Both tasks were untimed, and spoken words were only presented once.

Results

Camel and Cactus Task results: DNe was in the normal range for the CCT task when the materials were presented as pictures or written words, suggesting he did not have a substantial impairment of semantic cognition across modalities. However, he was impaired on tasks involving auditory materials.

A McNemar test showed no significant difference between written and picture versions of the CCT ($p = .109$). In contrast, DNe’s performance on the spoken version of the task was significantly worse than both the written ($p = .001$) and picture versions ($p < .001$). We examined the extent to which DNe was impaired in relation to controls by using the “Singlims” procedure (Crawford & Garthwaite, 2002), which uses a modified t-statistic to examine whether an individual is significantly below a control group, taking into account group size and standard deviation. This suggested his accuracy was only impaired in the spoken version of the task, not the written or picture versions (see Table 3.3).

Environmental sounds results: DNe showed a significant impairment in relation to controls in environmental sound and spoken word modalities, but showed normal performance with written words (shown in Table 3.3). Performance on spoken words and sounds was equivalent (McNemar test, p = .815).

Table 3.3: DNe's performance on semantic tasks across modalities

	Test	Max	Control mean (SD)	DNe	Singlims
Camel and Cactus task	Picture-picture matching	64	58.9 (3.10)	61	t = .646, p = .534
	Written word matching	64	60.7 (2.06)	56	t = 2.175, p = .058
	Spoken word-written word matching	64	(assumed same as written version)	36*	**t = 11.432, p < .001**
Environmental Sounds task	Sound-picture matching	48	41.2 (2.5)	33*	**t = 3.127, p = .012**
	Spoken word-picture matching	48	47.8 (0.6)	36*	**t = 18.751, p < .001**
	Written word-picture matching	48	(assumed same as spoken version)	47	t = 1.271, p = .235

* Denotes impaired performance. Bold represents significant impairment. Camel and Cactus task and Environmental Sounds test (Bozeat, Lambon Ralph, Patterson, Garrard & Hodges, 2000). A non-parametric t-test (Singlims) was used to compare DNe's performance to the control mean (Crawford, Garthwaite & Ryan, 2011).

Summary

DNe's results again show an input processing deficit. His performance on standard measures of semantic processing was only impaired in the auditory modality (both spoken word and environmental sound stimuli). In aphasia patients, there is often a coupling between spoken and written comprehension (Behrns, Wengelin, Broberg, & Hartelius, 2009; Warrington & McCarthy, 1983), suggesting similar control demands across these modalities.

3. Effect of semantic variables on comprehension.

SA patients show better performance on highly imageable items compared with items which are more abstract in meaning (Hoffman, et al., 2010; Jefferies, et al., 2007). Conversely, they show no effect of word frequency (Hoffman, Jefferies, et al., 2011; Hoffman, Rogers, et al., 2011; Jefferies, et al., 2007). This is also one of the key characteristics of 'access' patients, who show a lack of frequency effects (Crutch & Warrington, 2005a), with worse performance on abstract words compared to concrete words (Crutch & Warrington, 2005a; Warrington & McCarthy, 1983). We assessed DNe's performance a synonym judgement task which manipulated items according to imageability and frequency (Jefferies, et al., 2009).

Method

A synonym judgement task involved matching a probe word with a target word presented alongside two unrelated distractors. This had 96 items in two frequency bands (*high* and *low*: 128 (102) and 4.6 (4.5) counts per million in the Celex database respectively) and three imageability bands (*high*: 622/700, SD = 14; *medium*: 452/700, SD = 26; and *low*: 275/700, SD = 17), producing sixteen trials in each of the six frequency-by-imageability conditions (see Jefferies, et al., 2009). For example, a low imageability, low frequency item involved matching SUFFIX with INFLECTION, PERPETRATOR or TEMERITY. A low imageability, high frequency item involved matching CONSIDER to THINK, DEVELOP or DETERMINE. A high imageability, low frequency item involved matching CHESTNUT with CONKER, SWAMP or EAGLE. Finally, a high imageability, high frequency item involved matching MONEY with CASH, CAR or CHURCH. Responses were untimed. In two versions of the task, examined in separate sessions, the probe was presented as either a spoken or written word. In both versions, the response options were presented as written items and also read aloud by the researcher.

Results

Table 3.4 shows DNe's performance on spoken and written synonym judgement tasks. There was a significant overall difference between DNe's performance on the spoken and written tasks: $\chi^2(1) = 14.527$, $p < .001$. In the written task, DNe showed an effect of imageability, with higher performance on more imageable words: $\chi^2(2) = 25.59$, $p < .001$. Modified t-tests, using the singlims procedure (Crawford & Garthwaite, 2002), established the degree of deficit at each level of imageability and frequency are presented in

Table *3.4*. An imageability effect was found in the spoken version of the task: $\chi^2(2) = 12.673$, p = .002. There was no effect of frequency in either the written version: $\chi^2(1) = .549$, *p* = .459; or spoken version: $\chi^2(1) = 1.191$, *p* = .275, consistent with SA and 'access' patients' performance.

Table 3.4: DNe's scores on the synonym judgement task

	Test	Max	Control mean (SD)	DNe	Singlims
Written synonym judgment	Overall	96	94.5 (1.76)	75*	**t = 10.813, p <.001**
	Low imageability	32	30.8 (1.32)	15*	**t = 11.681, p <.001**
	Medium imageability	32	32 (0.65)	29*	**t = 4.504, p <.001**
	High imageability	32	31.85 (0.49)	31	**t = 1.693, p = .107**
	Low frequency	48	47.4 (0.99)	36*	**t = 11.238, p <.001**
	High frequency	48	47.1 (1.00)	39*	**t = 7.856, p <.001**
Spoken probe synonym judgment	Overall	96	(assumed same as written)	65*	**t = 16.357, p <.001**
	Low imageability	32		14*	**t = 21.421, p <.001**
	Medium imageability	32		26*	**t = 9.008, p <.001**
	High imageability	32		25*	**t = 13.643, p <.001**
	Low frequency	48		30*	**t = 17.152, p <.001**
	High frequency	48		35*	**t = 11.760, p <.001**

*Denotes impaired performance. Max = number of items in each task. Bold represents significant impairment. Synonym judgement task (Jefferies, Patterson, Jones & Lambon Ralph, 2009). "Singlims" procedure (Crawford & Garthwaite, 2002) uses a modified t-statistic to examine whether an individual is significantly below a control group, taking into account group size and standard deviation.

Summary

DNe's performance on this task suggested impairment beyond an auditory input processing deficit. Although there was a significant difference between accuracy on spoken and written tasks, combined with impaired ability to access the meanings of even highly imageable probe items when these words were spoken aloud, DNe showed characteristics of SA and 'access' patients in the written domain, indicating that semantic variables impact on his performance in non-auditory modalities. An impairment was perhaps not seen on the written word form of the CCT because this task did not involve judgments about abstract items. Abstract words may be more challenging for DNe to comprehend for at least two reasons: (1) since their processing draws less upon sensory-motor features, they may make more demands on auditory-verbal mechanisms (Pavio, 1986); (2) these words may also pose greater demands on executive-semantic mechanisms, since they can have a wider range of meanings in different situations – they have a large number of lexical associates, appear in a large number of linguistic context and have a large number of meanings or senses (Hoffman, Rogers, et al., 2011). The absence of frequency effects even in the written domain, in line with the performance of SA and 'access' cases, is consistent with this hypothesis, since frequent words are also thought to draw more heavily on semantic control, counteracting their normal processing advantage in patients with semantic control deficits (Hoffman, Jefferies, et al., 2011; Hoffman, Rogers, et al., 2011). This is because high frequency items activate spurious or irrelevant associations. Almaghyuli et al. (2012) showed that frequency of distractors influences performance – so that there is higher performance on high frequency items when they are presented with low frequency items – as these words have less varied meanings and occur in fewer contexts (e.g., KEEP with SAVE, DERIVATION or ENIGMA). These findings motivate further investigation of the impact of semantic control demands on comprehension across modalities, given that background neuropsychological testing reveal executive deficits restricted to the verbal domain.

4. Semantic control manipulations across modalities

DNe completed three tasks that manipulated semantic control demands in different ways, (1) by increasing the semantic distance between categorically related items, (2) by manipulating semantic ambiguity through comparisons of the dominant or subordinate meaning of homonyms, and (3) by comparing semantic matching across closely or weakly associated items. All 3 tasks assessed performance across modalities. These assessments were designed for the use in SA patients, who show an effect of semantic distance and semantic ambiguity (these tasks have not been run on 'access' patients so far). All tasks had unlimited response time.

Task 1: Nearest Neighbour Judgements

The semantic nearest neighbour task, involved matching a probe word to a target word in the same semantic category: the 'nearest neighbour' (Noonan, et al., 2010). This was therefore not an association matching task, but instead selection was based on how many features overlapped with the probe item. There were 4 conditions, in a 2 by 2 design, manipulating semantic similarity and modality. The degree of semantic control required was manipulated by varying semantic similarity of the probe with the target, whilst keeping the distractors the same. When the probe and the target were closely related, they shared much of their semantic structure, making it relatively easy to determine the target word, e.g., HAT, with CAP, FUTON or SPADE. When the probe and the target were distantly related, additional semantic control was required to work out the relevant semantic link, since there were overlapping features, e.g., HAT, with STOCKING, FUTON, or SPADE. Further details of the test and further examples of the stimuli can be found in Noonan et al. (2010). We contrasted two modalities, spoken and written. The response options were always presented as written words to reduce verbal short term memory demands, but the probes were either read aloud or shown as a written word. The same 64 words were tested in all conditions of relatedness and modality, over different testing sessions, which led to 256 trials.

Results

Table ***3.5*** shows DNe’s performance on the nearest neighbour task. A McNemar test revealed a significant difference between performance on written and spoken versions ($p < .001$). DNe’s high performance on the written task produced no significant difference between close or distant category decisions: χ^2 (1) = 2.133, p = .144. However, in the spoken version of the task, there was a semantic control effect – close category decisions were significantly more accurate than distant category decisions: χ^2 (1) = 7.850, p = .005.

Table 3.5: DNe's performance on semantic control tasks across modalities

	Test	Max	Control mean (SD)	DNe	Singlims
Ambiguity test	Written probe – dominant meaning	30	29.5 (0.53)	25*	**t = 7.937, p <.001**
	Written probe - subordinate meaning	30	28.875 (0.64)	16*	**t = 18.941, p <.001**
	Spoken probe – dominant meaning	30	(assumed the same as written probe)	23*	**t = 11.563, p <.001**
	Spoken probe – subordinate meaning	30		12*	**t = 24.859, p <.001**
Nearest neighbour task	Written probe - close	64	64 (0)[a]	62*	
	Written probe - distant	64	62.625 (1.685)	58*	**t = 2.588, p = .036**
	Spoken probe – close	64	(assumed the same as written probe)	56*	**t = 75.425, p <.001**
	Spoken probe - distant	64		39*	**t = 13.219, p <.001**

* Denotes impaired performance. Bold represents significant impairment. Ambiguity and nearest neighbour task (Noonan, Jefferies, Corbett & Lambon Ralph, 2010). Max = number of items in each task. "Singlims" procedure (Crawford & Garthwaite, 2002) uses a modified t-statistic to examine whether an individual is significantly below a control group, taking into account group size and standard deviation. [a] = no singlims test conducted as the SD for controls was 0.

Task 2: Comprehension of ambiguous words

A semantic ambiguity task (Noonan et al., 2010) examined the ability of DNe to selectively focus on the less dominant meanings of polysemous words. A word with multiple meanings is thought to activate these meanings in parallel (Onifer & Swinney, 1981; Rodd, Gaskell, & Marslen-Wilson, 2004; Simpson & Burgess, 1984). Less frequent meanings, however, show a processing disadvantage (Simpson, 1985). Therefore, control processes are required to select less frequent meanings, and avoid the dominant interpretation (Rodd, et al., 2005; Zempleni, et al., 2007). The semantic ambiguity task involved matching a homonym to a related word, in four conditions, in a 2 x 2 design, manipulating dominance (e.g., *dominant* or *subordinate*), and modality for the probe word (*written* and *spoken*). As before, response options were always presented as written words. In half of the trials, the target referred to the dominant meaning of the probe (e.g., FILM to be matched with MOVIE, COAL, PRINCE, or GOLF. The other half of the trials used the subordinate meaning (e.g., FILM, to be matched with SKIN, COAL, PRINCE or GOLF). There were 30 items, presented at both levels of meaning, and in both modalities, on different testing sessions (totalling 120 trials).

Results

DNe's scores in the ambiguity task are presented in Table 5. There was no overall difference between performance on the written and spoken tasks (p = .424). In both modalities, he showed a semantic control deficit – that is, lower accuracy on non-dominant than dominant meaning trials. This was significant in the written modality: χ^2 (1) = 4.800, p = .028, and the spoken modality: χ^2 (1) = 8.297, p = .004. Modified t-tests (Crawford & Garthwaite, 2002) showed DNe was impaired in all conditions in relation to controls (see

Table ***3.5***).

Task 3: Strong and weak association matching

To investigate if DNe had a semantic control deficit for non-verbal materials, we used a task manipulating semantic control demands across four conditions, with two variables, association strength between the probe and target (strong and weak) and modality (spoken word vs. picture). Association strength is often used to manipulate semantic control demands in the functional neuroimaging literature (Badre & Wagner, 2002, 2007; Thompson-Schill, et al., 1997; Wagner, Paré-Blagoev, et al., 2001), since strong associations are thought to be retrieved relatively automatically, while weak associations require more effortful controlled semantic retrieval followed by a comparison of different possible semantic links. This task used items from Krieger-Redwood (2012). Stimuli were acquired from the MRC psycholinguistic database. The EAT (Edinburgh Association Thesaurus) was used to acquire associations. The 'highly' related items were ones with the highest number of responses (e.g., 57% of people said “cat” for DOG). The ‘weakly’ related items were ones with the lowest number of responses (e.g., 1% of people said “paw” for DOG).

There was no significant difference between frequency of the probe (M = 51, SD = 100) and either the target in the strong condition (M = 67, SD = 166), or weak condition (M = 60, SD = 90): F<1, or any of these 3 items paired together in a t-test ($t \leq 1.124$, $p \geq .263$). There was also no effect of imageability between the probe (M = 592, SD = 49), or target in the strong condition (M = 577, SD = 84) or weak condition (M = 579, SD = 67): $F(2,140) = 1.521$, $p = .222$. However, there was a difference between the target and probe for the weak condition: $t(172) = 2.095$, $p = .038$, and approaching significance for the strong condition: $t(154) = 1.837$, $p = .068$, but there was no difference between the strong and weak condition targets: $t < 1$. In the spoken version, pre-recorded spoken words were presented. In the picture version, items were sourced from Wikimedia commons, a freely licensed media file repository (with all images in the public domain). Picture stimuli were coloured pictures all fitted to a standard 255 x 149 pixel size.

This task involved matching strong associates, such as KNIFE with FORK, or weak associates, such as SHOE with BRUSH. The target was presented alongside two unrelated distractors such as CLOUD and ARROW. There were 90 items. This task is shown in Figure 3.3.

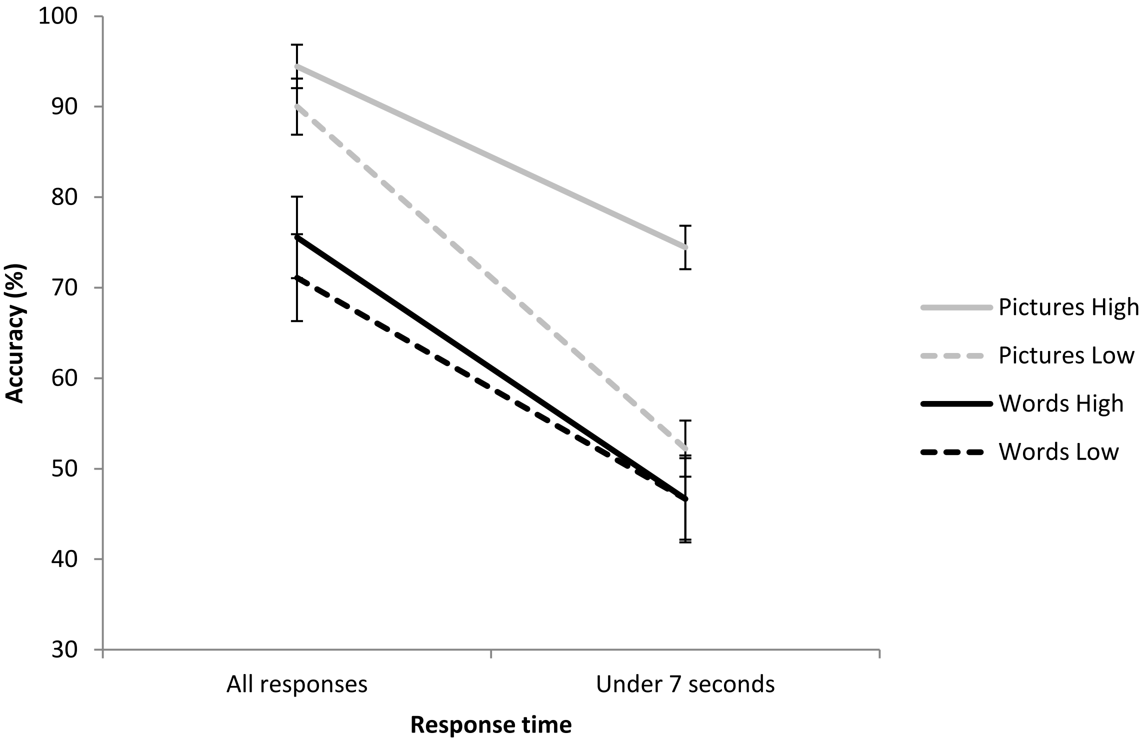
Weak associates (left) and strong associates (right). Pictures are sourced from the Wikimedia commons. Commons is a freely licensed media file repository, all images are in the public domain.

Figure 3.3: Example of the Picture Semantic Association test

<u>Results</u>

DNe's performance is shown in Figure 3.4. With an unlimited time to respond, DNe was able to detect the majority of picture associations (92% correct overall), and made some errors on spoken word associations (73% correct overall), but there was no significant difference between overall performance on these two tasks: χ^2 (1) = .635, p = .425. In both tasks, his performance did not vary according to strength of association. In the word task, he scored 76% and 71% for high and low association conditions, respectively: $\chi^2(1) = .455$, $p = .500$. In the picture task, he scored 94% and 90% for the high and low association conditions, respectively: $\chi^2(1) = 1.239$, $p = .266$.

It was noted, however, that DNe often responded extremely slowly. Therefore, we assessed only those trials completed within seven seconds. Accuracy fell on both tasks: from 92% to 63% in the picture task, and from 73% to 47% in the spoken word task. There was no significant difference between these modalities: $\chi^2(1) = .004$, $p = .951$. For the word task, DNe scored 47% for both high and low association conditions. For the picture task, DNe scored 74% and 52% for the high and low association conditions respectively. This effect of association strength was significant: $\chi^2(1) = 9.569$, $p = .002$.



Error bars showing standard error of mean. Chance level = 33%.

Figure 3.4: The effect of association strength on accuracy in spoken word and picture tasks.

Summary

DNe showed sensitivity to semantic control manipulations across modalities. Manipulations of semantic distance between probe and target, ambiguity and association strength all produced evidence for a semantic control deficit in written, spoken and picture modalities. DNe's impairment cannot be explained entirely by an auditory input processing deficit, since he shows parallel deficits across modalities like SA patients (Jefferies & Lambon Ralph, 2006). Nonetheless, his performance is notably worse overall on spoken word tasks, consistent with the view that a control deficit co-occurs with an input processing deficit. These two deficits appear to interact in tasks involving comprehension of spoken words, and produce a larger semantic control deficit in the auditory domain.

5. Cyclical matching across modalities

Cyclical matching experiments were examined across four modalities: written words, spoken words, environmental sounds and pictures. This method was developed from previous experiments (Gardner, et al., 2012; Warrington & Crutch, 2004;

Warrington & McCarthy, 1983). DNe matched a probe item (presented in one of the above modalities) with a target picture presented alongside three distractor pictures. The same items were presented repeatedly across several cycles, such that recently-selected targets became distractors, and distractors became targets. Jefferies et al. suggested that control demands increase across this task, because over cycles the target and distractors become highly activated, and so choosing among competing items becomes more difficult. A reduction in accuracy across cycles, referred to as a 'refractory effect', is found in SA patients with impaired semantic control. Warrington and colleagues also find refractory effects in 'access' patients, and suggest that items, after activation, become temporarily unavailable.

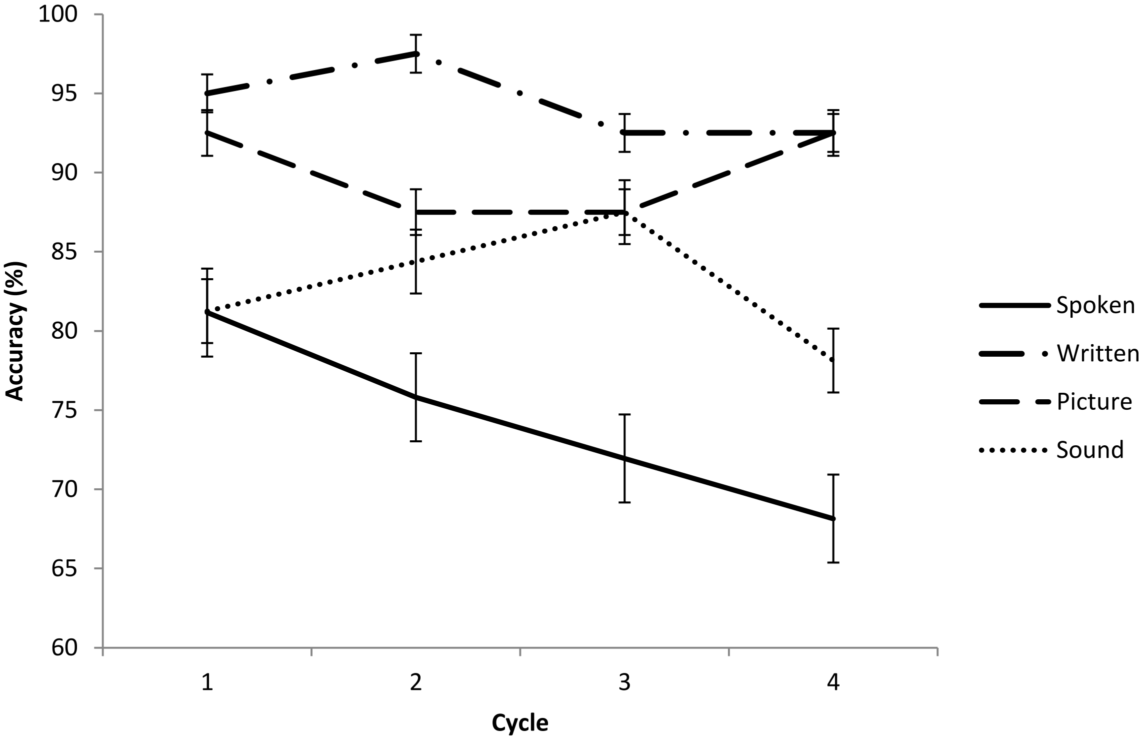
In the written word, non-verbal sound and picture conditions, the distractor items were semantically related. In the verbal-spoken domain only, (1) the effect of semantic relatedness was assessed, comparing accuracy on related and unrelated sets. These required matching of the probe word 'kettle' with a picture of a kettle alongside either related items, such as WHISK, JUG and CORKSCREW, or unrelated items, such as BED, FORK and MOTORBIKE. (2) The effect of phonological relatedness was also assessed. A phonological-related trial used a spoken probe, such as 'watch', to be matched to a picture of a watch displayed alongside pictures of items beginning with the same phoneme, for example, WHEEL, WELL and WHIP. In the unrelated condition, distractors did not begin with the same phoneme, for example, FENCE, HOUSE and STAR.

Procedure

An array of four pictures was displayed; the probe item was presented together with the four-item array, either through speakers or as a picture or written word at the top of the screen. The participant indicated his response by pointing to one of the pictures, and the experimenter pressed a key which advanced the task onto the next trial. The experimenter recorded accuracy (our primary dependent variable) while response time (RT) was recorded by the computer. As soon as a response was given, the next trial was presented. The participant had ten seconds to respond, before the next trial was presented and an error was recorded. There were four practice items before the start of each block. There were 160 items in the written task, picture task and spoken semantically-unrelated tasks (all using the same stimuli as targets and distractors). This included 10 sets of semantically related items, with 16 trials for each set (4 trials per cycle, with 4 cycles). There were 128 items in the environmental sounds task (8 sets of 16 items). There were 288 items in the spoken semantically related task, using a spoken word version of the environmental sounds task (with 8 sets) and the picture task (with 10 sets). There were 256 items in the spoken phonologically related and unrelated conditions (16 sets of 16 items for each condition). Beyond the change in modality, other key aspects of the task remained consistent: there were always 4 cycles, in a 4 alternative forced choice design. There was an RSI of 0 seconds, between a response and the presentation of the following trial. The related and unrelated sets in the semantic and phonological manipulations employed the same items but assigned to different sets.

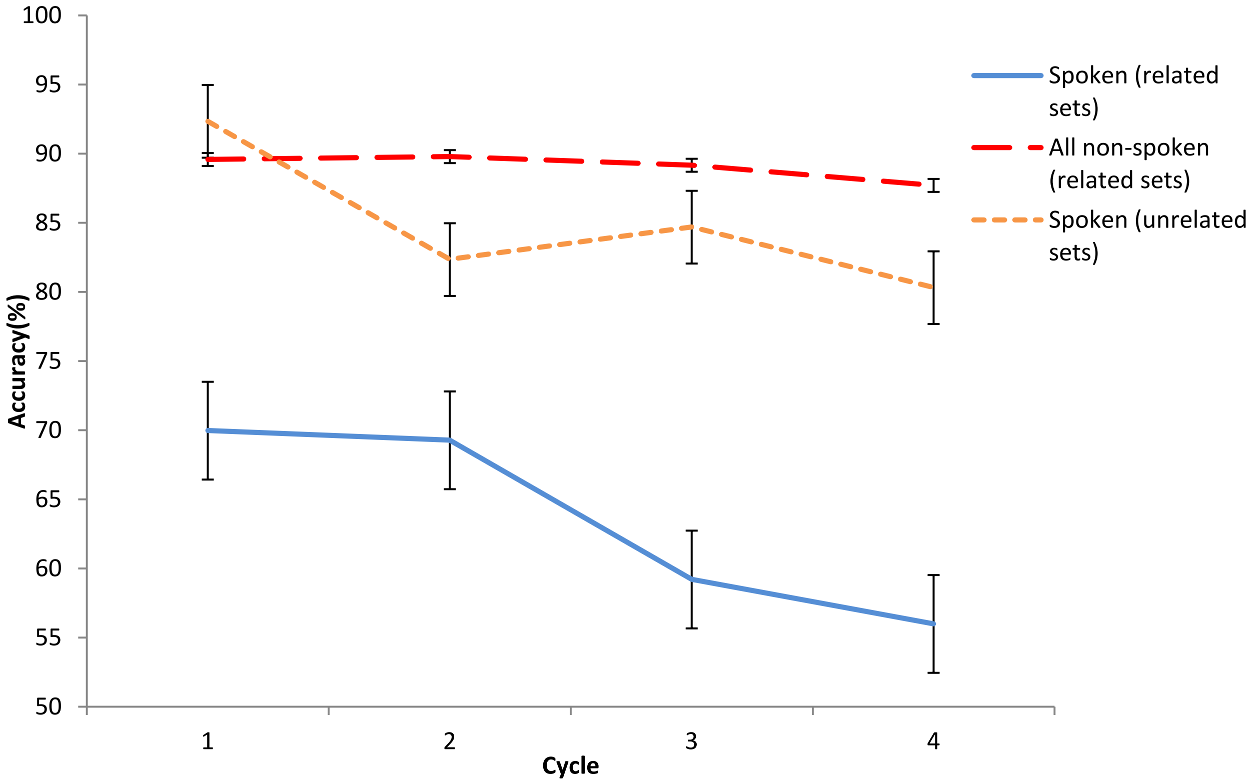
Results

DNe showed evidence of refractory effects, defined as declining accuracy across cycles, in all verbal-spoken versions of the task, but not in any non-verbal or non-auditory versions of the task. This included the environmental sounds, picture and written word tasks. DNe showed a gradual decline in performance over cycles in all spoken word versions of this task, including with both phonetically related and semantically related sets (see Figure 5). When analysing all spoken-verbal trials, the decline in performance was significant in a McNemar test between cycles 1 and 4 ($p = .001$). Equivalent analyses across all non-auditory tasks and/or non-verbal tasks (written, environmental sounds and picture tasks) yielded no effect of cycle. Using a McNemar test, and analysing data across both semantic and phonological spoken-word tasks, both related (p = .030) and unrelated ($p = .011$) sets showed significant refractory effects between cycles 1 and 4 (see Figure 3.6). When analysing related and unrelated sets together, the semantic ($p = .030$) and phonological conditions ($p = .023$) both showed refractory effects between cycles 1 and 4 (see Figure 3.7). The effect of relatedness of the semantic and phonological task is shown in Figure 3.8. There was no effect of cycle for the combined data from non-spoken modalities between any pair of cycles. There was also no refractory effect for any individual non-spoken task across any pairs of cycles ($p > .5$).



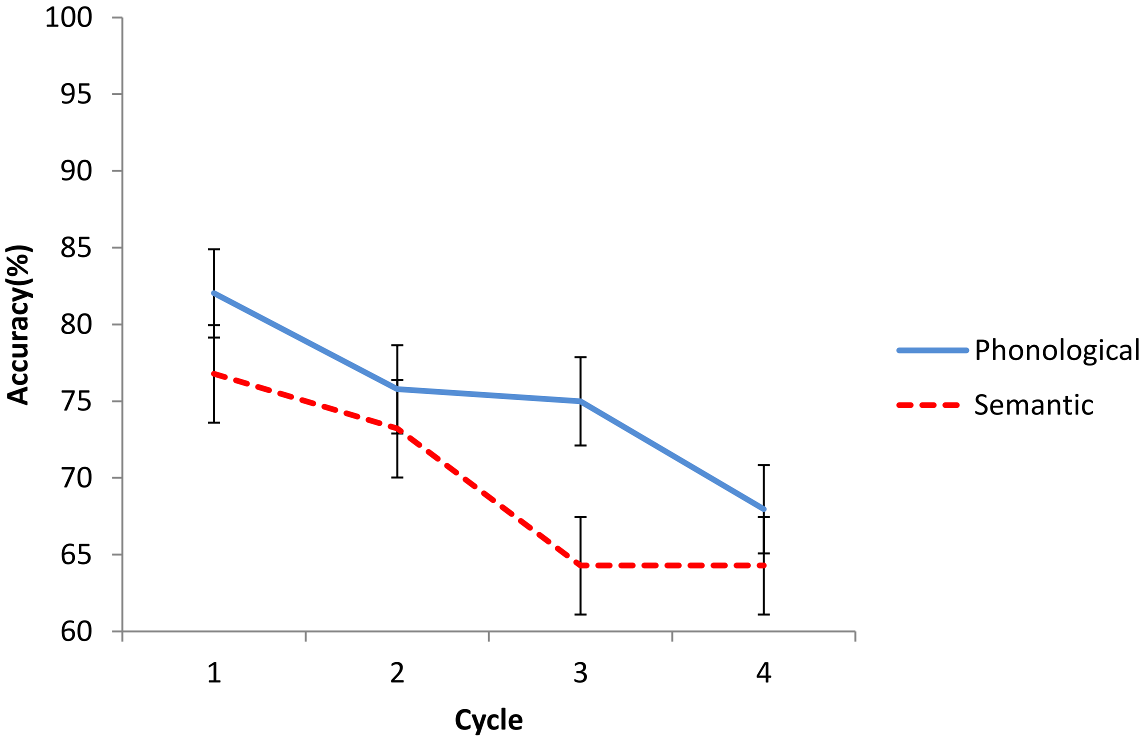
Error bars show standard error of mean. Spoken condition includes all spoken tasks: phonologically related and unrelated, and semantically related and unrelated sets.

Figure 3.5: DNe's semantic matching performance on the same items over four cycles across modalities.



Non-spoken modalities include written, environmental sounds and picture tasks. Error bars show standard error of mean.

Figure 3.6: DNe's cyclical semantic matching performance comparing related and unrelated distractors for spoken word-picture matching compared with non-spoken modalities



Phonological and semantic tasks, combining data from related and unrelated conditions. Error bars show standard error of mean.

Figure 3.7: DNe's refractory performance in phonological and semantic tasks

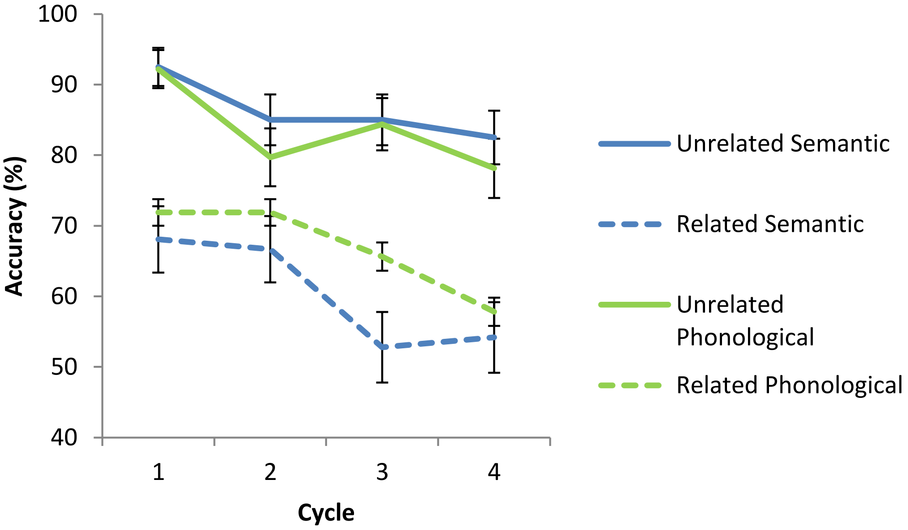


Figure 3.8: DNe's refractory performance with regards relatedness

A set of five logistic regressions analysed the predictive value of individual variables. Each model included two variables: modality/task (e.g., phonologically related versus unrelated sets) and cycle (see Table 3.6).

Table 3.6: Predictor variables for multiple logistic regression

Data entered into model	Task (A v. B)	Cycle
1. Cycle and modality: spoken v. nonspoken	**Wald = 47.489, *p* < .001**	**Wald = 11.067, *p* = .001**
2. Cycle and modality: environmental sounds v. spoken	**Wald = 6.088, *p* = .014**	**Wald = 11.263, *p* = .001**
3. Cycle and *non-spoken* modalities: pictures v. written words	Wald = 2.074, *p* = .150	Wald = .218, *p* = .641
4. Cycle and *non-spoken* modalities: pictures v. environmental sounds	Wald = 3.140, *p* = .076	Wald = .025, *p* = .876
5. Cycle and *non-spoken* modalities: written words v. environmental sounds	**Wald = 9.029, *p* = .003**	Wald = .366, *p* = .545
6. Cycle and *spoken tasks*: related v. unrelated, combining semantic and phonological sets	**Wald = 51.116** ***p* <.001**	**Wald = 12.557** ***p* < .001**
7. Cycle and *spoken tasks*: semantic v. phonological, combining related and unrelated sets	Wald = 3.740 *p* = .053	**Wald = 11.919** ***p* = .001**

This shows 7 logistic regression analyses, each looking at the effect of cycle, and a comparison between two tasks (or groups of tasks) from the refractory paradigm. Bold represents significant impairment.

(1) The first logistic regression included data from all tasks, and revealed a significant effect of cycle and task (results in Table 3.6). The data was then considered separately for verbal and non-verbal tasks. (2) A logistic regression using data only from the non-verbal tasks (including environmental sounds, written words and pictures) found no evidence for a predictive effect of cycle. Despite employing the auditory modality, the environmental sounds task resembled the pattern for

pictures in this experiment. (3) In contrast, the logistic regression with data from all verbal tasks (including semantic and phonological tasks with both related and unrelated distractors) found a strong effect of cycle. Dissecting this data in further analysis, we found the effect of cycle was replicated across all four spoken word conditions. (4) There was no difference between overall accuracy on semantic and phonological trials, suggesting DNe was equally impaired at both tasks. (5) There was a significant effect of relatedness of distractors, showing DNe's performance was significantly worse in the related condition (including data from both the semantic and phonological tasks) – although this did not interact with cycle. All the results are provided in Table 3.6.

Summary

DNe shows some similarities to SA patients. He shows strong refractory effects in the verbal domain, and his accuracy is affected by relatedness of the distractors, as in SA (Jefferies, et al., 2007). However, unlike both SA patients and at least some 'access' patients, DNe does not show refractory effects with environmental sounds (Crutch & Warrington, 2008b; Gardner, et al., 2012). With this task, he shows a striking modality effect with specific impairment of the spoken word domain. In addition, DNe shows a deficit in all spoken word tasks, including phonologically related items. These findings are consistent with an input processing deficit hypothesis, combined with a semantic control deficit, which results in greater impairment on later cycles, particularly notable on related sets which generate stronger competition.

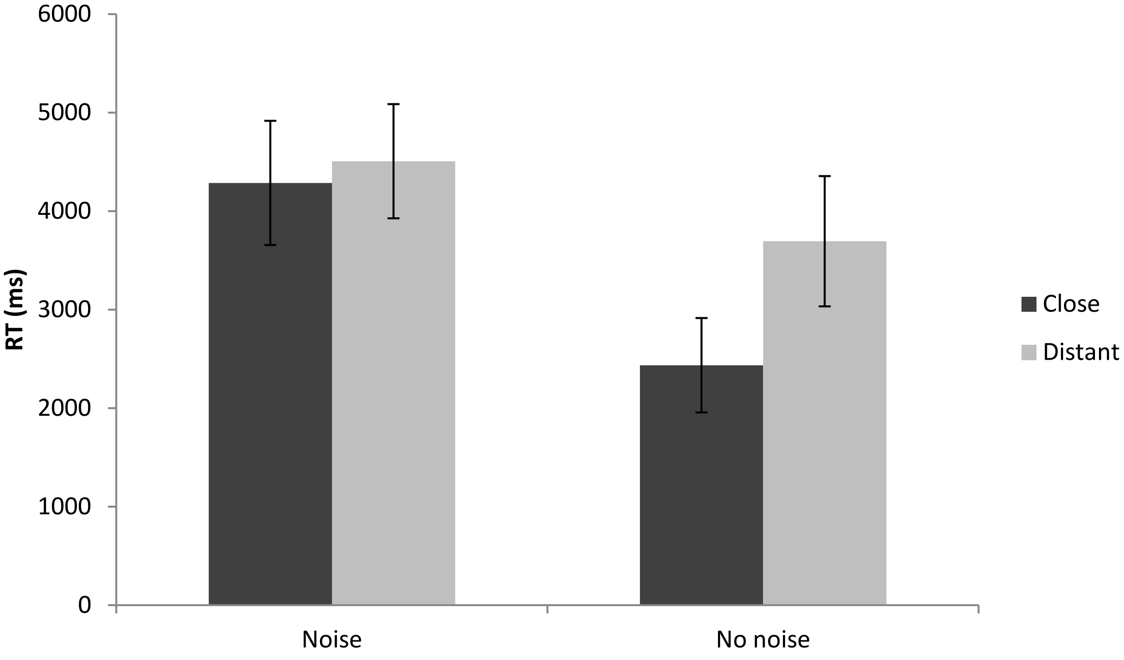
6. Effect of degraded speech input on controls

The evidence so far points to an input processing deficit, potentially combined with a semantic control deficit. The input processing deficit is revealed by DNe's more severe impairment in auditory-verbal semantic and phonological tasks compared with written and non-verbal tasks. However, it is unclear if this input processing deficit could give rise to the refractory effects and deficits on control-demanding tasks that DNe showed in the auditory-verbal domain. This pattern might instead reflect the interaction of the input deficit paired with a semantic control deficit, since in challenging tasks, degraded auditory input cannot be overcome via executive mechanisms.

In order to explore this issue, we tested the auditory-word and environmental sounds cyclical tasks in a group of twelve age-matched control subjects (age mean = 72 years, SD = 11years), without brain damage, and with an average education until 18 years. There were 4 males and 8 females. We presented words and/or sounds for comprehension both in white noise and in no noise. In the white noise condition, the sound files used in the 'no noise' condition were embedded in white noise, generated by Adobe Audition software. The amplitude of the noise was half that of the semantic stimulus, meaning the noise covered 50% of the sound from the audio file – leaving it partially audible. The tasks used were the nearest neighbour task (Study 3) and two refractory tasks involving environmental sounds and spoken word matching (Study 5). The order of these tasks was counterbalanced across subjects, and the tasks were run over two sessions.

Results

The data from the nearest neighbour task is shown in Table 3.7. As participants produced many errors in the 'noise' conditions, we focused analysis on accuracy, as RT showed a similar pattern (see Figure 3.9).



Error bars show standard error of mean.

Figure 3.9: Reaction time of controls in the Nearest Neighbour Task (Noonan et al., 2010).

In relation to accuracy, there was a strong effect of noise: $t(11) = 18.569$, $p < .001$. The difference between close and distant semantic category judgements was significant both in the noise condition: $t(11) = 4.046$, $p = .002$, and no noise condition: $t(11) = 4.267$, $p = .001$. There was an overall effect of both noise: $F(1, 11) = 344.819$, $p < .001$, and semantic distance: $F(1, 11) = 39.063$, $p < .001$. However, there was no interaction: $F(1, 11) = 1.782$, $p = .209$. Participants were greatly affected by noise, but this did not interact with semantic control demands. This is in contrast to the effects shown by DNe, who showed an effect of semantic control demands but only in the written domain.

Table 3.7: Nearest neighbour task for healthy participants in white noise and no noise conditions, with close and distant targets

	Close	Distant
White noise	43 (9.4)	35 (11.3)
No noise	99 (1.1)	94 (4.5)

Data shown are means (and standard deviation), accuracy correct as a percentage.

A 2 by 2 by 4 within subjects ANOVA was performed on the refractory data, examining the factors of task (word-picture or sound-picture matching), condition (noise or no noise) and cycle (1-4). The effect of task was non-significant: $F < 1$. There was a strong effect of noise: $F(1, 11) = 92.268$, $p < .001$, although this did not differ between tasks (task by noise interaction: $F(1, 11) = .151$, $p = .705$). The effect of cycle was significant: $F(3, 9) = 6.350$, $p = .013$, although this corresponded to improved accuracy across cycles, the opposite of DNe’s data. This was particularly prominent in the noise condition, since performance was at ceiling in the no noise condition, leading to a significant interaction between cycle and noise: $F(3, 9) = 9.841$, $p = .003$. The effect of cycle was greater in the word-picture than sound-picture matching tasks, reflecting an interaction with task: $F(3,9) = 5.023$, $p = .026$. This caused a three-way interaction of task by noise by cycles: $F(3, 9) = 5.575$, $p = .019$. The reaction time data is displayed in Figure 3.10.

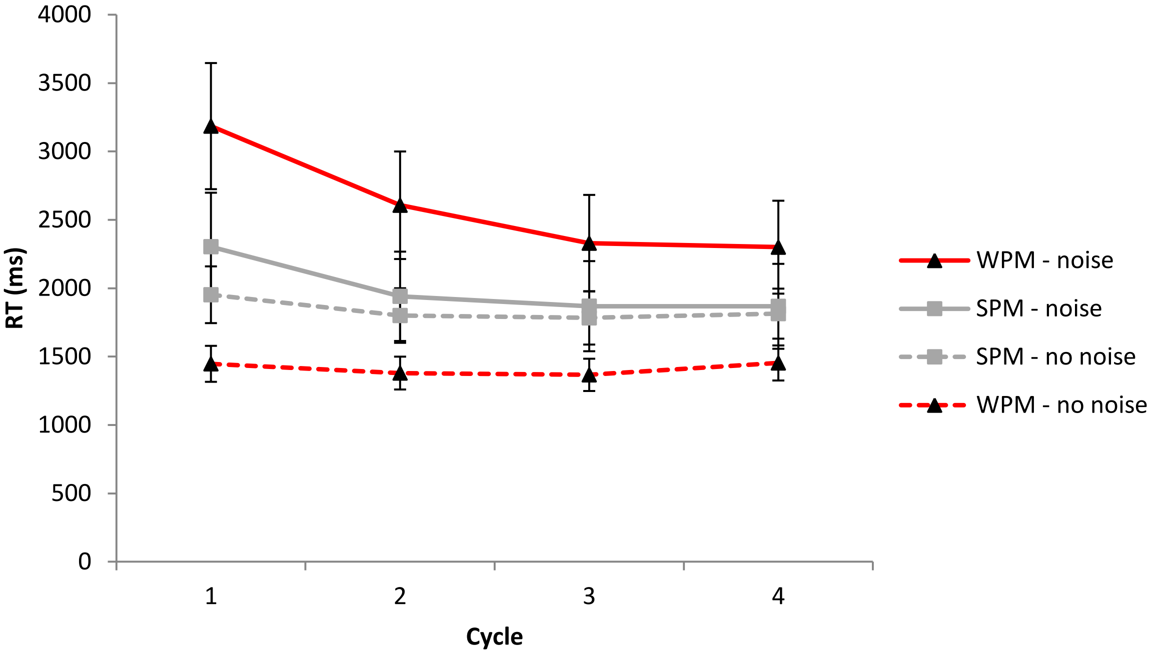
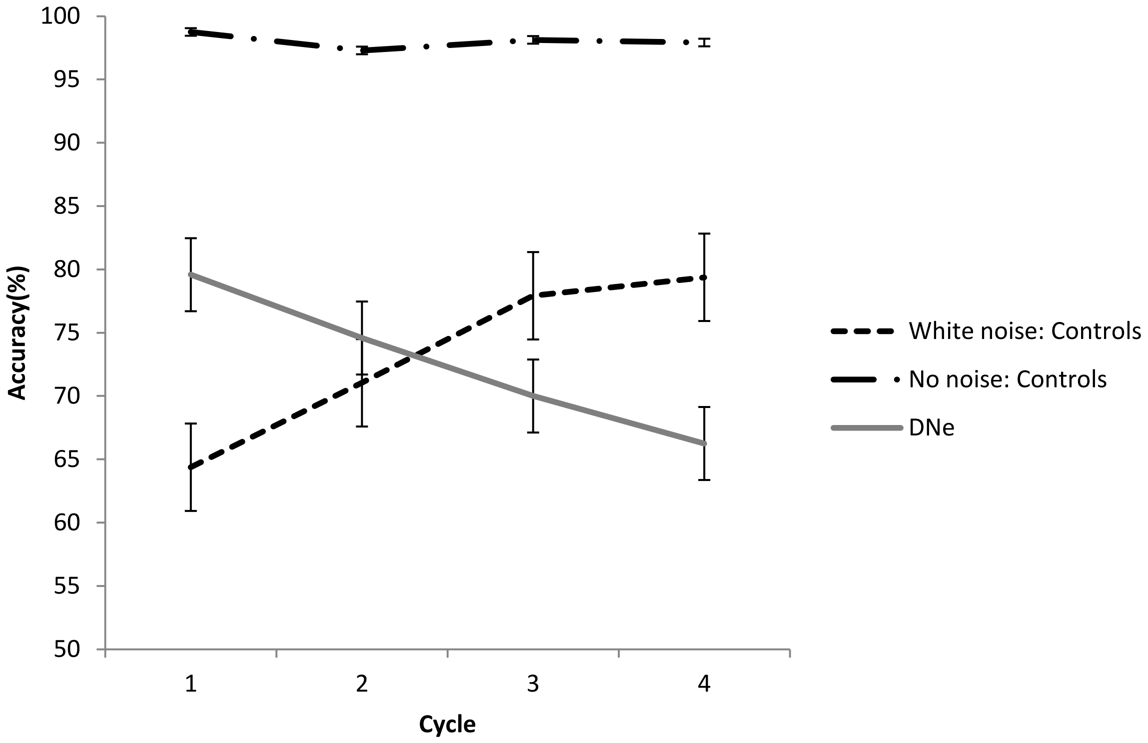


Figure 3.10: Reaction time of controls in the refractory tasks. Error bars show standard error of mean.

To unpick this three-way interaction, we examined each task separately.

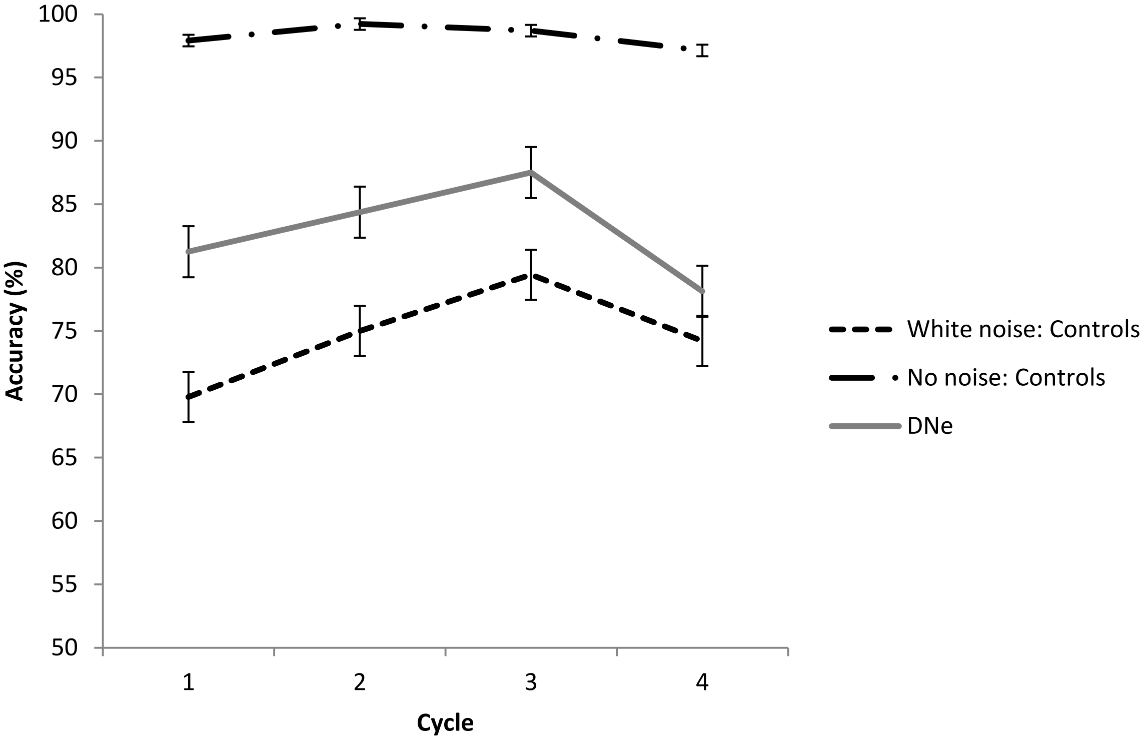
The spoken-word refractory task data is shown in Figure 3.11. A repeated-measures ANOVA revealed a significant effect of cycle: *F*(3,9) = 7.935, *p* = .007, noise: *F*(1,11) = 43.870, *p* < .001, and a significant cycle by noise interaction: *F*(3, 9) = 12.391, *p* = .002. In the spoken word no-noise condition, there was ceiling performance, and no significant cycle effect: *F*(3, 9) = 1.138, *p* = .385. In the noise condition, there was a significant increase in accuracy over cycles, the opposite of a refractory pattern: *F*(3, 9) = 9.911, *p* = .003. This suggests participants were impaired by noise, but only in the initial presentations. This is in contrast to DNe who shows a reduction in accuracy over cycle.



Also presenting DNe's scores for the spoken word refractory task (with no white noise). Error bars show standard error of mean.

Figure 3.11: Data from healthy participants performing a spoken word refractory task with words presented in white noise and no noise conditions

The environmental sounds refractory task data is shown in Figure 3.12. A repeated measures ANOVA revealed a significant effect of cycle: *F*(3,9) = 3.936, *p* = .048, noise: *F*(1,11) = 158.880, *p* < .001, and an interaction between cycle and noise approaching significance: *F*(3,9) = 3.127, *p* = .080. There was no significant effect of cycle in the no noise condition: *F*(3, 9) = 1.703, *p* = .235. In the noise condition, there was an improvement in performance over cycles which approached significance: *F*(3, 9) = 3.232, *p* = .075. A similar pattern was found for the spoken word and environmental sounds tasks. Again, this is in contrast to DNe, who shows a different refractory effect in these two tasks (see Study 5).



Also presenting DNe's scores for the environmental sounds word refractory task (with no white noise). Error bars show standard error of mean.

Figure 3.12: Data from healthy participants in a sound refractory task with sounds presented in white noise and no noise conditions

Summary

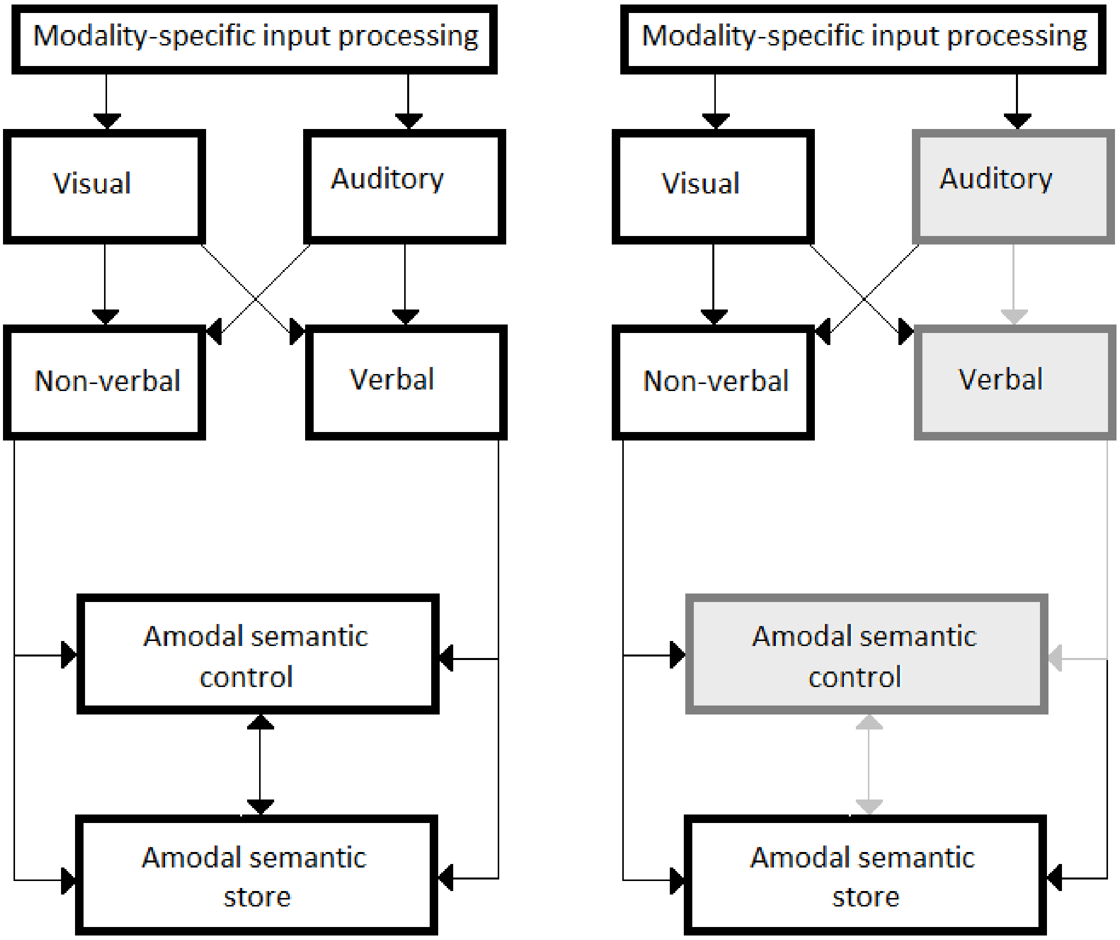
Healthy controls do not show the same pattern as DNe when they have an input deficit, externally generated using white noise. Controls did not show an interaction between semantic control demands (high v. low) and input deficit (white noise v. no noise conditions), suggesting that strong effects of semantic control demands cannot be produced from an input processing deficit but require an additional deficit of semantic control mechanisms.

Discussion

While there has been vigorous debate about the contribution of amodal and modality-specific representations in conceptual knowledge for many years, the role of modality in relation to the semantic control network has not been widely discussed. Jefferies and Lambon Ralph's (2006) model involves a modality-general control system interacting with amodal conceptual representations giving rise to semantic control deficits in words, pictures and action tasks in patients with semantic aphasia (SA). However, case studies AZ and BBB described by Warrington and colleagues (1983, 2004) show refractory effects which are modality specific: performance only declines across cycle in auditory word tasks in what they term semantic ‘access’ patients. We had the rare opportunity to study such a patient, DNe, who in preliminary testing showed refractory effects only in tasks involving spoken words. This case study was used to assess (1) whether sensitivity to control manipulations was specific to the auditory-verbal domain, and (2) if there was an association between executive and comprehension impairments along modality specific lines. Such a pattern might motivate revision of both Jefferies and Lambon Ralph’s multimodal model of semantic cognition, and Warrington et al.’s account, in which refractory effects are not associated with executive control.

At first glance, DNe shows a pattern similar to semantic ‘access’ patients. He showed significantly poorer performance in the verbal modality than the visual modality (Warrington & Crutch, 2004). This was clearest in cyclical matching tasks, where he showed reduced performance across cycles only in auditory-verbal tasks. However, DNe showed deficits in all phonological tasks, which suggests an auditory input processing deficit, and he also showed subtle effects of semantic control manipulations across modalities, indicating that he may have additional impairment of multimodal semantic control, like SA cases (Jefferies & Lambon Ralph, 2006).

Below, we explore the possibility that this pattern of impaired semantic and executive control within the auditory-verbal domain might be explained in terms of the combined effects of a relatively mild, general control deficit, paired with an auditory processing deficit. This, while not explicitly discussed by Jefferies and Lambon Ralph (2006), is consistent with their account in which semantic cognition comprises three components: (1) an amodal semantic hub, (2) modality-specific ‘spokes’ that interact with the hub and provide it with its inputs, and (3) a semantic executive control mechanism, which brings task relevant features to the fore. The first two elements are derived from a model of semantic representation proposed by Rogers et al. (2004), describing multiple layers distinguishing cortical areas which includes sets of units dedicated to specific visual or verbal processes, and amodal semantic units. They argue that the whole system involves interactions among perceptual representations in different modalities – and so damage to visuosemantic processing may have consequences for the system's ability to hold on to its semantic representations. Maintenance of stable semantic representations depends on preserved connectivity between the semantic system and the perceptual/motor representations with which it is connected. Activation of semantic representations is not rigid, however, and is directly shaped by context (Jefferies & Lambon Ralph, 2006, see also Figure 3.13).



If input processing is disrupted, this will affect semantic control predominantly in that domain (shown in the right panel).

Figure 3.13: Conceptualisation of the Jefferies and Lambon Ralph (2006) model incorporating input modality.

According to this model, presented in Figure 3.13, these three elements are highly interactive: an auditory input processing deficit would be expected to produce noisy or insufficient activation of an intact amodal semantic representation, leading to a deficit primarily in a single modality. The functional consequences of an additional amodal semantic control deficit would then be difficulty in semantic tasks with high control demands, particularly for auditory-verbal materials which generate error-prone conceptual activation, since executive resources are required to overcome processing difficulties in these circumstances, for example, matching an ambiguous homonym such as PEN with its subordinate meaning SHEEP.

Crutch and Warrington (2011a) argue that there are both unimodal and amodal representations, as well as multimodal representations which activated to more than one modality (not necessarily equally). They argue that patients who show different performance in two different modalities have unequal damage to multimodal representations, with representations tuned towards written information exhibiting a 'storage-type' impairment, and representations tuned towards spoken information exhibiting an 'access-type' impairment, due to the nature of the input. They suggest that executive control cannot account for a difference in 'access' patterns across modalities.

However, it is possible to account for DNe's performance in two alternative ways. One hypothesis is that (1) there are separate control mechanisms specific to verbal and non-verbal domains. DNe could have severe damage to the verbal control system, with only partial damage to the non-verbal systems, producing milder deficits on high-semantic control tasks employing pictures. Although incorporating the idea of semantic control, this is similar to Warrington and Crutch's account of parallel modality specific semantic 'systems', which are not a simple disconnection of a single modality (Warrington & Crutch, 2004). (2) An interaction of control and input, which stems from an input processing deficit, which could also lead to the discrepancy between the verbal and visual domain. Noisy activation from an impaired verbal input leads to activation errors of semantic items, and in healthy volunteers, leads to increased activation in semantic control regions (Davis & Johnsrude, 2003; Sharp et al., 2010). If DNe has an impairment of both input processing and semantic control, he would show particular difficulty in high demand conditions, such as fast presentations or weakly related items. Evidence gathered from this study will help us scrutinize these two potential explanations for DNe's performance.

General and specific control networks

There is a clear evidence for modality general control regions, which go beyond semantics. A large 'multi-demand' network has been described, with the same regions showing significant activation to a wide range of 'control' tasks (Duncan, 2010). Duncan and Owen (2000) analysed 20 studies which tested executive control: tasks involving response conflict, novelty, working memory, delayed memory and perceptual difficulty (see also Duncan, 2006). Although the foci of activation were somewhat distributed, there was similarity of activation across demands and experiments, which suggested a dorsal frontoparietal network, including inferior frontal sulcus, dorsolateral prefrontal cortex, supplementary motor areas, adjacent cingulate cortex and areas in and around the intraparietal sulcus (Dosenbach, et al., 2008; Duncan, 2006, 2010; Duncan & Owen, 2000; Nagel, et al., 2008; Wager, 2004).

Additional literature suggests partially overlapping yet somewhat different regions are implicated in linguistic/semantic control. The semantic control network, like the 'multi-demand' network, involves areas in and around (and inferior to) the inferior frontal sulcus and intraparietal sulcus mentioned above, but also involves 'semantic specific' regions - the pMTG (Dosenbach, et al., 2008; Duncan, 2006, 2010; Nagel, et al., 2008) and anterior IFG (Devlin, et al., 2003; Noonan, et al., submitted). Whitney et al. (2011) used TMS to assess the roles of these regions in both semantic and non-semantic tasks. The semantic control tasks involved controlled retrieval of distant associates (e.g., SALT with SUGAR), and feature selection (e.g., matching according to colour BEETROOT with BLOOD). The non-semantic control task involved matching a probe letter (e.g., 'b') to a local letter feature, 'b' presented within a conflicting global Navon letter (e.g., 'K'). TMS to pMTG and IFG found disruption only to semantic control tasks, not the non-semantic Navon task. Stimulation of the dAG did disrupt the non-semantic Navon task, as well as specific aspects of semantic control: feature selection and not 'controlled retrieval' of distant associations (Whitney, et al., 2012). This suggests that the dAG/IPS may overlap with regions involved in allocating attention to internal and external representations beyond the semantic domain. The large region that comprises the IFG may be further distinguished, with the most anterior parts being predominantly semantic, while posterior parts are involved in phonological decisions and resolving linguistic conflict

(Devlin, et al., 2003; Gold & Buckner, 2002; Gough, Nobre, & Devlin, 2005; Snyder, Feigenson, & Thompson-Schill, 2007).

While there is partial differentiation of function across the neural network underpinning semantic and non-semantic control, there are two reasons why it is unlikely that either DNe or other auditory-verbal ‘access’ patients have a verbal-specific control deficit. Firstly, our case study and the ‘access’ patients described in the literature have large lesions, and it is perhaps implausible to link their lesions to aspects of the control network that are more specific to semantics – e.g., damage to anterior LIFG or pMTG. Additionally, although semantic specific control is nearly always tested in the verbal domain (Dumontheil, et al., 2011; Duncan, 2006, 2010; Hon, Epstein, Owen, & Duncan, 2006; Nagel, et al., 2008), both LIFG and pMTG have been implicated in non-verbal semantic cognition, in picture and action tasks. This makes it unlikely that even selective damage to pMTG or anterior LIFG would result in refractory effects specific to verbal comprehension – instead, one might expect multimodal semantic control deficits, like those seen in SA. While pMTG is thought to be important in the interface of phonological processing and semantic representations (Hickok & Poeppel, 2004, 2007; Turken & Dronkers, 2011), it is also involved in semantic judgements of non-verbal items, such as actions relating to pictured objects (Kellenbach, et al., 2003), and in word and picture semantic association tasks (Hoffman, Pobric, et al., 2011). The LIFG is associated with language production (Schnur, et al., 2005); but it is also involved in control beyond this domain (Hagoort, 2005; Thompson-Schill, 2003), in particular during semantic memory retrieval (Badre, et al., 2005; Thompson-Schill, et al., 1997; Wagner, Paré-Blagoev, et al., 2001), visual target search (Fink, et al., 2006), action recognition (Hamzei, et al., 2003) and face recognition tasks (Rajah, et al., 2008). Thus, this literature suggests that sites involved in semantic control that do not form part of the multi-demand control network are nevertheless not restricted in their processing to particular modalities, but instead contribute to our understanding of words, pictures and actions. Additionally, evidence from Warrington et al. suggests ‘access’ patients may not be at ceiling level on visual tasks (indeed, on one visual object matching task, performance of case study VER is just 68%, Warrington & McCarthy, 1983). This suggests that there is little evidence for distinct modality-specific control systems.

‘Noisy’ activation of semantics from audition

Semantic comprehension requires both input and control processes to be intact. If auditory processing is impaired, as in DNe, this could potentially increase the control demands of word comprehension tasks, reducing the executive resources available for overcoming task demands in high control conditions. This could produce the pattern of results seen in semantic ‘access’ patients – an apparent control deficit only in the auditory domain.

Bilateral STS is crucial for auditory processing of speech (Hickok & Poeppel, 2007; Scott & Johnsrude, 2003). When speech is unrecognisable, ATL activation is reduced, suggesting that incomprehensible speech fails to activate semantic stored representations within this region (Scott, et al., 2000). Additionally, studies involving degraded speech show an increased activation in linguistic control areas, such as LIFG (Davis & Johnsrude, 2003; Zekveld, Heslenfeld, Festen, & Schoonhoven, 2006). For example, increasing perceptual difficulty leads to increased activation around BA 45 in the LIFG (Sharp, et al., 2010), the same region which responds to post-retrieval selection of semantic competitors (Badre & Wagner, 2007). Similarly, older people with age-related hearing loss show correlated impairments in executive control (Larsby, Mathias, Bjorn, & Stig, 2005; Li & Lindenberger, 2002; Pichora-Fuller, Schneider, & Daneman, 1995), with expectancy-based attentional control modulating auditory identification (George et al., 2007; Murphy, Schneider, Speranza, & Moraglia, 2006), and exaggerated effects of semantic priming, suggesting contextual information helps to compensate for disturbances of sensory processing (Aydelott, Leech, & Crinion, 2010; Sheldon, Pichora-Fuller, & Schneider, 2008). Therefore, distorted input from auditory speech areas, as well as problems with linguistic control (preventing the patients from compensating for the degraded input) could give rise to ‘verbal-only’ access deficits.

We attempted to test the hypothesis that DNe’s refractory and semantic control impairments could result from degraded auditory input alone using age-matched controls (Study 6). We found that controls showed no interaction between perceptual noise and task demands in a semantic distance task, and they showed improved performance over trials in the noise-embedded verbal refractory task. This suggests that an auditory input deficit alone would not produce the pattern shown by DNe. Moreover, in more demanding semantic tasks, DNe showed an effect of semantic control manipulations in picture and written modalities, suggesting he has impairments that go beyond auditory processing.

Degraded input may increase control demands, since executive control processes could compensate for ‘noisy’ activation. In patients like DNe, this type of compensation is not possible. As predicted by Jefferies and Lambon Ralph’s (2006) model, disruption of auditory input paired with a mild amodal semantic control deficit leads to particular difficulty on control-demanding auditory-verbal tasks combined with ‘access’ impairment in this domain. The semantic control network is distributed, and includes the pMTG which is close to the auditory cortex. Therefore, this hypothesis may explain several case studies in the literature that show an ‘access’ or control deficit in only one modality.

4. CHAPTER FOUR

Does posterior temporoparietal cortex support semantic control? A direct comparison of semantic deficits following temporoparietal, prefrontal and bilateral anterior temporal lobe lesions.

Acknowledgements: Experimental data from several SA patients presented (PG, NY, BB, HN, SC and KA); was collected by Dr. Paul Hoffman, and background data from these patients, plus SD data, was taken from Jefferies and Lambon Ralph (2006). Two semantic control tasks, the Ambiguity and Semantic Distance task were designed by Dr. Krist Noonan and collaborators in Manchester and Cambridge. Data from 9/13 SA patients on these two tasks was taken from Noonan et al. (2010).

Abstract

For the first time, we explored the effect of lesion location on behavioural performance of semantic aphasia (SA) patients, who have damage to the prefrontal cortex (PF+) and/or temporoparietal cortex (TP-only). Past research suggests SA patients with these two lesions may show similar deficits of semantic control, yet the functional neuroimaging literature proposes a unique role for the prefrontal cortex. To explore this apparent controversy, five TP-only, and ten PF+ SA patients, were compared to ten semantic dementia (SD) patients, who have damage to semantic representations, on a range of tasks which assessed sensitivity to semantic and executive control. SD patients showed clear evidence of degraded knowledge on every semantic task: in contrast both SA groups showed a qualitatively different pattern. Relative to SD, both TP-only and PF+ patients: (1) showed inconsistency across items when the task demands changed; (2) were more influenced by semantic selection and inhibition demands on a semantic association task; (3) exhibited attenuated effects of lexical frequency; and (4) showed evidence of poor semantic regulation in their verbal output – performance on picture naming was substantially improved when provided with a phonological cue. Despite these similarities, some differences emerged. PF+ patients were less fluent, showed more associative picture naming errors, and overall somewhat stronger SA characteristics (e.g., they were more inconsistent, and less affected by frequency). Additionally, it would found that patients with damage to posterior temporal regions as opposed to frontoparietal cortex were less affected by a task requiring dampening down of a prepotent distractor, suggesting posterior temporal regions are not involved in this aspect of semantic control. Taken together these findings suggest that semantic impairment in TP-only and PF+ cases is underpinned by damage to a semantic control network instantiated across anterior and posterior cortical areas, and helps to constrain theories about the contribution of each cortical region to semantic control.

Introduction

Semantic deficits following different aetiologies of brain damage have suggested that a large network of regions is implicated in semantic cognition. These can be segmented according to function – with regions implicated in either semantic representation (damaged in semantic dementia, SD; Lambon Ralph & Patterson, 2003) or selection and retrieval of these items in a context specific way (disrupted in semantic aphasia, SA; Jefferies & Lambon Ralph, 2006).

As noted in Chapter 1, a highly selective deficit in semantic memory is seen in SD and arises from degradation of conceptual representations. Patients show impaired conceptual knowledge in the context of relatively spared functioning in other cognitive areas – such as episodic memory and executive functioning (Hodges, et al., 1992b; Snowden, Goulding, & Neary, 1989). Due to the degenerative nature of this brain disorder, SD patients are strongly influenced by item frequency and familiarly – with low frequency items being degraded first (Funnell, 1995; Lambon Ralph, et al., 1998). They show strong item-specific consistency across different tests of semantic knowledge (Bozeat, et al., 2000), suggesting degradation of the underlying semantic representation of an item.

In comparison to SD patients, SA patients show: (1) performance that is predicted by control participants' ratings of executive difficulty (Noonan, et al., 2010); (2) item consistency only on tasks which have similar control requirements, for example consistency on an association task which uses either picture or written word modalities, but not between association judgements and word-picture matching; Jefferies & Lambon Ralph, 2006); (3) minimal effects of frequency/familiarity, when task demands are held constant (Hoffman, Rogers, et al., 2011); (4) impaired performance on picture naming, which is greatly improved when given the initial phoneme as a cue (Jefferies, Patterson, et al., 2008); (5) effects of semantic control demands which are similar across modalities, with impaired performance on non-verbal action tasks, picture tasks and verbal tasks (Corbett, Jefferies, & Lambon Ralph, 2009; Jefferies & Lambon Ralph, 2006); and (6) correlations between poor semantic performance and backgrounds measures of executive functioning (Baldo, et al., 2010; Baldo, et al., 2005; Jefferies & Lambon Ralph, 2006).

SA patients often have large lesions, and at least two lesion types have been previously described (Gardner, et al., 2012), including (i) those with lesions to left inferior frontal gyrus (LIFG) which also extend to posterior temporal and/or inferior parietal regions (PF+ patients), and (ii) those with lesions restricted to posterior brain regions, incorporating posterior temporal and/or inferior parietal regions (TP-only patients). Little is known about how these patients differ.

However, across semantic control tasks, TP-only and PF+ patients show striking similarity in the impact of semantic control demands on performance.

Those with prefrontal damage have impairments of selection (see selection theory; Badre et al., 2005). For example, Thompson-Schill et al. (1998) have shown that focal inferior prefrontal damage can affect the ability to generate verbs for nouns, but only in ‘high selection’ demand conditions (e.g., for nouns with many potential verbs, such as CAT, compared to nouns with a single dominant response, such as SCISSORS). Generating sentences when the stimulus has multiple conceptual propositions that compete for selection are impaired in frontal patients (Robinson, et al., 2005). Patients have impairments at processing/selecting the correct linguistic context, showing impairments at tasks using homonyms which are words with multiple meanings according to context (Bedny, et al., 2007). Lesions to LIFG also leads to lack of semantic priming of ambiguous words, suggesting difficulty processing context-appropriate meanings in the presence of competing meanings (Metzler, 2001). Campanella et al. (2012) studied a single patient following the resection of a left frontal glioma, and showed that this patient is less accurate with distantly related items (compared to closely related items), inconsistency of concepts, but showed no effect of frequency. This lack of frequency effect has been explained in terms of selecting the appropriate linguistic context. Hoffman and colleagues argue that highly frequent words are more semantically diverse – so have meaning in many contexts (e.g., FIRE can be used to describe a personality, being sacked, or a physical fire (Hoffman, et al., 2010; Hoffman, Rogers, et al., 2011). Therefore, although there is a natural advantage for high frequency words, this is counteracted in frontal patients by the need to select the appropriate linguistic context for the word.

Lesions to posterior regions – including posterior temporal cortex and angular gyrus – produce semantic deficits too. Performance on semantic tasks is associated with damage to these regions (Berthier, 2001; Dronkers, et al., 2004; Saygin, et al., 2003; Schwartz, et al., 2009). More specifically, posterior regions are related to semantic control, with damage to this region disrupting performance on more control demanding tasks in relation to less demanding tasks – including tasks involving selecting distantly related items compared to closely related items, being aided by a phonetic cue in a picture naming task, and showing impairments on non-verbal action tasks with multiple subcomponents (Corbett, Jefferies, Ehsan, et al., 2009; Corbett, Jefferies, & Lambon Ralph, 2009; Corbett, et al., 2011; Jefferies, Hoffman, et al., 2008; Noonan, et al., 2010).

However, there are two notable behavioural distinctions between those with and without prefrontal damage. (1) Berthier (2001) found that ‘anterior’ patients were significantly less fluent than ‘posterior’ patients – a finding which is supported by fMRI data which suggests the posterior semantic control region posterior middle temporal gyrus (pMTG) is only responsive to comprehension tasks, and not expressive tasks (Noonan, et al., submitted). (2) Additionally, Chapter 2 found a difference in performance using a cyclical matching task (the ‘refractory’ task). SA patients with PF+ damage show refractory effects - or a decline in accuracy across cycles. Those with TP-only damage do no show this pattern (Campanella, et al., 2009; Gardner, et al., 2012; Jefferies, et al., 2007; Schnur, et al., 2009).

This subtle difference in behaviour found in PF+ and TP-only patients raises the possibility that, while both regions underpin semantic control, they provide functionally distinct contributions, accentuated by the refractory task. However, the difference found in the refractory task could be related to a number of different factors which are unusual in this cyclical task in comparison to other semantic tasks where no difference is found. These include *repetition* of related stimuli, *switching* between targets over a period of time, having a *limited time* to respond, *dampening down* items which are prepotent or having *previously relevant* items as distractors.

The posterior temporal cortex

The posterior temporal cortex has been implicated in a number of different disorders of language or semantics, which has led some to question its role in semantic control, and rather to suggest it has a role in representation. The pMTG is sometimes considered to be a repository of semantic representations (Binder, et al., 2009; Martin, 2007). The idea for a representation particularly for tools in the pMTG has been supported by fMRI studies (Beauchamp, Lee, Haxby, & Martin, 2002; Kable, et al., 2005; Martin & Chao, 2001). However, questions have been raised about the nature of these fMRI tasks. Devlin and colleagues (Devlin, Russell, et al., 2002) used three tasks to show no uncorrected significance for man-made objects over animals. Even when assessing just manipulable objects, with an ROI over the pMTG, this did not reach a corrected significance level (see also Gerlach, Law, Gade, & Paulson, 2000). They suggest some previous work has used uncorrected statistical thresholds, or stimuli which are not controlled for frequency or visual complexity (see also Tyler et al., 2003). Equally, there are tasks or participants where null results for tools have been found (Chao, et al., 1999; Moore & Price, 1999; Perani et al., 1999). Devlin et al. (Devlin, Moore, et al., 2002) did find consistent pMTG activation for tools in comparison to animals – but only for more complex semantic tasks (see also Price & Friston, 2002; Tyler, et al., 2000). This suggests there may be an interaction between activation for tools and control (Davey & Jefferies, in prep). For example, pMTG activation for action word generation was specific to a generation task and over and above that shown when naming an object (Martin, et al., 1995). Tyler et al. (2003) found activation for the names of animals and biological actions are largely overlapped, with no evidence of category specificity for living compared with nonliving categories. This matches our findings from patients. SA patients show deficits for actions (Corbett, Jefferies, Ehsan, et al., 2009; Corbett, Jefferies, & Lambon Ralph, 2009; Corbett, et al., 2011), but also for words and pictures with no action component (Noonan, et al., 2010), with performance on these tasks not correlated with category (Gardner, et al., 2012). This suggests that damage to posterior regions leads to deficits in demanding semantic tasks which is not dependent on category. However, it remains plausible that *restricted* damage to posterior temporal cortex could lead to a category-specific deficit (Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996; Patterson, et al., 2007).

Another group of researchers, based on patient data, suggest damage to a posterior temporal region leads to pure anomia – considered to result from a disconnection between preserved semantic knowledge and phonological word forms (Foundas, Daniels, & Vasterling, 1998; Hillis et al., 2005; Hillis, Tuffiash, Wityk, & Barker, 2002; Raymer et al., 1997). Indeed, some semantic control studies find greater activation in this region for verbal in comparison to non-verbal tasks (Krieger-Redwood, 2012), although it is important in both modalities (Hoffman, Pobric, et al., 2011). Damage to left BA 37 (inferior temporal region) correlates with lexical processing impairments in stroke patients (DeLeon et al., 2007). It is assumed that in these patients, input from semantics is disrupted, leading to insufficient activation required for word production (Lambon Ralph, et al., 2000). Comprehension is usually good (Gainotti, Silveri, Villa, & Miceli, 1986; Lambon Ralph, 1998), with patterns of performance suggestive of mild SA. For example, naming errors are semantically appropriate (Benson, 1979, 1988; Damasio, et al., 1996; Lambon Ralph, Moriarty, & Sage, 2002), and there is also mild inconsistency on an item-by-item basis (Lambon Ralph, 1998). Performance is increased by phonemic cueing (Lambon Ralph, 1998; Patterson, Purell, & Morton, 1983), and patients have the ability to produce tip-of-the-tongue information about unnamed items (Lambon Ralph, et al., 2000). Therefore, these patients appear to have a conflict between their spoken production and word comprehension. Indeed, another group of patients have the opposite deficits – impaired auditory comprehension with intact repetition and fluent speech – in transcortical sensory aphasia (TSA; Goldstein, 1948). Some of our SA patients show these symptoms (cf. Table 4.1). Boatman et al. (2000) used electrical interference via electrodes to seizure patients, and found regions associated with TSA characteristics in MTG particularly, but also other regions of the temporal lobe, temporo-occipital cortex and the parietal lobe. Characteristics of pure anomia patients are similar to SA patients (albeit milder), and so this literature does not conflict with our claims that posterior temporal regions are involved in semantic control.

Wernicke's aphasia patients (who show similar symptoms to TSA without the ability to repeat) have a brain damage to posterior superior temporal cortex (pSTG; Eggert, 1977), posterior middle temporal gyrus (pMTG; Dronkers, et al., 2004; Ogar et al., 2011) and angular gyrus (AG; Chertkow, et al., 1997). Because damage is focal around pSTG, their deficits in auditory processing are often more pronounced, although often paired with semantic control deficits across domains (Robson, Sage, & Lambon Ralph, 2012). This suggests that it is possible to have damage to a 'spoke' (e.g., the auditory spoke), as well as damage to semantic control mechanisms (e.g., pMTG), which lead to a more pronounced deficit in one domain, paired with multimodal semantic control deficits (Goodglass, Kaplan, & Barresi, 2001; Ogar, et al., 2011).

Representation interacting with control?

As alluded to above - patients may share similar lesions but show different behavioural characteristics. The major difference of opinion comes at the distinction between representation and semantic control. Semantic control is comprised of both multi-demand areas, involved in domain general control (Duncan, 2010; Duncan & Owen, 2000), and 'semantic' regions involved in processes like controlled retrieval/integration which are specific to semantic control (Noonan, et al., submitted). There is evidence for category effects and domain effects mentioned above, but also numerous examples of domain-general effects in pMTG too (Devlin, Russell, et al., 2002; Hoffman, Pobric, et al., 2011; Noonan, et al., 2010). It is plausible that the area of the pMTG involved in control and representation is different. SA patients may have lesions which do not distinguish the contributing cortex for representation and control.

Given distributed network, a key question remains over the role of each component. Neuropsychological evidence is useful in distinguishing which areas are necessary for particular functions. However, given that the majority of SA patients' lesions encompass several semantic regions, neuroscientific evidence has been useful in discerning separable roles. The most important aim of this study is to provide good evidence that posterior SA patients can show SA characteristics, given that previous literature contains too few posterior cases to analyse sufficiently as a separate group (Jefferies & Lambon Ralph, 2006).

Given this distributed network, a key question concerns the role of each component. This is likely to be at least partially distinct. Critically however, no study to date has directly compared TP-only, PF+ and SD patients. Although all semantic control tasks by their very nature require semantic representation, we are able to differentiate the contribution of both representation and control by looking at the pattern of performance across a battery of tasks. For example, those with a representational deficit for certain items will show consistency of errors on the same items in different tasks, no improvement after phonological cues in picture naming, and little effect of semantic control manipulations in tasks tapping the same items. Additionally, a representational deficit is also paired with word frequency effects, as low frequency items are more likely to degrade first. Currently, it is unclear whether TP-only patients will show effects of semantic storage variables comparable to that seen in SD patients, or whether they will be more similar to PF+ patients. PF+ show difficulty shaping the relevant aspects of their conceptual knowledge to perform the task at hand, but they do not show impairment of semantic representation (Metzler, 2001; Samson, et al., 2007; Swick & Knight, 1996; Thompson-Schill, et al., 1998). Therefore PF+ cases provide an ideal comparison group to test the degree of semantic control impairment in TP-only patients.

The aim of this study is to assess two controversies in the literature. Firstly, a number of theories propose that temporoparietal areas are specifically involved in semantic storage, either through representing individual sensory/motor features (Martin, 2007), or by mediating access to broadly distributed conceptual representations (Hickok & Poeppel, 2004, 2007). This study critically evaluates the nature of semantic knowledge deficits in TP-only patients in an attempt to better understand the contributions of temporoparietal cortex to semantic cognition. If temporoparietal areas are involved solely in semantic representation we would expect comprehension problems in this group to be qualitatively similar to patients with SD. In contrast, if temporoparietal areas also contribute toward semantic control then we might expect greater similarly between TP-only patients and PF+ cases with multimodal comprehension problems. Previous studies have not been able to address these issues because they have either used a small number of cases or employed assessments which have not allowed the separation of conceptual representation from semantic control (Berthier, 2001; Jefferies & Lambon Ralph, 2006). Secondly, there is limited work comparing PF+ and TP-only patients, with previous work grouping together patients with heterogeneous lesions into a single analysis (Corbett, Jefferies, Ehsan, et al., 2009; Corbett, Jefferies, & Lambon Ralph, 2009; Jefferies & Lambon Ralph, 2006; Noonan, et al., 2010; Soni, et al., 2009; Soni, et al., 2011). However, differences in neuroimaging literature suggest that despite many similarities, a detailed neuropsychological investigation of semantic and executive control in TP-only and PF+ patients has the potential to elucidate the role of these regions in specific aspects of semantic cognition. Therefore, for the first time, we will directly compare TP-only and PF+ patients on a range of tasks which assess performance on non-semantic and semantic control experimental tasks.

Methods

Participants

There were twenty five patients separated into three groups, ten SD patients, and fifteen SA patients, five of whom were TP-only (lesions only affecting temporoparietal regions), and ten of whom were PF+ patients (lesions affecting prefrontal cortex and/or temporoparietal regions).

Stroke patients: SA patients were recruited from stroke clubs and speech and language therapy services in Manchester and York, UK. Patients were selected for the study if they showed impairments on both word and picture association tasks (the Camel and Cactus Task, CCT). All of the patients had chronic impairments resulting from a CVA at least one year prior to testing. The group included patients with fluent and less fluent profiles (Table 4.1 provides background aphasialogical and demographic information).

Table 4.1: Semantic aphasia patient demographic information

Patient	Age	Edu	Group	Aetiology	Aphasia Type	BDAE Compreh	BDAE Fluency	BDAE Repetition	Nonword repetition	Word Repetition	Cookie theft WPM
HN	80	15	TP-only	Ischemia	Anomic/ TSA	NT	NT	NT	56	86	59
SC	80	16	TP-only	Haemorrhage	Anomic/ TSA	37	90	60	87	98	84
EW	74	15	TP-only			NT	NT	NT	NT	80	NT
ME	40	16	TP-only	Subarachnoid haemorrhage	TSA	33	100	100	93	100	63
KS	59	16	TP-only	Haemorrhage	TSA	43	97	100	73	94	84
PG	63	18	PF+	Subarachnoid haemorrhage	TSA	20	40	80	73	91	27
NY	67	15	PF+		Mixed transcortical	47	37	40	40	81	42
KH	73	14	PF+		Mixed Transcortical	30	30	40	43	80	29
JM	69	18	PF+	Haemorrhage	TSA	22	63	40	87	95	26
BB	59	16	PF+	Subarachnoid haemorrhage	Mixed Transcortical	10	17	55	83	96	11
KA	78	14	PF+	Thomboembolic/partial haemorrhage	Global	0	23	0	0	0	NT
LS	75	15	PF+		TSA	13	90	90	90	96	30
GH	56	15	PF+		Global	NT	NT	NT	30	75	3
DB	83	16	PF+		TSA/Wernicke's	13	90	30	70	85	11
EC	66	16	PF+		Global	NT	NT	NT	NT	NT	0

Edu = age of leaving education. Aphasia classifications were derived from the Boston Diagnostic Aphasia Examination (BDAE; Goodglass, 1983). Fluency percentile is derived from phrase length, melodic line and grammatical form ratings. Repetition percentile is average word and sentence repetition.Transcortical sensory aphasia (TSA) was defined as good or intermediate fluency/repetition and poorer comprehension. Word/nonword repetition (%): Tests 8 and 9 from PALPA (Psycholinguistic Assessments of Language Processing in Aphasia, Kay et al., 1992). Cookie theft description assesses fluency (words-per-minute), Nicholas & Brookshire, 1993.

Stroke lesion analyses: Scans were available for 13/15 SA patients. CT/MRI scans were manually traced onto Damasio's standardised templates (Damasio & Damasio, 1989). Lesion analyses revealed that 5/13 SA patients had infarcts confined to temporal/parietal cortices (HN, SC, EW, ME & KS). 8/13 patients had damage which extended into the frontal lobes (NY, KH, BB, KA, LS, DB, GH & EC). CT/MRI scans were not available for PG or JM. However, radiological reports were present in both cases. PG's report indicated a left frontal lesion but made no definitive statement about more posterior damage. JM's lesion was extensive effecting left hemisphere frontal, temporal and parietal cortices. Both PG and JM were included in the PF+ group. Table 4.2 presents a breakdown of the patients' lesions to the left hemisphere, relative to areas involved in semantics: prefrontal regions (BA 9, 46, 47, 45, 44), temporal regions (BA 22, 21, 20, 36, 38) and parietal lobe (BA 39, 40). These are defined by previous functional neuroimaging and neuropsychological studies of semantic cognition (Chertkow, et al., 1997; Demb, et al., 1995; Hart & Gordon, 1990; Thompson-Schill, et al., 1997; Vigneau et al., 2006; Wagner, Paré-Blagoev, et al., 2001).

Table 4.2: Lesion analysis for stroke patients

Patient	Group	Lesion size (% of template damaged)[a]	Prefrontal					Posterior temporal			Temporal			Parietal		
				DLPFC	orbIFG	trIFG	opIFG	pSTG	pMTG	pITG	FG	sTP	POT	AG	SMG	OL
			BA9	BA46	BA47	BA45	BA44	BA22	BA21	BA20	BA36	BA38	BA37	BA39	BA40	BA19
HN	TP-only	6	-	-	-	-	-	-	2	1	-	-	2	-	-	2
SC	TP-only	8	-	-	-	-	-	-	2	2	-	-	2	2	1	1
EW	TP-only	2	-	-	-	-	-	-	-	1	-	-	1	-	-	-
ME	TP-only	5	-	-	-	-	-	-	1	2	2	-	1	-	-	1
KS	TP-only	2	-	-	-	-	-	1	2	-	-	-	2	-	-	1
NY	PF+	14	-	1	2	2	2	2	-	-	-	-	-	1	1	-
KH	PF+	8	1	-	-	-	2	-	1	2	2	-	2	1	-	2
BB[b]	PF+	3	-	-	2	2	2	1	-	-	-	-	-	-	-	-
KA	PF+	6	-	-	-	-	2	2	1	-	-	-	1	-	1	-
LS	PF+	17	-	1	-	2	2	-	2	2	-	-	2	2	2	2
DB	PF+	12	1	1	1	2	2	2	1	-	-	-	-	-	1	-
GH	PF+	12	-	-	2	1	1	2	1	-	-	-	2	1	2	1
EC	PF+	17	-	-	2	1	2	2	1	-	-	1	1	-	1	-

Quantification of lesion: 2 = complete destruction/serious 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; sTP = superior temporal pole; pSTG = posterior superior temporal gyrus; pMTG = posterior middle temporal gyrus; ITG = inferior temporal gyrus; FG = fusiform gyrus; POT = posterior occipitotemporal area; SMG = supramarginal gyrus; AG = angular gyrus; OL = occipital lobe. [a] Lesion size was estimated by overlaying a standardised grid of squares onto each patient's template and working out the percentage of squares damaged relative to the complete undamaged template. [b] BB showed additional signs of ventricular enlargement in the left hemisphere. No scan available for JM or PG, though radiographers report reveals PF+ lesion.

All patients with lesions affecting the frontal lobe had damage to BA 44. Most also had damage to BA 47 and 45 (although KH and KA did not). Most also had damage extending to BA 21 (pMTG; except BB and NY). All TP-only patients had damage to BA 37 (occipital temporal cortex). The majority also had damage to BA 21 (pMTG; except SC and EW).

There was a significant difference between the lesion size of PF+ patients (M = 11%, SD = 5.1), and TP-only patients (M = 5%, SD = 2.6), $t(11) = 2.632$, $p = .023$. Factor analysis was used to extract one composite semantic score. A single factor accounted for 54% of the variance in four semantic tasks: naming, WPM, CCTp and synonym tasks. This factor analysis was also run for four executive control tasks: BSRA, digit span (forwards and backwards), and RCPM. This single factor accounted for 58% of the variance. The composite semantic score and executive score correlated with each other: $r = .623$, $p = .013$. Lesion size did not significantly correlate with the composite semantic score: $r = -.463$, $p = .111$, or composite executive score: $r = -.388$, $p = .190$.

SD patients: Ten SD patients took part in this study; all were identified through the Memory and Cognitive Disorders Clinic at Addenbrooke's Hosptial, Cambridge, UK. These patients, first described by Bozeat et al. (2000) fulfilled all of the published criteria for SD (Hodges, Patterson, Oxbury, & Funnell, 1992a; Hodges, et al., 1992b): they had word-finding difficulties in the context of fluent speech and showed impaired semantic knowledge and single word comprehension; in contrast, phonology, syntax, visual-spatial abilities and day to day memory were relatively well preserved. MRI revealed focal bilateral atrophy of the inferior and lateral aspects of the anterior temporal lobes in every case.

For two tasks (synonym judgement task and semantic distance task) data was not available from the main SD cohort. For the synonym judgement task, SA patients were compared with an additional cohort of eleven SD patients recruited in Cambridge, Bath and Liverpool, UK. These cases have also been described in detail elsewhere (Jefferies, et al., 2009). With regards the semantic distance task, four SD patients recruited in Manchester and Bath were used. Two have been previously described in this paper – GE was from the 'synonym' cohort, JW from the main SD cohort. The other two patients have been described elsewhere, both NH (Hoffman & Lambon Ralph, 2011; Mayberry, Sage, Ehsan, & Lambon Ralph, 2011), and TM (Jefferies, Rogers, & Lambon Ralph, 2011) The SD groups were matched on background semantic performance – there were no difference across any of the four tests from 64-item semantic battery (naming, WPM, CCTp, CCTw; $t < 1$).

1.Non-semantic executive control

Neuropsychological tests were used to assess cognitive abilities in our patient cohort, in visual and non-visual domains. This included tests of working memory, attention, and reasoning. We expected that SA patients would show significantly worse performance than SD patients, due to their lesions affecting semantic and non-semantic control mechanisms in prefrontal and temporoparietal cortex. However, we predicted that PF+ patients would be particularly impaired, as this region is implicated strongly in non-semantic control.

Procedure

The tasks used were: (1) the Visual Object and Space Processing battery, VOSP (Warrington & James, 1991), using the space perception subparts 5-8: dot counting, position discrimination, number location and cube analysis. (2) Forward and backward digit span (Wechsler, 1987). (3) An Elevator Counting task, which involved counting tones played with or without distracting tones, from the Test of Everyday Attention, TEA (Robertson, et al., 1994). (4) The Ravens Coloured Progressive Matrices test (RCPM: Raven, 1962), which assesses non-verbal reasoning using pattern and rule completion. (5) The Wisconsin Card Sorting test, WCST (Stuss, et al., 2000), which examines the flexibility of rule-based categorisation after feedback. (6) And finally, the Brixton Spatial Rule Attainment task (BSRA: Burgess & Shallice, 1997), involves the detection of spatial patterns, and switching in light of feedback.

Results

Table 4.3 shows the background data for each patient. When looking at the correlation between lesion size and each task, there was no significant correlation between naming, WPM, CCTp, CCTw, category or letter fluency, any subtest of VOSP, WCST, TEA with distraction, digit span (forwards or backwards), or RCPM. However, there was a significant correlation with lesion size and synonym judgement accuracy (r = -.743, p = .004); and TEA (r = -.560, p = .026).

Table 4.3: Background neuropsychological data for all patients

	Semantic Composite Score	Executive control Composite Score	Naming	WPM	CCTp	CCTw	Synonym Judgement	Category Fluency	Letter Fluency	Digit Span: forwards	Digit Span: Backwards	VOSP dot counting	VOSP position discrimination	VOSP number location	VOSP cube analysis	RCPM	WCST	BSRA	TEA: counting with distraction	TEA: counting without distraction
Max			64	64	64	64	96	-	-	-	-	10	20	10	10	36	6	54	10	7
Cut off			59	63	53	57	91	62	18	5	2	8	18	7	6	13[a]	1†	28	2.6	4.2
ME	-0.50	-0.05	4*	62*	13*	33*	80*	25*	14*	6	3	3*	15*	2*	4*	13	0*	11*	9	7
KS	0.14	1.92	21*	46*	44*	NT	81*	NT	NT	8	4	NT	NT	NT	NT	31	NT	28	9	5
SC	0.63	0.56	28*	63	47*	56*	71*	17*	24	6	2	10	17*	10	9	22	6	25*	1*	7
EW	1.19	0.87	45*	57*	45*	48*	86*	34*	20	4*	2	10	20	10	7	30	1	33	NT	NT
HN	1.39	0.58	51*	50*	54	54*	89*	49*	14*	6	2	8	19	9	4*	20	6	28	9	7
EC	-1.90	-1.35	1*	40*	32*	20*	41*	0*	0*	0*	0*	3*	14*	10	6*	12*	NT	24*	1*	1*
LS	-1.80	-0.65	5*	48*	15*	16*	47*	11*	8*	4*	1*	6*	16*	8	4*	16	0*	14*	3	2*
KA	-1.20	-1.98	0*	35*	46*	36*	60*	0*	0*	0*	0*	0*	14*	6*	NT	12*	1	6*	5	5
BB	-0.50	-0.11	9*	53*	38*	30*	63*	13*	0*	5	0*	10	18	8	2*	24	1	23*	4	0*
DB	-0.10	0.85	39*	46*	51*	46*	54*	14*	0*	4*	2	6*	0*	10	3*	31	0*	31*	2*	2
GH	0.29	-0.37	19*	60*	45*	29*	71*	15*	2*	2*	0*	10	4*	0*	0*	32	NT	18*	6*	1*
JM	0.32	-0.69	30*	61*	37*	37*	69*	17*	1*	3*	2	10	19	5*	3*	14	2	12*	3	0*
KH	0.55	-0.8	29*	62*	46*	41*	61*	18*	0*	4*	2	10	18	9	3*	12*	0*	7*	6	3*
PG	0.70	0.64	44*	58*	44*	40*	69*	4*	2*	6	2	5*	20	9	10	23	0*	26*	0*	3*
NY	0.73	0.59	51*	60*	36*	39*	69*	25*	5*	3*	2	10	20	10	5*	26	2	34*	2*	3*
JP			59	64	61	62	NT	79	27	6	5	10	NT	10	NT	9	NT	NT	NT	NT
WM			57*	63	56	52*	NT	67	29	8	7	10	20	9	10	22	NT	NT	NT	NT
SL			45*	60*	52*	34*	NT	45*	45	6	3	10	NT	10	NT	NT	NT	NT	NT	NT

JC	43*	58*	47*	37*	NT	36*	23	8	4	10	20	10	9	23	NT	NT	NT	NT
AT	17*	57*	51*	43*	NT	32*	20	8	5	10	NT	10	NT	34	NT	NT	NT	NT
DS	17*	58*	43*	44*	NT	13*	7*	6	4	10	20	9	10	33	NT	NT	NT	NT
DC	11*	36*	31*	18*	NT	10*	16*	7	2	10	17	10	10	8	NT	NT	NT	NT
JH	6*	18*	30*	NT	NT	12*	19	6	5	10	20	10	10	31	NT	NT	NT	NT
JW	9*	23*	22*	NT	NT	7*	NT	5	5	10	NT	NT	NT	35	NT	NT	NT	NT
IF	1*	18*	19*	10*	NT	7*	16*	5	5	10	20	NT	6	31	NT	NT	NT	NT

SA patients are arranged within each group according to composite semantic severity scores. This is a single factor extracted from naming, WPM, CCTp and synonym judgement tasks (which all SA patients have done). Executive control composite scores are a single factor extracted from BSRA, RCPM and digit span (forwards and backwards), which all SA patients have done. * = impaired performance. NT = not tested. † Cut-off for 50–74 year olds (regardless of educational level). ^{a} = norms standardised on children. WPM = spoken word to picture matching; CCTw/p = camel and cactus test of associative semantic knowledge presented with words and pictures, respectively; VOSP = visual object and space processing battery; RCM = Raven’s Coloured Matrices; WCST = Wisconsin card sorting test – number of categories attained; Brixton spatial rule attainment task – accuracy; TEA = elevator counting with and without distraction from the test of everyday attention. Category fluency scores refer to the total number of items produced across six semantic categories. Letter fluency refers to the combined scores from the letters F, A and S.

Table 4.4 compares SD and PF+ patients. Where data is available, it is clear that SD patients have no significant impairments on executive control tests, unlike PF+ patients, and the difference between groups is significant or approaching significance on all t-tests.

Table 4.4: Statistical comparison of SD and PF+ patients

Task	Significance level
VOSP	t(18) = 4.713, p < .001
Digit span: forwards	t(18) = 4.685, p < .001
Digit span: backwards	t(18) = 6.400, p < .001
Interaction: digit span forwards and backwards	F(1,18) < 1
RCPM	t(17) = 1.160, p = .262
Naming	t(18) < 1
WPM	t(18) < 1
CCTp	t(18) < 1
CCTw	t(18) < 1
Category fluency	t(18) = 2.214, p = .040
Letter fluency	t(17) = 5.924, p < .001

VOSP = Visual Object and Space Processing battery (Warrington & James, 1991); digit span (Wechsler, 1987), TEA = Test of Everyday Attention (TEA; Robertson, Ward, Ridgeway & Nimmo-Smith, 1994), Ravens Coloured Progressive Matrices (RCPM, Raven, 1962), Brixton Spatial Rule Attainment task (BSRA; Burgess & Shallice, 1997). Naming = Cambridge 64 item naming task (Bozeat et al., 2000); WPM = 64 item word-picture matching task (Bozeat et al., 2000); CCTp/CCTw = Camel and Cactus task – in picture or word form (Bozeat et al., 2000). All significant effects reflect SD patients’ higher performance. N.T. = too few SD patients to make a comparison (n = 1).

Table 4.5 compares SD to TP-only patients. There was fewer data to compare between these groups, but analyses nevertheless showed a significant difference between groups, particularly on the most executively demanding task, the backwards digit span.

Table 4.5: Statistical comparison of SD and TP-only patients

Task	Significance level
VOSP	t(13) = 3.555, p = .004
Digit span: forwards	t(13) = < 1
Digit span: backwards	t(13) = 2.818, p = .015
Interaction: digit span forwards and backwards	F(1,13) = 2.909, p = .112
RCPM	t(12) < 1
Naming	t(13) < 1
WPM	t(13) = 1.103, p = .290
CCTp	t(13) < 1
CCTw	t(10) = 1.090, p = .301
Category fluency	t(12) < 1
Letter fluency	t(11) < 1

VOSP = Visual Object and Space Processing battery (Warrington & James, 1991); digit span (Wechsler, 1987), TEA = Test of Everyday Attention (TEA; Robertson, Ward, Ridgeway & Nimmo-Smith, 1994), Ravens Coloured Progressive Matrices (RCPM, Raven, 1962), Brixton Spatial Rule Attainment task (BSRA; Burgess & Shallice, 1997). Naming = Cambridge 64 item naming task (Bozeat et al., 2000); WPM = 64 item word-picture matching task (Bozeat et al., 2000); CCTp/CCTw = Camel and Cactus task – in picture or word form (Bozeat et al., 2000). All significant effects reflect SD patients' higher performance. NT = too few SD patients to make a comparison (n = 1).

Finally, Table 4.6 compares TP-only and PF+ patients. The tasks which placed the largest demands on verbal working memory, digit span and elevator counting, showed significant differences between the groups. This may be due, in part, to impaired verbal output in the PF+ group.

Table 4.6: Statistical comparison of PF+ and TP-only patients

Task	Significance level
VOSP	t(13) = 1.044, p = .316
Digit span: forwards	t(13) = 2.915, p = .012
Digit span: backwards	t(13) = 2.839, p = .014
Interaction: digit span forwards and backwards	F(1,13) = 3.123, p = .101
TEA: without distraction	t(12) = 3.244, p = .007
TEA: with distraction	t(12) = 3.768, p = .003
Interaction: TEA with and without distractor	F(1,12) = 2.408, p = .147
RCPM	t(13) < 1
WCST	t(10) = 2.144, p = .058
BSRA	t(13) = 1.117, p = .284
PALPA 9 (word repetition)	t(12) = 1.1372, p = .193
Naming	t(13) < 1
WPM	t(13) < 1
CCTp	t(13) < 1
CCTw	t(12) = 2.543, p = .026
Synonym judgment	t(13) = 3.847, p = .002
Category fluency	t(12) = 3.360, p = .006
Letter fluency	t(12) = 8.087, p < .001

VOSP = Visual Object and Space Processing battery (Warrington & James, 1991); digit span (Wechsler, 1987), TEA = Test of Everyday Attention (TEA; Robertson, Ward, Ridgeway & Nimmo-Smith, 1994), Ravens Coloured Progressive Matrices (RCPM, Raven, 1962), Wisconsin card sorting task (WSCT; Milner, 1964); Brixton Spatial Rule Attainment task (BSRA; Burgess & Shallice, 1997); PALPA (Psycholinguistic Assessments of Language Processing in Aphasia; Kay, Lesser & Coltheart, 1992). Naming = Cambridge 64 item naming task (Bozeat et al., 2000); WPM = 64 item word-picture matching task (Bozeat et al., 2000); CCTp/CCTw = Camel and Cactus task – in picture or word form (Bozeat et al., 2000). All significant effects reflect TP-only patients' higher performance.

Cross task comparisons

We compared two different tasks to compare changes in task demands, to assess whether one subgroup is more influenced by one factor than another. These factors were (1) speech output, (2) self-generation, (3) modality, and (4) complexity. (1) To assess the factor 'speech output', we compared a task with this factor (naming) with one without this factor (WPM) which is similar in other ways – they both involve matching a single word onto a picture, and include the same concepts. We compared naming and WPM, and found a significant effect of task: *F*(1,22) = 57.516, *p* < .001, but no interaction: *F*(2,22) = 1.186, *p* =

.324, or main effect of group: *F*(2,22) < 1. This reflects a higher performance in the WPM than naming task across patients. (2) For the factor 'self-generation', we compared naming (without self generation), and category fluency (with self generation). In a comparison of naming and category fluency, there was no effect of task: *F*(1,21) < 1, or group: *F*(2,21) = 1.324, *p* = .287, but there was an interaction: *F*(2,21) = 3.666, *p* = .043. TP-only and SD patients are similar at both tasks, whereas PF+ patients are worse at the category fluency task. (3) In a comparison of modality, we compared CCTp and CCTw, and found no effect of task: *F*(1,19) = 1.295, *p* = .269, or group: *F*(2,19) < 1, but was an interaction: *F*(2,19) = 7.733, *p* = .003. Using Bonferroni corrected, two-tailed t-tests, we found SD were worse at the CCTw than CCTp: *t*(7) = 3.208, *p* = .030; as were PF+ patients: *t*(9) = 3.040, *p* = .028. TP-only patients show the reverse pattern, although the numbers were too low to run a similar t-test. (4) In a comparison of complexity, comparing a simple task (WPM) with a more complex task (CCTw). In this comparison, there was a significant effect of task: *F*(1,19) = 36.189, *p* < .001, but no interaction: *F*(2,19) = 1.136, *p* = .342, or main effect of group: *F*(2,19) = 1.162, *p* = .334. Performance was higher across patients in the WPM task in relation to CCTw.

Summary

Where comparison was possible (e.g., RCPM), SD patients show very little sign of executive control impairments. In contrast, all PF+ showed deficits on at least 4/11 executive control subtests, although these differed across subjects. All TP-only patients showed deficits on at least 1/11 control subtests, and were less impaired than PF+ patients on executive control tasks. No TP-only patient shows impairment on the backwards digit span, a demanding working memory task, and the majority of TP-only patients show normal performance on the elevator counting task, and Raven's non-verbal reasoning task. This reflects the importance of PFC for domain-general executive control, though it does not rule out a contribution from posterior areas – particularly the inferior parietal regions.

There was significantly higher performance from TP-only patients in some semantic tasks (the CCTw and synonym judgement task). This may reflect TP-only patients' preserved ability to select the appropriate linguistic context for high frequency words which are semantically diverse (Hoffman, et al., 2010; Hoffman, Rogers, et al., 2011) – which is needed in CCTw and the synonym task, two tasks where there was a notable difference between PF+ and TP-only patients. It may also reflect visual impairments in TP-only patients (particularly notable in patient ME on the VOSP task), leading to comparatively worse performance in picture tasks. Notably, performance on category and letter fluency was also significantly higher in TP-only patients than PF+ patients, perhaps reflecting preserved ability to switch between items, as well as higher fluency overall.

2.Item consistency

SA patients have been shown to be inconsistent across tasks tapping the same concepts (Jefferies & Lambon Ralph, 2006), with performance affected by the task demands and not predictable from the items themselves. For example, patients may be accurate in a word-picture matching task for the item CAT, but fail to match this item to an associated picture (e.g., MILK) in an association task. In contrast, SD patients show strong item consistency, reflecting degraded item knowledge (Bozeat, et al., 2000; Patterson, et al., 2007). SD patients are always consistent when the items are the same (Jefferies & Lambon Ralph, 2006), and show correlations even when items are different, suggesting there is a single semantic factor which is similar across these tested items (e.g., concrete, frequent items). We predicted that SD patients would show strong item consistency across tasks, and PF+ would not show this effect. We predicted that TP-only patients would also be inconsistent, similar to PF+ patients. However, given their control deficits are less severe in the tasks above; they may not show as strong an effect as PF+ patients. We tested the same items across different semantic tasks which tapped different input and output modalities and which involved different control demands (Adlam, et al., 2010; Bozeat, et al., 2000).

Procedure

64-items were taken from 8 semantic categories: domestic animals, foreign animals, birds, fruit, large household items, small household items, vehicles and tools; which can be split into two main categories: living and manmade. There were four test components: (1) spoken word-picture matching (WPM, target presented with 9 semantically related distractors, as black and white line drawings), (2) picture naming (black and white line drawings) and the Camel and Cactus Test (CCT) – assessed using both (3) picture and (4) word versions (Bozeat et al.2000). The CCT is a test of associative semantic knowledge similar to the Pyramid and Palm Trees test (Howard & Patterson, 1992). Patients were asked to decide which of four pictures/words were most associated to a probe picture/word (e.g., camel with cactus, rose, tree, or sunflower). In addition, we used ratings from Jefferies and Lambon Ralph (2006), provided by normal participants that assessed (a) the ease with which the relevant semantic relationship could be identified (e.g., understanding that a camel goes with a cactus because they are both found in the desert—and not because camels eat cacti); (b) the strength of association between the probe and the target (how often are camels and cacti thought of together?) and (c) the difficulty of rejecting the distractors. The participants rated each trial on a scale of 1–5.

Results

An omnibus logistic regression was carried out on all the data, with the following predictive variables: participant ID, task (CCTp, CCTw, WPM and naming), familiarity, patient group (SD, TP-only and PF+) and the group by task interaction. This found significant values of all these variables, including the interactive term: Wald > 37.2, $p \leq .001$.

Task consistency

We predicted that Both SA and SD patients would show within task consistency (between CCTp and CCTw), as the tasks demands were similar in these tasks, and only the modality changed. A logistic regression assessed whether a predictor variable (e.g., CCTw) could predict performance on a second task (CCTp), and vice versa. The variables entered into the model were: participant ID, predictor task, familiarity rating, patient group, group by predictor task interaction. If one task significantly predicts another, this suggests consistent performance across assessments. With between task consistency (e.g., WPM and CCTp), we predicted less consistency in the SA groups in relation to SD patients. The results are displayed in Table 4.7 (raw data is in Table 4.8).

Table 4.7: Logistic regression across all patients

Predictor variable (task)	Predictive variable (task)	Task	Group	Task x group	Patient ID	Familiarity
CCTw	CCTp	**27.646*** **	**7.9** **	N.S.	**105.727 *** **	**5.603* **
CCTp	CCTw	**29.041 *** **	N.S.	**8.448* **	**114.841 *** **	N.S.
CCTw	WPM	N.S.	N.S.	N.S.	**117.586 *** **	**5.396* **
WPM	CCTw	N.S.	N.S.	N.S.	**151.764 *** **	N.S.
CCTw	Naming	N.S.	N.S.	N.S.	**109.526 *** **	**5.658* **
Naming	CCTw	N.S.	**19.203 *** **	N.S.	**316.279 *** **	**30.485 *** **
CCTp	WPM	**3.914* **	N.S.	N.S.	**138.230 *** **	N.S.
WPM	CCTp	**4.178* **	N.S.	N.S.	**204.645 *** **	**4.866* **
CCTp	Naming	N.S.	N.S.	N.S.	**132.849 *** **	N.S.
Naming	CCTp	N.S.	**25.919 *** **	N.S.	**358.105 *** **	**42.906 *** **
WPM	Naming	**20.688 *** **	N.S.	**6.410* **	**143.643 *** **	N.S.
Naming	WPM	**17.497 *** **	**8.587 *** **	N.S.	**306.620 *** **	**38.713 *** **

* = p < .05; ** = p < .01; *** = p < .001. Values are Wald values. N.S. = accuracy on one task did not predict accuracy on the other assessment. N.T. = not tested, due to the main effect of familiarity being non-significant.

Table 4.8: Performance on four semantic tasks with differing control demands

	CCTp	**CCTw**	**Naming**	**WPM**
PF+	60.78 (48.86)	52.34 (49.98)	43.59 (49.63)	76.41 (42.49)
TP-only	63.13 (48.32)	75.00 (43.39)	47.19 (49.99)	83.20 (37.46)
SD	63.13 (48.28)	58.01 (49.40)	41.41 (49.29)	71.09 (45.37)

Data are shown in percentage with means (and standard deviations) for each group of subjects.

To further explore this data, a logistic regression was run for each group (shown in Table 4.9, Table 4.10 and Table 4.11). We predicted that SD patients would show more item consistency, and more of an effect of familiarity than TP-only and PF+ patients, due to degraded representations of less familiar items, independent of task demands.

Table 4.9: Logistic regression for PF+ patients

Predictor variable (task)	Predictive variable (task)	Task	Familiarity
CCTw	CCTp	**27.709*** **	N.S.
CCTp	CCTw	**27.710*** **	N.S.
CCTw	WPM	N.S.	N.S.
WPM	CCTw	N.S.	N.S.
CCTw	Naming	**13.307*** **	N.S.
Naming	CCTw	**13.307*** **	N.S.
CCTp	WPM	**4.299* **	N.S.
WPM	CCTp	**4.297* **	N.S.
CCTp	Naming	**5.312* **	N.S.
Naming	CCTp	**5.314* **	N.S.
WPM	Naming	**13.259*** **	N.S.
Naming	WPM	**13.283*** **	N.S.

* = p < .05; ** = p < .01; *** = p < .001. Values are Wald values. N.S. = accuracy on one task did not predict accuracy on the other assessment.

Table 4.10: Logistic regression for TP-only patients

Predictor variable (task)	Predictive variable (task)	Task	Familiarity
CCTw	CCTp	**16.129*** **	**6.861** **
CCTp	CCTw	**16.210*** **	N.S.
CCTw	WPM	N.S.	N.S.
WPM	CCTw	N.S.	N.S.
CCTw	Naming	**10.357*** **	N.S.
Naming	CCTw	**10.368*** **	**4.559* **
CCTp	WPM	N.S.	N.S.
WPM	CCTp	N.S.	N.S.
CCTp	Naming	**28.505*** **	N.S.
Naming	CCTp	**28.561*** **	**13.265*** **
WPM	Naming	**8.531** **	N.S.
Naming	WPM	**8.588** **	**11.747*** **

* = p < .05; ** = p < .01; *** = p < .001. Values are Wald values. N.S. = accuracy on one task did not predict accuracy on the other assessment.

Table 4.11: Logistic regression for SD patients

Predictor variable (task)	Predictive variable (task)	Task	Familiarity
CCTw	CCTp	**63.886*** **	N.S.
CCTp	CCTw	**63.852*** **	**3.871***
CCTw	WPM	**38.000*** **	N.S.
WPM	CCTw	**37.910*** **	**6.004***
CCTw	Naming	**40.191*** **	N.S.
Naming	CCTw	**40.265*** **	**11.765*** **
CCTp	WPM	**58.985*** **	**3.943***
WPM	CCTp	**58.939*** **	**8.794** **
CCTp	Naming	**47.259*** **	N.S.
Naming	CCTp	**47.406*** **	**13.694*** **
WPM	Naming	**81.324*** **	**3.835***
Naming	WPM	**81.394*** **	**9.308** **

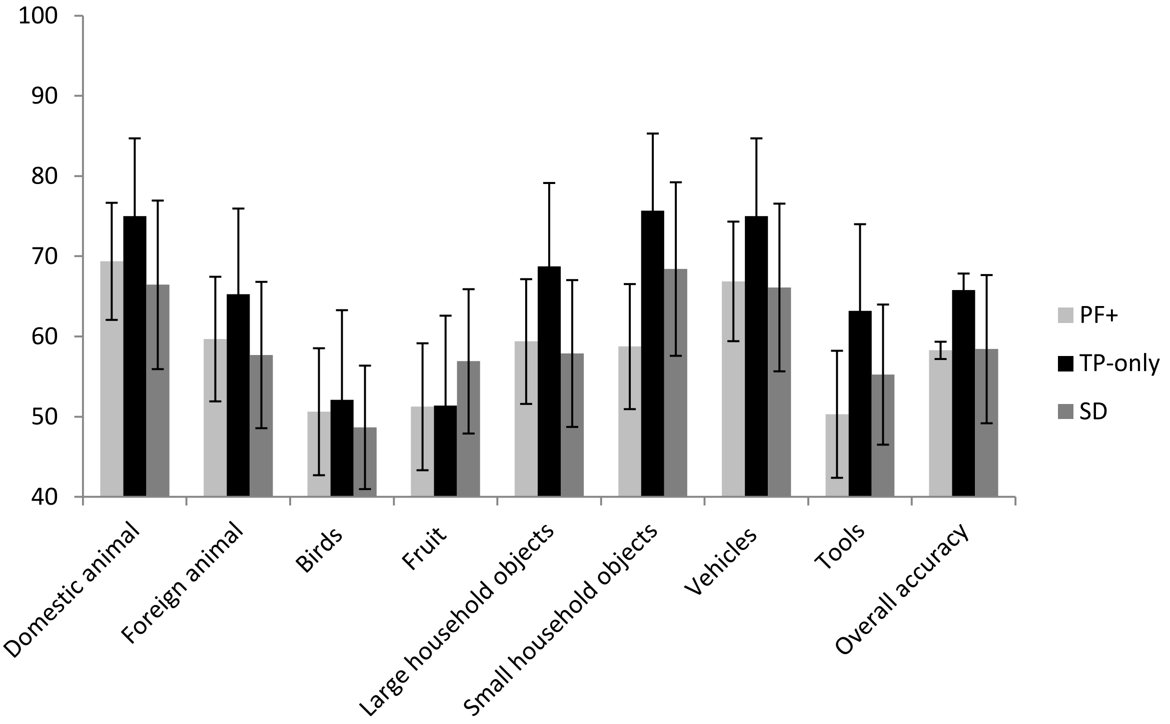
* = p < .05; ** = p < .01; *** = p < .001. Values are Wald values. N.S. = accuracy on one task did not predict accuracy on the other assessment.

Summary

There was strong consistency across all patient groups for within task consistency (CCTp vs. CCTw), reflecting the similar task demands. There was huge variation between all patients, and individual patient had a higher predictive value than any other variable. Nonetheless, when separating patient into subgroups, there was clearly higher consistency in SD patients compared to the two SA groups. Additionally, TP-only patients showed some predictive value of familiarity, something which has commonly been associated with SD patients.

Category effects: four semantic tasks (CCTp, CCTw, WPM & naming)

The Cambridge Semantic Battery (Adlam, et al., 2010; Bozeat, et al., 2000), involves four tests that include the same concepts, drawn from 8 categories and divided equally into natural and man-made objects. We categorised all items as either manmade or natural. Accuracy scores for each category are show in Figure 4.1. A logistic regression included patient ID, group, familiarity, category, and category by group. This found a significant effect of category: Wald = 7.572, *p* = .006, group: Wald = 24.221, *p* < .001, and category by group interaction: Wald = 10.900, *p* = 012, as well as a main effect of familiarity: Wald = 22.244, *p* < .001, and participant: Wald = 878.053, *p* < .001.



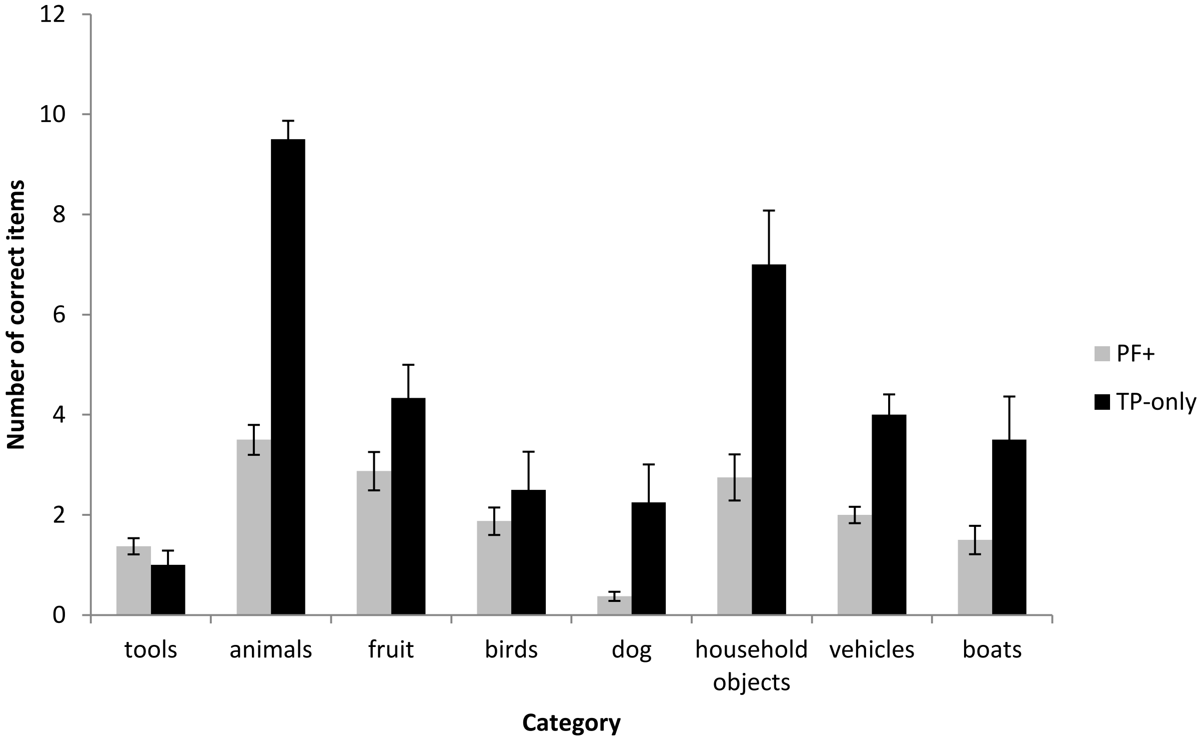
Tasks used in this graph: Camel and Cactus (picture and word versions), word-picture matching and naming (Bozeat et al., 2000; 2002).

Figure 4.1: Category effects across four semantic comprehension tasks

The effect of category was looked at for each group (with a model including patient ID, familiarity and category). The effect of category was not significant for PF+ patients (Wald < 1), but was for TP-only patients: Wald = 7.841, *p* = .005 (where familiarity was not). For SD patients, the effect of familiarity was significant: Wald = 48.221, *p* < .001, the effect of category was not (Wald < 1). Contrary to many theories, the effect of category on TP-only patients reflected higher performance on manmade (71%) compared to living items (61%). However, the effect of familiarity was much less influential in TP-only patients than SD patients.

Category effects: verbal fluency

We then analysed the scores we had which were distinguished according to category (from TP-only and PF+ patients, Figure 4.2). When comparing living and non-living categories, there was a significant effect of category: *F*(1,10) = 5.834, *p* = .036, and significant effect of group: *F*(1,10) = 9.472, *p* = .012, but no interaction: *F* < 1. This reflected higher performance for living items, and an overall higher score from TP-only patients. TP-only patients showed more fluctuation of response across categories in relation to PF+ patients, who were impaired across categories.



Error bars show standard error of mean

Figure 4.2: Correct items on category fluency, according to category

Bonferroni-corrected independent-groups t-tests were used to further explore this data. Significant values represent higher performance from TP-only patients. There was a significant different between PF+ and TP-only patients for fluency in the categories animals: *t*(10) = 6.197, *p* < .001, and vehicles: *t*(10) = 2.981, *p* = .034. There were no other significant differences (including no group effect for tool fluency).

Summary

For the category effects analysis of responses to the Cambridge Semantic Battery, PF+ patients showed no category effects, whereas TP-only patients do. There was larger variance in the data from TP-only patients, with an overall higher level of accuracy in relation to PF+ and SD patients. This may be due to some effect of visual feature overlap in TP-only patients (many of whom have damage to visual cortex). In WPM/naming, PF+ and TP-only patients were similar for the living categories, but TP-only patients showed higher scores on non-living categories, suggesting their relatively poorer performance for living things might have been linked to visual overlap. The two categories which had lowest scores across comprehension tasks – fruit and birds – are difficult to visually distinguish. Indeed, categories with high visual overlap (e.g., animals) activate extra visual areas, thought to be required to differentiate the category exemplars (Tyler, et al., 2003), leading some to suggest that category-specific deficits are a reflection of perceptual deficits (Humphreys & Riddoch, 2003). Overall, PF+ patients don't show category effects because their executive deficits are 'blind' to category, whereas TP-only patients show effects which are driven by visual impairment.

In relation to verbal fluency, TP-only patients typically showed higher performance on categories which were highly familiar, and which easily subcategorise (e.g., animals → farm animals, zoo animals, pets), whereas PF+ patients showed blanket impairment in this task. The natural advantage some categories have is missing in PF+ patients, due to reduced verbal fluency.

Factors which affected performance

Jefferies and Lambon Ralph (2006) collected ratings from healthy participants, who scored each item from 1-5, with a high rating meaning lower control demands or an easier relationship to work out. There were three questions: (1) ease of determining the relevant semantic relationship, (2) co-occurrence of probe and target, and (3) ease of rejecting distractors. In SA, reduced consistency across tasks in relation to SD patients could reflect the extent to which semantic control is required in each trial. Jefferies and Lambon Ralph (2006) found that SD patients, like SA patients, showed an effect of co-occurrence of the probe and target (inter-item frequency), but they did not show an effect of the other two factors, which were more associated with semantic control.

Logistic regression was used to assess each group separately. This model included patient ID, rating and familiarity. For question 1, there was a significant predictive effect of ratings for the PF+ group (Wald = 17.863, $p < .001$), TP-only patients (Wald = 23.914, $p < .001$), and SD patients (Wald = 13.279, $p < .001$). The effect, although significant in all patients, is weaker in SD patients, as shown in Figure 4.3.

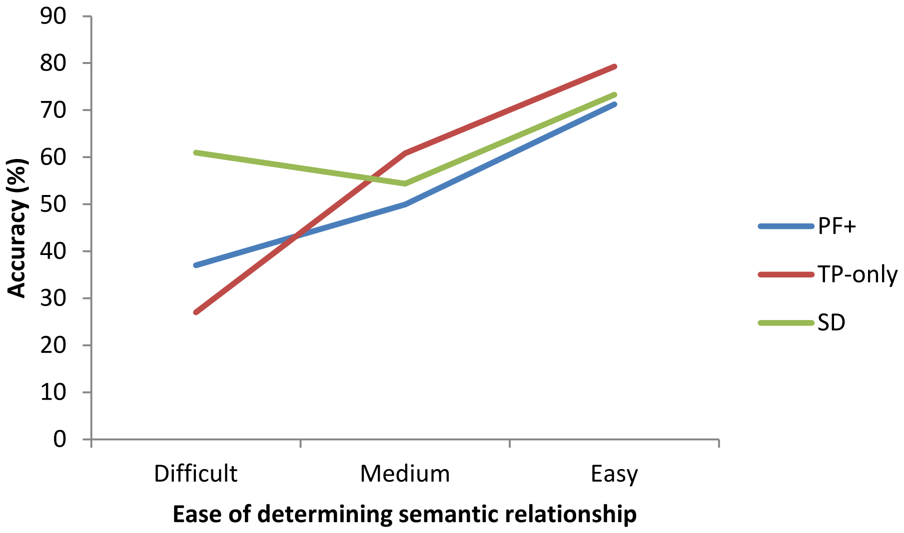


Figure 4.3: Impact of ease of determining semantic relationship between probe and target on performance in PF+, TP-only and SD patients.

For question 2, there was a significant predictive effect of ratings for PF+ (Wald = 12.709, *p* < .001), TP-only (Wald = 20.691, *p* < .001), and SD patients (Wald = 18.179, *p* < .001). This is shown in Figure 4.4.

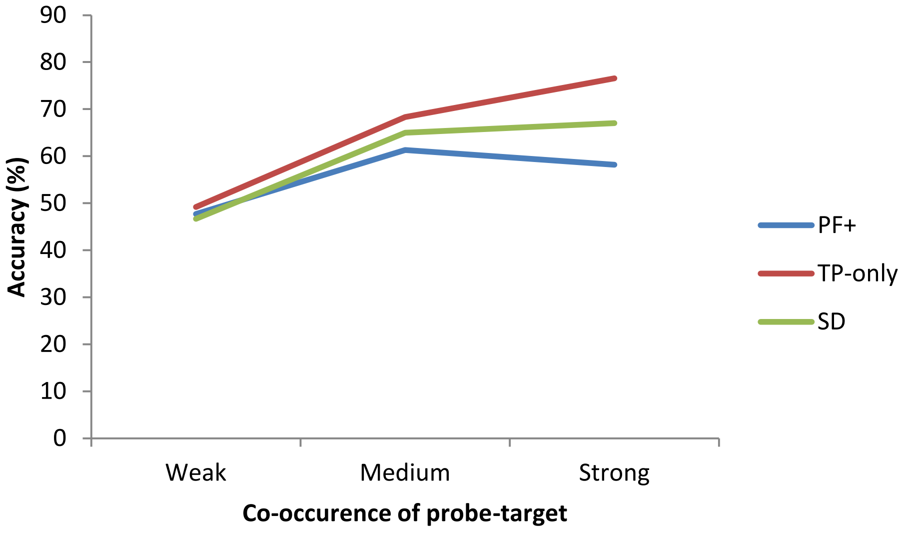


Figure 4.4: Impact of co-occurence of the probe and target on accuracy in PF+, TP-only and SD patients.

For question 3, there was a significant effect in PF+ (Wald = 10.623, *p* = .001), TP-only (Wald = 16.376, *p* < .001), and SD patients (Wald = 10.167, *p* = .001). This is shown in Figure 4.5.

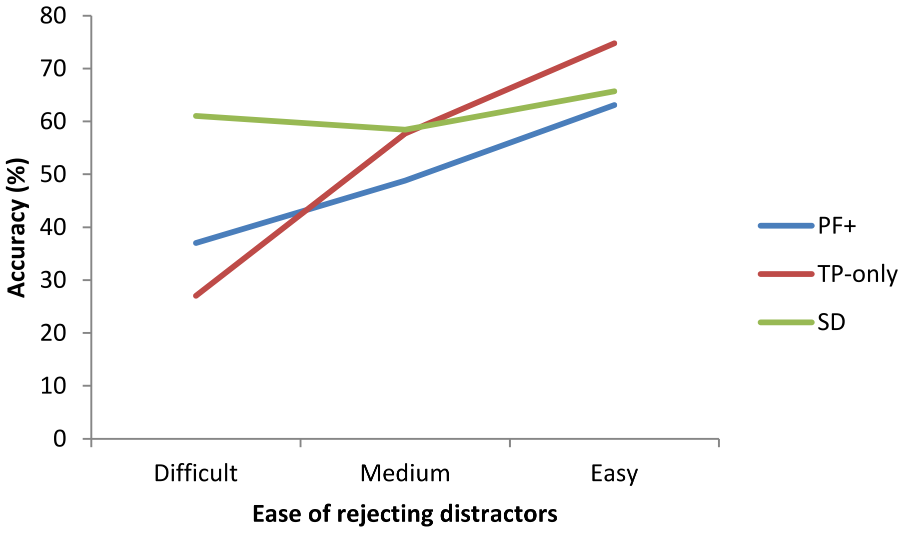


Figure 4.5: Effect of ease of rejecting distractors on accuracy in PF+, TP-only and SD patients.

Groups were paired to find whether an interaction between group and factor was significant. A model including familiarity, group, rating, rating by group was run. (1) Comparing PF+ and SD patients, the interaction of rating and group was not significant for question 1, 2, but for question 3 the interaction of group and factor was (Wald = 4.777, *p* = .029). (2) In a comparison of TP-only and SD patients, there was no significant predictive interaction of group and factor for question 2, but was for question 1 (Wald = 6.901, *p* = .009) and 3 (Wald = 10.132, *p* = .001). (3) A comparison of TP-only and PF+ patients found the interaction of rating and subgroup was not significant for question 1 or 3, but was for question 2 (Wald = 7.486, *p* = .006). TP-only patients show higher performance on items which co-occur in relation to PF+ patients, who only show a marginal effect of this variable.

Summary

The impact of several factors which influence the ease of making semantic associations was found to be important in all patients, but was particularly strong in TP-only patients. The impact may have been less statistically strong in PF+ patients due to their lower performance, which may have reduced the impact of these control factors on performance.

3.Naming

Previous investigations of SA patients have shown that their picture naming performance bears the hallmarks of a regulatory control impairment. Specifically, SA patients make associative errors that are almost never seen in SD, suggesting SA patients have difficulty directing activation to the correct target item, and away from competitors and miscues (Jefferies, Patterson, et al., 2008; Soni, et al., 2009). We determined the extent to which SA patients performance could be modulated by the amount of intrinsic constraint provided across different verbal production tasks (e.g., picture naming, category and letter fluency). Picture naming has the largest external constraint, as it gives an image of an item with one, or in some cases a few, possible correct responses. Letter fluency has the least constraint, with many possible correct items from different semantic categories. Category fluency is in-between these two tasks; it has more constraint than letter fluency, because it involves activating and selecting a select number of items based on the named category. However, there are more potential correct responses than in picture naming. Therefore, we predict that SA patients (potentially PF+ more than TP-only patients) will be worse at tasks with less external constraint, in relation to tasks with higher constraint, due to the manipulation of task demand.

Procedure

Category fluency was examined in both groups using six category labels (i.e., ANIMALS, BIRDS, FRUIT, HOUSEHOLD OBJECTS, TOOLS, and VEHICLES). Letter fluency was also assessed using the letters ‘F’, ‘A’ and ‘S’. In both fluency tasks patients were given one minute to produce as many exemplars as possible. SA patients were additionally tested on the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983) and provided with the prescribed phonemic cue for items they could not name.

Results

Picture naming errors

The 64 item naming test was used to examine patterns of naming errors in our SD and stroke groups. The three groups were at the same level of accuracy: $F < 1$, and there was a significant main effect of category: $F(7,15) = 10.222$, $p < .001$, but no interaction with group: $F(14,32) = 1.658$, $p = .116$. This stems from higher performance overall on domestic animals which are highly familiar, in relation to foreign animals and birds; and higher performance on small household objects and vehicles than large household objects or tools.

In an analysis across all errors, the majority of errors were semantic or omission (see

Table 4.12), which lead to a main effect of error type: F(5,17) = 161.728, p < .001. There was also a significant interaction of error and group: *F*(10,36) = 2.110, *p* = .050, but no main effect of group: *F* < 1.

Table 4.12: Type of picture naming errors across PF+, TP-only and SD patients

	PF+	TP-only	SD
Total correct	40.63 (29.0)	47.31 (29.4)	41.41 (34.4)
Errors			
Semantic	28.81 (19.6)	55.42 (27.5)	45.12 (14.8)
Phonological	11.38 (12.0)	5.93 (13.3)	6.54 (8.2)
Unrelated	4.97 (7.0)	3.56 (7.1)	0.39 (0.8)
Preservative	13.45 (14.4)	1.78 (3.2)	10.52 (13.2)
Omission	66.40 (29.5)	30.41 (23.9)	37.24 (23.3)
Descriptive	1.59 (3.1)	2.90 (3.9)	0.19 (0.6)
Semantic errors			
Co-ordinate	61.71 (20.9)	61.59 (16.5)	74.03 (25.7)
Superordinate	10.97 (12.8)	29.01 (22.0)	24.72 (25.4)
Associative	27.32 (16.5)	9.40 (12.4)	1.30 (4.1)

Scores are shown as a percentage. Means (and standard deviations) of the proportion of each type of error for each patient group. KA is not included in the analysis due to being unable to complete the 64 item naming task.

To further explore this significant interaction, one-way ANOVAs were used to compare each of the six error types across patients (in terms of proportion of error): semantic, phonological, unrelated, preservative, omission or descriptive.

There was no difference in (i) phonological or (ii) omission errors between groups (*F* < 1). (iii) There was also no difference in semantic errors overall: *F*(2,23) = 2.894, *p* = .078, although there was a trend towards less semantic errors in PF+ patients than TP-only patients or SD patients. (iv) There was no significant effect of group in unrelated errors: *F*(2,23) = 1.617, *p* = .222, (v) perservative errors: *F*(2,23) = 1.403, *p* = .268 or (vi) descriptive errors: *F*(2,23) = 1.913, *p* = .172.

A further analysis on the semantic errors examined the production of co-ordinate, superordinate or associative errors as a proportion of total semantic errors (see Figure 4.6). There was a significant effect of type of error: *F*(2,20) = 35.037, *p* < .001, and a significant interaction of group and error: *F*(4,42) = 4.444, *p* = .004, but no main effect of group: *F* < 1.

There was no difference between groups on coordinate errors: *F*(2,23) = 1.027, *p* = .375; superordinate errors: *F*(2,23) = 1.868, *p* = .179; but was for associative errors: *F*(2,23) = 13.069, *p* < .001.

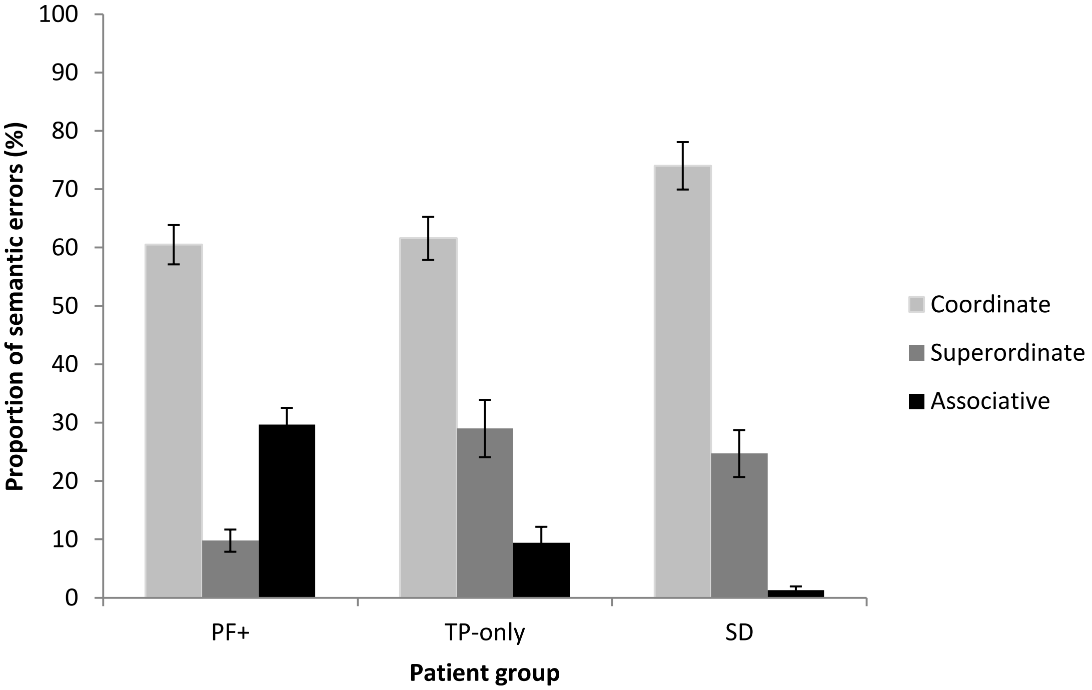


Figure 4.6: Type of semantic errors produced in picture naming across PF+, TP-only and SD patients. Error bars show standard error of mean.

Bonferroni-corrected independent samples t-tests found no significant differences between TP-only and PF+ patients, for coordinate: *t* < 1, superordinate: *t*(12) = 2.187, *p* = .147, or associative errors: *t*(12) = 2.298, *p* = .120. TP-only patients show slightly more superordinate errors, whereas PF+ patients show more associative errors, although this does not come out statistically. In a comparison between PF+ and SD patients, PF+ patients make more associative errors: *t*(12) = 5.054, *p* < .001, but there was no difference superordinate or coordinate errors (*t* < 1.7, *p* ≥ .372). In a comparison between TP-only and SD patients, there was no significant difference of coordinate or superordinate errors (*t* < 1), or associative errors: *t*(13) = 1.923, *p* = .231.

Cueing effects in naming

The BNT also allowed us to examine the effects of phonological cues on naming performance. BNT performance in the two stroke groups was examined using a 2 (group) x 2 (cueing) ANOVA. There was a main effect of cueing: *F*(1,8) = 64.733, *p* < .001. This was significant in each individual patient, from both TP-only and PF+ groups (see Table 4.13).

Table 4.13: BNT scores for each individual patient

		Accuracy (/64)		Cueing
		No cue (/60)	Final cue (/60)	
PF+	JM	19	42	**p < .001**
PF+	NY	23	52	**p < .001**
PF+	KH	20	37	**p < .001**
PF+	BB	1	43	**0 < .001**
PF+	KS	3	52	**p < .001**
PF+	DB	24	42	**p < .001**
PF+	GH	15	48	**p < .001**
PF+	PG	34	57	**p < .001**
TP-only	KS	10	NT	NA
TP-only	SC	8	44	**p < .001**
TP-only	ME	1	46	**p = .001**

McNemar scores for the effect of cueing in each SA patient. NT = not tested. NA = not available.

In both PF+ and TP-only groups, initial naming performance was poor (28.9% and 10.6% respectively) but improved substantially following cues (77.7% and 75%). No group difference or interaction between group and cueing was detected: *F*(1,8) = 1.684, *p* = .231.

Summary: Both TP-only and PF+ groups showed clear evidence of regulatory control problems in their verbal output. Their picture naming errors revealed a tendency to be pulled toward associative responses (e.g., SQUIRREL → “nuts”). This was particularly noticeable in PF+ patients. Deficits in control mechanisms could lead to associative errors, due to inability to inhibit the most readily accessible response, usually a strong associate of the target. This also reflects considerable remaining knowledge about the target items. Conversely, degraded semantic representations lead to more superordinate errors, as specific item knowledge is reduced. However, TP-only patients make more superordinate errors than PF+ patients, and make the same number of superordinate errors as SD patients. It is not clear why this is the case, although it may again be related to visual overlap between items of the same category, leading patients to name an item as simply ‘fruit’ rather than a more specific item such as ‘apple’. In both SA patients, errors in naming were greatly reduced when phonemic cues helped the patient to direct activation toward the correct target and away from potential competitors.

Verbal fluency

In an omnibus 3 by 3 ANOVA (letter fluency, category fluency, naming by group), there was a main effect of task: $F(2,17) = 8.642$, $p = .003$, but not group: $F(2,18) = 1.982$, $p = .167$, or an interaction: $F(4,26) = 2.018$, $p = .113$. In an ANOVA comparing letter and category fluency there was a significant effect of task: $F(1,18) = 14.540$, $p = .001$, and a significant effect of group: $F(2,18) = 6.025$, $p = .010$, but no interaction: $F < 1$. This reflects higher performance from SD patients, followed by TP-only and then PF+ patients; and higher performance overall on the category task.

In a one-way ANOVA comparing category fluency, there was no group difference between SD, PF+ and TP-only: $F(2,21) = 1.955$, $p = .169$. In terms of letter fluency, a one-way ANOVA revealed a significant group difference: $F(2,20) = 17.684$, $p < .001$. Bonferroni corrected t-tests showed that PF+ patients were more impaired than the TP-only patients: $t(10) = 3.264$, $p = .027$, and SD patients: $t(15) = 6.622$, $p < .001$; TP-only and SD patients were not significantly different: $t(11) = 1.583$, $p = .426$ (see Figure 4.7).

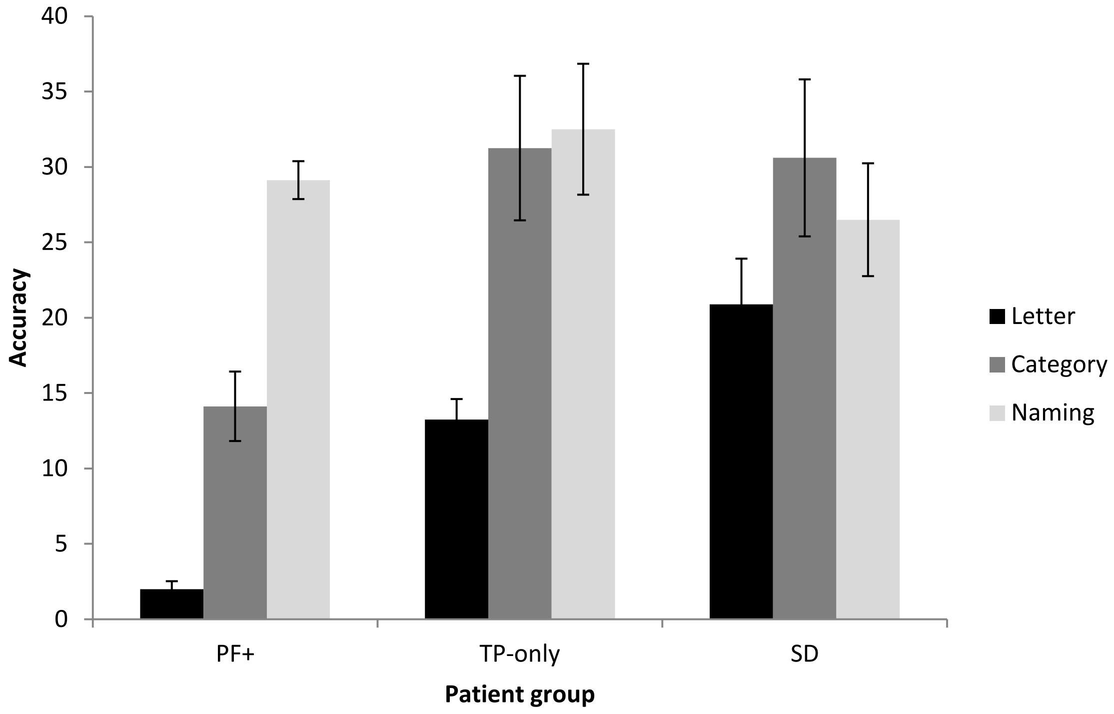


Figure 4.7: Naming, category and letter fluency accuracy in PF+, TP-only and SD patients

In Bonferroni-corrected, independent-samples t-tests, which looked at group difference per task, TP-only patients were significantly more fluent than PF+ patients on both letter fluency: $t(10) = 3.264$, $p = .027$, and category fluency: $t(10) = 3.078$, $p = .036$, but not naming: $t < 1$. Although SD patients are more fluent than PF+ patients, this was only significant for letter fluency: $t(15) = 6.622$, $p < .001$. There were no differences between SD and TP-only patients.

Summary: Both TP-only and PF+ patients are worse at letter fluency than category fluency or naming, which is the task which requires the most self-directed regulation. However, PF+ patients show significantly lower fluency in relation to TP-only patients, both in category and letter fluency. This suggests PF+ show a classic pattern associated with executive control deficits, and SD patients performed poorly on semantic tasks regardless of their regulatory requirement. TP-only patients showed strong cueing for picture naming, but seem able to produce category/letter exemplars.

4.Frequency/imageability effects

Procedure

Synonym judgement was assessed in SA patients, and a separate cohort of 11 SD patients, using a 96 item synonym judgement task from Jefferies et al. (2009) which orthogonally varied frequency (high and low) across three imageability bandings (high, medium and low). There were three response options, one target and two distractors. The distractors were unrelated, but both target and distractors were matched to the probe word for frequency and imageability.

Results

Table 4.14: Synonym judgment scores

	LI: LF	MI:LF	HI:LF	LI:HF	MI:HF	HI:HF
SD	5.5 (3.11)	7.3 (3.98)	10.5 (4.76)	10.0 (4.75)	13.7 (3.00)	13.6 (1.96)
PF+	8.3 (2.5)	9.0 (3.37)	13.3 (2.21)	8.1 (1.85)	9.6 (2.50)	12.1 (1.85)
TP-only	8.4 (2.30)	14.0 (1.41)	15.8 (.45)	11.6 (2.97)	14.8 (1.64)	15.0 (1.22)

LI = low imageability, MI = medium imageability, HI = high imageability, LF = low frequency, HF = high frequency. 96 items are split into 6 categories of imageability and frequency, each with a maximum score of 16. Data shows means (and standard deviations) across the three groups.

Results are shown in Table 4.14. There was significant correlation of this task with lesion size, in overall score (r = -.697, p = .008). There was also a correlation of lesion size with high frequency scores (r = -.757, p = .003), low frequency scores (r = -.571, p = .041), high imageability items (r = -.738, p = .004), and low imageability items (r = -.672, p = .012). This suggests lesion size correlates with the task generally, rather than a particular aspect of it (such as less imageable items).

A 3 (group) x 2 (frequency) x 3 (imageability) ANOVA revealed a main effect of group, F(2,23) = 3.631, p = .043, frequency: F(1,23) = 25.355, p < .001, and an interaction of frequency and group: F(2,23) = 22.269, p < .001. There was also a main effect of imageability: F(2,22) = 75.253, p < .001, which showed a marginal interaction with group: F(4,46) = 2.513, p = .054. There was an interaction of frequency and imageability: F(2,22) = 5.406, p = .012, but no three way interaction: F(4,46) = 1.312, p = .280.

There was an overall effect of group when comparing TP-only and PF+ patients: F(1,13) = 14.067, p = .002, TP-only and SD patients: F(1,14) = 4.672, p = .048, but not PF+

and SD patients: *F*(1,19) < 1. This shows that TP-only patients show higher performance overall.

Individual group performance is shown in Figure 4.8, Figure 4.9 and Figure 4.10. SD patients showed higher performance for high than low frequency words. In a comparison of frequency (high vs. low), there was a main effect of frequency: *F*(1,23) = 25.355, *p* < .001; group: *F*(2,23) = 3.631, *p* = .043; and interaction: *F*(2,23) = 22.269, *p* < .001. In an ANOVA comparing two groups, SD and PF+ patients showed a significant interaction of group and frequency: *F*(1,19) = 36.787, *p* < .001; and a similar interaction was found for SD and TP-only patients: *F*(1,14) = 15.097, *p* = .002. The two SA groups showed a similar effect of frequency: *F*(1,13) = 2.438, *p* = .142. In Bonferroni-corrected paired-samples t-test for each group, there was no significant difference between high and low frequency for PF+ or TP-only patients, but there was a significant difference for SD patients: *t*(10) = 7.910, *p* < .001. This suggests the frequency effect is significantly greater in SD patients than TP-only or PF+ patients.

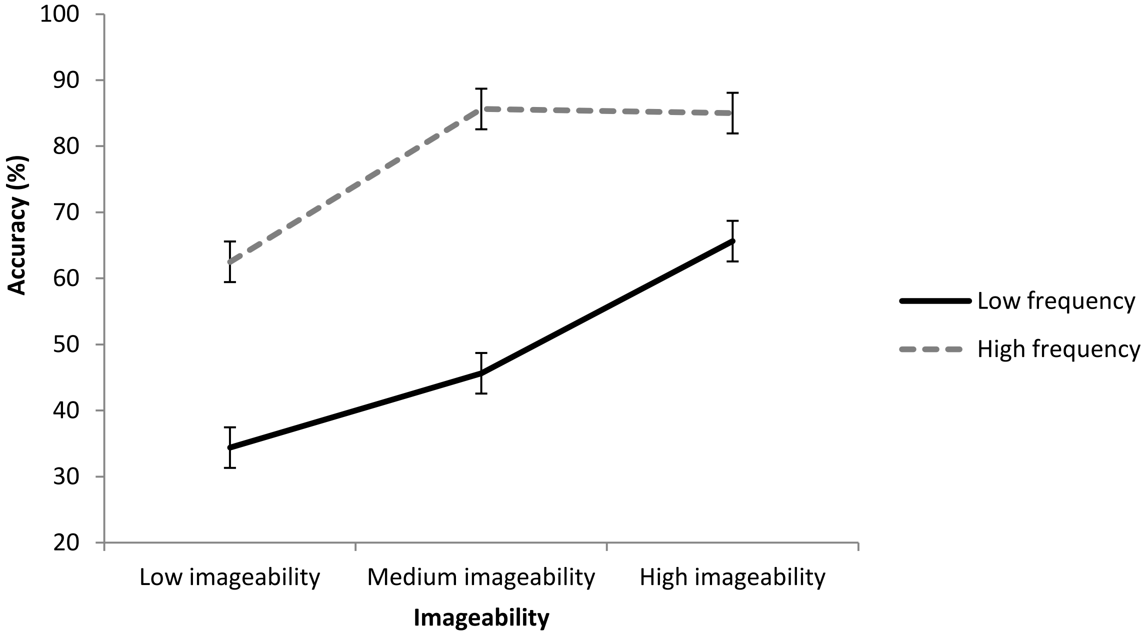


Figure 4.8: SD imageability x frequency scores. From the synonym judgement task (Jefferies et al., 2009).

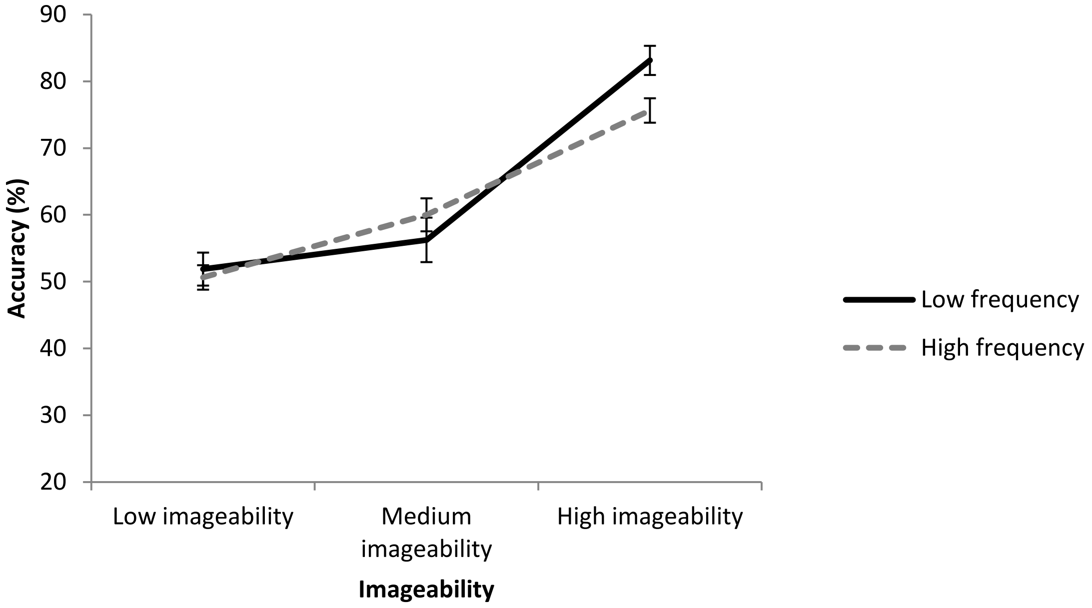


Figure 4.9: PF+ imageability x frequency performance. From the synonym judgement task (Jefferies et al., 2009).

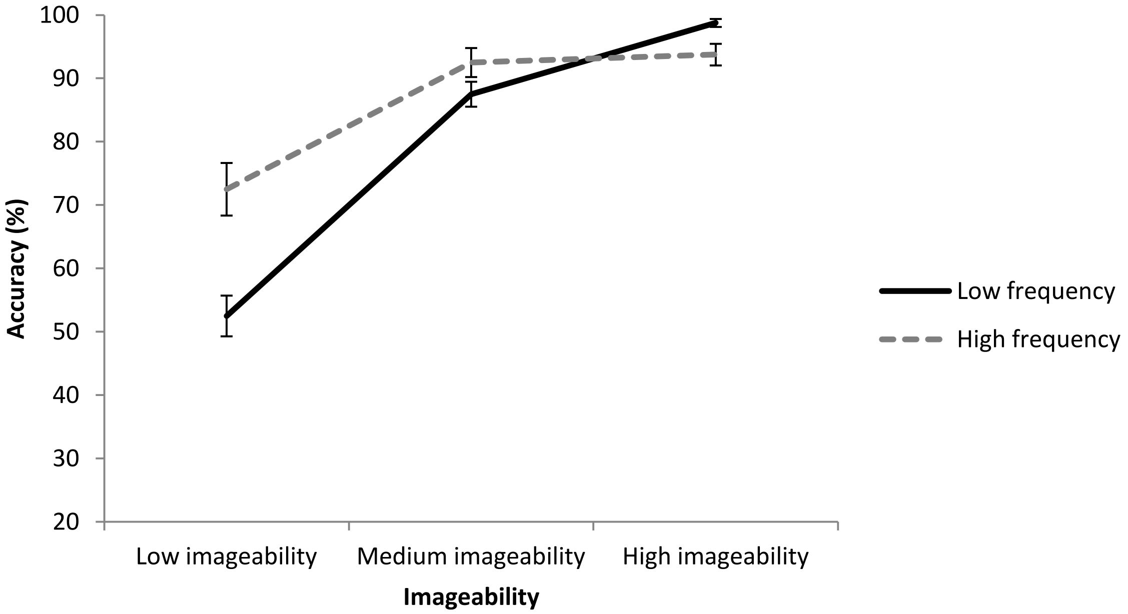


Figure 4.10: TP-only imageability x frequency performance. From the synonym judgement task (Jefferies et al., 2009).

All the patients showed higher performance on more imageable words. There was a main effect of imageability: $F(2,22) = 75.253$, $p < .001$; a significant group difference:

F(2,23) = 3.631, *p* = .043; and a trend towards significant interaction between imageability and group: *F*(4,46) = 2.513, *p* = .054. When comparing two patient groups, there was an interaction of imageability and group for PF+ and TP-only patients: *F*(2,12) = 4.052, *p* = .045; but not for PF+ compared to SD patients: *F*(2,18) = 3.11, *p* = .069, or TP-only compared to SD patients: *F*(2,13) < 1. Bonferroni-corrected t-tests found that TP-only patients showed higher performance than PF+ cases on high imageability words: *t*(13) = 3.080, *p* = .027, and medium imageability words: *t*(13) = 4.004, *p* = .006, but not low imageability words: *t*(13) = 1.774, *p* = .297.

Summary: All patients were influenced by imageability, but TP-only patients only showed impaired performance for low imageability words, whereas SD and PF+ patients showed impairments for medium imageability words as well (reflecting higher performance overall in TP-only patients). SD patients were very sensitive to frequency. TP-only patients showed some effects of frequency, but not to the same extent as SD patients. PF+ patients had identical performance on high and low frequency items. High frequency items appear in more linguistic contexts. Thus – although a normal sample would show a high frequency word advantage, patients with control deficits do not show this effect - as high frequency words also require selecting the appropriate linguistic context. This leaves performance on high and low frequency words the same. This selection process of high frequency words appears to be particularly dependent on the PFC – given the trend towards higher performance on high frequency words in TP-only patients but not PF+ patients.

5.Semantic control tasks

Four tasks assessed different aspects of semantic control in PF+ and TP-only SA groups. The first two tasks were taken from Noonan et al. (2010), and the second adapted from Whitney et al. (2011).

(i) Semantic distance

The degree of semantic control required was manipulated by varying semantic similarity of the probe with the target, whilst keeping the distractors the same. When the probe and the target were closely related, they shared much of their semantic structure, (e.g. HAT, with CAP, FUTON or SPADE). When the probe and the target were only distantly related, additional semantic control was required to work out the relevant semantic link (e.g. HAT, with STOCKING, FUTON, or SPADE). Distantly related items were more demanding as all of the items were equally distantly related to the target. Further details of the test and further examples of the stimuli can be found in Noonan et al. (2010).

Procedure

The semantic distance task (Noonan et al., 2010) involved matching a probe word to the target word in the same semantic category. There were two levels of relatedness, either matching a closely or distantly related item. The same 64 words were tested in both conditions of relatedness, over different testing sessions, which led to 128 responses. This included data from 12 patients, 8 PF+ (DB, GH, EC, PG, NY, BB, KA, LS), and 4 TP-only (KS, HN, SC, ME). For this task, we were also able to compare these patients with a separate cohort of 4 SD patients (GE, TM, NH and JW).

Results

There was a correlation with lesion size in SA and closely related words: r = -.751, p = .008; but not distantly related word: r = -.504, p = .114. There was no correlation of the difference between close and distant responses and lesion size. Data from the nearest neighbour task is presented in Figure 4.11. When assessing all patients (SD, PF+ and TP-only), we found a main effect of semantic closeness: *F*(1,13) = 56.041, *p* < .001, and an interaction of group and closeness: *F*(2,13) = 4.483, *p* = .033, but no main effect of group: *F*(2,13) = 1.335, *p* = .297.

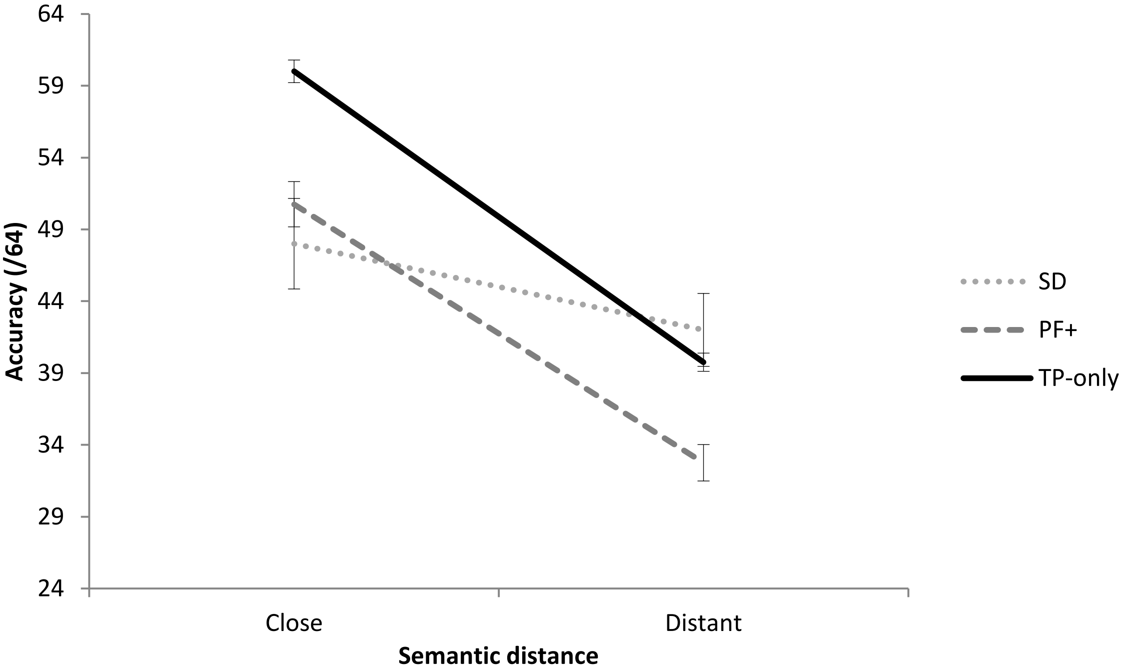


Figure 4.11: Semantic distance effects in the nearest neighbour task (Noonan et al., 2010).

In a comparison of PF+ and SD patients, this interaction remains significant: *F*(1,10) = 6.174, *p* = .032 (with no main effect of group: *F* < 1; but a main effect of closeness: *F*(1,10)

= 24.695, *p* = .001). This is also true of a comparison of TP-only and SD patients, with a significant interaction: *F*(1,6) = 9.565, *p* = .021, and main effect of closeness: *F*(1,6) = 32.458, *p* = .001, but no effect of group: *F* < 1. In a comparison of PF+ and TP-only patients, there was a main effect of semantic closeness: *F*(1,10) = 67.646, *p* <.001; but no main effect of group: *F*(1,10) = 3.509, *p* = .091; or interaction: *F*(1,10) = .234, *p* = .639. Both TP-only and PF+ patients showed the same effects of task demand. Nonetheless, individuals from both SA groups of patients showed an effect of semantic control manipulation (see Table 4.15).

Table 4.15: Effects of semantic control manipulations in individual patients

		Accuracy (/64)		Semantic distance	Accuracy (/30)		Semantic ambiguity
		Close	Distant		Dominant	Subordinate	
PF+	PG	54	51	p = .644	19	17	p = .804
PF+	KH	NT	NT		19	10	**p = .022**
PF+	NY	50	34	**p = .010**	23	13	**p = .031**
PF+	BB	58	38	**p < .001**	14	13	p = 1
PF+	KA	54	28	**p < .001**	21	8	**p < .001**
PF+	LS	44	29	**p = .012**	11	10	p = 1
PF+	DB	49	22		12	5	
PF+	GH	61	36		24	14	
PF+	EC	36	24		12	6	
TP-only	KS	57	33		21	13	
TP-only	HN	64	52		26	23	
TP-only	SC	60	35	**p < .001**	26	20	p = .109
TP-only	ME	59	39	**p = .001**	23	10	**p = .002**

Results show p values from related-samples McNemar test

(ii) Semantic ambiguity

A semantic ambiguity task used polysemous words to select the less dominant meaning of these words when appropriate to the task (in relation to the dominant meaning). A word with multiple meanings is thought to activate these meanings in parallel (Onifer & Swinney, 1981; Rodd, et al., 2004; Simpson & Burgess, 1984). Less frequent meanings, however, show a processing disadvantage (Simpson, 1985). Therefore, control processes are required to select less frequent meanings, and avoid the dominant interpretation (Rodd, et al., 2005; Zempleni, et al., 2007). The semantic ambiguity task (Noonan et al., 2010) involved matching a homonym to a related word that was either associated with either the dominant or subordinate meaning.

Procedure

A semantic ambiguity task (Noonan et al., 2010) involved matching a homonym with a related word. There were two levels of relatedness, dominant, e.g., matching FIRE with HOT, and subordinate, matching FIRE with RIFLE. There were 30 items, each presented in both conditions of relatedness, on different testing sessions (totalling 60 responses). This included data from 13 patients, 9 PF+ (DB, GH, EC, PG, KH, NY, BB, KA, LS), and 4 TP-only (KS, HN, SC, ME).

Results

There was no correlation between lesion size and the effect of semantic ambiguity, either the difference between dominant and non-dominant responses, or the accuracy scores for either ($r \leq -.441$, $p \geq .151$). Results from the ambiguity task are shown in Figure 4.12. An ANOVA revealed a main effect of semantic ambiguity: $F(1,11) = 29.041$, p <.001. There was a significant effect of patient group: $F(1,11) = 6.902$, $p = .024$, but no interaction: $F(1,11) = .131$, $p = .724$. The lack of interaction suggests that although TP-only patients' performance was higher than PF+ patients, both groups showed an equivalent influence of semantic control demands. This is shown in the individual patient analysis, displayed in Table 4.15.

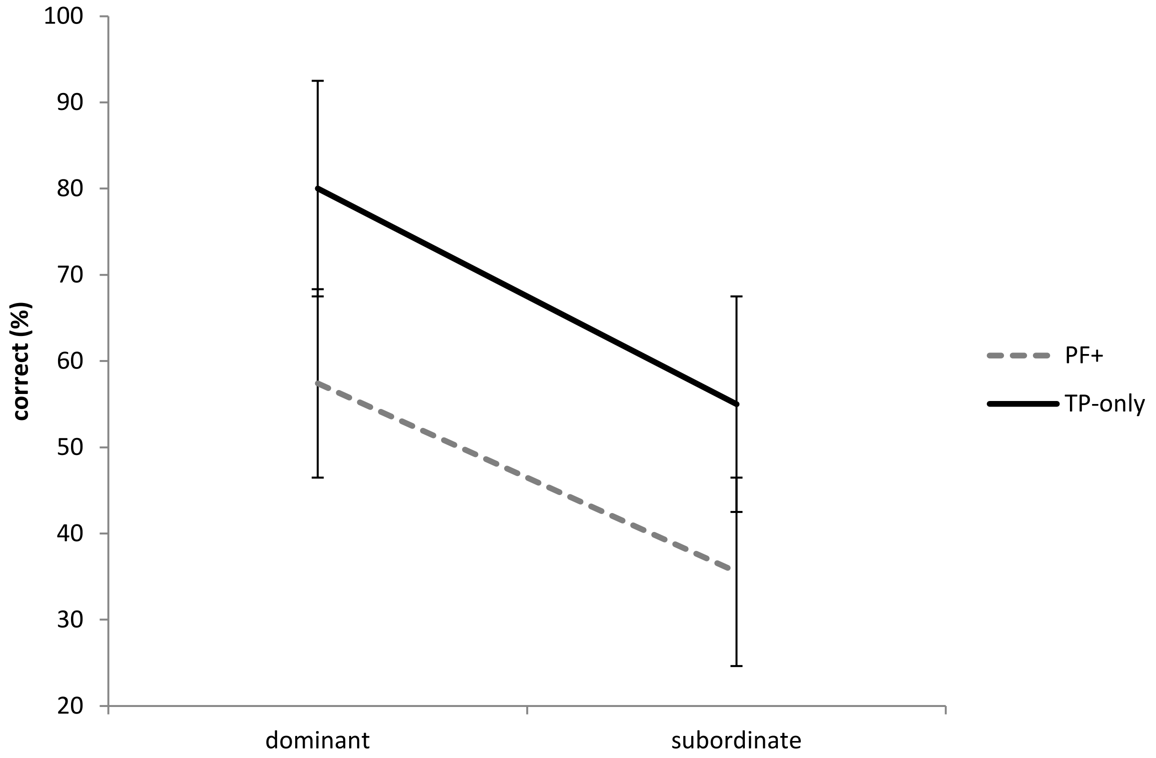


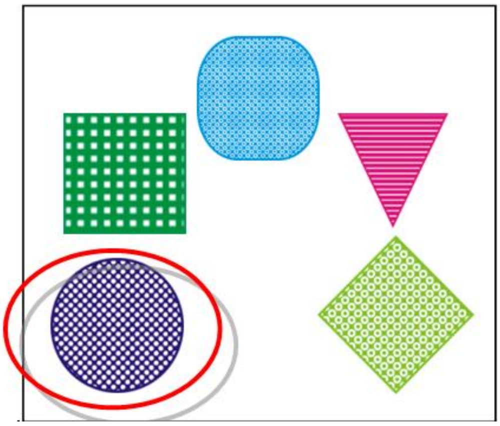
Figure 4.12: Ambiguity task results (task from Noonan et al., 2010).

(iii) Feature selection

A third task used stimuli from Whitney et al. (2011; see also Badre et al., 2005). This manipulated two aspects of semantic control. The first involved choosing a target concept which was weakly related to a probe, compared to semantic decisions based on strong associations. This involves semantic control, as in the weakly related condition, the probe does not automatically activate the target via spreading activation (Collins & Loftus, 1975; Masson, 1991; Neely, 1990; Wagner, Paré-Blagoev, et al., 2001), and so additional executive control resources are required. The second task was feature selection, which involved decisions based on one aspect of an item (e.g., colour), not global semantic similarity: SALT with DOVE, CORN or PEPPER. This required selection of the appropriate feature, and inhibition of the irrelevant association (Badre, et al., 2005; Thompson-Schill, et al., 1997).

Procedure

The feature selection task had four components: each component had 2 practice trials and 32 experimental trials: (i) a strong global association task, matching a probe such as TORTOISE with a target TURTLE presented among two unrelated distractors, e.g., MOLD and MANTLE; (ii) a weak global association task, matching HOUSE with TENT presented with two unrelated distractors; (iii) a semantic feature selection task, matching an aspect of an item (colour, shape, size or texture) with another item. For example, when matching according to colour, participants were given an item e.g., BLOOD, which was to be matched with a similarly coloured item e.g., BEETROOT. On one version of the semantic feature selection task (iiia) there was a prepotent distractor. Participants were presented with the target, one distractor which was globally associated to the target (e.g., CELERY) and one unrelated distractor (e.g., HAY). On a second version of the task (iiib) participants did not have to inhibit a related distractor, and were instead presented with two unrelated distractors. Participants were told the feature (e.g., colour) before the block, and this was presented throughout the trials as a reminder. Because patients were very poor at this task, a reminder (verbally prompting the feature to be matched) was given at the beginning of each trial. Each feature selection was presented in a block of eight, with four features, totalling 32 items. Each feature additionally had two practice trials. (iv) A figure feature selection task involved matching a probe figure with a target figure along a particular feature (colour, shape, size and texture). Similarly to the semantic version, this task had 32 items in blocks of eight. This task had 4 choices. Features between the probe and target were similar, but not identical (to avoid visual matching). For example, when matching colour, participants were asked to match the most similar colours, such as red with pink (see Figure 4.13 and Figure 4.14). This task was run on 9 patients: 5 PF+ (DB, GH, PG, NY, BB), and 4 TP-only (KS, HN, SC, ME).



The probe is presented at the top, with four possible responses underneath. The probe was to be matched to the target according to a certain feature. The correct response for colour feature matching is circled.

Figure 4.13: Figure feature selection task - example trial.

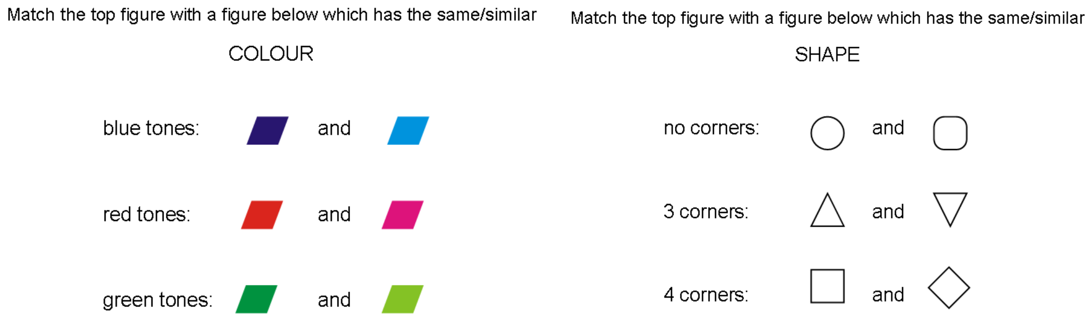


Figure 4.14: Example instruction screens for the figure selection task showing which items to match on the features ‘colour’ and ‘shape’.

<u>Results</u>

This task involved semantic global associations (high and low), semantic feature selection (with/without prepotent distractor) and figure feature selection. Lesion size did not correlate with the global association tasks (high or low), the semantic feature selection task or figure feature selection task. Data was then analysed in a number of ways. (1) A comparison between high and low global associations (Figure 4.15) revealed a strong effect of condition: $F(1,7) = 27.275$, $p = .001$, but not group: $F(1,7) = 3.662$, $p = .097$. There was no interaction: $F(1,7) = 3.332$, $p = .111$. However, as is evident from the graph, Bonferroni-corrected t-tests found the difference between high and low associations was greater for PF+ patients: $t(4) = 4.737$, $p = .018$, than TP-only patients: $t(3) = 2.777$, $p = .138$. (2) In an analysis comparing low global associations and semantic feature selection, the low global associations were significantly easier: $F(1,7) = 48.638$, $p < .001$, and this did not interact with group: $F < 1$. There was a significant main effect of group: $F(1,7) = 5.723$, $p = .048$. (3) The effect of a prepotent distractor was assessed using ANOVA (Figure 4.16). This found an effect of task: $F(1,7) = 11.001$, $p = .013$, and a main effect of group: $F(1,7) = 6.792$, $p = .035$, but no interaction $F < 1$. (4) A comparison of semantic (with prepotent distractor) and figure feature selection task finds no significant effects: $F(1,7) < 2.7$, $p \geq .144$. This suggests that the tasks had similar control demands, and that both groups were equally impaired. (5) A comparison of semantic feature selection (without prepotent distractor) and figure feature selection found performance on the semantic task significantly higher: $F(1,7) = 31.478$, $p = .001$, but no main effect of group $F(1,7) = 3.940$, $p = .088$, or interaction: $F(1,7) = 1.032$, $p = .343$.

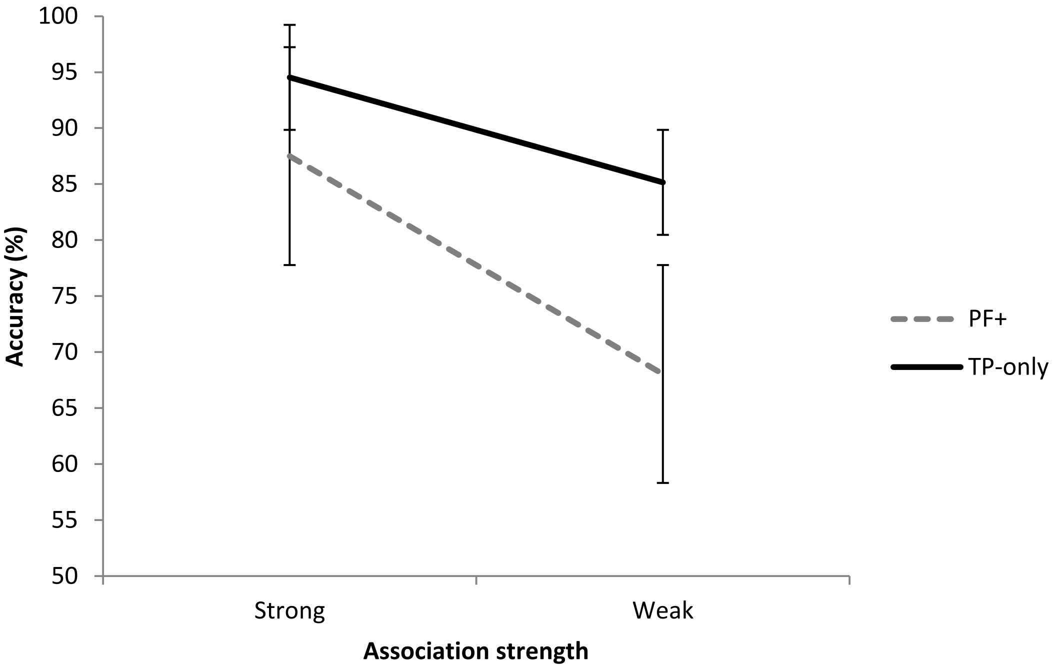


Figure 4.15: Strong versus weak global semantic associations (Feature selection task; Whitney et al., 2011).

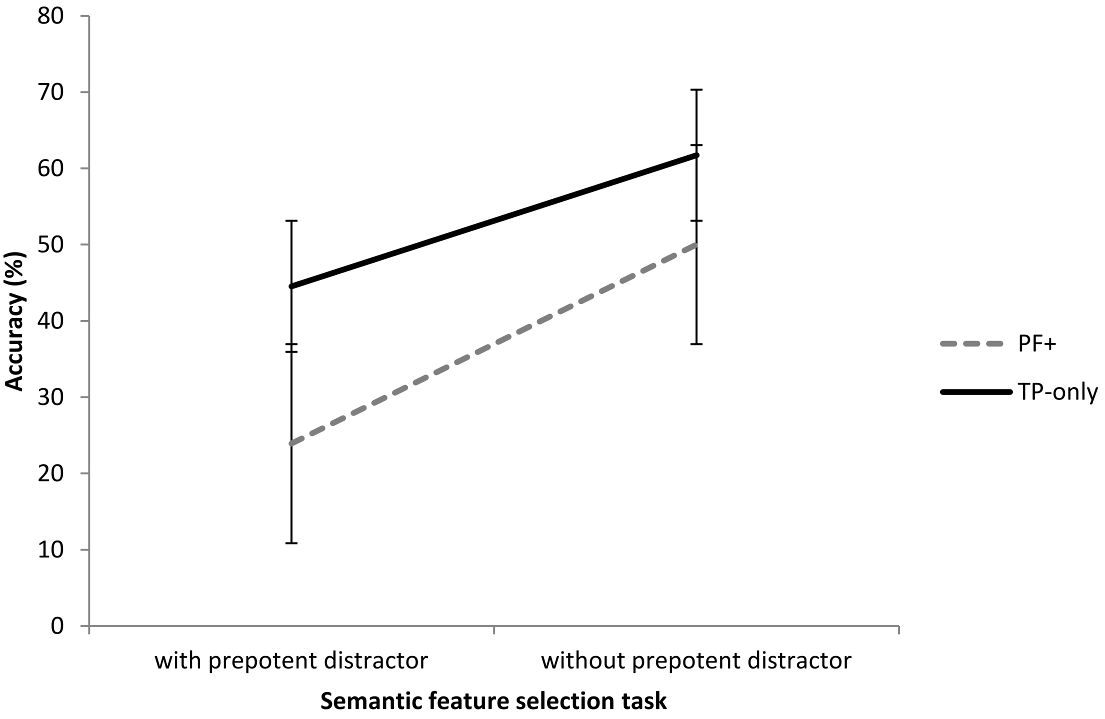


Figure 4.16: Semantic feature selection with and without a prepotent distractor (Feature selection task; Whitney et al., 2011).

Individual analyses were run across patients (Table 4.16). It was noted that none of the TP-only patients showed a difference between high and low semantic global associations, and this difference was only found in some PF+ patients.

Table 4.16: Individual differences between semantic feature selection tasks

	Prefrontal					TP-only			
	GH	*DB*	*PG*	*NY*	*BB*	*HN*	*SC*	*ME*	*KS*
High-Low	N.S.	N.S.	**0.039**	**0.007**	N.S.	N.S.	N.S.	N.S.	N.S.
Low-SF	**< .001**	**0.006**	**< .001**	**0.035**	**0.001**	**0.002**	**< .001**	**0.012**	**0.017**
SF-SF(ND)	**0.021**	N.S.	**0.004**	**0.006**	N.S.	N.S.	**< .001**	N.S.	**0.013**
SF-FF	N.S.	N.S.	N.S.	N.S.	N.S.	**0.002**	N.S.	N.S.	N.S.
SF(ND)-FF	N.S.	N.S.	**0.027**	N.S.	N.S.	**0.031**	**0.013**	N.S.	**0.003**
High	94 (25)	75 (44)	97 (18)	84 (37)	88 (34)	97 (18)	97 (18)	100 (0)	84 (37)
Low	81 (40)	59 (50)	75 (44)	50 (51)	75 (44)	97 (18)	81 (40)	91 (30)	72 (46)
Semantic feature (SF)	13 (34)	28 (46)	19 (40)	22 (42)	31 (47)	66 (48)	16 (37)	63 (49)	34 (48)
Semantic feature without distractor (SF(ND))	38 (49)	41 (50)	56 (50)	53 (51)	16 (37)	59 (50)	63 (49)	59 (50)	66 (48)
FF	28 (46)	31 (47)	22 (42)	44 (50)	22 (42)	28 (46)	31 (47)	44 (50)	22 (42)

Results show p values from McNemar tests. SF = semantic feature selection with prepotent distractor; SF(ND) = semantic feature selection with no prepotent distractor; FF = figure feature selection. Scores are presented as percentage correct (with SD).

<u>Summary</u>

TP-only patients show a subtle but consistent higher performance in all tasks with high and low semantic control demands. However, this never interacts with task demands, which suggests TP-only patients show the same semantic control deficits as PF+ patients in the two aspects of semantic control which were tested: global associations and feature selection.

(iv) Switching task

The final task examined the aspect of semantic control involved in switching. There were ‘switching’ and ‘non-switching’ blocks: all the decisions involved matching according to either semantic associations or categorical relationship, but in the switching condition, the matching criteria were switched on every trial (so that on one trial, the participant had to match according to an association: e.g., TREE with AXE; an on the next trial, the participant had to match according to an category, e.g., TREE with FLOWER). In the ‘non-switching’ condition, the type of matching was fixed for the whole block.

This task was used because the PFC (and not the pMTG) has been implicated in switching between tasks (Dove, Pollmann, Schubert, Wiggins, & Yves von Cramon, 2000; Hirshorn & Thompson-Schill, 2006; Troyer, Moscovitch, & Winocur, 1997), with reduced verbal switching in patients with frontal lobe damage (Troyer, Moscovitch, Winocur, Alexander, & Stuss, 1998; Troyer, Moscovitch, Winocur, Leach, & Freedman, 1998). This may be because switching involves selecting a weakly activated item over already active representations, with the LIFG critical for this response conflict (Thompson-Schill, 2005). Additionally, recent evidence has found a difference between PF+ and TP-only patients in the refractory task (Gardner, et al., 2012), which involves switching from a target which is still present, in a cyclical matching task.

Procedure

A single item (e.g., AXE) was presented as a picture, for matching with one of three words, the target word being either categorically related (e.g., HAMMER) or associatively related (e.g., TREE). The two distractor words were unrelated. Words which were targets were matched for frequency and imageability with words which were used as distractors, using the CELEX Lexical Database (Baayen, Piepenbrock, & Van Rijn, 1995) and MRC psycholinguistic database (Wilson, 1988). There was no frequency/imageability difference for the targets used in categorical and associative tasks: $t < 1$, with target frequency being 27 and 37 words per million for categorical and associative words respectively, and 585/700 and 580/700 imageability ratings for categorical and associative words respectively. Probes were the same across conditions. There was no frequency/imageability difference for the distractors used in categorical and associative tasks: $t < 1$, with distractor frequency being 24 and 31 words per million for categorical and associative words respectively, and 591/700 and 596/700 imageability ratings for categorical and associative words respectively. Using the

Edinburgh Associative Thesaurus (EAT; Kiss, Armstrong, Milroy, & Piper, 1973), we used categorical and associative items which were infrequently paired with the target word (associative: $M = 4.4$, categorical: $M = 3.4$). The difference between conditions was not significant: $t < 1$.

Each item was presented in a block of eight trials, with four associative and four categorical relationships. These were presented in two ways: (i) in a no-switching condition, all four associative and four categorical relationships were matched in blocks for each item (counterbalancing which relationship is presented initially); and (ii) in a switching condition, the four associative and four categorical relationships were interleaved within the block of eight trials for each item. There were a total of 14 items, with eight trials for each item, and the same items presented in both conditions across different testing sessions. This task was run on 9 patients, 5 PF+ (NY, DB, GH, PG, BB) and 4 TP-only (SC, HN, KS, ME).

Results

Lesion size did not correlate with performance on categorical or associative trials, or on switch in relation to non-switch conditions. An omnibus ANOVA including switching (switch or no switch task), condition (categorical or associative) and group (TP-only or PF+) was performed. The effect of switch had no main effect: $F(1,7) = .134$, $p = .725$. The effect of condition was significant: $F(1,7) = 31.237$, $p = .001$, driven by higher performance in the categorical compared with associative matching condition. The main effect of group was not significant: $F(1, 7) = 2.623$, $p = .149$, and there was no interaction between switching and group: $F(1,7) = .339$, $p = .579$; or condition and group: $F(1,7) = 1.379$, $p = .279$, and no three way interaction: $F(1,7) = .600$, $p = .464$.

We analysed the ‘no switch’ condition in more detail. Although this presented all categorical and all associative items together, there was still a ‘switch’ trial between these two blocks. Over 8 trials, the first 4 items were one condition (e.g., associative) and the last 4 in another condition (e.g., categorical). Therefore, performance on item 4 (after 3 trials of one condition) was compared to item 5 (the first item of a new condition). This is shown in Figure 4.17.

There was a significant main effect of switch: $F(1,7) = 29.068$, $p = .001$, but no effect of group or interaction ($F < 1$). In independent samples t-tests, there was a significant difference between groups on the ‘switch’ trial (item 5): $t(6) = 2.516$, $p = .046$, but not on the ‘no-switch’ trial (item 4): $t(6) = 1.837$, $p = .116$. PF+ patients showed a significant drop in performance on the ‘switch’ trial in relation to TP-only patients.

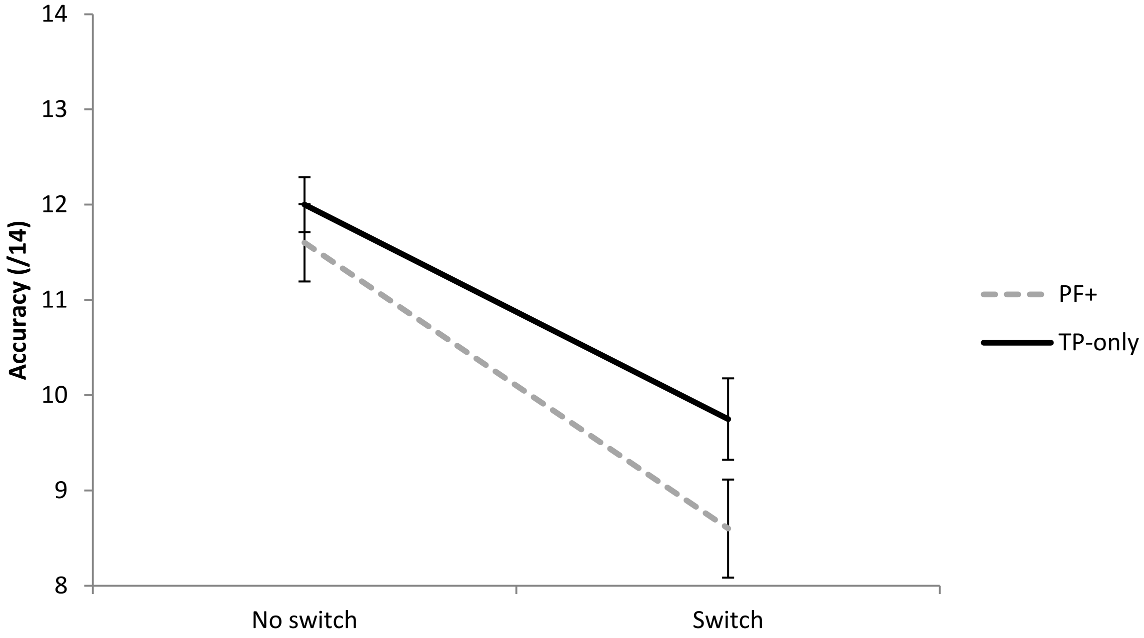


Figure 4.17: Performance on ‘switch’ trials (trial 5), and ‘no switch’ trials (trial 4)

Individual McNemar tests found no significant difference between switch and no-switch conditions (Table 4.17). There was a trend towards PF+ patients being more likely to show lower performance in the associative than categorical version of the task in relation to TP-only patients. This was not significant in an independent t-test: associative: *t*(7) = 1.935, *p* = .094; categorical: *t*(7) = 1.104, *p* = .306.

Table 4.17: Individual differences in switching task

	PF+					TP-only			
	GH	*DB*	*PG*	*NY*	*BB*	*HN*	*SC*	*ME*	*KS*
switch-no switch	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
categorical-associative	0.052 *	**< .001**	**0.035**	N.S.	**< .001**	**< .001**	N.S.	N.S.	N.S.
switch	72	60	79	63	76	87	88	70	75
	(45)	(49)	(41)	(49)	(43)	(34)	(33)	(46)	(43)
no switch	81	55	77	57	78	89	86	73	72
	(39)	(50)	(42)	(50)	(42)	(31)	(35)	(44)	(45)
categorical	82	70	84	65	90	96	90	77	77
	(38)	(46)	(37)	(48)	(30)	(19)	(30)	(42)	(42)
associative	71	46	71	54	63	79	83	66	71
	(45)	(50)	(45)	(50)	(48)	(41)	(38)	(48)	(46)

Results show p values from McNemar tests. Scores are presented as percentage correct (with SD). * = $p < .06$.

Summary

Both groups show a similar impairment overall, with both affected by whether the relationship was categorical or associative. There was some evidence that TP-only patients showed higher performance, but only on the most demanding tasks, such as the associative matching during the switching task, and during the ‘switch’ trial after a build up of presentations in another relationship.

Frontoparietal vs. pMTG+

A comparison was made which grouped these patients differently: rather than separating according to whether they had prefrontal lesions or not, we compared patients who had lesions to either prefrontal and/or angular gyrus (GH, PG, NY, BB, SC), the ‘frontoparietal’ group, with those with damage to temporal regions, which sometimes extended to prefrontal cortex, the ‘pMTG+’ group (DB, HN, KS, ME, KA). The main difference between these groups was the involvement of the parietal lobe: none of the pMTG+ group had impairment of the angular gyrus (BA 39), with only DB showing damage to prefrontal regions BA 47/45.Overall, pMTG+ patients had damage which was more inferior (all involving pMTG). Frontoparietal patients had damage to PFC and angular gyrus, and marginally fewer had pMTG implicated. A comparison between TP-only, PF+, pMTG+ and frontoparietal patients is displayed in Figure 4.18.

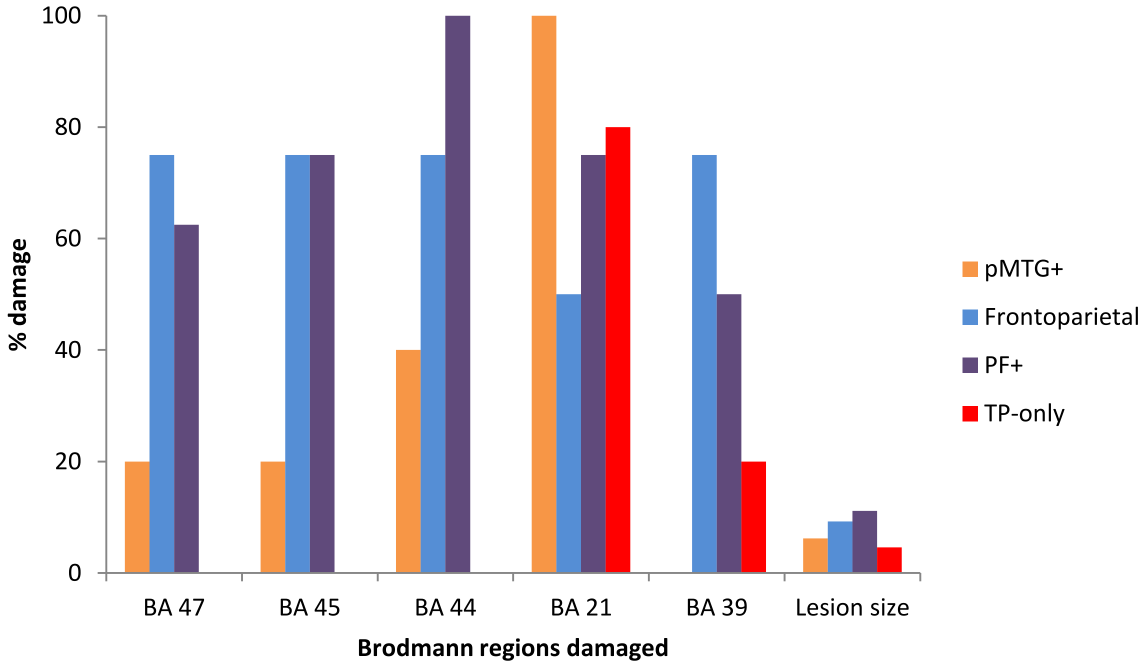


Figure 4.18: A comparison of key brain regions implicated in semantic control between the four SA patient groups.

We assessed performance on the above four semantic control tasks, and report the significant interactions between group and task. In the semantic feature selection task, we found two significant interactions. (1) The effect of a prepotent distractor was assessed using ANOVA (comparing semantic feature selection with and without prepotent distractor). Here there was a significant effect of task: $F(1,7) = 23.148$, $p = .002$, a significant effect of group: $F(1,7) = 5.974$, $p = .044$, and a significant interaction: $F(1,7) = 10.327$, $p = .015$. This shows those with damage to pMTG+ were less susceptible to prepotent distractors, whereas the group with damage to frontoparietal regions are less able to direct their attention away from prepotent responses. This is shown in Figure 4.19.

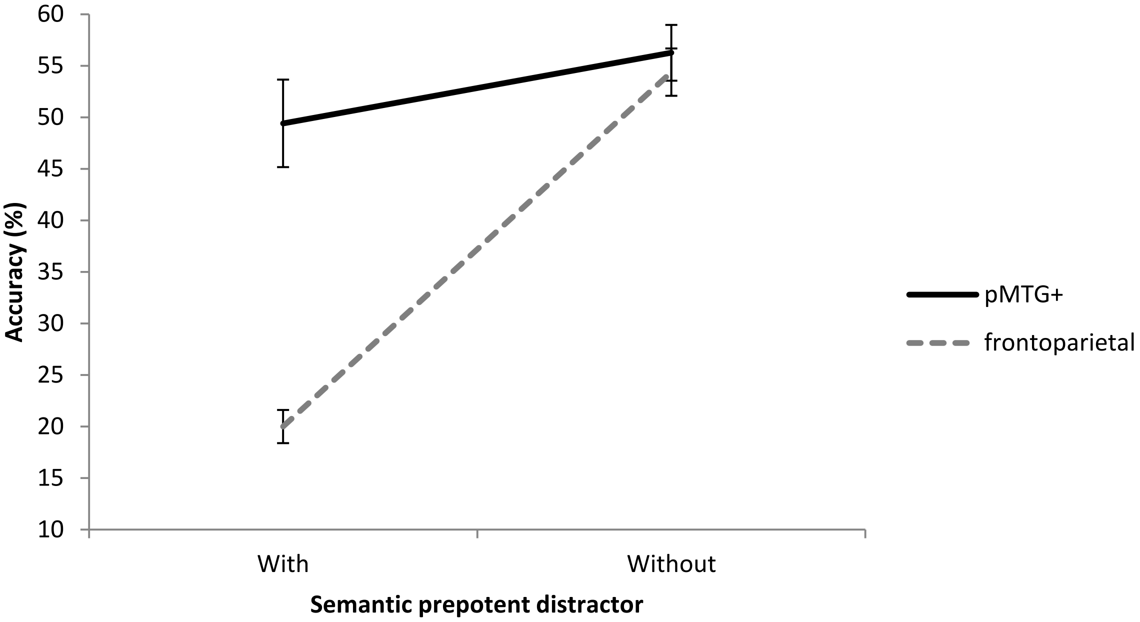


Figure 4.19: pMTG+ vs. frontoparietal patients on semantic feature selection with and without a prepotent distractor

(2) A comparison of semantic (with prepotent distractor) and figure feature selection task finds no effect of task: *F*(1,7) = 1.178, *p* = .314, but a significant effect of group: *F*(1,7) = 6.832, *p* = .035, and an interaction of group and task: *F*(1,7) = 10.551, *p* = .014. This is shown in Figure 4.20. Both groups are equally as impaired figure feature selection task. However, those with frontoparietal damage are more impaired at the semantic feature selection task (with prepotent distractor), whereas those with pMTG+ damage show higher performance on this task.

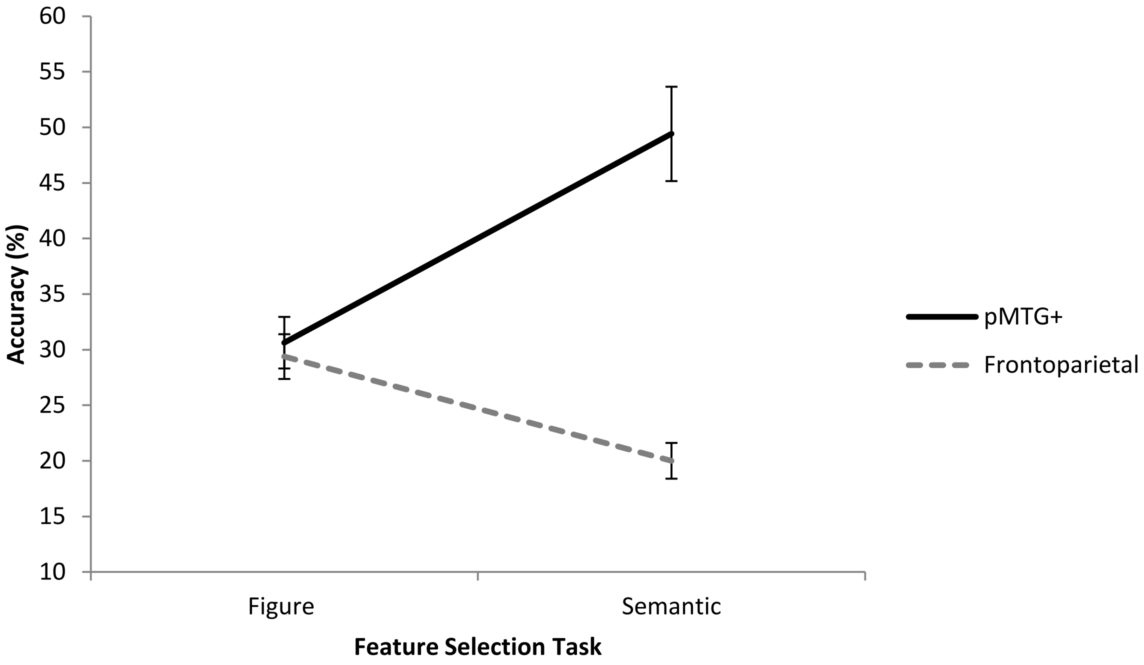


Figure 4.20: pMTG+ vs. frontoparietal patients on semantic (with prepotent distractor) and figure feature selection tasks

<u>Summary</u>

When comparing those with frontoparietal to those with pMTG+ damage, some notable differences emerged. There was no difference between strong and weak associations, but the effect of a prepotent distractor had a big effect of the frontoparietal group, which was not shown in the pMTG+ group. Additionally, those in the frontoparietal were impaired at both a figure and semantic feature selection task, but those with pMTG+ damage showed a higher performance in the semantic feature selection task.

Discussion

The exact role posterior temporoparietal cortex plays in semantic cognition is unclear from the current literature. Recent work by our group has suggested that regions within this area, along with the PFC, supports the task selective regulation of semantic behaviour (Jefferies & Lambon Ralph, 2006; Noonan, et al., 2010; Whitney, Kirk, et al., 2011; Whitney, et al., 2012). It is likely that some regions of the temporoparietal lobe are important in representation of semantic knowledge (Hickok & Poeppel, 2004, 2007; Martin, 2007; Martin & Chao, 2001), but it is nonetheless maintained that areas exist which are critical for semantic control (Noonan et al., submitted). There is still opinion, however, that control is exclusively the domain of the PFC (Badre & Wagner, 2007; Demb, et al., 1995; Wagner, Paré-Blagoev, et al., 2001). The current study examined two research questions to address this conflict in the literature: (1) the performance of PF+ patients (with confirmed lesions in the prefrontal cortex and potentially also damage to temporoparietal areas) in comparison to TP-only (damage focused on the temporoparietal region and leaving PFC intact). Little research has compared these two groups in terms of semantic control performance. The majority of evidence suggests these roles play a similar part in semantic control (Noonan, et al., submitted; Whitney, Kirk, et al., 2011; Whitney, et al., 2012), with performance identical on a number of semantic control tasks. However, there is some suggestion that the prefrontal cortex plays a unique role in some aspects of semantic control (Gardner, et al., 2012; Noonan, et al., submitted). (2) TP-only patients were also compared to semantic dementia (SD) patients, who show deficits in the representation of semantic knowledge (Mummery, et al., 2000). SD patients therefore show consistency across the same items in different tasks. We wanted to assess whether our TP-only patients would show this effect. In particular, certain temporoparietal regions, such as the IPL and pMTG, are associated with tool and action knowledge, so we tested particularly whether there were category effects in TP-only patients. We used a multitude of tasks and analyses to unpick the nature of the semantic deficits in PF+, TP-only and SD patients. The results are summarised in Table 4.18.

Table 4.18: Overview of similarities and differences between patient groups

‘SA’ characteristics	Patient response		
	PF+	TP-only	SD
Executive control impairment	✓✓	✓	×
Inconsistency across items	✓✓	✓	×
No category effects	✓✓	×	×
No familiarity effects	✓✓	×	×
Picture naming errors: associative	✓✓	×	×
Cueing effects	✓✓	✓✓	×
Low verbal fluency	✓✓	×	×
Letter fluency < category fluency	✓✓	×	×
Imageability effects*	✓✓	✓✓	✓✓
No frequency effects	✓✓	✓	×
Semantic distance effects	✓✓	✓✓	×
Semantic ambiguity effects	✓✓	✓✓	
Semantic feature selection deficit	✓✓	✓✓	
Figure feature selection deficit	✓✓	✓✓	
Deficits with prepotent distractor	✓✓	✓✓	
Switching deficit	✓	×	

✓ = some evidence of this characteristic, ✓✓ = strong evidence of this characteristic, × = no significant evidence for this characteristic. * = imageability also a characteristic of SD patients.

Our current results are readily interpretable within a framework which views semantic cognition as composed of (at least) two principal components: (1) conceptual representations, underpinned by the anterior temporal lobes, specifically the basal fusiform gyrus (Binney, et al., 2012), which is an amodal system with links to modality-specific ‘spokes’, and is necessary to bind together disparate aspects of the same concept and group of concepts. (2) Additionally, there are regulatory control processes instantiated across a wide cortical network, including at least three main regions: the left inferior frontal gyrus (LIFG), posterior middle temporal gyrus (pMTG) and dorsal angular gyrus (dAG) (Noonan, et al., submitted).

A comparison of SD patients and SA patients is useful because their lesion sites show little overlap. SA usually occurs after a stroke, and the fusiform gyri are well protected from blood clots which can cause stroke (Visser, Jefferies, et al., 2010). Although the aSTG can be vulnerable to stroke (Phan, Donnan, Wright, & Reutens, 2005; Phan, Fong, Donnan, & Reutens, 2007; Schwartz, et al., 2009), the fusiform region which is thought critical to semantic representation is unaffected by stroke. Therefore, the exploration of SA patients' semantic memory deficit is on the assumption that the semantic representations of the fusiform gyri are intact, but the retrieval mechanisms that access this store are faulty. It is, of course, possible that 'spokes' are damaged in these patients, leading to an overall deficit which is greater in one domain than another (but nonetheless, semantic control deficits present in all domains).

Isolated PFC damage has been shown to lead to high-level difficulties controlling semantic competition (Metzler, 2001; Novick, Kan, Trueswell, & Thompson-Schill, 2009; Robinson, Shallice, Bozzali, et al., 2010; Thompson-Schill, et al., 1998). However, it is unclear how stroke patients with damage to temporoparietal regions (TP-only patients) fit in. Evidence suggests this region is multimodal (Hoffman, Pobric, et al., 2011; Vandenberghe, et al., 1996; Visser, Embleton, et al., 2012), and has rich connections with other temporal, frontal, parietal and occipital regions, allowing it to act as a contextual 'hub' (Turken & Dronkers, 2011). We would not dispute that these areas contribute toward specific representations of semantic feature knowledge. However, it is possible that these ventral and lateral temporal areas are distinct from those structures which critically underpin semantic control (Whitney, Jefferies, et al., 2011). Equally, it is plausible that different regions of the posterior temporal cortex are involved in both 'control' and 'representation' (Jefferies, in press). A deficit in tool and action knowledge by its very nature may be paired with a semantic control impairment – as these particular types of knowledge require interactive/ contextual knowledge, which is semantically demanding.

Some TP-only patients also have damage to angular gyrus, and it was not possible to distinguish posterior regions within the scope of this paper, due to the number of patients, as well as the generally large lesion sizes we found in our sample. Nonetheless, AG has also been implicated in semantic control (Noonan, et al., submitted).

As well as the difference between TP-only and SD patients, this paper also assesses the different contribution of the PFC and posterior regions to semantic control. There is much evidence to suggest PF+ and TP-only patients have similar control deficits (Corbett, et al., 2011; Jefferies & Lambon Ralph, 2006; Noonan, et al., 2010), which includes sensitivity to ambiguity and semantic distance (Noonan, et al., 2010). However, there is emerging evidence that LIFG, pMTG and dAG play different roles in semantic control (Noonan et al., submitted). Because of the lesion locations (with PF+ patients showing damage to prefrontal and posterior regions), it has been most fruitful to assess the role of the PFC in relation to the other regions. (1) TP-only and PF+ patients show a difference in performance on a refractory task (Gardner et al., 2012). PF+ patients show more preservations of earlier responses in picture naming (Schnur, et al., 2006; Schnur, et al., 2009), and decline in accuracy of repeated items with a build-up of competition between targets and distractors (Gardner, et al., 2012). (2) Additionally, while LIFG responded to the control demands of semantic tasks involving both production and comprehension, the contribution of pMTG is restricted to executive control of receptive tasks (Noonan et al., submitted).

Our studies found similarities and differences between PF+ and TP-only patients. The similarities provide critical support for the idea that both prefrontal and temporoparietal regions make important contributions to semantic regulation, but the nature and extent of this contribution may differ. Both groups showed a difference to SD patients in item consistency. When the nature of the task changed – e.g., when they had to make associative judgements rather than matching a word to a picture – performance of SA patients was variable on an item-by-item basis, as patients were not always able to make the appropriate computational shifts required for the different types of semantic assessments. This lack of flexibility also explains why SA patients' associative judgements were more strongly predicted by the requirement for task specific semantic retrieval compared with SD patients. SA patients were no longer able to explore and manipulate semantic knowledge online. This inconsistency across tasks was more prominent in PF+ than TP-only patients, but nonetheless substantially greater in SA patients than SD patients.

We also found evidence for attenuated affects lexical frequency in both stroke groups – compared to SD – although this effect was again much stronger in the PF+ group. The lack of frequency effect has been explained in terms of high frequency items being more semantically diverse (Hoffman, Jefferies, et al., 2011; Hoffman, Rogers, et al., 2011), so appearing in many contexts (e.g., FIRE to mean losing your job, describing someone's personality, or a physical bonfire, house fire or BBQ). Usually, high frequency words have a natural advantage (simply because of their regularity in language), but also have this additional control requirement involving choosing the appropriate linguistic context – which may cancel out the advantage in those with control impairments. Frequent exposure to an item may lead to poorer performance in SA patients if that concept has been paired with many strongly associated exemplars, across a range of different contexts – in this case semantic control is required to select the specific facet of the item's meaning which is appropriate for the particular task at hand.

PF+ patients made significantly more associative errors than either TP-only or SD patients in picture naming, which reflected their difficultly directing activation toward a target item they still retained knowledge of. Subsequently, constraining the task with phonemic cues boosted SA patients' performance and revealed they still retained the knowledge for many items they previously could not name. As the task became less constrained and internally generated organisation became more important (i.e., naming vs. category fluency, and category vs. letter fluency), PF+ patients showed a significant effect of self-generation, where TP-only patients did not.

It was found that TP-only and PF+ patients both showed an impairment on tasks which have high semantic control demands in relation to tasks with low semantic control demands. This impairment was the same in both SA patient groups across a range of control manipulations. Both groups showed poorer performance on distant category exemplars in relation to close category exemplars; subordinate in relation to dominant meanings to homonyms; and feature selection compared to global association. This suggests that both regions have an equal role in retrieval of distant meanings, or that an intact network, and connectivity of these regions, is crucial for semantic control.

There were, however, some points of difference, which point to a unique role for the PFC in some aspects of semantic control. (1) In particular, it seems to be crucial for **dampening down prepotent distracting and highly-relevant items**. This is true in associative picture naming errors – where the associated item has to be dampened down for correct picture naming (e.g., PIANO → LESSONS; BATH → WATER). Higher performance in the WPM from TP-only patients, for example, could also be explained by the role of the PFC in dampening down prepotent distractors. As all the distractors in the WPM are strongly related to the target, you would expect performance to be worse in PF+ than TP-only patients, and for this variable to have a stronger effect for PF+ than TP-only patients. (2) PF+ patients show less of an effect of frequency, a characteristic which is associated with semantic diversity. It is plausible, therefore, that the PFC is involved in **selecting the appropriate linguistic context** for an item – particularly difficult for high frequency words. This may explain the modality effect for the Camel and Cactus task (CCT), where performance was higher for the picture than word version in PF+ but not TP-only patients. In the picture task, participants were given the concrete, correct meaning for the item by its very nature, whereas in the written version, the word does not give the correct contextual meaning. (3) There is subtle evidence to suggest a role for the PFC in **switching**. The evidence is weak from the switching task, perhaps due to the highly imageable items chosen as stimuli. Nonetheless, the PF+ patients are more rigid in their response, leading to worse performance on the same items when switching is required, in relation to non-switching. Perhaps more convincingly, there were strong differences between these patients in category fluency – with TP-only patients being significantly more fluent than PF+ patients. This is a task which requires switching from the current item to another, semantically similar response. (4) PF+ patients showed more evidence for a deficit beyond semantics – of **executive control**. This is consistent with a recent meta-analysis (Noonan et al., submitted), which found that pMTG was not implicated beyond semantic control. The fact that some executive control impairments were found in the TP-only group may be related to AG damage.

A direct comparison of SD and TP-only patients on semantic representation of tool use found no evidence for item consistency in TP-only patients. TP-only patients' knowledge for manmade items was actually superior to knowledge of living things (a pattern not shown in PF+ and SD patients). TP-only patients, however, do show a category effect, but it is likely that this is due to other factors. Often, the lesion extends through some of the temporal lobe, to affect areas which process visual input. The two categories which TP-only patients are particularly impaired at naming, (FRUITS and BIRDS), have high visual overlap, and it is possible that the input from the visual stream is impaired, leading to a bias towards visually distinct items. It is also possible that a visual 'spoke' has been disrupted, leading to damage to stored representations for visual forms, that play a greater role in ANIMALS than TOOLS. We know this is restricted to the visual form, as categories which led to particularly high performance on a verbal fluency task were not necessarily visually dissimilar (ANIMALS and HOUSEHOLD OBJECTS). It is likely performance on this verbal fluency task reflects a pattern found in healthy controls, and is due to the ease of subcategorisation for each category.

We also compared frontoparietal patients with those with pMTG damage (pMTG+). Although it was difficult to distinguish the different regions involved in semantic control, separating the patients according to pMTG damage meant that we were able to compare a group who all had damage to pMTG with those with damage to other regions (see Figure 16). Our results suggest that the pMTG is not involved in all aspects of semantic control. Frontoparietal patients showed disruption to the semantic feature selection task with a prepotent distractor. As found in picture naming errors in this study (more associative errors in PF+ patients), and also the refractory task (with an effect in PF+ but not TP-only patients;

Gardner et al., 2012), PF+ patients may have particular difficulty dampening down a prepotent distractor.

The reason for this subtle difference in PF+ and TP-only patients in a number of different tasks may be that the TP-only patients show a smaller effect of semantic control. Their performance is usually higher than both SD and PF+ patients, suggesting a *milder* deficit of semantic control. A recent meta-analysis of neuroimaging studies revealed the left prefrontal cortex is strongly and consistently activated in executive-semantic tasks, while the TP-region shows a somewhat smaller peak of activation which is only significant in some studies/tasks (Noonan, et al., submitted). This may also explain why TP-only patients fail to show refractory effects. However, these patients show the same degree of semantic control impairments when performing other semantic tasks (e.g., feature selection), which instead suggests PFC and pMTG may make unique contributions to semantic control. Most interestingly, although the lesion size of TP-only patients is significantly smaller, this does not correlate with semantic or executive control impairments.

Another possibility is that PF+ patients have damage to a larger number of ‘nodes’ within the distributed semantic control network, compared with TP-only patients (major control regions being LIFG, pMTG and dAG). The majority of TP-only patients have damage to just 1 of these critical control regions, but PF+ patients have an average damage to 2.25 of these 3 regions. If the regions have different roles to play in semantic control, it may be that damage to more than one region does not cause a greater semantic control impairment on each task, but rather causes a greater semantic control impairment overall (as each task requires different elements of semantic control). It has recently been found that TMS over LIFG causes increased compensatory activation of pMTG in a semantic control task (Whitney, et al., submitted), suggesting flexible recruitment of semantic control regions according to control demands. The more regions which are damaged, the less able the system is to recruit other cortical regions to compensate during demanding tasks.

With a greater number of TP-only patients we have been able to confirm, for the first time, that the nature of the semantic impairment in TP-only cases is similar to PF+ cases and distinct from SD patients with degraded knowledge. Our TP-only patients did not show a profile consistent with a static storage disorder, or evidence of a category specific semantic impairment for tools, which may be expected if they had lost knowledge of specific semantic features. Instead our patients with temporoparietal lesions – to the same extent as those patients with PFC involvement – were impaired at regulating their semantic knowledge in a task appropriate fashion. We have also been able to show that those with frontoparietal (in relation to pMTG+ damage) are more impaired in semantic feature selection when a prepotent distractor is present. Subtle differences in TP-only and PF+ patients clearly exist. Future studies should assess the nature of the semantic control demands in each task, with stringent comparison tasks, to gauge which regions are uniquely involved in a particular aspect of control. Additionally, the effect of damage to more than one control region (or connectivity between regions), should be considered.

5. CHAPTER FIVE

The role of the right hemisphere in semantic control

Acknowledgements: This Chapter was conducted in collaboration with a 3rd year undergraduate project, where students helped to design the tasks and collect data from patients and controls. These students were Tom Wright and Kirsty Patterson (the face identity refractory task), Lauren Henshall (summation task), and Tharaki Siyaguna (metaphor task). Additional age-matched control data for other tasks presented in Chapter 5 was collected by Jen Ashton and Rhian Badrsley (face picture naming task and social synonyms task).

Abstract

Semantic cognition recruits a wide cortical network, in both the left hemisphere (LH) and right hemisphere (RH). This includes brain regions that contribute to (i) input processing, (ii) semantic representations and (iii) processes which mediate semantic retrieval and control over semantic activation (e.g., semantic control). In terms of processing, there are subtle domain specialisations between the hemispheres – although the hypotheses relating to the specialisation of the RH are wide ranging, from face processing to metaphor comprehension. Nonetheless, a wide cortical network including both right and left inferior frontal gyri has been proposed for semantic control, albeit with a smaller cluster in the RH. Semantic aphasia (SA) patients have damage to left inferior frontal and/or temporoparietal regions. They typically show near-normal performance on tasks which are low control demands, e.g., when given a phonemic cue in picture naming. However, their performance is reduced when the control demands are high e.g., when matching two distantly-related items. This pattern is seen across modalities. Our aim was to test RH patients to assess their semantic control deficits. There were three alternative predictions for RH performance in these tasks. (1) Impairments qualitatively similar to those found in SA patients, with performance correlating with semantic control demands of the task. - but found in semantic materials in which the RH is specialised in processing, e.g., metaphors. (2) A reduced semantic control deficit, with the RH playing a smaller, but still necessary role in semantic control. (3) No semantic control impairments, if an intact LH is able to take over the semantic control functions which usually recruit the RH. We analysed the effects of manipulating semantic control in tasks which are thought to be processed in the RH: face identity, face expression, social concepts, metaphors and summation of distant concepts, in 6 RH stroke patients and 12 age-matched controls. Evidence for a semantic control impairment can be seen in 2 of 7 semantic control tasks – a face emotion refractory task and a summation task. Performance was influenced by the nature of the task, rather than the material itself (on a picture naming face emotion task, no refractory effect was found). Two properties of these tasks –configural processing and inhibition of distracters – may be key to the semantic deficits found. From our data, it appears RH patients are largely able to overcome their control deficits through their intact left hemisphere control regions, except for when a task is particularly demanding of the RH semantic system.

Introduction

Semantic cognition involves a wide cortical network, in both initial sensory processing (Catani & Ffytche, 2005), representation (Martin, 2007; Patterson, et al., 2007) and controlled retrieval and selection of information guided by the task and context (Badre, et al., 2005; Jefferies & Lambon Ralph, 2006; Thompson-Schill, et al., 1997).

Semantic processing in the left and right hemispheres

Semantic representational damage is seen in semantic dementia (SD) and herpes simplex encephalitis, where patients nearly always have bilateral anterior temporal lobe (ATL) damage (Lambon Ralph, Lowe, & Rogers, 2007; Mion et al., 2010; Mummery et al., 2000; Nestor, Fryer, & Hodges, 2006; Noppeney et al., 2007). It is thought that both ATLs store similar semantic representations. For example, patients with unilateral damage – through resection for temporal lobe epilepsy, tumour resection or vascular accident (Lambon Ralph, Cipolotti, et al., 2010), have far less severe semantic impairments, suggesting that either hemisphere can compensate for the other. There are only exceptions found to this in particular cases such as for less frequent or abstract concepts, where the bilateral network appears to be necessary (Lambon Ralph, et al., 2012). This bilateral 'hub' is not only supported by patient data, but neuroimaging too. A recent meta-analysis (Visser, Jefferies, et al., 2010) revealed no significant difference in the distribution of peaks across the two hemispheres in words or pictures, although the LH shows slightly more peaks overall. Pobric et al. (2010a) showed that rTMS to either ATL produced significant increases in reaction time in both word and picture semantic association tasks. Therefore, it is thought that both hemispheres, and the connections between them, support amodal semantic representations in a bilateral 'hub' (Binney, Embleton, Jefferies, Parker, & Lambon Ralph, 2010; Lambon Ralph, Sage, Jones, & Mayberry, 2010; Rogers et al., 2004).

Although the hemispheres have many similarities, there are subtle differences. SD patients with more damage to the left hemisphere show more anomia (Lambon Ralph, et al., 2001), and there is some evidence that those with more right hemisphere damage are more impaired at naming faces (Dell, 1989; Snowden, et al., 2004). Mion and colleagues (2010) found that verbal semantic tasks correlated with damage to left fusiform and left parahippocampal gyrus, whilst a visual semantic association task correlated with damage to the right fusiform gyrus. In an fMRI study, Visser and Lambon Ralph (2011) found similar levels of activation in left and right vATL in picture and sound tasks, but much higher involvement of the LH in a spoken word task. This stems from a basic ‘right = visual’, ‘left = verbal’ premise. However, more detailed hypotheses for the RH have been put forward, and these are detailed below.

1. RH specialisation – faces and emotions

While initial processing of written words occurs within the visual-word form area (VWFA) in the left mid-fusiform (Cohen & Dehaene, 2004), faces produce specific activation in the fusiform face area (FFA) of the right mid-fusiform (Gauthier, et al., 2000), suggesting an early processing distinction between the hemispheres. fMRI and lesion studies have found RH dominance for a wide range of tasks requiring comprehension of emotional stimuli, including face expression processing (Blonder, Bowers, & Heilman, 1991; Bowers & Bauer, 1985; Kucharska-Pietura, Phillips, Gernand, & David, 2003; Nakamura et al., 1999), leading to theories which suggest expressions through non-verbal signals are mediated by the RH (Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000; Kolb & Taylor, 2000; Silberman & Weingartner, 1986). Emotional expressions in the face activate several distinct regions, including right or bilateral amygdala, cingulate gyrus, orbitofrontal cortex, and other prefrontal areas (Blair, Morris, Frith, Perrett, & Dolan, 1999; Brieter et al., 1996; Dolan et al., 1996; Morris et al., 1996; Nakamura, et al., 1999; Vuilleumier, Armony, Driver, & Dolan, 2001). The ‘right hemisphere hypothesis’ emphasises the dominance of this hemisphere in emotion processing (Adolphs, et al., 2000; Blonder, et al., 1991; Borod, 2000; George et al., 1996). Neuropsychological studies have found that in tasks which require the participant to select a word which best describes a face emotion, RH patients (compared to both LH patients and controls) showed impaired performance overall, even when taking into account face perception ability (Kucharska-Pietura, et al., 2003). In fMRI tasks which require judgement of an individuals’ emotion, both the right orbitofrontal cortex (Blair & Cipolotti, 2000; Blair, et al., 1999) and right lateral prefrontal cortex are activated (George et al., 1993; Nakamura, et al., 1999). Even in tasks where faces are presented for 250ms or masked, fearful faces activate the right fusiform gyrus to a greater extent than the left (Vuilleumier, et al., 2001).

2. RH specialisation – social judgements

However, it is not simply the case that the LH processes words and the RH processes faces. Disruption to the RH has been associated with deficits of social cognition (Adolphs, 1999; Ellis, Ellis, Fraser, & Deb, 1994). Theory of mind is the ability to infer the mental states of others, particularly in making non-literal inferences (Weed, 2008; Weed, McGregor, Nielsen, Roepstorff, & Frith, 2010). It has been found that RH stroke patients show impairments on cartoon tasks which require attribution of mental states (Happe, Brownell, & Winner, 1999). This role of the RH in theory of mind is congruent with its perceived role in emotion processing of faces (Adolphs, et al., 2000). Ruby and Decety asked participants questions based on their own or the perspective of another person. Imagining another's perspective activated frontopolar cortex and right inferior parietal lobe (Ruby & Decety, 2003, 2004). It has been found that patients with RH damage show greater empathy deficits than LH cases (Perry et al., 2001; Rankin et al., 2006; Shamay-Tsoory, Tomer, & Aharon-Peretz, 2005; Shamay-Tsoory, Tomer, Berger, & Aharon-Peretz, 2003; Shamay-Tsoory, Tomer, Berger, Goldsher, & Aharon-Peretz, 2005; Shamay-Tsoory, Tomer, Goldsher, Berger, & Aharon-Peretz, 2004). Atrophy to the right ATL is associated with behavioural changes, such as a lack of inhibition or empathy (Liu et al., 2004; Rankin, et al., 2006). Similarly, an fMRI study, in which participants were asked to make a relatedness judgement on two words which were either social (e.g., TACTLESS – IMPOLITE) or animal (e.g., NUTRITIOUS – USEFUL), found that only the right superior anterior temporal lobe survived an analysis which assessed activity for social versus animal concepts – suggesting it reflects social cognitive processes (Zahn et al., 2007). This study highlights the RH's involvement beyond picture tasks, in language comprehension. Indeed, in sentence processing, sentences with a moral content produce right anterior temporal – but not left anterior temporal activation (Moll, de Oliveira-Souza, Bramati, & Grafman, 2002; Moll, Eslinger, & Oliveira-Souza, 2001; Oliveira-Souza & Moll, 2000). Zahn et al. (2007) assessed hypometabolism across a cohort of 47 frontotemporal lobar degeneration and corticobasal syndrome patients in comparison to performance on animal or social concepts. Those with right superior ATL hypometabolism were significantly more impaired on social concepts than animal concepts. Additionally, this correlated with inappropriate social behaviours (see also Bartolomeo, Thiebaut de Schotten, & Doricchi, 2007; Konen, Behrmann, Nishimura, & Kastner, 2011; Mort et al., 2003). Therefore, it appears that rather than the RH being specialised for visual or particularly for face processing, it may be the nature of the stimuli itself (e.g., social) which leads to a deficit in RH patients.

3. RH specialisation – metaphors

A noticeable behavioural impairment in RH stroke patients is that they perform more poorly than LH aphasic patients on picture metaphor tasks, giving more literal responses, e.g., responding to 'he has a heavy heart' with a picture of someone carrying a heavy heart

(Winner & Gardner, 1977). This suggests that patients are unable to identify the appropriate situation in which a specific expression is suitable (Brownell, et al., 1990; Foldi, et al., 1983; Myers, 1983; Rehak, et al., 1992; Rinaldi, et al., 2004; Zaidel, et al., 2002). Much data has come from patients who show deficits in comprehending higher-level language (Gagnon, Goulet, Giroux, & Joanette, 2003; Gold & Faust, 2010; Kircher et al., 2004; Mitchell & Crow, 2005). fMRI data is less convincing – with some evidence that the RH contributes to metaphor processing (Bottini, et al., 1994; Faust & Mashal, 2007), verbal creativity and abstractness (Gold, et al., 2011), sarcasm (Giora, et al., 2000) and inferences (Jung-Beeman, Bowden, & Gernsbacher, 2000). For example, the right inferior temporal gyrus has been shown to activate more for conventional metaphors than literal sentences (Ahrens et al., 2007). However, some argue that both hemispheres have the ability to process metaphors alone (Faust & Weisper, 2000; Kacinik & Chiarello, 2007; Rapp, et al., 2007; Schmidt, et al., 2007).

RH specialisation - theories

Of course, it is possible to link together these disparate specialisations into overarching theories of the role of the RH. For example, the distinction between the right FFA and left VWFA has been interpreted in terms of the processes that are required for words and faces, as opposed to differences in modality or input (Bukach, Gauthier, & Tarr, 2006; Cohen & Dehaene, 2004; Gauthier & Palmeri, 2002; Palmeri & Gauthier, 2004; Price & Devlin, 2003; Tarr & Gauthier, 2000). This group of researchers suggest that faces require *configural processing* – using a holistic analysis rather than element-element analysis, and words or symbols instead need analytical analysis – assessing each element in turn (Dien, 2009).

Similarly, this could be a useful distinction for other RH specialisations – with the RH being specialised for a gestalt analysis over analytical processing. In relation to this, the *coarse semantic coding hypothesis* has been put forward to describe the RH role in metaphors (Jung-Beeman, 2005). This suggests the LH focuses on dominant, literal or contextually relevant meanings, and the RH activates a broader semantic field, which sustains the meaning of a wide range of distant associates. This is similar to the *graded salience hypothesis* (Giora, 1997), which suggests that the left hemisphere processes meanings which are particularly salient – be that through prior context, familiarity or dominant/ conventional meanings; and non-salient comprehension involves the RH (Giora, 2009; Giora, et al., 2000). These theories can be integrated (Mashal, et al., 2009), if one assumes that familiar items are often closely related – or become closely related – and novel items are distantly related. In relation to social judgments, t*he weak central coherence theory* (Norbury, 2005; Rundblad & Annaz, 2010), stems from the failure to integrate sources of information to establish meaning, for example, integrating different elements of a face (the eyes or mouth), and not being able to extract the overall expression. This means focusing on small details rather than large, globally coherent patterns of information (Frith, 1989). This directly relates to the idea that the RH is involved in face processing because it is interested in configural processing. Finally, *the stimulus-driven attention hypothesis* (Corbetta & Shulman, 2002) suggests that a largely lateralised RH system is involved in reorienting attention according to new or distinctive stimuli. Conversely, an area which is largely left lateralised is involved in goal-directed attention. This suggests that the RH is critical in focusing attention on aspects of a stimulus which are unusual, and shifting attention away from more typical interpretations of the stimuli.

All these theories share common strands, and suggest that the reason behind the deficits found in RH patients for faces, social judgements or metaphors can be explained by the role of the RH in making global or ‘coarse’ judgements, and being involved in unfamiliar or unusual stimuli.

Executive control

Control demands have been shown to be an important factor in semantic tasks (Jefferies & Lambon Ralph, 2006), though it is unclear how these relate to the processing specialisms of the RH which are described in the theories above. Semantic aphasia (SA) patients, with damage to left prefrontal and/or temporoparietal regions show little evidence that they have lost semantic representations. Instead they show: (1) lower performance on high demand tasks, such as matching items that are in the same category but not closely related, like ‘salt’ with ‘sugar’, but almost ceiling performance on tasks with low control demand, such as matching items which are of the same category and closely related, such as ‘salt’ with ‘pepper’ (Noonan, et al., 2010); (2) consistency of performance across semantic decisions which have the same level of difficulty and task demands, such as semantic association in word and picture modalities, but not across tasks with different demands, such as word to picture matching and association matching (Jefferies & Lambon Ralph, 2006); and (4) general executive control impairments which go beyond the semantic domain, and correlate with the degree of impairment on semantic tasks (Jefferies & Lambon Ralph, 2006). This suggests that SA patients have intact semantic representations but deregulated conceptual processing, such that they are unable to focus processing on relevant features and associations in the absence of external constraints, i.e., a semantic control deficit.

Because of these deficits, we find that SA patients show good performance on certain tasks, but impaired performance on the same task which has been manipulated to require more control. (1) SA patients are better able to perform a synonym judgement task, when the distractor foils are weakly associated to the probe (e.g., NEAT – TIDY, MESSY or LUCKY), in relation to a task where there is a distractor which is strongly related to the probe (e.g., HAPPY – CHEERFUL, SAD, or CONSCIOUS; Noonan et al., 2010). (2) Patients show strong effects of cues towards picture naming, whether they are phonemic (e.g., /b/ for bed), word or sentence cues (Corbett, et al., 2008; Jefferies, Patterson, et al., 2008). Additionally, they can be miscued towards a related but incorrect word (Soni, et al., 2009; Soni, et al., 2011). (3) SA patients are better at matching strongly related word, in relation to weakly related word. This occurs even if the probe word remains the same, e.g., performance is significantly better on matching LEAF-TREE compared to LEAF-PAGE (Noonan, et al., 2010). (4) Finally, a cyclical word-picture matching task has been used to show a decline in accuracy over repetitive presentation of the same, semantically related set of items (refractory effects; Warrington & McCarthy, 1983). Cyclical tasks typically use a target with distractors which are closely related, with the target on one trial becoming the distractor on another, and vice versa. This increases competition between the target and distractor, because all items are highly activated, so it becomes more difficult to reject the distractors (Jefferies, et al., 2007).

Prefrontal vs. temporoparietal regions

In SA patients, those with prefrontal and those with temporoparietal lesions show virtually identical semantic control impairments (e.g., Noonan et al., 2010; Jefferies et al., 2008; Corbett et al., 2011). Additionally, fMRI data reveals an executive control network which spans both prefrontal and parietal regions (Duncan, 2010). However, a recent meta-analysis (Noonan et al., submitted) did not find RH temporo-parietal activation for semantic control specifically. Therefore, although patients with prefrontal damage with or without temporoparietal damage (PF+) and those with damage restricted to the temporoparietal cortex (TP-only) may both show impairments on executive control tasks - consistent with the large network involved in executive control - there may be a difference in relation to semantic control – with PF+ patients showing more effects of semantic control demands than TP-only patients.

Executive control processes have been described as emerging from a bilateral network (Duncan, 2006, 2010; Duncan & Owen, 2000; Miller & Cohen, 2001), with fronto-parietal areas involved in domain general control, and contributing to the shaping of activation according to the task (Freedman, Riesenhuber, Poggio, & Miller, 2001). In terms of semantics, the RIFG, like the LIFG, has shown to be consistently activated by semantic tasks, though the LIFG is typically more responsive to verbal material (Noonan, et al., submitted; Vigneau, et al., 2011), including many key studies on semantic control (Badre, et al., 2005; Snyder, et al., 2011; Thompson-Schill, et al., 1997; Wagner, Paré-Blagoev, et al., 2001). However, little research has explored the role of the right hemisphere in semantic control. Our hypothesis is that, given the role of the RH in semantic processing as well as control, patients with RH stroke might show: (1) qualitiatively similar semantic control impairments to those found in SA patients, with performance correlating with semantic control demands of the task - but in semantic materials in which the RH is specialised in processing, e.g., metaphors. (2) It is also possible that, given the smaller peak of activation in RIFG compared to LIFG in semantic control tasks, we may find a reduced semantic control deficit, with the RH playing a smaller, but still necessary role in semantic control. (3) Finally, given the noticeable difference between LH and RH patients in language ability, and simple comprehension tasks, we may find no semantic control impairments, suggesting an intact LH is able to take over the semantic control functions which usually recruit the RH.

Some researchers have already pointed out the importance of executive function in communication impairments after RH lesion or dysfunction. Given that pragmatic and higher-order language comprehension requires flexibility, inhibition and intention decoding, this suggests that comprehension relies on executive control (Champagne-Lavau & Joanette, 2009; Martin & McDonald, 2003). There is some evidence to suggest this is the case (Leslie, Friedman, & German, 2004; Leslie, German, & Pollizi, 2005; Verte, Guerts, Roeyers, Ooosterlaan, & Sergeant, 2006). For example, performing a dual-task impairs the ability to perform a theory of mind task (Bull, Phillips, & Conway, 2008; McKinnon & Moscovitch, 2007), and verbal executive function correlates with pragmatic communication abilities in TBI patients (Douglas, 2010). Additionally, the type of error made in language can be reflected by corresponding executive deficits (McDonald, 1993). For example, a patient who makes frequent topic shifts and is highly garrulous also showed poor impulse control on cognitive tasks (and not preservative errors seen in other patients). Disinhibition may decrease ability to use indirect or subtle language (McDonald & Pearce, 1996).

Despite scepticism from proponents of the domain general theory of control, who argue that there is a bilateral system that is involved in all aspects of control (Hampshire, et al., 2010; Hampshire, et al., 2009), there is suggestion that the RIFG is linked to a particular aspect of executive control – inhibition (Aron, et al., 2004; Chikazoe, et al., 2007; Lenartowicz, et al., 2011). Inhibition is required when there are task eligible but incorrect items present. Milham et al. (2001) devised a stroop task which involved the traditional conflict of ink colour and written colour, with participants having to name the ink colour and ignore the written colour word. Additionally, they studied the effect of adding written colours which were never ink colours ("ineligible"). This condition did not activate RH regions of the prefrontal cortex, although homologue LH regions showed similar activation for both "eligible" and "ineligible". This suggests that the RH is needed in response to relevant conflicts, when an automatic behaviour needs to be overridden. Similarly in a "go no-go" task, where participants have to press a button when presented with one stimulus, but withhold this behaviour after presentation of another stimulus, the RIFG activation is seen in the "no-go" inhibition trials. This is particularly true in more complex versions of the task, such as when the subject has to remember a sequence of presentation of stimulus (e.g. "X-Y-X-Y"), and inhibit responding to previously relevant items (e.g. "X-Y-Y-X") which requires a high degree of inhibitory control (Garavan, et al., 1999).

This study

Because the RIFG has been linked to both executive control (either domain general or more specific aspects of control), as well as semantics, it is important to test the hypothesis that RH patients are more impaired on semantic tasks when the semantic control demands are maximised. The aim of this study was to assess the semantic deficits in RH stroke patients in relation to the semantic control demands of the task. There were three potential outcomes to these studies. (1) A deficit of semantic control which is more pronounced for material thought to be processed predominantly in the RH. For example, RH patients may show no impairment on picture naming of everyday objects, even when these are presented repeatedly at a fast rate, requiring control to selection, inhibit, and then reselect items (in a cyclical task). Nevertheless, they might show refractory deficits when naming face emotions. (2) A weak control deficit across tasks which are specifically recruiting this hemisphere, with only subtle differences to controls on the highest demand tasks. This would suggest the RH has a smaller, but still necessary role in control. This prediction is based on the weaker RH activation for semantic cognition in neuroimaging literature. Nonetheless, we wanted to test whether RH patients would show some of the patterns of LH cases for domains in which they are impaired, e.g., inconsistency, refractory effects, cueing and distractor strength. (3) Patients may show no semantic control impairments compared with healthy controls. This could be the case, since the semantic control network activates predominantly LH regions. Patients may be able to utilise intact LH regions to take over the semantic control functions which usually recruit the RH. This finding would also suggest that the RH is not necessary for semantic control, as patients are able to cope with demanding semantic tasks using their LH network.

Two additional hypotheses will be tested. Firstly, domain general executive control will be assessed, in tasks which are traditionally used to assess inhibition, as well as other executive control tasks, such as non-verbal reasoning which do not assess inhibition. We will compare scores on these tasks and predict that RH patients will be worse at tasks which require inhibition. Secondly, we will assess the role of the prefrontal cortex where possible. We hypothesised that patients with known damage to this region would show both executive and semantic impairments, with semantic control impairments much greater than those without known prefrontal damage.

Methods

Participants

There were 6 RH stroke patients, and between 10 and 12 aged-matched controls of similar educational background (different controls were used for each task). SA patients were recruited from stroke clubs in Yorkshire, UK. Patients were selected for the study if they showed impairments on two or more subsets of the Right Hemisphere Language Battery (Bryan, 1995).

Stroke lesion analyses: Scans were available for 4/6 patients (FBu, CNe, DJe, ARi). PSm was not able to be scanned due to a metal stent, but a radiographer’s report from the time revealed an acute infarct in the territory of the right middle cerebral artery. EHo did not wish to be scanned and no radiographers report was available. CT/MRI scans that were available were manually traced onto Damasio’s standardised templates (Damasio & Damasio, 1989). This is shown in Table 5.1. Three patients showed damage to prefrontal regions (CNe, DJe and ARi). We grouped these patients into those with known prefrontal damage (PF+). A second, comparison group was formed for the purpose of this study. This included FBu, without prefrontal damage. It also included PSm and EHo, both of whom did not have hemiplegia, suggesting their lesions may be relatively small and/or with a posterior focus. For the purposes of this analysis, we labelled these patients ‘other’. Because of the small sample size and insufficient data for accurate lesion location analysis, we only assessed RH patients in these subgroups briefly.

Comparison SA group: We compared RH patients to our SA patients presented in Chapter 4. 15 SA patients were recruited from stroke clubs and speech and language therapy services in Manchester and York, UK. These SA patients showed impairments on both word and picture association tasks (the Camel and Cactus Test, CCT). All of the patients had chronic impairments resulting from a CVA at least one year prior to testing. They were matched for age and years of education ($t > 1$), but had damage exclusively to the left hemisphere. On one executive control task (the trail making task), no data was available for this group of SA patients. Therefore, a group of 8 SA patients were used to compare to the RH group. This group of SA patients did not differ significantly from the previously reported SA group in terms of their semantic or executive abilities, age and years of education ($t > 1$).

In terms of our experimental tasks, we also thought it would be fruitful to explore the effects of semantic control manipulations in both RH and SA patients. Therefore, we compared our new tasks run in RH patients with tasks previously run with our SA patients which use the same semantic control manipulations (all patients reported in these experimental paradigms have also been described in detail in Chapter 4). For example, we compared our RH patients face emotion picture naming task with and without cues with our SA patients’ performance on the Boston Naming Task with and without cues (BNT; Kaplan, et al., 1983). Although we expected that in some cases, the RH and SA tasks could not be matched for overall accuracy (as they were different tasks), they could still be compared for the degree of performance on high vs. low demand conditions to check for an interaction of group and semantic control demands.

Controls: We used a cohort of 19 aged-matched controls from a participant database at the University of York. Participants had no prior history of brain injury, and showed unimpaired cognitive functioning on the Mini-Mental State Examination (Folstein, et al., 1975). Independent t-tests showed that the age of the controls did not differ from the patients. Of this cohort, there were 12 controls in Experiment 2, 10 in Experiment 3, 11 in Experiment 4 and 12 in Experiments 5 & 6. The numbers of controls in each experiment varied slightly due to hearing ability (we only used those with good hearing when the task had auditory probes or cues), as well as availability.

Table 5.1: Lesion analysis for stroke patients

Patient	Group	Lesion size (% of template damaged)		DLPFC	orbIFG	trIFG	opIFG	PMC	STG	MTG	ITG	FG	POT	AG	SMG	TP	OL
			BA9	BA46	BA47	BA45	BA44	BA6	BA22	BA21	BA20	BA36	BA37	BA39	BA40	BA38	BA19
ARi	PF+	4	-	-	-	-	2	2	1	-	-	-	-	-	-	-	-
CNe	PF+	7	-	-	-	1	-	2	2	1	-	-	2	1	2	-	-
DJe	PF+	11	-	-	-	-	2	1	2	2	-	-	2	2	2	-	-
FBu	‘other’	3	-	-	-	-	-	1	1	1	-	-	-	-	-	-	-

Quantification of lesion: 2 = complete destruction/serious 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; sTP = superior temporal pole; pSTG = posterior superior temporal gyrus; pMTG = posterior middle temporal gyrus; ITG = inferior temporal gyrus; FG = fusiform gyrus; POT = posterior occipitotemporal area; SMG = supramarginal gyrus; AG = angular gyrus; OL = occipital lobe. No scan available for PS or EH.

1.Background neuropsychology

Rationale

SA patients who showed deficits in semantic control also showed impaired performance on domain-general control tasks. It has been shown that the RH is involved in a domain general control network (Duncan, 2010). Therefore, we wanted to see if damage to the RH after stroke would produce difficulties on standardised assessments of working memory, attention and reasoning to the same extent as has been found after LH stroke. This included working memory, attention, reasoning and processing. We also assessed our RH cases on the semantic battery we have used with LH cases (although only used the most demanding tasks).

Procedure

We used a number of semantic and non-semantic background assessments. Semantic: (1) *The Camel and Cactus task*, picture version (CCTp; Bozeat, et al., 2000) used 64 items, and involved matching a probe with one of four related items (e.g., does CAMEL go with CACTUS, TREE, SUNFLOWER, or ROSE?). (2) *A synonym judgement task* involved matching a probe word with a target word presented alongside two unrelated distractors. This had 96 items in two frequency bands (high and low) and three imageability bands (high, medium and low), producing sixteen trials in each of the six frequency-by-imageability conditions (see Jefferies, et al., 2009). For example, a low imageability, low frequency item involved matching SUFFIX with INFLECTION, PERPETRATOR or TEMERITY. A low imageability, high frequency item involved matching CONSIDER to THINK, DEVELOP or DETERMINE. A high imageability, low frequency item involved matching CHESTNUT with CONKER, SWAMP or EAGLE. Finally, a high imageability, high frequency item involved matching MONEY with CASH, CAR or CHURCH. Responses were untimed.

RH language: (3) *The right hemisphere language battery* (RHLB, Bryan, 1994) involved six subtests: (i & ii) A metaphor word and picture task, involving matching a probe item (a spoken sentence), with one of four possible interpretations. For example, in the word task, the experimenter reads: "*He didn't take the changes lying down. (1) He didn't want to lie down, (2) He protested against the changes,* or *(3) change made him tired*". The picture task has a spoken sentence to be matched with a target presented with 3 distractors as an image. There were 10 items in each test. (iii) An inference test, involved reading a short paragraph and answering questions requiring inferences about the story. This used three paragraphs (and a practice paragraph) with four questions about each one. (iv) Word-picture matching, involved 20 items where the name of the item was matched with a corresponding picture. (v) A humour test involved 10 items. A sentence was read out, and the participant was required to pick which of four possible sentences was the best punchline for the joke. For example, the experimenter read out: "*A judge had just finished telling the prisoner that he was free to go, as the jury found him not guilty of fraud. The prisoner then asked: (A) When can I leave sir? (B) What about my friends? (C) Does that mean I can keep the money? (D) What time is it please?*" These responses were: (A) neutral, (B) emotional, (C) correct, or (D) unrelated. (vi) A test of emphatic stress, where the researcher read a sentence which described a picture, and the participant described a similar picture with the same prosody. There were 10 items. (4) *The Familiar and Novel Language Comprehension test* (FANL, Kempler & Van Lancker Sidis, 1996), used 20 items, with a four-choice picture test of (i) novel (literal) phrases and (ii) familiar metaphoric phrases. A sentence was presented verbally and participants were asked to pick the picture which reflects the sentence (e.g., metaphoric – 'he's got his head in the clouds'; literal – 'he's chasing after a white duck').

Visual/Neglect: (5) *The Visual Object and Space Processing battery, VOSP* (Warrington & James, 1991), involved a number of perceptual tasks, including counting, location analysis and position discrimination. (6) *The Bells Cancellation test* is a test of neglect, and involved marking all images of a BELL on a sheet of paper.

Executive Control: (7) *Forward and backward digit span* (Wechsler, 1987), assessed working memory. (8) *An Elevator Counting task* involved counting varying length tones which were played with or without distraction, from the Test of Everyday Attention (Robertson, et al., 1994). (9) *The Ravens Coloured Progressive Matrices test* (RCPM: Raven, 1962), assessed non-verbal ability using pattern and rule recognition of shapes and colours. (10) *The Brixton Spatial Rule Attainment task* (BSRA: Burgess & Shallice, 1997), involved adapting patterns of responses based on feedback. (11) *The Hayling test* was single word sentence completion, with participants ending the sentence with either the logical conclusion, or a word which was unconnected to the sentence. (12) *The trails test* involved linking letters and numbers in order, in an easy condition (e.g., 1-2-3...) and difficult condition (e.g., 1-A-2-B-3-C..., Reitan, 1958).

Results

Results are shown in Table 5.2. Factor analysis was used to extract a single factor across multiple tasks which tap the same concept (e.g., semantic, executive, visual and RH language). The scores in the table represent the regression co-efficient for each patient on the basis of this factor, with scores of 0 representing mean performance, scores above this being higher than average, and negative scores being below average. There were only 6 cases, so any correlates run had limited power. There were no significant correlations between these four factors, except between visual and executive factors: *r* = .857, *p* = .029. This may reflect some of the demanding aspects of the visual tasks (e.g., cube analysis), as well as the visual executive tasks (e.g., RCPM), which may have overlapping demands.

Table 5.2: Background neurology of RH patients

	Max	Normal cut off	*CNe*	*ARi*	*DJe*	*FBu*	*PSm*	*EHo*
Semantic								
CCT pictures	*64*	52	52	56	55	57	58	54
Synonym task - words	*96*	91	95	88*	89*	94	79*	87*
Low imageability	*32*	27.6	31	29	26*	30	16*	24*
Medium imageability	*32*	30.8	32	30*	32	32	32	31
High imageability	*32*	30.9	32	29	31	32	31	32
Low frequency	*48*	44.9	48	45	44*	48	38*	45
High frequency	*48*	44.4	47	43*	45	46	41*	42*
Semantic factor			1.35	-0.36	0.13	0.67	-1.60	-0.18
Executive functioning								
BSRA	*55*	28	38	21*	31	27*	27*	24*
Hayling - sensible	*15*	11	14	14	15	12	13	13

Hayling unconnected	*15*	11	1*	6*	7*	1*	1*	5*
RCPM (A, AB, B)	*36*	21.7	26	30	24	35	23	21*
TEA	*7*	6	6	NT	6	NT	7	6
TEA (with distraction)	*10*	3	0*	NT	5	NT	2*	7
Trail making (A)	*24*		24	24	NT	24	24	NT
Trail making (B)	*23*		7*	22	NT	23	17*	NT
Digit Span forwards	*8*	5	4*	7	6	5	4*	5
Digit Span backwards	*7*	2	3	4	3	2	2	NT
Executive factor			-1.38	1.44	-0.32	0.82	-0.52	-0.29
Visuospatial								
VOSP-screening	*20*	17.8	18	20	19	18	20	NT
VOSP-incomplete letters	*20*	16.9	18	20	19	20	20	NT
VOSP-silhouettes	*30*	10.0	13	24	21	17	23	NT
VOSP-object decision	*20*	10.5	16	18	18	14	19	NT
VOSP-progressive silhouettes	-	6.0	15	10	10	13	11	NT
VOSP - dot counting	*10*	9.5	9*	10	10	8*	10	10
VOSP - position	*20*	17.1	19	20	20	20	19	20
VOSP - number location	*10*	4.7	7	10	5	10	10	9
VOSP – cube analysis	*10*	5.4	4*	10	8	9	7	3*
Bells cancellation test	35	32	32	35	33	33	34	32
Visual factor			-1.31	1.49	-0.18	0.52	0.30	-0.82

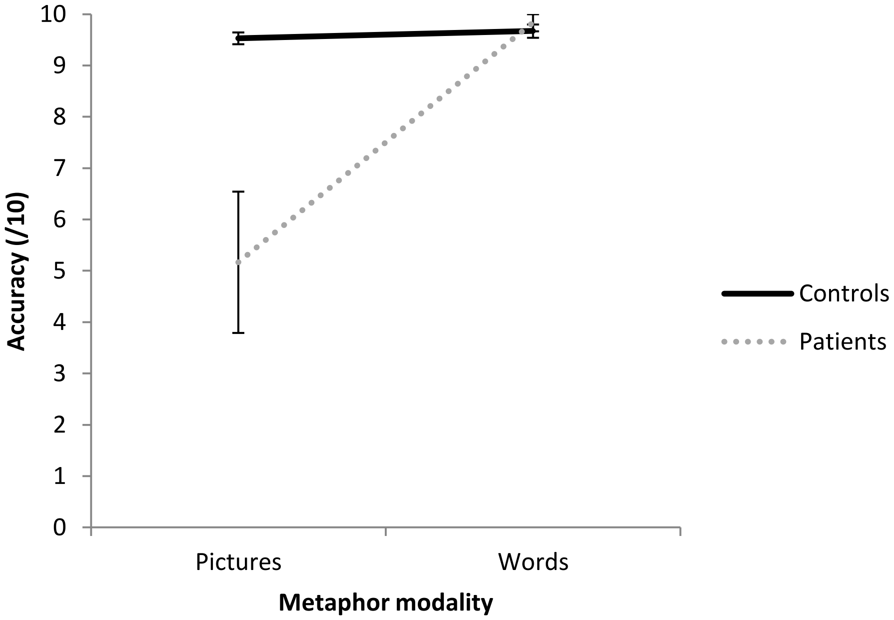
RH language								
Metaphor pictures	10	8.3	10	6*	6*	0*	3*	6*
Metaphor words	10	8.3	10	10	10	10	9	10
Lexical semantic (WPM)	20	19.4	18	19	20	19	19	18
Inferences	12	8.0	12	9	10	11	9	12
Humour test	10	8.8	5*	9	0*	9	3*	7*
Emphatic stress	10	10	9*	8*	5*	6*	4*	7*
FANL – metaphors (pictures)	20	16.7	13*	16*	15*	NT	16*	15*
FANL - literal phrases (pictures)	20	16.6	16*	18	15*	NT	18	17
Language factor			1.27	0.21	-0.83	-0.08	-1.40	0.83

WPM = spoken word to picture matching; CCT = camel and cactus test of associative semantic knowledge; VOSP = visual object and space processing battery; RCPM = Raven's Coloured Progressive Matrices; BSRA = Brixton spatial rule attainment task; TEA = elevator counting with and without distraction from the test of everyday attention. Raven's Progressive Matrices norms calculated from Luszcz, M.A. (1992). Predictors of memory in young-old and old-old adults. *International Journal of Behavioral Development, 15*(1), 147-166. Bells Cancellation test (Gauthier, Dehaut & Joanette, 1989). RHLB = right hemisphere language battery (Bryan, 1994). FANL = Familiar and Novel Language Comprehension Test (Kempler & Van Lancker Sidis, 1996). Semantic, executive, visual and language factor scores created from the tasks in each subset where all participants have a score.

(1) *The Camel and Cactus Task* was analysed by examining the extent to which patients were impaired in relation to controls by using the "Singlims" procedure (Crawford & Garthwaite, 2002). This uses a modified t-statistic to examine whether an individual is significantly below a control group, taking into account group size and standard deviation. Singlims tests revealed no significant difference from controls in any patient, suggesting they are performing at a normal level. (2) *The synonym judgement task* was analysed using modified t-tests, which revealed a significant difference from controls in four patients: ARi (t = 3.604, p = .002), EHo (t = 4.830, p < .001), DJe (t = 3.125, p = .007), and PSm (t = 9.595, p < .001). All four of these patients showed significantly impaired performance on low or medium imageability words but normal performance on high imageability words – a similar pattern to that found in SA patients. In an omnibus ANOVA, there was no significant effect of frequency: F < 1;

imageability: *F*(2,4) = 4.096, *p* = .108, or interaction: *F*(2,4) = 1.201, *p* = .390. For imageability, there was marginally higher performance in high imageability compared with low imageability words: *t*(5) = 2.245, *p* = .075; and medium imageability compared with low imageability words: *t*(5) = 2.342, *p* = .066; but not medium imageability compared with high imageability words: *t*(5) = 1.000, *p* = .363.

(3) A paired-samples t-test comparing scores on the *right hemisphere language battery subtasks* involving metaphor pictures and metaphor sentences found a significant difference between the two: *t*(5) = 3.5, *p* = .017, reflecting a lower performance in the picture task across RH patients. A Revised Standardised Difference Test (RSDT) revealed a significantly lower performance in the picture task compared with the written sentences for ARi, EHo and DJe (*t* = 6.321, *p* < .001), FBu (*t* = 15.258, *p* < .001), and PSm (*t* = 9.640, *p* < .001). Controls did not show this modality difference, as shown in Figure 5.1, displaying our patient data, and control data from 30 age-matched participants presented in Bryan (1995).



Error bars show standard error of the mean.

Figure 5.1: Scores on the picture and word versions of metaphor subtasks from the Right Hemisphere Language Battery (Bryan, 1995).

(4) Modified t-tests were run for the FANL tasks. Patients do slightly worse at the metaphor task (M = 15.0, SD = 1.2), in relation to the literal task (M = 16.7, SD = 1.3), which is an opposite trend to healthy controls. For the literal phrases, there was a significant impairment for CNe (t = 2.357, p = .040), and DJe (t = 3.093, p = .011). This was not significant for PSm or ARi (t < 1), or EHo (t = 1.620, p = .136). For the metaphors, there was significant impairment for all patients: DJe and EHo (t = 3.395, p = .007), ARi and PSm (t = 2.524, p = .030), and CNe (t = 5.135, p < .001). A RSDT revealed significantly worse performance on the metaphor task for ARi (t = 2.320, p = .043); CNe (t = 3.818, p = .003); EHo (t = 2.502, p = .031); PSm (t = 2.320, p = .042); but not DJ (t < 1).

(5&6) *The VOSP task* and *Bells Cancellation task* revealed high performance across the subtasks, with some errors in the dot counting and cube analysis. Overall, no neglect was evident. (7) *Digit span* performance was normal, and those who scored below the normal cut off on the forwards digit span were within the normal range on the backwards digit span. (8) *Elevator counting task* showed performance was not at ceiling, but was nonetheless within the normal range. (9) *Raven's Coloured Progressive Matrices* showed a range of scores, within the normal range, with one exception, EHo, who was marginally beneath it (see Table 2). (10) *The Brixton Spatial Rule Attainment task* found 4 of the 6 patients outside the normal range, two noticeably so. (11) *The Hayling sentence completion task* was performed poorly. When asked to complete with a sensible word, most patients were within normal range. However, they were unable to come up with an unconnected word to the sentence. (12) *The trails making task* also found impairments in the majority of patients on the more difficult switching condition.

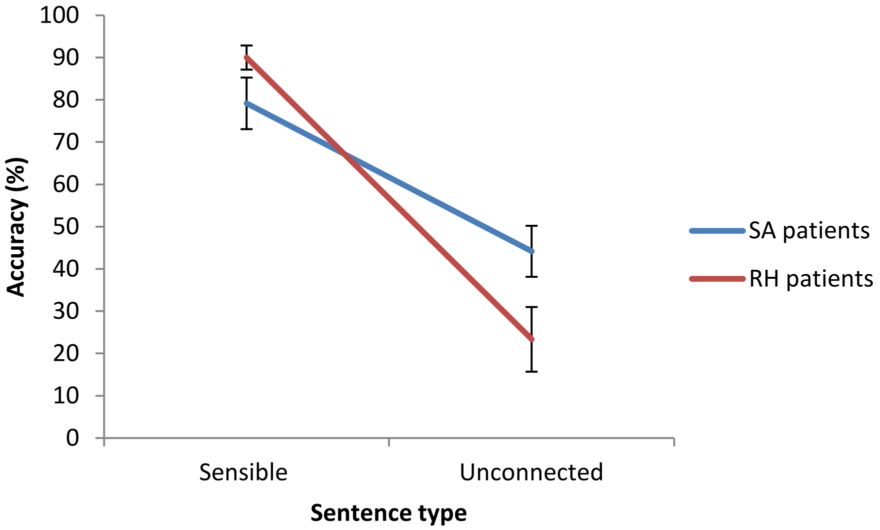
Comparative executive performance to SA patients

Semantic: In the CCTp, RH patients were significantly more accurate that our SA patients: F(1,19) = 10.230, p = .005. This was also true for the synonyms task: F(1,19) = 13.068, p = .002. In an omnibus ANOVA of the effects of frequency and imageability across groups, there was a significant main effect of imageability: F(2,18) = 33.002, p < .001, but not frequency: F < 1. There was also a main effect of group: F(1,19) = 15.617, p = .001. Imageability interacted with group: F(2,18) = 7.660, p = .004, but frequency did not: F < 1. There was no three way interaction. Although both groups showed higher performance with high imageability items (means: RH = 31, SA = 27), in relation to low imageability items (means: RH = 26, SA = 18), the difference was greater in our SA patients.

Visual: There was no significant difference between groups on the dot position task: *F*(1,19) = 2.437, *p* = .135, position discrimination task: *F*(1,19) = 3.642, *p* = .072, number location task: *F* < 1, or cube analysis: *F*(1,19) = 2.618, *p* = .122.

Executive: In the *RCPM*, there was no significant difference between groups: F(1,19) = 2.393, p = .138. This was also true for the *BSRA*: *F*(1,17) = 2.299, *p* = .148. In an ANOVA comparing *digit span* forwards and backwards, there was a main effect of task: F(1,18) = 43.286, p < .001, but no interaction: F < 1, or main effect of group: F(1,18) = 2.250, p = .151. Comparing *TEA* with and without distraction, there was no main effect of task: *F*(1,15) = 2.573, *p* = .130; or main effect of group: F(1,15) = 1.399, p = .255; or interaction: F < 1. Using the second SA group, we compared performance on the trail making task. Over both groups, task B was significantly more difficult than task A: *F*(1,11) = 17.994, *p* = .001, but this did not interact with group: *F* < 1. There was no main effect of group: *F*(1,11) = 1.727, *p* = .216, suggesting RH patients are performing similarly to our SA patients.

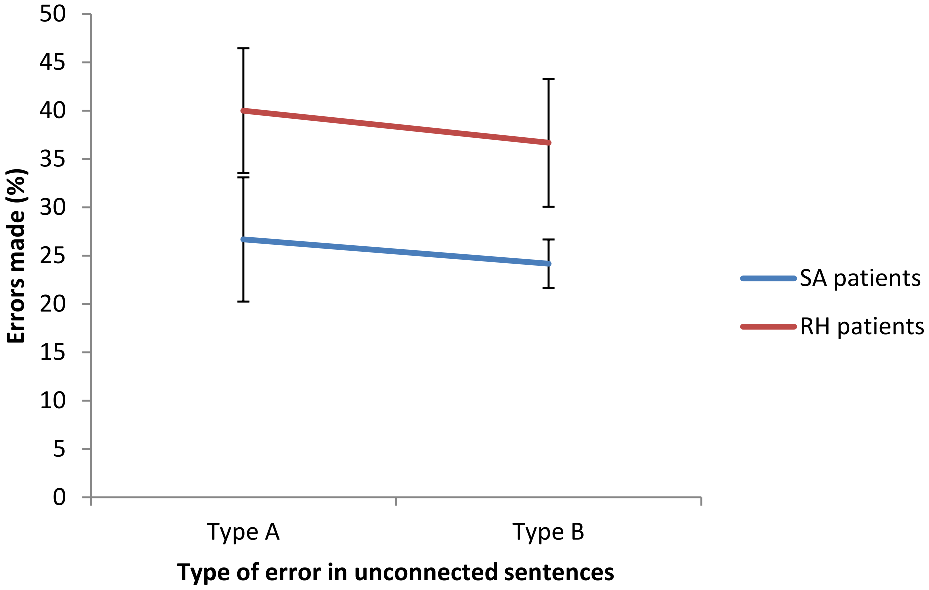
In the Hayling task, a repeated measures ANOVA was run on both sensible and unconnected sentence completion in 8 of our SA patients and our RH patients. Although there was no group difference in performance (*F* < 1), performance on the ‘sensible’ sentence completion was higher than the ‘unconnected’ sentence completion: *F*(1,12) = 172.402, *p* < .001, and there was a significant interaction with group: *F*(1,12) = 16.726, *p* = .001. RH patients showed more errors in the unconnected sentences condition, but had higher accuracy in the sensible sentences condition. This is shown in Figure 5.2.



Error bars show standard error of the mean.

Figure 5.2: Sentence completion accuracy with sensible or unconnected words from the Hayling Test (Burgess & Shallice, 1997).

With regards to the type of error made in the unconnected sentences task, Type A errors represent strongly connected words (e.g., AT LAST THE TIME FOR ACTION HAD... ‘come’), and Type B errors are somewhat connected (e.g., MOST CATS SEE VERY WELL AT... ‘dawn’). This time, a group difference was found: $F(1,12) = 9.169$, $p = .011$, but there was no main effect of error type or interaction ($F < 1$). This is shown in Figure 5.3. When looking at each error type as a proportion of total errors, there was no significant effects ($F < 1$).



Unconnected sentence completion version of the Hayling Test (Burgess & Shallice, 1997). Error bars show standard error of the mean.

Figure 5.3: Number of connected (Type A) and somewhat connected (Type B) errors

<u>Summary</u>

RH patients show that in relation to SA patients, their semantic comprehension impairments are much milder (show by significantly better performance on CCTp and synonym judgement tasks). However, like SA patients, they show no frequency effects, and show some evidence of an imageability effect. There was no difference between groups on visual tasks. However, all RH patients were impaired on at least one metaphor task which used pictures. Additionally, there was a striking pattern of performance on executive control tasks. In all 5 tasks which we were able to run a comparative analysis on, there was no interaction between group and task, suggesting a similar effect of executive control impairment in both groups. There was also no group differences, suggesting the impairments are similar across patient groups.

RH patients also showed a notable impairment at the Hayling sentence completion task (finishing a sentence with an unconnected word). They were able to inhibit naming the target end to the sentence (e.g., cats see very well.... ‘at night’) but instead named a close associate or synonym of that word (e.g., cats see very well ... ‘in the evening’). Patients showed an impairment on control (e.g., Hayling sentence completion, BSRA, Trail Making, TEA) which was not matched by their semantic impairment (e.g., CCTp, synonym task).

2.Cyclical matching task: face emotions

Rationale

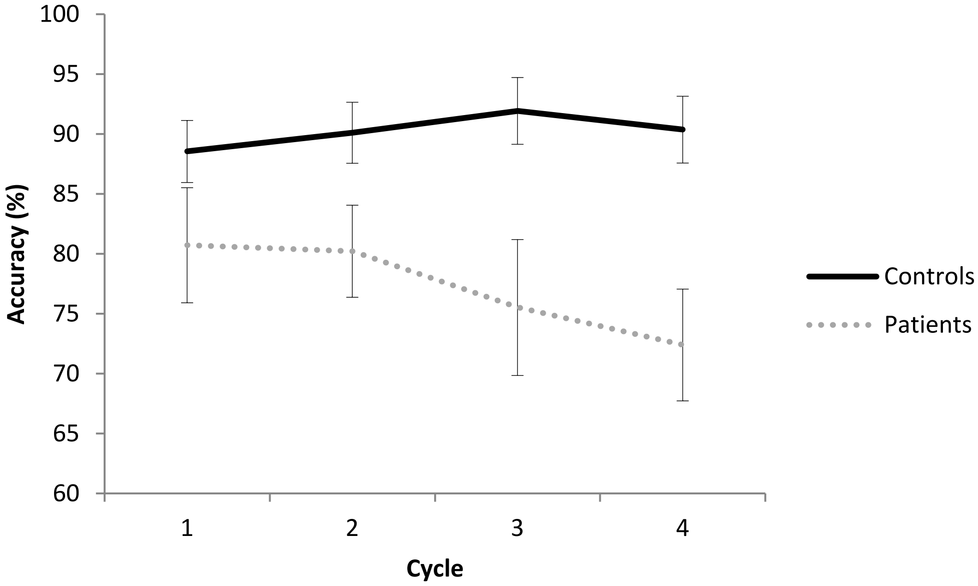
Our SA patients show a decline in accuracy, or refractory effects, after multiple presentations of the same items (Gardner, et al., 2012; Jefferies, et al., 2007). The semantic distance of the target and distractors is of particular importance (Crutch & Warrington, 2003a, 2004, 2007, 2010b), with stronger effects for closely related targets over distantly related targets (Jefferies, et al., 2007). The RH has been linked to knowledge of faces (Snowden, et al., 2004) particularly face emotions (Bowers, Blonder, Feinberg, & Heilman, 1991; Harciarek & Heilman, 2009). Additionally, test-retest correlations of face emotion recognition were weak in these patients, although it was high in healthy controls (Zgaljardic, Borod, & Sliwinski, 2002). Inconsistent performance to the same stimuli has been shown in SA patients, and is thought to be a trait of 'access' rather than storage deficits (Crutch & Warrington, 2011a; Jefferies & Lambon Ralph, 2006). This suggests that there may be reason to believe RH patients are impaired at accessing the meaning of emotions. Therefore, we tested the hypothesis that our RH patients would show a refractory effect for face emotions.

Procedure

The cyclical emotion matching task involved matching a spoken emotion to a picture of a face. The 7 emotions were: HAPPY, SAD, ANGRY, FEARFUL, SURPRISED, CONTEMPTUOUS and DISGUSTED. Faces were from the Radboud Faces Database (Langner et al., 2010). There were 8 sets, each with 4 different emotions that were probed. Each set used the same identity and orientation of face, to maximise the visual overlap between items. There were four pictures displayed, one target with three distractors. Each target was presented four times, with the target and distractors rotating across the 16 trials. The experimenter moved on the trial when patient made a response. After 10 seconds without a response, the next trial was presented. As soon as a response was made, the next trial was presented.

Results

There was a main effect of cycle: *F*(3,14) = 6.310, *p* = .006, and an interaction of cycle with group: *F*(3,14) = 8.416, *p* = .002. Additionally, there was a main effect of group: *F*(1,16) = 7.341, *p* = .015. This is shown in Figure 5.4.



Error bars show standard error of mean.

Figure 5.4: Accuracy across cycles for the refractory emotion matching task in controls and patients

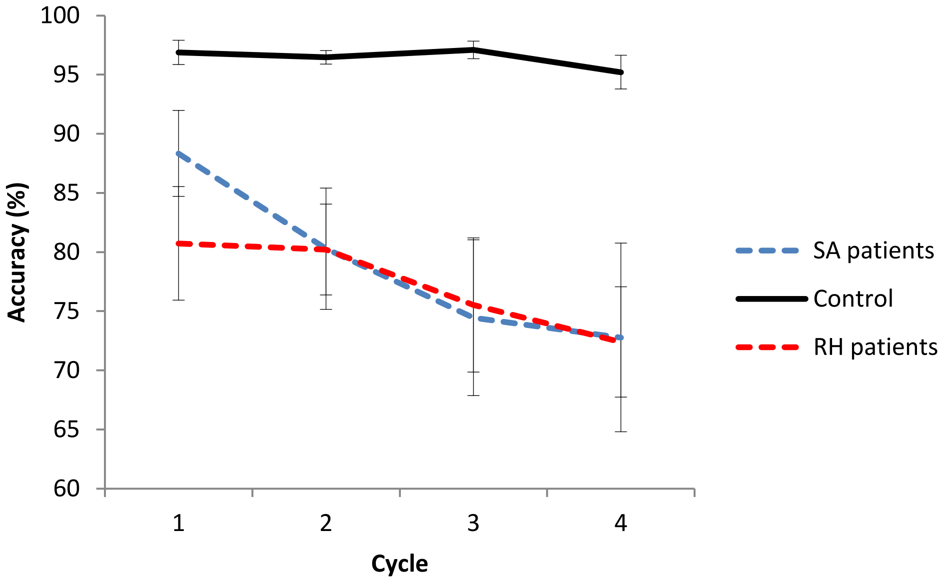
Tests of the four a priori hypotheses were conducted using Bonferroni adjusted alpha levels of .0125 per test (.05/4). Independent samples t-tests found no significant effect of group at cycle 1: *F*(1,16) = 1.492, *p* = .240, cycle 2: *F*(1,16) = 3.251, *p* = .090, but a group difference at cycle 3: *F*(1,16) = 8.582, *p* = .010, and cycle 4: *F*(1,16) = 12.484, *p* = .003. This shows patients were performing at a normal level initially, but significantly declined over cycles. In a repeated measures ANOVA for each group, there was a marginal effect of cycle for the controls: *F*(3,9) = 2.936, *p* = .092, showing their increased in accuracy over cycles. For patients, there was also an effect of cycle: *F*(3,3) = 16.533, *p* = .023, but this reflects their decline in accuracy over cycles.

Each patient was analysed individually, to see if the refractory effect was consistent across patients. Using McNemar, no patient showed significant differences across any cycle (*p* ≥ .07). The patients who showed a marginal effect of cycle, DJe, CNe and ARi, had known prefrontal damage. The PF+ group was compared to the ‘other’ group using logistic regression. This included cycle and group. No significant effect of group was found: Wald = 1.926, *p* = .165, although the effect of cycle was significant: Wald = 6.970, *p* = .008.

Consistency analysis using logistic regression found no consistent performance when using a cycle to predict another cycle in any comparison.

Comparison with SA patients

A comparison with SA patients was made, using the data from controls and LH patients from Chapter 2 (Gardner, et al., 2012), which was a simple word-picture matching task, matching an spoken word (e.g., ‘fork’) with a picture of the same item (e.g., FORK, SPOON, SPATULA, or KNIFE). This is shown in Figure 5.5. In an ANOVA comparing RH and SA patients, there was an effect of cycle: *F*(3,11) = 4.491, *p* = .027, but no interaction of cycle and group: *F*(3,11) = 1.283, *p* = .328. There was no main effect of group (*F* < 1).

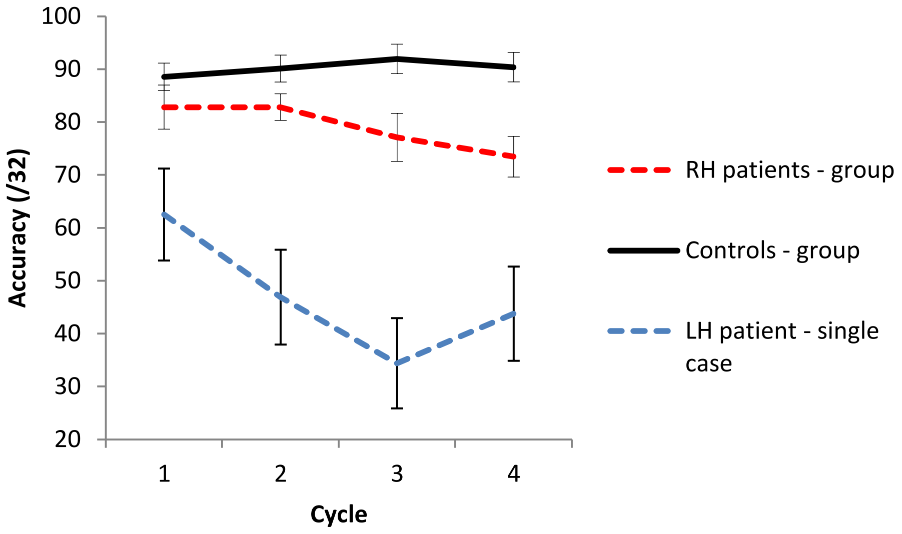


Refractory task used for SA cases (showing controls from this experiment): word-picture matching task (Experiment 1 from Chapter 2). Refractory task used for RH cases: emotion word-picture matching. Error bars show standard error of mean.

Figure 5.5: The effect of cycle on accuracy for SA patients and RH patients

Finally, we compared a single LH case with RH patients on the same task (comparing face emotion matching), to see if the refractory effects were comparable. The patient, DB, has been described before (Gardner, et al., 2012), and has an extensive LH lesion (see Chapters 2 & 4). He was chosen to perform this task because he shows refractory effects in other tasks, and the largest refractory effects have been found in the most severe cases (Gardner, et al., 2012).

Figure 5.6 shows that the single case was markedly more impaired than the RH patients, with a greater drop in accuracy across cycles. In relation to this SA patient, RH patients appear more similar to controls.



Error bars show standard error of mean.

Figure 5.6: Accuracy across cycles for controls, RH patients and a single SA case

Summary

RH patients show a similar refractory effect in this domain compared to LH patients in a simpler semantic task (although this is not significant in any individual patient). There is some evidence that this is driven by PF+ patients (as is the case with SA cases), suggesting the prefrontal cortex is particularly involved in selecting a target amongst prepotent distractors. For the first time (in our knowledge), the prefrontal right hemisphere has been shown to be involved in this cyclical task, when using items highly specific to RH processing.

3.Face emotion picture naming

Rationale

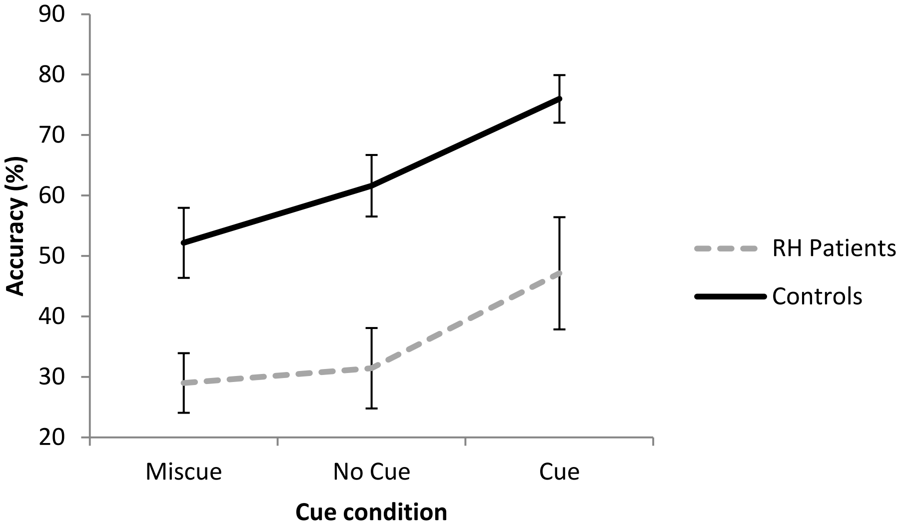
SA patients show impairments in picture naming, which is dramatically improved with phonemic cueing (e.g., /b/ for bed) and impaired by miscueing a semantically related alternative, such as /l/ for tiger (Corbett, et al., 2008; Jefferies, Patterson, et al., 2008; Soni, et al., 2009; Soni, et al., 2011). Given that a significant refractory effect was found for face emotion matching, we tested the hypothesis that picture naming of face emotions would also be impaired and affected by cues RH stroke patients.

Procedure

Pictures were selected from the Radboud Faces Database. These emotions were surprise, fear, sadness, anger and disgust. Happy was left out due to it being easily perceived in the previous refractory task, and as there is debate about whether happy emotions are represented in the RH (Nijboer & Jellema, 2012). Pictures were presented for 3 seconds, and the patients' naming response was recorded. During each presentation, there was either (i) a cue (the first phoneme of the emotion), (ii) a miscue (the first phoneme of a different emotion), or (iii) no cue (presenting a 'click' sound at the beginning of the trial). Each participant was given a list of the 5 emotions before the test, which they were allowed to refer to at any point during the task. There were 262 items, 87 in the cue and no cue condition, and 88 in the miscue condition (results were analysed as percentage correct).

Results

In an ANOVA, the effect of cue was significant: $F(2,13) = 11.331$, $p = .001$, as was the effect of group: F(1,14) = 13.346, p = .003, but the interaction was not significant: $F(2,13) = 1.122$, p = .355. This is shown in Figure 5.7. In an ANOVA comparing miscues with no cues, there was a significant effect of task: $F(1,14) = 6.845$, $p = .020$, group: $F(1,14) = 10.885$, $p = .005$, but no interaction: $F < 1$. In a comparison of cues and no cues, there was a significant effect of task: $F(1,14) = 21.226$, $p < .001$, group: F(1,14) = 33.321, $p < .001$, but no interaction: $F(1,14) = 2.382$, p .145. Finally, comparing cues with miscues, there was an effect of task: $F(1,14) = 24.406$, $p < .001$, and group: $F(1,14) = 12.171$, $p = .004$, but no interaction: $F < 1$.



Error bars show standard error of mean

Figure 5.7: Effect of cueing condition on emotion picture naming performance

Although patients were worse overall, the effect of cueing was equivalent in patients and controls. Individual ANOVAs (for patients and controls), found no significant effect of cue condition for patients: *F*(2,4) = 3.122, *p* = .152, but there was for controls: *F*(2.8) = 9.091, *p* = .009. McNemar tests were used to assess the effect of cueing in each patient (see Table 5.3). There was individual variability, with those with low scores overall not showing any significant difference between conditions.

Table 5.3: Effects of cueing on performance

	DJe	**ARi**	**CNe**	**EHo**	**FBu**	**PSm**
Cue v. miscue	**0.014***	**< .001***	0.839	0.176	0.263	**< .001***
Cue v. no cue	1	**< .001***	0.678	1	0.256	**< .001***
Miscue v. no cue	**0.01***	0.76	1	0.280	1	1
Cue	51	87	39	45	47	53
Miscue	30	44	37	34	36	25
No cue	49	48	36	44	38	23
Overall	43	60	37	41	40	34

McNemar tests showing p values. Accuracy scores are as a percentage.

Actual word errors

We analysed the proportion of word errors across each patient. These are shown in Table 5.4. Semantic errors include either (i) co-ordinate errors, e.g., a word which was given to them at the beginning (‘surprised’ for FEARFUL); (ii) associative errors, e.g., giving words which are related to the picture (‘smell’ for DISGUSTED), and (iii) novel words which were not given as one of the five options (‘determined’ for ANGRY).

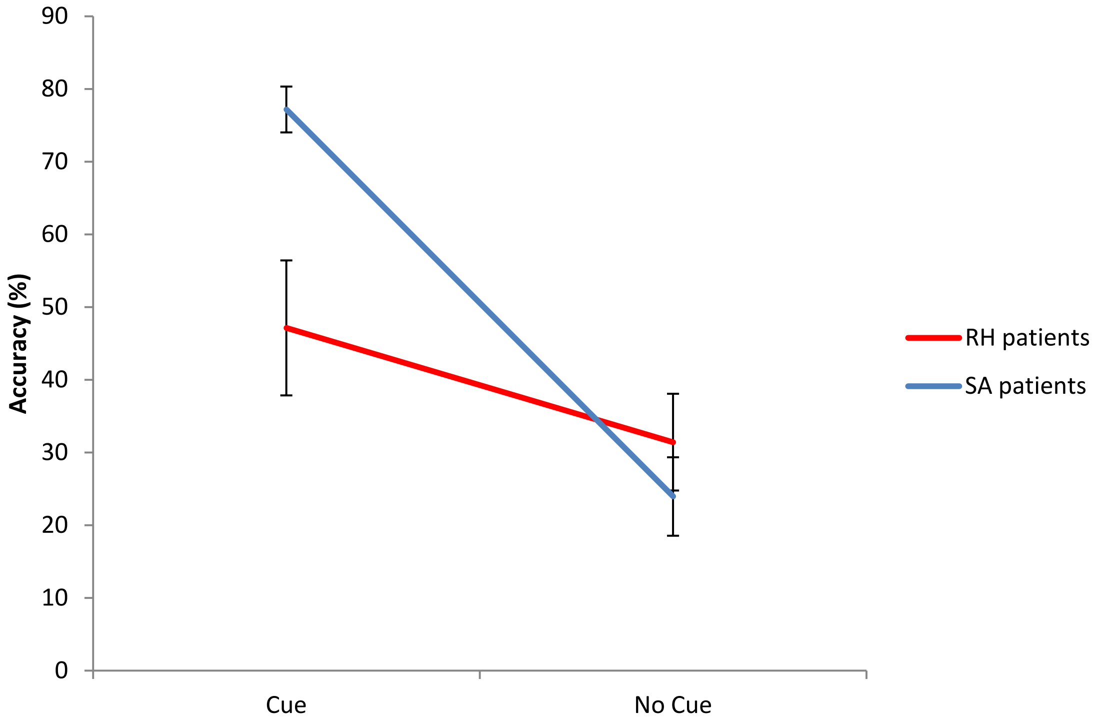
Table 5.4: Proportion of errors made in RH patients in face emotion picture naming

	DJe	**ARi**	**CNe**	**EHo**	**FBu**	**PSm**	**Average**
Perservative	34	19	8	15	23	17	19
Omission	20	49	74	26	39	13	37
Semantic	46	32	18	59	38	70	44
Semantic							
Co-ordinate	76	44	21	29	27	27	37
Novel	24	56	46	58	66	54	51
Associative	0	0	33	13	7	19	12

Errors are shown as %, with errors classified as either preservative, omission or semantic. The semantic errors were further divided into those which were co-ordinate, novel or associative errors.

Comparison to SA patients' cueing effects

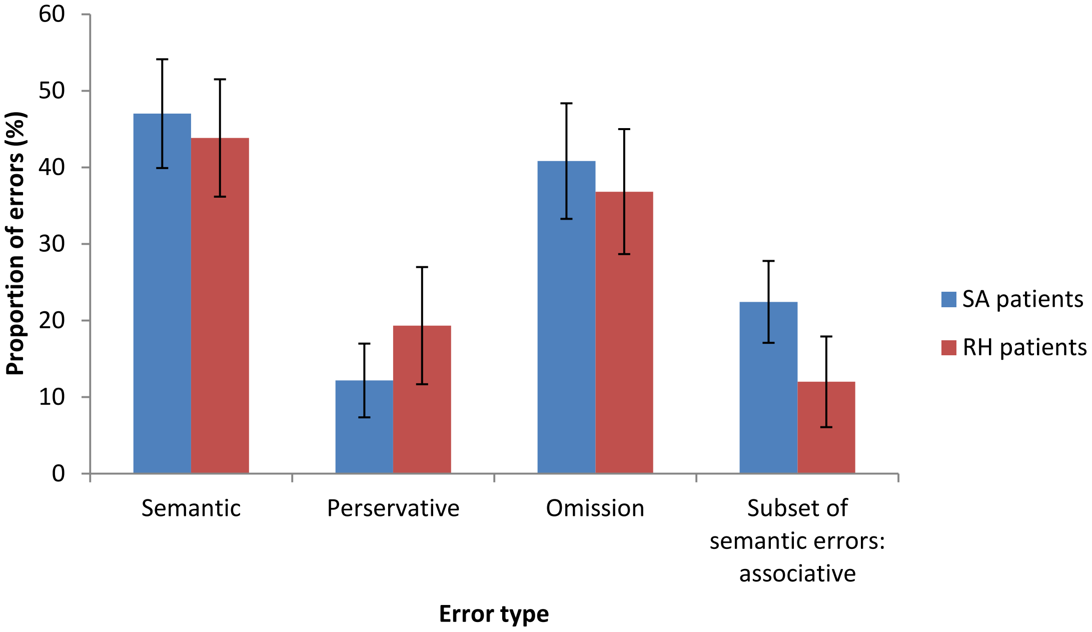
We compared our RH patients in this task to our SA patients described previously (Chapter 4) doing the Boston Naming Test (BNT; Kaplan, et al., 1983) which was run with and without a cue. This is shown in Figure 5.8. These were different tasks, so we did not run a direct comparison. However, we wanted to assess whether the direction of deficit was the same in both patient groups. In our SA patients, there was a significant improvement in performance after a cue: $t(9) = 8.757$, $p < .001$. In our RH patients, the effect was the same, although there was only marginal significance: $t(5) = 2.359$, $p = .065$.



Task used for SA patients: Boston Naming Test (BNT; Kaplan, et al., 1983, shown in Chapter 4). Task used for RH patients: face emotion picture naming. Error bars show standard error of mean.

Figure 5.8: A comparison between SA and RH patients on picture naming tasks with and without a phonemic cue.

In terms of picture naming errors, there was a trend towards more associative errors in SA patients, and more preservative errors in RH patients (shown in Figure 5.9). However, the standard deviations were large, and the group differences for each error type were not significant. Removing participants who were extreme outliers, 2 standard deviations above the mean, removed just one patient for the preservative errors (SA patient LS), which led to a significant difference in preservative errors between groups: *F*(1,17) = 8.668, *p* = .009. There were no other significant effects found using this method.



Error bars show standard error of mean.

Figure 5.9: Picture naming errors in SA and RH patients (error bars show standard error).

Summary

Patients were affected by cueing to the same extent as controls. Individual variation was large, and performance overall was low – for controls it was 68%, and RH patients 42% across all conditions. Given that both groups made significant numbers of errors even in uncued naming, it is perhaps unsurprising that some participants did not show a miscueing effect – the single phoneme might have been insufficient to strongly activate the name of the competitor emotion. In contrast, the cueing effect was strong in the basic picture naming task used with SA patients (Chapter 4), where there was a clear target word response. The empirical data is therefore insufficient to determine whether the SA cases show stronger cueing effects per se, or whether this apparent difference was a function of the tasks that the patients were tested on. In relation to picture naming errors, there was a trend towards significantly more preservation errors in RH patients, and more associative errors in SA patients. However, they both show a large number of semantic and omissions overall.

4.Social synonym matching

Rationale

Our SA patients have shown an effect of manipulating the target and distractor strength on performance – with higher performance on tasks where there is a closely related target (e.g., PRUNE – PLUM) compared to a weakly related target (e.g., PRUNE – SHRUB; Noonan et al., 2010). These authors also found that patients making a synonym judgement (e.g., HAPPY – CHEERFUL) were more impaired when there was a strong antonym distractor present (e.g., SAD; Noonan et al., 2010).

The RH involvement in emotion processing has been extended to involvement in social interpretation more generally (Semrud-Clikeman, Goldenring Fine, & Zhu, 2011). The RH has been shown to be involved in the Heider and Simmel task – consisting of 'social' and 'non-social' animations of small geometric shapes, with 'social' shapes seeming to interact and react to the other shapes' response (Ross & Olson, 2010). fMRI has found that the ability to perceive eye-gaze of other people from photos or videos is strongly lateralized to the RH (Pelphrey, Viola, & McCarthy, 2004). The 'theory of mind' network is thought to involve the temporoparietal region of the right hemisphere, and activity in this region is higher in autistic individuals comprehending social passages requiring social inferences, which authors suggest reflect increased processing demands in these patients in relation to controls (Mason, Williams, Kana, Minshew, & Just, 2008). We explored the hypothesis that meanings for social words may be impaired, and that within a task tapping linguistic social judgements, sensitivity to control demands can be assessed.

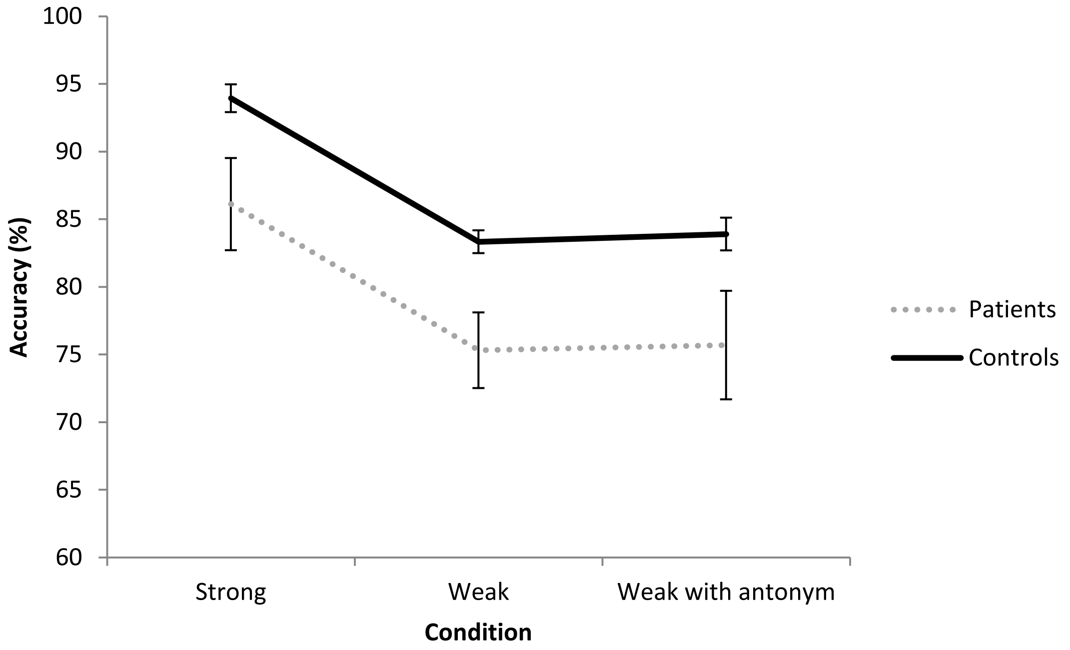
Procedure

Words were taken from Zahn et al. (2007), and the target and distractors were matched for frequency and imageability. Participants were required to match a social word (e.g., HAPPY) with a (i) a strongly related synonym (e.g., CONTENT, DUTIFUL or FIRM), (ii) a weakly related synonym (e.g., FRIENDLY, DUTIFUL or FIRM), (iii) a weakly related synonym with antonym distractor (e.g., FRIENDLY, SAD or FIRM). We predicted that the strongly-related synonym matching is a relatively automatic process, via spreading activation from the target (Collins & Loftus, 1975; Masson, 1991; Neely, 1990; Wagner, Paré-Blagoev, et al., 2001). However, weakly related matching tasks require additional executive control resources, as they do not automatically activate. The weakly related matching task was made more demanding by adding a prepotent distractor. All words were written, and trials moved on after 7 seconds if there was no response (and the next trial was presented immediately after a response). There were 48 items in each condition, with the same probe being used in all three conditions, presented at the same time as the target and two distractors.

Results

An ANOVA revealed a significant effect of condition: *F*(2,14) = 24.635, *p* < .001, and group: *F*(1,15) = 4.634, *p* = .048, but no interaction of condition with group: *F* < 1. This is shown in Figure 5.10.

.



Error bars show standard error of mean.

Figure 5.10: performance on social synonym tasks across different semantic control conditions.

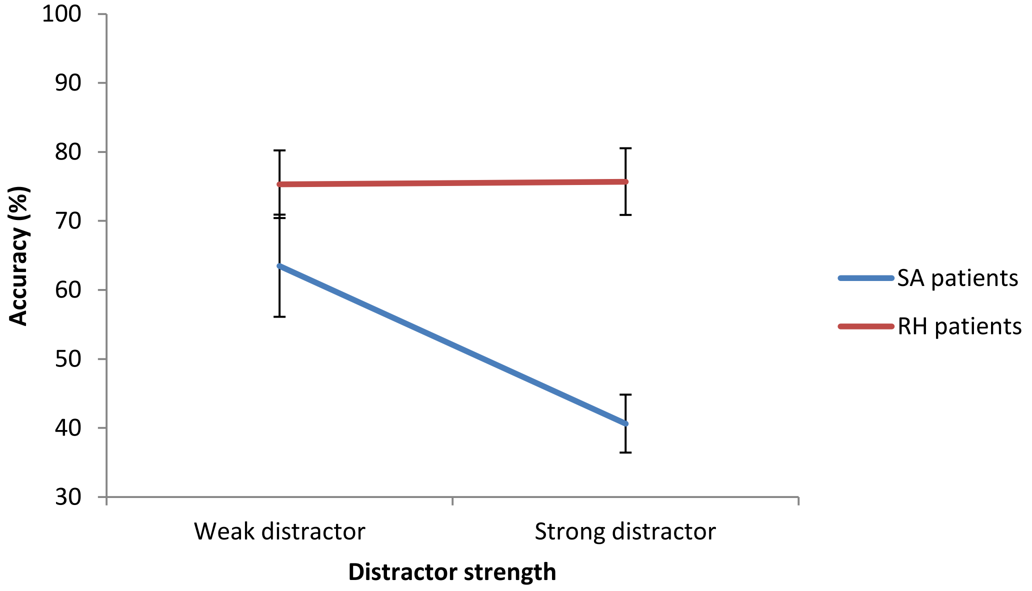
An ANOVA for each group individually revealed that the effect of condition was significant for both patients: *F*(2,4) = 75.726, *p* = .001, and controls: *F*(2,9) = 12.952, *p* = .002. McNemar tests were carried out on each patient. No significant effects were found for any patient (p ≥ .065).

Comparison to SA patients

We were able to assess whether both groups of patients show an effect of the manipulation of semantic control, but because the tasks we were comparing were different, it is not clear whether a larger effect in one group means that they show more semantic control deficits, or whether the task was more sensitive to semantic control.

Firstly, we wanted to see whether both groups showed an effect of distractor strength. The SA task was developed by Noonan et al. (2010), examining synonym matching in the presence of an antonym distractor, and run on 7 of our cohort of SA patients. This task had a demanding condition, involving matching a word such as HAPPY with a synonym CHEERFUL when presented with a strong antonym distractor e.g., SAD, and an unrelated distractor CONSCIOUS. In a less demanding condition, the distractors strength was manipulated, so that it was only weakly related to the probe (e.g., NEAT to be paired with TIDY, MESSY or LUCKY).

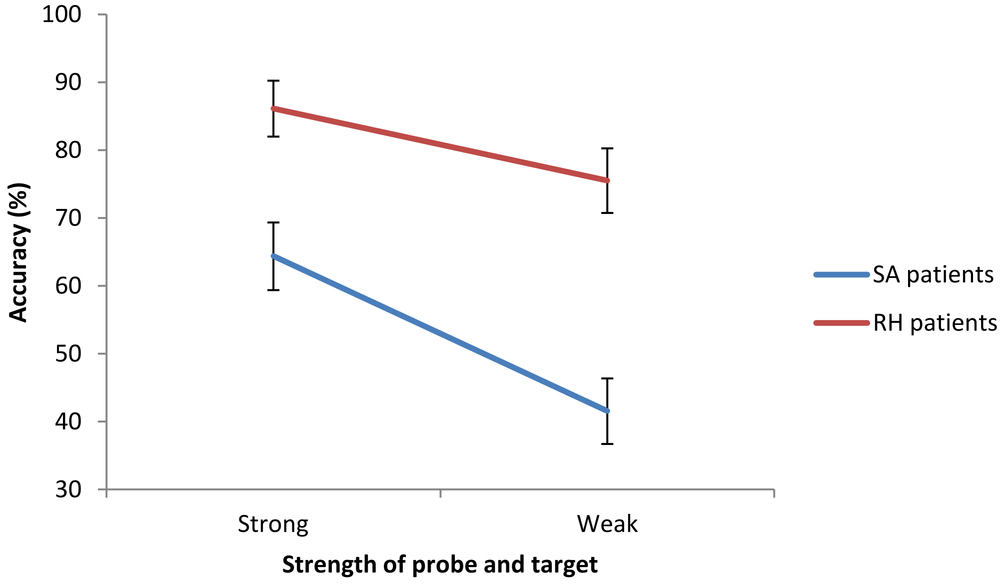
This compares with our RH task which manipulated distractor strength. In one condition, there were unrelated distractors (‘weak’), whereas in another (‘weak with antonym’), there was an antonym present. Both RH tasks used the same probe and target. The results are displayed in Figure 5.11. RH patients do not show an effect of distractor type (t < 1), whereas SA patients do: *t*(6) = 3.7, *p* < .01.



Errors bars show standard error of mean

Figure 5.11: Comparison of SA and RH patients in performance on a task with and without strong antonym distractors

A further comparison was made with SA patients comparing performance according to strength of association between the probe and target. To do this, we averaged RH performance on the ‘weak’ association tasks to have one accuracy estimate for ‘strong’ and one for ‘weak’ associations. We compared this performance to SA patients on a task which also manipulated the strength of association between the probe and target (Ambiguity Task; Noonan et al., 2010, data from 13 of our SA patients as presented in Chapter 4). This is shown in Figure 5.12. Again, the tasks were very different, and may have tapped semantic control in a different way, and been more or less demanding to the control network. SA patients show a significant effect of strength of probe and target: *t*(12) = 5.905, *p* < .001; as do RH patients: *t*(5) = 5.114, *p* = .004.



Error bars show standard error of the mean.

Figure 5.12: Comparison of SA and RH patients on tasks which manipulate the strength of association between the probe and the target

Summary

There was a significant effect of the semantic control manipulation, but for both RH patients and controls. The average score for patients, across all tasks, including the more challenging versions of the task, was 79%, suggesting patients found this set of tasks relatively easy. Additionally, in comparison with SA patients, our RH show a similar effect of strength of probe-target, but do not show an effect of strength of distractor in this task. This suggests SA patients may have a more global semantic control deficit, whereas RH patients may have specific impairments of control.

5.Metaphor task

SA patients show a strong effect of distractor strength, being more impaired when the distractors are closely related to the target, compared to when they are semantically unrelated (Jefferies, et al., 2007). Jefferies and Lambon Ralph (2006) found there were three semantic control factors which affected SA performance in an association matching task: (i) ease of determining the relevant semantic relationship, (ii) co-occurence of the probe and target, and (iii) ease of rejecting distractors. These factors affected SA patients' performance far more than SD patients who did not have semantic control deficits (see also Chapter 4). We therefore used this paradigm (related vs. unrelated distractors) to test the deficits of metaphoric knowledge in our RH patients.

There is evidence that the RH plays a role in language tasks which involve metaphors (Anaki, et al., 1998; Faust & Mashal, 2007; Pobric, et al., 2008), a theory which stems from RH lesion patients' literal interpretations of metaphors (Winner & Gardner, 1977). There is much debate about whether this is true, particularly given the mixed fMRI data, where some researchers suggest the RH is either less involved than the LH, being involved as an addition to the LH because of the demands of the task (Lee & Dapretto, 2006; Rapp, et al., 2012; Stringaris, et al., 2006). However, studies using a split visual field have found presenting metaphors for comprehension to the 'left hemisphere' compared with the 'right hemisphere' led to an increased reaction time for comprehension (Anaki, et al., 1998; Faust & Mashal, 2007; Faust & Weisper, 2000; Schmidt, et al., 2007). We explored the hypothesis that deficits found for metaphor tasks in our RH sample were related to the semantic control demands of these tasks.

Procedure

Participants were asked to match word pairs (taken from Pobric, et al., 2008) according to either their literal meanings or using conventional metaphors. The initial word was presented as a probe, and the target word presented underneath with three distractors. The distractors were either related or unrelated to the target. Distractors across conditions were matched to the target for frequency and imageability, and across tasks (metaphor and literal pairs) for frequency and imageability.

For example, in the conventional metaphors task, BAD was to be paired with EGG, MILK, BUTTER, or MEAT in the related condition; and BAD with EGG, POT, LIPS, or OWL in the unrelated condition. In the literal task, the word BAD with BOY, INDIVIDUAL, MALE, or GENT in the related condition, and BAD with BOY, FUNDING, GRAIN or REEF in the unrelated condition.

Results

An 2 x 2 x 2 omnibus ANOVA including distractor type (related or unrelated), task (literal or metaphoric words), and group revealed a main effect of distractor: $F(1,16) = 63.844$, $p < .001$, and group: $F(1,16) = 7.916$, $p = .012$. The effect of task (either literal or metaphoric) approached significance: $F(1,16) = 4.327$, $p = .054$. However, the interactions were non-significant, both for distractor and group: $F(1,16) = 1.303$, $p = .270$, and word type and group: $F < 1$. The three-way interaction was also non-significant: $F < 1$. The data is shown in Table 5.5. This indicates that patients were impaired at both the literal and metaphoric word task in relation to controls.

An ANOVA for metaphoric word pairs included distractor type (related or unrelated) and group, revealed a main effect of distractor type: $F(1,16) = 24.968$, $p < .001$, and a main effect of group: $F(1,16) = 5.869$, $p = .028$, but no interaction: $F(1,16) = 1.198$, $p = .290$. Both groups were more accurate with unrelated distractors. For literal word pairs, there was also a main effect of distractor type: $F(1,16) = 30.577$, $p < .001$, and group: $F(1,16) = 7.463$, $p = .015$, but no interaction: $F < 1$.

Table 5.5: Accuracy across different distractor types and word pairs

	Metaphors – unrelated distractors	Metaphors – related distractors	Literal pairs – unrelated distractors	Literal pairs – related distractors
Controls	91.1 (4.1)	86.0 (7.4)	97.3 (2.4)	91.0 (5.2)
Patients	85.5 (7.5)	77.7 (6.3)	92.3 (4.0)	85.1 (7.1)

Mean scores (and standard deviation) shown as a percentage.

An ANOVA on the patient data found a significant overall effect of distractor: $F(1,5) = 34.091$, $p = .002$, but no main effect of word type: $F(1,5) = 3.073$, $p = .140$, or interaction: *F* < 1. This reflected higher performance with unrelated distractors across both metaphors and literal pairs, with no significant difference between these two tasks. This pattern was identical for controls, who showed a main effect of distractors: *F*(1,11) = 33.904, *p* < .001, but not of word type: *F*(1,11) = 1.288, *p* = .281, or an interaction: *F* < 1. When using Bonferroni-corrected t-tests to assess group differences per task, there were no significant differences apart from the literal word-pairs with unrelated distractors: t(16) = 3.350, p = .016. Indeed, McNemar analyses (Table 5.6), found few significant effects in individual patients. This may be because all patients performed at a high level, with the average score being 86% across all tasks (percentage accuracy also shown in Table 5.6).

Table 5.6: Individual effects of condition

	CNe	**DJe**	**ARi**	**EHo**	**PSm**	**FBu**	**Group average**
Metaphors – unrelated vs. related distractors	.057	.581	.180	.078	.824	**.035***	
Literal – unrelated vs. related distractors	**.035***	.063	1	.424	.078	1	
Metaphors unrelated vs. literal unrelated distractors	0.774	.021	1	.180	.078	.388	
Metaphors related vs. literal related distractors	1	.238	.344	.054	.839	.359	
Metaphors related vs. literal unrelated	**.031***	**.003***	.344	**.003***	.167	.359	
Metaphors unrelated vs. literal related	.167	.607	1	.832	1	.388	
Metaphors – unrelated	90	87	96	82	75	93	87.2
Metaphors – related	78	82	88	69	78	79	79.0
Literal – unrelated	92	98	95	91	89	88	92.2
Literal - related	78	90	94	85	75	88	85.0

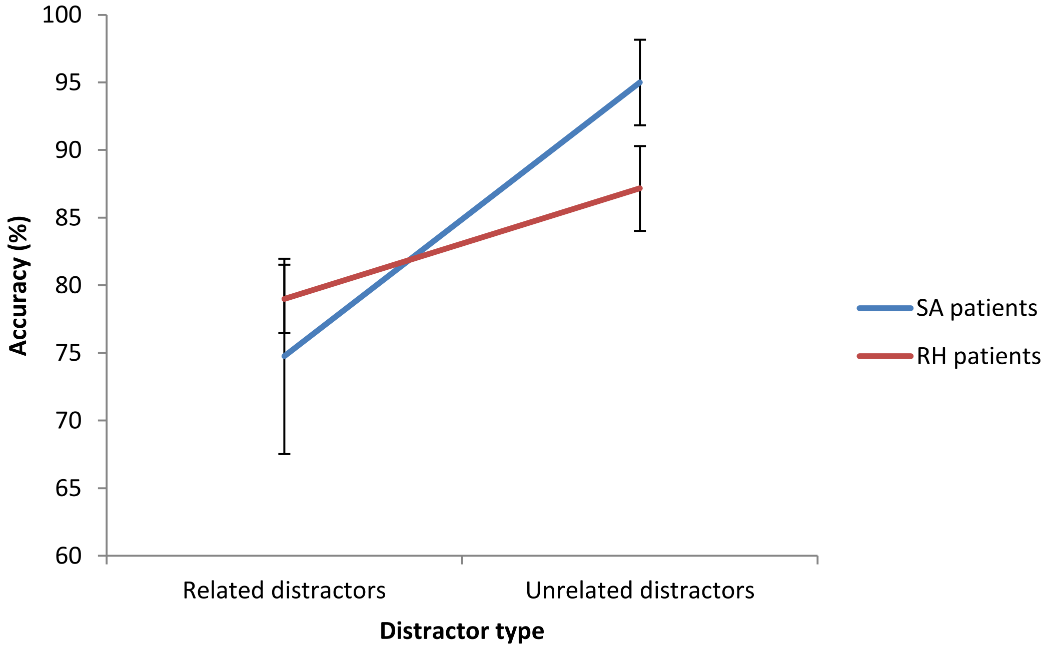
Table shows p values from McNemar tests. Scores on each task are shown as a percentage.

Comparison with SA patients

As stated previously, we were cautious about comparing our RH data to SA data, as the two groups did not do the same task. Nonetheless, we were interested to see whether both groups would show some effect of semantic control manipulation of distractor type, particularly as there were discrepancies between the groups on the Social Synonym Task (with RH patients not showing an effect of distractor manipulations).

In our RH task, there were distractors which were related and unrelated to the target. We compared our results from the metaphor word matching task with a cohort of 8 of the SA patients presented in Chapter 4. The SA patients had also performed a task which manipulated the distractor strength, published by Jefferies et al. (2007). This was a word-picture matching task, differing from our metaphor task in that there were five picture distractors. Nonetheless, both groups differed from the controls on these tasks, suggesting an impairment.

As is evident from Figure 5.13, both groups show the same direction of effect when the distractors were manipulated. SA and RH patients were better at correctly selecting the target among unrelated distractors. This is significant for SA patients: *t*(7) = 17.7, *p* = .004, and RH patients: *t*(5) = 3.024, *p* = .029.



Task used for SA patients: word-picture matching (Jefferies et al., 2007). Task used for RH patients: metaphor word-pair matching. Error bars show standard error of mean.

Figure 5.13: The effect of distractor type on performance of SA and RH patients

Summary

Patients were not poorer at metaphors comprehension in relation to literal pairs – a pattern they shared with controls. Both groups were affected by the distractor type, with lower scores in related distractor conditions. The level of task difficulty may have negated any significant group by task interactions between RH patients and controls, with each patient performing at a high level across all conditions. Additionally, RH patients may be less impaired at word tasks overall. Words are significantly easier for these patients in relation to pictures in the metaphor tasks of the Right Hemisphere Language Battery, which may have reduced the effects of semantic control manipulations.

6.Summation task

To manipulate semantic control demands, we used a technique that has been successful with SA patients: phonemic cueing. From the assumption that SA patients retain the appropriate meanings, but have difficulty constraining their semantically-driven behaviour, and we would expect to see benefit from external constraints such as the correct initial phoneme (Corbett, et al., 2008; Jefferies, Patterson, et al., 2008). Activation spreads to distractors (Dell, 1989; Dell & O'Seaghdha, 1992; Dell, et al., 1997), and so other semantic co-ordinates and associations will equally be activated, leading to worse performance after miscueing of semantically related words, e.g., /w/ for ‘bath’ (Soni, et al., 2009; Soni, et al., 2011).

In this final task, we explored the *coarse semantic coding hypothesis* in more detail (Jung-Beeman, 2005). This theory suggests the LH focuses on dominant, literal or contextually relevant meanings, and the RH activates a broader semantic field, which sustains the meaning of a wide range of distant associates. Many visual field experiments have confirmed the RH is predisposed to ‘coarse coding’, showing faster processing of distantly related words in comparison to the LH (Anaki, et al., 1998; Faust & Mashal, 2007; Mashal & Faust, 2009). In particular, Beeman et al. (1994) suggests that the RH is required to group together disparate words to create an overarching meaning (e.g., EYES – CLOSED – NIGHT → SLEEP; or FOOT – CRY – GLASS → CUT). Each word is only distantly related to the target, but together they accumulate support for the meaning of the target word.

In this final task, we tested the RH ability to comprehend written words in relation to the coarse semantic coding hypothesis, and in conditions where semantic control demands are manipulated.

Procedure

We tested this hypothesis in a 2 by 2 design, using stimuli from Beeman et al. (1994). Participants were asked to pick a target word amongst distractors. The probe was either (i) three weak associates of the target, or (ii) one strong associate. This uses a similar method to Beeman et al., who judged the priming effects of weak associates (e.g., SUBWAY – NOISE – BUILDING → CITY) compared to a single strong probe with two unrelated distractors (e.g., WHETHER – TOWN – NONE → CITY).

The probe word/s were presented one at a time (for 1 second), and then the target and 3 distractors appeared. These were presented for an unlimited time until a response was made. The distractors were either (iii) related to the target or (iv) related to the probe. This is shown in Table 5.7. Distractors related to the probes were related to each probe word, but not the summed meaning of all three words together. Distractors related to the target were synonyms of the target word. The target was the same across conditions, with distractors matched to the target for frequency and imageability.

Table 5.7: Distractors in the summation task

Condition	**Probe(s)**	**Target**	**a. Distracters related to each probe**	**b. Distractors related to target**
1. Weak Associates	Cat	Scratch	Whiskers	Scrape
	Attacks		Hit	Rub
	Paw		Foot	Scar
2. Strong associates	Itch	Scratch	Whiskers	Scrape
			Hit	Rub
			Foot	Scar

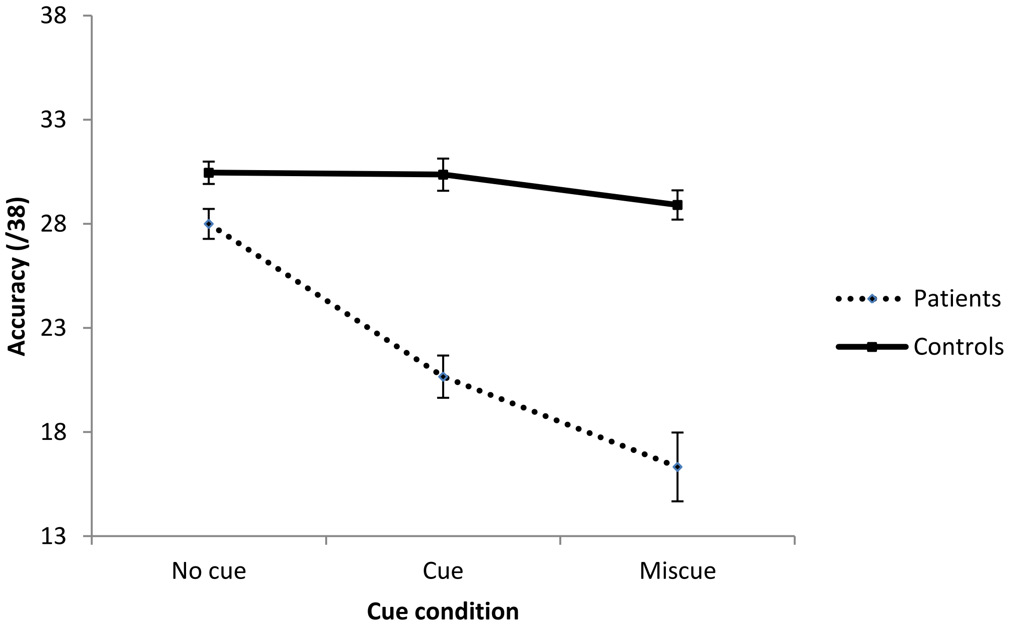
Additionally, for the weak associates with distractors related to the target (1b in Table 5.7), two further conditions were added. This included (v) semantic cueing and (vi) semantic miscueing of the probes. Examples are shown in Table 5.8. ‘Cues’ were related to the correct association between the probe and the target (e.g., AGGRESSIVE to link CAT with SCRATCH). Cue words were chosen that were not strongly related to either the probe or target (≤ 2% of people respond to the cue with this word), according to the Edinburgh Associative Thesaurus (EAT; Kiss, et al., 1973). Instead they were chosen to cue the correct semantic context of the word – by relating the two words together. The miscue was created to produce the opposite effect – by cueing the semantic context of the probe word which is irrelevant for comprehending the target.

Table 5.8: Example stimuli from the summation task

Condition	**Probe(s)**	**Cue words**	**Target**	**Distracters related to the target**
Weak Associates-cued	Cat Attacks Paw	Aggressive Cut Pad	Scratch	Scrape Rub Scar
Weak Associates-miscued	Cat Attacks Paw	Kitten Military Fur	Scratch	Scrape Rub Scar

Results

An ANOVA on cue condition (cue, miscue, or no cue), and group, found a significant effect of cue: *F*(2,14) = 12.096, *p* = .001, and a significant cue by group interaction: *F*(2,14) = 7.064, *p* = .008, and a significant effect of group: *F*(1,15) = 16.987, *p* = .001. This is shown in Figure 5.14. Separate ANOVAs were run to assess the interaction of the two cue conditions with group. An ANOVA for cued and miscued tasks revealed a significant main effect of condition: *F*(1,15) = 15.243, *p* = .037; group: *F*(1,15) = 19.412, *p* = .001, but no interaction: *F*(1,15) = 1.297, *p* = .273. For cued and uncued, there was a significant effect of condition: *F*(1,16) = 7.152, *p* = .017, and group: *F*(1,16) = 10.599, *p* = .005; and an interaction: *F*(1,16) = 6.834, *p* = .019. This reflects patients impaired performance in the cue condition in comparison to the no cue condition. Finally, in a comparison of miscue with no cue, there was an effect of condition: *F*(1,15) = 25.667, *p* < .001, group: *F*(1,15) = 12.297, *p* = .003, and an interaction: *F*(1,15) = 15.062, *p* = .001. This again reflects patients' impaired performance on the miscue condition in relation to the uncued condition. Patients were impaired with any added words – either cues or miscues – in relation to no cues. This pattern of results suggests that patients were distracted by any additional meanings, particularly those which are not relevant to the task.



Error bars show standard error of the mean.

Figure 5.14: Effect of cue condition in the summation task on the two groups

A 2 x 2 x 2 ANOVA on all the uncued conditions was run (data shown in Table 5.9). This examined group, distractor type (related to target or probe), and strength of association (weak or strong). There was a significant effect of strength of association: *F*(1,15) = 44.747, *p* < .001, distractor type: *F*(1,15) = 4.987, *p* = .041, and group: *F*(1,15) = 9.406, *p* = .008. Strength of association interacted with group: *F*(1,15) = 6.443, *p* = .023, as did distractor type and group: *F*(1,15) = 9.349, *p* = .008, with performance on distractors related to the probe significantly lower than distractors related to the target in the patient group, and performance on weak associates worse than strong associates in this group. Strength of association and distractor type interacted: *F*(1,15) = 18.673, *p* = .001, and there was a three-way interaction: *F*(1,15) = 4.838, *p* = .044. This reflects patients' impaired performance for weak associates with distractors related to the probe, a difference which is not replicated in the strong association task, or with controls. In this task, distractors related to the target could actually help participants, cueing them to the weak association being probed.

Table 5.9: Data from the summation task

Association strength	**Distractors**	**Patients**	**Controls**
Strong	Related to the target	31.3 (2.9)	32.6 (2.7)
	Related to the probe	32.0 (1.4)	34.7 (1.5)
Weak	Related to the target	28.0 (3.5)	30.0 (3.7)
	Related to the probe	19.2 (9.0)	29.5 (3.6)

Means show accuracy (/38) with standard deviation

Indeed, for weak associations, distractors related to the target actually produced a higher response – particularly for patients. There was a significant effect of distractor: *F*(1,15) = 13.897, *p* =.002, group: *F*(1,15) = 9.162, *p* = .008, and an interaction: *F*(1,15) = 9.194, *p* = .008. This may be because for weak associations, the distractors related to the target may guide selection towards the correct interpretation of the items, as they are not too different from the target itself. Distractors which are related to the probe items individually led to performance on a par with the miscue condition for patients, suggesting patients get easily distracted by semantic meanings which are not directly related to the task – whether these are presented as distractors or miscues. Indeed, in the strong associates task, there was marginally worse performance when the distractors were related to the target: *F*(1,15) = 3.721, *p* = .073. Although there was higher performance in controls: *F*(1,15) = 4.979, *p* = .041, these variables did not interact: *F*(1,15) = 1.053, *p* = .321.

PF+ vs. 'other'

A preliminary analysis was run to compare subgroups of RH patients. We compared those with known prefrontal lesions with those whose lesion was either unknown, or was more posterior. Of course, this means those in the ‘other’ group may have had prefrontal lesions too, which is why the analysis should not be treated as anything more than preliminary.

A logistic regression was used to compare those with a known prefrontal lesion (ARi, CNe and DJe) with the ‘other’ patients without known prefrontal damage (FBu, EHo, and PSm). Across all tasks, when patient ID, task, group and task by group were entered into the analysis, there was a main effect of group (Wald = 6.302, *p* = .012), patient ID (Wald = 69.468, *p* < .001), and task (Wald = 64.597, *p* < .001), but no interaction (Wald = 9.764, *p* = .082). We analysed the main effect of group for each subtask (in a logistic regression model including patient ID and group). For the weak probes with distractors related to the probe, the group effect was significant (Wald = 6.215, p = .013). For the other tasks, this was non-significant.

A logistic regression with patient data from the cue and miscue elements of the summation task was run (with predictor variables patient ID, task, group, and task by group interaction). This found a significant predictive value of task: Wald = 11.084, *p* = .001, and group x task interaction: Wald = 5.018, *p* = .025. This shows that performance by PF+ patients was more impaired on the cue task, but that performance fell for both groups for the miscue task. For the PF+ group, there is very little difference between the cue and miscue condition, suggesting that for this group, additional words are equally distracting. Conversely, the ‘other’ group only showed significant impairments in the miscue task.

Individual McNemar analyses were carried out (Table 5.10). This shows the variation in accuracy between patients on each task, particularly in relation to cueing condition. Three patients showed the predicted pattern, with lower performance in the miscue condition in relation to the other conditions: FBu, EHo and DJe. CNe was impaired with the presence of either a cue or miscue in relation to no cue. ARi showed significantly higher performance in the miscued than cued condition, an unexpected finding. PSm showed a milder effect of condition throughout (noted by the lack of significant differences in all comparisons).

Table 5.10: McNemar tests of each patient's performance on the summation task

	DJe	ARi	CNe	PSm	EHo	FBu
Cued v. miscued	**.049***	**.007***	.629	.180	**.039***	**.013***
Cued v. no cue	.523	**.003***	**.002***	.791	.481	.289
Miscue v. no cue	**.002***	.549	**.001***	.096	**.017***	**.001***
Weak v. strong (related distractors)	.065	1	.581	.146	.118	.388
Weak v. strong (unrelated distractors)	**.001***	.125	**.001***	.267	**.001***	.180
Weak related v. weak unrelated distractors	**.004***	.388	**.001***	.804	**.012***	.581
Strong related v. strong unrelated distractors	.688	.625	1	.508	.581	1
Cued	61	53	32	68	50	63
Miscued	37	82	24	53	29	34
No cue (weak related)	71	89	74	74	61	74
Weak (unrelated)	39	79	21	68	29	66
Strong (related)	89	87	82	89	79	84
Strong (unrelated)	84	92	79	82	71	82

Significance values (p) are from McNemar tests. Scores for each task displayed as a percentage.

Consistency

We used logistic regression to predict the performance on one task based on another. These tasks use the same items. It has been found (Chapter 4) that SA cases can show inconsistency even for the same items, when the demands of the task change but are consistent when the demands don't change (e.g., during the same task presented in different modalities). Our RH data is shown in Table 5.11. Unlike SA cases, there was high consistency between tasks, with performance on one task predicting performance on another - with the exception of the lowest demand condition – strongly associated words with unrelated distractors.

Table 5.11: Logistic regression showing the predictive value of performance on each task

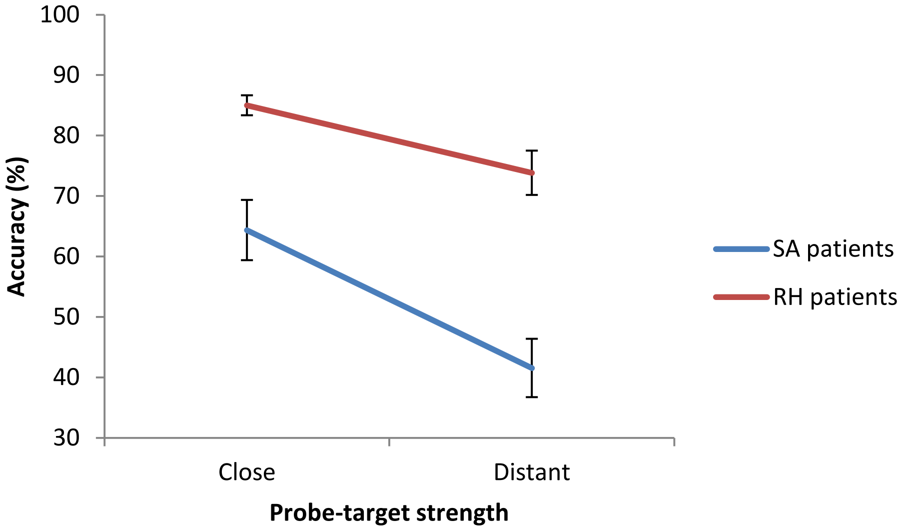
	Strong Related to target	Strong related to probes	Weak Related to target	Weak Related to probes	Cued related to target	Miscued related to target
Strong Related to target		W = 9.398, p = .002		W = 4.496, p = .034	W = 3.953, p = .047	W = 4.583, p = .032
Strong related to probe	W = 9.398, p = .002					
Weak Related to target				W = 4.699, p = .030		W = 4.186, p = .041
Weak Related to probe	W = 4.496, p = .034		W = 4.699, p = .030		W = 16.449, p < .001	W = 31.351, p < .001
Cued related to target	W = 3.953, p = .047			W = 16.449, p < .001		W = 9.708, p = .002
Miscued related to target	W = 4.583, p = .032		W = 4.186, p = .041	W = 31.351, p < .001	W = 9.708, p = .002	

Each row presents a predictor variable, with the predictive variable as a column. Wald (W) and p values are presented for significant results. Cells coloured in orange have no significant predictive values.

Comparison with SA patients

This summation task was quite different to ones tested in SA patients in many respects. However, one dimension which manipulates semantic control demands – probe-target strength – could be compared, albeit in a preliminary way.

SA patients performed an Ambiguity Task (Chapter 4), where the strength between the probe and target was manipulated, with one strongly related condition, and one weakly related condition. Similarly, in this task, we had one strong single probe versus the multiple weak probes on the summation task. Figure 5.15 shows that both SA and RH patients are worse at a task where the probe and target are distantly related, in comparison to a strong probe-target association. This is similar to the findings of the Social Synonym task presented above, and is significant for SA patients: $t(12) = 5.905$, $p < .001$, and RH patients: $t(5) = 3.953$, $p = .011$.



Task for SA patients: Ambiguity task (Noonan et al., 2010; Chapter 4). Task for RH patients: summation task (close = single strong associate, distant = 3 weak associates). Error bars show standard error from mean.

Figure 5.15: The effect of probe-target strength on performance comparing SA with RH performance.

Summary

RH patients behaved differently to controls on this task. Firstly, they were negatively affected by either a cue or miscue in relation to no cue, whereas controls performed at the same level for all three conditions. RH patients showed a significant drop in performance for distractors related to the probes in the weak association task in comparison to distractors related to the target (with controls maintaining their performance throughout). PF+ patients showed the effect of ‘distraction’ more than the ‘other’ group – most notable with distractors related to the probes. These results suggest a role for the RH in inhibition, with our patients showing reduced ability to orient their attention towards a correct semantic context when other distracting meanings were presented. Additionally, RH patients showed a similar direction of response to SA patients, who were both worse at distantly related probes and targets in relation to a strong probe-target relationship.

Overall summary

We manipulated semantic control demands in five semantic tasks using the following methods: changing the distractors to be either related or unrelated to the target (SA patients show impairments with related distractors), adding a cue or miscue (SA patients show improvements with a phonemic cue, and are impaired with a miscue), changing the association strength between the probe and target (SA patients are better at tasks where there is a strong association between the probe and target), and cyclical presentations (SA patients show a refractory effect when items are presented repeatedly). We also assessed RH patients on a battery of semantic, executive and language tasks.

Firstly, we found that although semantic performance was high, executive impairments were not significantly different from our SA patients. In our experimental tasks, we found evidence of a semantic control impairment in comparison to controls, on: the summation task and the face emotion refractory task. Both these tasks require inhibition (in the summation task, participants had to inhibit distractors as well as miscues, and in the face emotion refractory task, participants had to inhibit a previously relevant item). They also require configural processing (the summation task involves grouping distantly related words to a single meaning, and the face emotion task requires linking multiple facial features to produce an overarching emotion). There are at least three possible ways to interpret the data: (1) the role of the RH in semantic control is relatively weak, (2) the role of the RH in semantic control is specific to certain aspects of control or certain processes, (3) some of our tasks lacked the sensitivity to determine the role of the RH. The significant effects of control manipulation on two tasks suggest that the RH has some part to play in semantic control, and evidence for this will be reviewed in the discussion.

Discussion

Semantic processing is thought to recruit both hemispheres, in initial sensory processing (Catani & Ffytche, 2005; Poeppel, 2001), representation (Lambon Ralph, et al., 2001; Lambon Ralph, Pobric, & Jefferies, 2009b; Snowden, et al., 2004) and control (Badre, et al., 2005; Noonan, et al., submitted; Snyder, et al., 2011; Thompson-Schill, et al., 1997; Wagner, Paré-Blagoev, et al., 2001). However, studies into semantic control have so far exclusively considered patients with left hemisphere brain damage (SA patients; e.g., Jefferies & Lambon Ralph, 2006, Jefferies et al., 2007, Noonan et al., 2010). The aim of this study was to analyse the effect of a RH lesion on semantic control. We examined a range of phenomena previously shown in SA cases, including cueing, inconsistency, sensitivity to distractor strength, manipulations of probe-target strength, and cylical presentations. There were three potential patterns of performance that these patients were hypothesised to show: (1) a deficit to the same degree as SA patients, but with semantic material processed and represented in the RH, (2) a weaker control deficit, with only subtle deficits – given that data suggests a smaller peak of activation in the RH for semantic control (and representation), (3) or no control impairments in relation to controls – suggesting the RH is an 'overflow' hemisphere for semantics, and although it is used in the healthy population, is not necessary for semantic control (but see TMS studies, e.g., Pobric, et al., 2010a; Pobric, et al., 2008).

Overall, our evidence suggests that RH patients have deficits which are qualitatively similar to our SA patients. This is unsurprising, given that bilateral processes are thought to be involved in semantic control (Noonan, et al., submitted). Nonetheless, our evidence does not negate the theories which specify a specific role for the RH in certain processes (e.g., inhibitory or configural), as RH patients were impaired on tasks which have these demands. It is likely that there are subtle specialisations between the hemispheres, leading to semantic control effects which may be stronger in certain tasks than others.

We found some evidence that RH patients were impaired to similar level as our SA patients. This was most notable in our comparison of executive control tasks, where the same tasks were performed at an equivalent level in both patient groups, even though the SA cases showed more substantial deficits on simple semantic tasks. In fact, our RH patients showed worse performance on the Hayling sentence completion task, when asked to finish a sentence with an unconnected word. There was also evidence that SA patients show a similar degree of refractoriness to our RH patients in a cyclical task, but only when comparing two different tasks using materials which each group found difficult.

There was evidence that RH patients showed impairments which were in the same direction as our SA cases, even if the tasks we were comparing were different. We found evidence that our RH patients shown an effect of probe-target strength, in both the summation task and the social synonyms task. There was a negative effect of miscueing for our RH patients in both the face emotion naming and summation task. The effect of cueing led to higher performance than miscueing in both tasks, but did not lead to higher performance than no cue in the summation task. There was an effect of relatedness of the distractor in some, but not all tasks – for the summation task, distractors relating to the probe impaired performance, and for the metaphor task, performance was worse with related distractors. However, for the social synonyms task, this pattern was not found.

The effects which semantic control manipulations have on the patients gives the first evidence that RH patients show a semantic control deficit. The RH has been shown to reliably activate during semantic control tasks (Noonan, et al., submitted), and the domain-general control network is bilateral (Duncan, 2010). Therefore, the RH appears to play a part in control beyond inhibition. However, our RH patients did show deficits for inhibitory tasks, supporting the notion that this region is associated with inhibitory processing (Aron, et al., 2004; Konishi, et al., 1999).

However, it was noted that RH patients show a weak semantic control deficit in relation to controls. This could be related to the tasks used in comparisons – which, although they shared similar semantic control manipulations, may have been more or less sensitive to control. Often, we were unable to compare the same task in the two groups (our SA patients would have been at floor on the majority of these tasks). For example, the face emotion picture naming may have found less of an effect of cueing because of the different stimuli used (in the SA case, the picture had a single possible response, e.g., ‘chair’, so cues would be more helpful. In our RH patients, the picture had several potential responses, e.g., ‘sad’, ‘unhappy’, ‘upset’, ‘miserable’, ‘sorrow’, ‘gloomy’, 'tearful', 'mournful', 'dejected', so a cue of /s/ would be less helpful). Additionally, a phonemic cue may not have been very helpful, given uncued errors were frequent. In terms of relatedness of distractors, both the probe and target were related to the distractor in the SA task which involved matching a spoken word (e.g., 'chair') to a picture presented among distractors (e.g., CHAIR, TABLE, BED, or BOOKCASE). In the metaphor task, this was not the case (e.g., 'politican' with PLATFORM, STAGE, CHAIR, or FLOOR). In the metaphor task, the distractors are related to each other and the target, but not the probe (e.g., FLOOR and POLITICIAN are unrelated). Additionally, in the social synonyms task, the effect of an antonym distractor may have been weakened by not all the stimuli having a prominent 'antonym' (e.g., RESPONSIBLE-FOOLISH) which may have meant the antonym was not as distracting as those used in the Noonan et al. (2010) task, which used non-social as well as social synonym-antonym pairs. The effect of strength of probe-target association was weaker in RH patients, possibly because it was less easy to find a 'weak' synonym for a social word (e.g., strong: AGGRESSIVE-ANGRY; weak: AGGRESSIVE-CRUEL), as in both conditions, the connection between the words is relatively easy. In the comparison task, SA patients had the same word probe with one dominant and one subordinate meaning (e.g., strong: PLANT-VEGETABLE, weak: PLANT-FACTORY).

In relation to controls, it was only two tasks – the summation task and refractory task – where RH patients showed a significant effect of semantic control manipulations and controls did not. On these tasks, RH patients and controls performance was not significantly different with low semantic control demands (e.g., on the first cycle of the refractory task, and in the summation task with strong associates), but performance became impaired with the same items presented under high semantic control conditions.

As predicted by some researchers (Aron, et al., 2004; Garavan, et al., 1999), our RH patients show impairments on tasks which require inhibition. For example, they show refractory effects (Experiment 2), which requires inhibiting previously relevant distractors in order to correctly select the target. In the summation task (Experiment 6), participants show *worse* performance with cues. This may be because cues activate extra semantic associations which are unnecessary for the task. However, there are some tasks where patients do not show control effects where inhibitory processes are required (such as the social synonym judgement task, involving inhibiting an antonym distractor, or the picture naming task, where RH patients had the same level of accuracy in the 'miscue' condition as the ‘no cue’ condition). This may reflect elements of the task itself – mentioned above.

Additionally, our findings support the hypotheses that the RH is involved in configural processing, with patients showing impairments on tasks which have this demand (Bruyer, 2011; Jung-Beeman, 2005; Jung-Beeman, et al., 2000; Maurer, Le Grand, & Mondloch, 2002). Configural processing refers to perceiving relations among the features of a stimulus, such as a face (Maurer, et al., 2002; Thompson, 1980). Although this term often refers to faces, it can be used to describe sentence processing (but see Bruyer, 2011; Leder & Carbon, 2006). This is because readers construct holistic meanings of a sentence, with contextual information incorporated into an overall representation, and information about specific word concepts that are irrelevant or inappropriate to the meaning of the sentence as a whole are not included in the representation (Anderson & Bower, 1972; Jung-Beeman, 2005; Merrill, Sperber, & McCauley, 1981). It is unclear how this relates to control – whether it is a distinct process or whether it is part of the control mechanism.

Another finding of was that RH patients were always significantly worse than controls on our experimental semantic tasks (regardless of semantic control demands). This suggests impairments on the tasks which could reflect (1) impaired semantic processing/representation, (2) slower performance, (3) inattention to all the possible options or (4) a mixture of two or more of these. We suggest an impairment of top-down allocation of attention, as described below.

(1) Although it is likely there was some impaired semantic processing, performance was at or near normal on the background semantic tasks (although these tapped different semantic representations to our experimental tasks). Additionally, performance on all tasks did show an effect of semantic control (similar to that found in SA patients), but this was no different to that seen in age-matched controls. (2) Patients do show slower performance, and in tasks with a time limit, this produced errors. (3) However, the most interesting finding was from assessing the type of errors made in our patients. In particular, SA patients made perserveration errors on around 10% of trials in the Boston Naming Test (BNT; Kaplan, et al., 1983, see Chapter 4), whereas RH patients made these errors on around 20% of the trials. This perseverance could be explained by an inhibition deficit of the most recently activated item. Corbetta and Shulman (2002)

suggest that there is a largely lateralised system in the RH activated to ‘bottom-up’ stimulus detection, which requires reorientation of attention (such as presentation of stimuli that induce task-contingent shifts of attention). Several diverse executive control tasks which require seemingly diverse cognitive functions are right lateralized, including sustained attention (Coull, Frackowiak, & Frith, 1998; Coull, Frith, Frackowiak, & Grasby, 1996; Manly et al., 2003), inhibition (Garavan, et al., 1999; Menon, et al., 2001) and oddball tasks (McCarthy, Luby, Gore, & Goldman-Rakic, 1997). Fassbender et al. (2006) suggest that response inhibition tasks involve a combination of neural amplification and active inhibition (Burle, Vidal, Tandonnet, & Hasbroucq, 2004). The same region is involved in maintenance of a task set as inhibition of a prepotent response (Aron, et al., 2003; de Zubicaray, Andrew, Zelaya, Williams, & Dumanoir, 2000; Garavan, et al., 1999; Kawashima et al., 1996; Konishi, et al., 1999). It has been suggested that this frontoparietal network is involved in allocating top-down attentional resources – and that inhibition is part of this attentional process (Fassbender et al., 2006). Recruitment of the RH during response inhibition tasks may reflect increase in more general attentional processes (Hampshire, et al., 2010; Hampshire, et al., 2009). Therefore, if our patients have deficits in this top-down allocation of attention, we would expect impairments on tasks which have extra stimuli present (either in the form of cues or miscues), distractors which are irrelevant (leading to diversion of attention), inhibitory tasks (such as the Hayling sentence completion task, and the refractory task), and those which require configural processing (e.g., the processing and maintenance of several items into a single factor, such as face emotion processing). Response inhibition is thought to be central in attentional control, as inhibiting response to distracting stimuli is important to maintain task behaviour.

And finally, this study explored the effect of right prefrontal damage on performance on a range of tasks. The analyses should be taken as preliminary, given the small patient numbers and an incomplete set of MRI/CT scans. However, in the summation task, PF+ patients were more disrupted by distractors related to the probe. This did not relate to overall accuracy, given the ‘other’ subgroup were often worse at tasks than PF+ patients. This suggests that these deficits are linked to the wider semantic control network described by Noonan and colleagues (submitted), which found evidence for a right prefrontal (but not temporoparietal) role in semantic control more generally.

The key findings of this study were: (1) RH patients showed a notable non-semantic executive control deficit similar to our SA patients. (2) RH patients showed effects of semantic control which were similar to our SA patients – for distractors, cues/ miscues, probe-target strength and cyclical matching. The effects are often as significant as those found in SA patients, although the effects are hard to compare across different tasks. Therefore, there is evidence for a semantic control deficit. Nonetheless, our data does not exclude the possibility that RH patients may have a greater deficit for tasks involving inhibition and configural processes, which supports the previously mentioned theories of the RH. (3) RH patients were impaired overall (not dependent on control demands), and they made many preservation errors in picture naming. This suggests our RH patients have top-down attentional deficit, additional to the semantic control deficits found.

Taken as a whole, this study gives the first evidence that damage to the RH control network leads to a pattern of semantic impairment which is qualitatively similar to SA but distinct from SD patients – leading to effects of cueing, distractor strength, probe-target strength and refractoriness. Further research is needed to to dissect the role of different regions of the RH in control, to find whether there is a unique role of the RH is in semantic cognition more generally, and discover whether the mixture of configural processing and inhibitory demands in semantic tasks always leads to a semantic control deficit in RH patients.

6. CHAPTER SIX

Discussion chapter

Introduction

Semantic cognition involves retrieval of meanings in a context dependent way, allowing us to interact with items in a task flexible manner (Binney, et al., 2010; Jefferies & Lambon Ralph, 2006; Whitney, et al., 2012). Correct retrieval of a meaning requires at least three cognitive mechanisms: (i) conversion and combination of sensory properties into meaning (Andrews, et al., 2009), (ii) storage linking items together according to meaning (Patterson, et al., 2007), and (iii) control mechanisms which allow flexibility and specificity of retrieval from the store in a context appropriate way (e.g., Jefferies & Lambon Ralph, 2006; Rogers & McClelland, 2004). A qualitative difference has been found in comparisons between a representational deficit (shown in semantic dementia; SD), and a semantic control deficit (shown in semantic aphasia; SA; Jefferies & Lambon Ralph, 2006). However, the semantic control network involves a distributed network, including posterior sites and the right hemisphere (Noonan, et al., submitted). This thesis explored the role of different regions in semantic control, by assessing behavioural deficits in verbal and non-verbal domains, shown in patients with different lesion locations. The motivation for this thesis was to further analyse the effect of these two variables (modality and lesion location) on performance on semantic tasks in patients after stroke.

Chapter 2 presented work comparing SA patients with anterior (PF+) and posterior (TP-only) lesions on a refractory task across modalities, with evidence of a multimodal refractory effect in PF+ patients, and no refractory effects in TP-only patients. In **Chapter 3**, case study DNe was described, who showed a deficit which was significantly greater in the verbal compared with visual domain. He nonetheless showed semantic control impairments in all modalities, although his semantic control impairments in non-verbal domains was only evident in the most demanding tasks. **Chapter 4** reviewed SD, PF+ and TP-only patients' performance on a multitude of executive control, semantic control and background neuropsychological tasks. It was concluded that, although PF+ and TP-only patients were more similar to each other than they were to SD patients, there were certain situations where TP-only patients showed weaker semantic control effects, and thus were less stereotypically 'SA' than PF+ patients. **Chapter 5** examined executive and semantic control deficits in right hemisphere (RH) patients, with evidence of an executive impairment to the same extent as our SA patients. Semantic control impairments were much subtler in RH patients, and sometimes opposite to the direction of impairment we would have expected, given our SA patients' performance. The findings from these chapters will be discussed in relation to theoretical conclusions, and future directions.

Theme 1: The effect of lesion location on semantic control

Although much research has focused on the left inferior frontal gyrus (LIFG) in semantic control (Badre, et al., 2005; Schnur, et al., 2005; Schnur, et al., 2009; Thompson-Schill, et al., 1997; Thompson-Schill, et al., 1999), evidence suggests that semantic control involves a large-scale neural network (Corbett, Jefferies, & Lambon Ralph, 2009; Noonan, et al., submitted; Whitney, et al., submitted; Whitney, Kirk, et al., 2011; Whitney, et al., 2012). A recent meta-analysis (Noonan, et al., submitted) revealed that as well as LIFG involvement, sites consistently showing a response to semantic demands include the right IFG (RIFG), posterior middle temporal gyrus (pMTG) and dorsal angular gyrus (dAG), bordering and/or within the intraparietal sulcus (IPS). It has been suggested that these regions play an essential role in semantic control. Semantic aphasia (SA) patients with prefrontal and/or temporoparietal lesion show no notable differences on a range of semantic tasks (Berthier, 2001). Tasks which manipulate semantic control reveal similar deficits for both lesion locations (Corbett, Jefferies, & Lambon Ralph, 2009; Noonan, et al., 2010). Additionally, SA patients with anterior and posterior lesions show equal improvement with the provision of external constraints, such as cues (Jefferies, Patterson, et al., 2008). TMS to pMTG or LIFG has been shown to have an equivalent negative effect on semantic control task performance (Whitney, Kirk, et al., 2011; Whitney, et al., 2012). Additionally, a recent TMS study has shown stimulation of LIFG leads to compensatory increases in activation of pMTG in semantic conditions with high demands (Whitney, et al., submitted). This, and fMRI evidence of coupled activation cited above, suggests these regions work in concert to regulate semantic activation.

Chapter 4 assessed 5 TP-only and 10 PF+ patients, in relation to semantic dementia (SD) patients, on a range of semantic and executive control tasks. **Chapter 4** shows that PF+ and TP-only patients have many similarities: (1) both show *executive control* impairments beyond the semantic domain (although these are more severe in the PF+ group). The TP-only patients typically showed damage to dAG/IPS regions, thought to be involved in domain-general control, as well as damage to posterior temporal areas.

Therefore, the finding does not contradict the view that pMTG is involved uniquely in semantic control. (2) TP-only and PF+ show *inconsistency* across tasks with different task demands, showing good consistency across tasks with similar demands (such as the picture and word version of the camel and cactus task, CCT), but no consistency between tasks of different demands (such as word-picture matching and picture naming). (3) Both TP-only and PF+ are both as influenced by *semantic control* manipulations over a range of tasks, such as matching dominant and subordinate meanings to homonyms; matching close and distant exemplars of the same semantic category; and semantic feature selection in comparison to global association tasks. (4) PF+ and TP-only patients showed the same effect of cueing during a picture naming task – showing the same degree of impairment before cue, and the same improvement after a phonemic cue was given.

However, there were some notable differences found in **Chapter 4**. In particular, TP-only patients showed some positive effects of *word frequency*, which were not seen in PF+ patients. These are much more subtle than those found in SD patients, who show much higher performance in high frequency compared to low frequency words. As well as frequency effects, TP-only patients also showed an effect of familiarity, which this time was at a similar level to SD patients. This was found in relation to performance on the CCT, picture naming and word-picture matching tasks. The lack of frequency or familiarity effects in PF+ patients is thought to relate to the fact that high frequency words tend to appear in a wide range of linguistic contexts and therefore require more constraint to direct activation to aspects of knowledge which are relevant (Almaghyuli, et al., 2012; Hoffman, Jefferies, et al., 2011). This role for semantic control in high frequency words is thought to counter-act the normal advantage enjoyed by high frequency words, due to their higher resting activation levels (Dell, 1989). Thus, it appears that TP-only patients are able to use ‘post-retrieval selection’ to capture the appropriate meaning of a word in these tasks.

In our comparison between PF+ and TP-only patients, we were also interested in naming tasks. This is because the functional neuroimaging meta-analysis (Noonan, et al., submitted) highlighted a second difference between the LIFG and pMTG – between receptive and expressive tasks. The LIFG is strongly involved in picture naming (Belke, et al., 2005; Krieger-Redwood & Jefferies, in prep.; Schnur, et al., 2009; Schwartz, et al., 2006), and was found to be equally activated by receptive and expressive tasks. Conversely, the pMTG was only active for receptive tasks. Patients with damage to LIFG were notably more impaired than those with damage to posterior regions at expressive tasks, such as word fluency (Berthier, 2001). **Chapter 4** did find a difference in the type of picture naming error made. TP-only patients made more superordinate errors than PF+ patients, something found more commonly in SD patients. Additionally, PF+ patients made significantly more associative errors. This adds to evidence that suggests that the prefrontal regions are involved in dampening down prepotent distractors. An associative error is the prepotent response to a picture, and so patients with difficulty dampening down this prepotent response will produce the most associative errors. In contrast, superordinate errors would occur with patients who have difficulty retrieving item specific information – a role of the temporoparietal cortex. It is unlikely that these superordinate errors reflect loss of knowledge, since these patients show hugely significant increase in accuracy after cueing. They also show non-verbal cueing effects, similar to PF+ patients (Corbett, et al., 2011).

Chapter 2 used a cyclical matching task to assess semantic control impairments in patients with prefrontal damage (PF+) and those restricted to the temporoparietal cortex (TP-only). The cyclical task presents the same small set of semantically related items to be matched with a probe word, picture or sound (e.g., 'cat' with a picture of a CAT, presented with DOG, RABBIT and HAMSTER). The target on one trial (e.g., CAT) becomes a distractor on another trial (where the target is DOG). Both the target and distractors become highly activated, leading to competition for selection between the presented items. Three groups of researchers (Campanella, et al., 2009; Jefferies, et al., 2007; Schnur, et al., 2009) have found refractory effects associated with lesion of the LIFG, but reduced or non-existent refractory effects in patients with temporoparietal lesions (TP-only patients). **Chapter 2** provides further support for the difference between PF+ and TP-only patients, and confirms that TP-only patients who show impairments on other control tasks, do not show effects of cycle in this task. It also suggests that modality effects are not correlated with lesion location, as refractory effects were found in PF+ patients in picture, spoken word and environmental sound tasks – and not in TP-only patients in any modality. This difference in performance according to lesion location is likely to reflect a functional difference between the contribution of LIFG and regions within our patients' temporo-parietal lesions to semantic control – with the LIFG playing a role in aspects of semantic control which the temporoparietal region is not involved in. Badre et al.'s (2005) model involves the temporoparietal region in retrieving items, particularly when they have multiple meanings. The LIFG is activated for these tasks, but additionally is involved in selecting among previously activated and competing items (cf. Thompson-Schill, et al., 1997; Wagner, Paré-Blagoev, et al., 2001). The TP-region is not thought crucial for “selection”. It is thought that inhibition of previously relevant items uniquely involves the inferior prefrontal cortex (Grison, Paul, Kessler, & Tipper, 2005).

Given the refractory effect produces a difference in performance between PF+ and TP-only patients, it would be interesting to further explore the reasons behind this difference. In **Chapter 4**, we found some evidence that the reason for this difference was related to the dampening down of prepotent distractors. However, it could be related to a number of different factors which are unusual about the refractory task: *repetition* of related stimuli, *switching* between targets over a period of time, having a *limited time* to respond, *dampening down* items which are prepotent or having *previously relevant* items as distractors. A carefully designed fMRI study could assess the impact of each factor in a semantic task, looking at the activation of LIFG and pMTG, to assess the reason behind the refractory effect.

Evidence from **Chapter 2 and 4** suggests that the temporoparietal region is not involved in all aspects of semantic control. TP-only patients did not show decreased accuracy on the *refractory task*, showed effects of *word frequency* and produce *superordinate picture naming errors*, and those with damage to pMTG were *less susceptible to prepotent distractors*. Dampening down prepotent distractors seems to be a particular role of the LIFG (Hoffman, et al., 2010), given the data from the refractory task (Schnur, et al., 2009). Nonetheless, the posterior semantic control regions (pMTG/ dAG) contribute to semantic control of tasks which use ambiguous words (Hoenig & Scheef, 2009; Rodd, et al., 2005; Zempleni, et al., 2007), figurative meanings (Chen, et al., 2008; Lee & Dapretto, 2006; Rapp, et al., 2004; Shibata, Abe, Terao, & Miyamoto, 2007), or associations (Badre, et al., 2005; Gold et al., 2006; Noppeney, Phillips, & Price, 2004; Thompson-Schill, et al., 1997; Wagner, Maril, et al., 2001; Wagner, Paré-Blagoev, et al., 2001). This suggests that strategic aspects of semantic processing such as these emerge from the interplay of anterior and posterior cortical areas and not PFC in isolation. Indeed, PFC and temporoparietal cortices are well situated for interactive reciprocal communication; tractography has revealed a number of distinct white matter pathways connecting the two cortical territories (Glasser & Rilling, 2008; Parker et al., 2005; Saur et al., 2008).

Overall, evidence from these chapters suggests partially distinct and partially overlapping roles for semantic control areas within the whole semantic network. Most interestingly, left TP-only patients show that there are semantic control tasks which the LIFG can achieve without an intact pMTG/dAG (TP-only patients maintain the ability to inhibit/ dampen down prepotent distractors, and these patients are significantly more fluent). Nonetheless, TP-only and PF+ patients show an equal deficit in high demand conditions in relation to low demand conditions. This suggests that either these regions have overlapping functions, or that the connectivity between the regions is vital for this role (Fiebach, Rissman, & D'Esposito, 2006; Friederici, 2009; Matsumoto, Nair, LaPresto, Najm, & Bingaman, 2004; Parker, et al., 2005).

The separate/joint role of different semantic control regions could be further explored in patients using tDCS. Anodal (excitatory) stimulation of LIFG in TP-only patients may increase their ability to perform semantic control tasks. This would imply that regions have overlapping functions, and upregulating the LIFG compensates for the loss of pMTG. It may also be, however, that anodal stimulation of LIFG in PF+ patients would also reduce deficits, suggesting that perilesional brain regions can take over the role of the damaged LIFG, in line with patient neuroimaging studies (Crinion & Leff, 2007). These regions have been shown to activate in recovered stroke patients (Cao, Vikingstad, George, Johnson, & Welch, 1999; Warburton, Price, Swinburn, & Wise, 1999; Zahn et al., 2004; Zahn et al., 2002), along with homotopic language regions (Rosen, et al., 2000). Early functioning is predicted by RH activation, whereas later recovery is predicted by LH activation. However, the RH might remain important for semantic control recovery in SA patients. Additionally, it is not clear if damage to LIFG can be fully compensated for by activation of other regions, or whether LIFG is necessary for some aspects of semantic control (e.g., those highlighted by Badre et al. as ‘post-retrieval selection’). This could be tested by assessing the difference between controls and patients after tDCS on a range of semantic control tasks.

The role of connectivity between regions could be further explored by assessing performance relative to connectivity rather than lesion location or size (Catani & Mesulam, 2008; de Zubicaray, et al., 2011; Duffau, 2008; Glasser & Rilling, 2008). The TP-only group shows highly varied performance, and this may be due to greater or lesser residual connectivity from pMTG to LIFG. Quantifying the relationship between the connection of pMTG and LIFG with behavioural scores on semantic control tasks is novel. However, the importance of this connectivity has recently been shown in a TMS study (Whitney et al., submitted). In this study, rTMS to LIFG to ‘knock out’ this region led to increased activation of pMTG, but only in a high demand condition of the semantic task. This suggests that a lesion in one region can be compensated for by activated in the remaining regions of the semantic control network.

The role of connectivity between the LIFG and pMTG could be further explored using a double pulse rTMS study, while healthy participants are performing a semantic control task, such as those described in Noonan et al. (2010). Participants are known to perform at the same level with rTMS to either LIFG or pMTG (Whitney et al., 2011). However, it is not clear whether rTMS to both regions would produce a super additive deficit in performance. If this is the case, it would suggest some compensatory performance from the unstimulated site in semantic control – further reason to suggest an overlap of function of these two regions.

Chapter 5 considers the role of other semantic control regions highlighted in a recent meta-analysis (Noonan, et al., submitted). In particular, the role of RH regions was assessed. While studies focus on the LIFG in semantic cognition, consistent activation has been found in the RIFG. There is evidence for a bilateral domain-general executive control network (Duncan, 2006, 2010; Duncan & Owen, 2000), as well as a bilateral semantic control network, reported in studies which often emphasise the role of the LIFG (Badre, et al., 2005; Devlin, et al., 2003; Hoffman, et al., 2010; Moss et al., 2005; Robinson, Shallice, Bozzali, et al., 2010; Schnur, et al., 2009; Snyder, et al., 2011; Thompson-Schill, et al., 1997; Wagner, Paré-Blagoev, et al., 2001).

Chapter 5 found evidence of both non-semantic and semantic control deficits, suggesting the RH has some role to play in control. Deficits in executive control were found in RH patients to the same extent as our SA cases. However, these did not correlate with semantic performance as they do in SA patients, suggesting a somewhat different deficit. We also found refractory effects to the same extent in SA patients and RH patients, but only for items which each group found difficult (e.g., for SA patients, everyday objects, for RH patients, face emotions).

There were many *differences* between these two groups, with suggestion that RH patients are qualitatively different from SA cases. RH patients were at normal level on a range of background semantic tasks testing basic concepts, and showed significantly higher accuracy than SA patients. In terms of semantic control manipulations, SA patients showed a larger effect of this manipulation on almost all of the comparisons, although the tasks which SA and RH patients were tested on differed. The most notable difference, however, was the opposite pattern of behaviour found with regards distractors and cues: RH patients showed worse performance in the presence of semantic cues in relation to no cue, and unrelated compared to related distractors.

It was hypothesised that the RH patients have difficulty in top-down allocation of attentional resources (Corbetta & Shulman, 2002), which gives rise to deficits in tasks requiring configural processing, as well as inhibitory responses – with target detection and inhibition highly related processes which have both been linked to the RIFG (Hampshire, et al., 2010; Hampshire, et al., 2009). For example, there was impaired performance when the task involves inhibition. Impaired performance with unrelated distractors and cues may be due to activation of extra semantic meanings, which were unnecessary for the task. Participants also showed impairment on the Hayling sentence completion task, and the face emotion refractory task, both of which have an inhibitory element. However, some tasks which require inhibition (e.g., such as the social synonym judgement task with antonym distractors) did not show a difference between 'high' and 'low' conditions, suggesting RH patients have something more than an inhibitory deficit.

There was also impairment on tasks requiring configural processing. Configural processing refers to any phenomenon that involves perceiving relations among the features of a stimulus, such as a face (Maurer, et al., 2002; Thompson, 1980). Although this term often refers to faces, it can be used to describe sentence processing (Anderson & Bower, 1972; Jung-Beeman, 2005; Merrill, et al., 1981). Whether top-down allocation of attention to both configural processes and inhibitory processes are part of the same disorder, or whether they are separate, remains to be seen. However, the additive effect of configural processing and inhibition in a single task seemed to lead to the effects of semantic control seen in RH patients. (1) The face emotion refractory task involves configural processing of the face, as well as inhibition of previously activated items. (2) The summation task involves configuration of weakly related probe words (e.g., LEGS – REST – BENCH → SIT), as well as inhibition of distractors and cues/miscues. In these tasks, patients showed identical performance to controls in conditions where there was not the conjunction of these two control demands (e.g., in the refractory task, cycle 1; and the summation task without cues/micues). The inhibitory/configural processing account may also explain the increased of perservation in RH patients on the face emotion picture naming task in relation to SA patients on a naming task. This may be because RH patients have either (i) not noticed the change in face stimuli, reflecting a configural processing deficit, or (ii) been unable to inhibit repeating the activated expression word, or both.

It could be argued that it is these elements of a task, rather than the stimuli themselves (e.g., faces and distantly related words), which produce the deficits. If so, RH patients would show semantic control impairments even on basic items, such as household objects, when the task is demanding in these ways, such as if they were presented in a go-no go task which uses Gestalt Completion items as its stimuli (Ekstrom, French, & Harman, 1976). This is something which has not yet been tested, although the RH has already been hypothesised to be involved in configural processing and inhibition (Aron, et al., 2004; Garavan, et al., 1999; Huberle & Karnath, 2012; Konishi, et al., 1999; Menon, et al., 2001; Snyder, Shpaner, Molholm, & Foxe, 2012; Wasserstein, Zappulla, Rosen, & Gerstman, 1987).

Given the preliminary nature of **Chapter 5**, the role of the RH could be further explored. Both RH vs. LH and anterior/posterior comparisons (in both hemispheres) would benefit from a larger series of patients, to provide a greater opportunity to explore the roles of specific regions. Predictions about more focal sites (e.g., IPS vs. pMTG; RIFG vs. RpMTG) could then be tested with TMS.

Additionally, the tasks used in the RH chapter do not explore all aspects of semantic control. For example, none of the tasks use visual-only stimulus (e.g., either the probe or target uses a written or spoken word). It has been argued that the RH is particularly involved in visual semantics (e.g., Mion et al., 2010; Snowden et al., 2004), and it may be that the involvement of language in each task is reducing the effect of the semantic control impairment that would otherwise be found in these patients. A picture-picture task which manipulates semantic control demands would be an important test for these patients. The role of the RH in social cognition almost always focuses on visual interpretations of people or scenes, and the RH's role in social words is predicted only by a single group (Zahn et al., 2007). This is also true of metaphors, some believe the RH plays a role in metaphor picture interpretation rather than sentence comprehension (Winner & Gardner, 1977). Each of these semantic tasks could be retested using visual stimuli.

There are some tasks which, according to fMRI tasks, lead to bilateral activation, but which RH patients perform at a normal level. However, RH patients did show impairments on tasks with configural and inhibitory requirements. Therefore healthy subjects could be tested on a task requiring (i) configural and inhibitory processing, and (ii) neither of these components but of equally high demand. With rTMS over RIFG, we could assess the necessity of the RIFG in these tasks. Some role for RIFG in semantic processing has already been shown using this method (Pobric, et al., 2008)

As the domain-general control network includes a bilateral system, it may well be the case that the RH patients show deficits in tasks that require configural processing and inhibition, but do not use semantics (e.g., the feature figure selection task described in **Chapter 4**). It still remains a question, however, whether RH patients show an impairment on the more demanding tasks (e.g., that the RH is an 'overflow' hemisphere), or whether it is specifically involved in these certain aspects of control. Given the exploratory nature of **Chapter 5**, the findings are open to interpretation and require further research. It is not yet fully clear, for example, whether the deficit involves particular stimuli (e.g., face emotions and distantly related concepts), or whether it is a deficit purely related to the task demands. Another suggestion given in **Chapter 5** is that patients showed perservation of speech (e.g., referring to each face presented as 'surprised'). This may account for their impaired performance overall on most tasks (e.g., perservation of motor action towards a particular space). It is not yet clear if this is an additional deficit of RH patients, e.g., an inattentional deficit, occurring from not being aware of new stimuli being presented (Corbetta & Shulman, 2002). This may interacts with semantic control demands (e.g., inhibition), or whether it works in parallel to semantic control (e.g., it is not influenced by the demands of the task).

The data from this thesis provides new evidence into the role of different areas of the semantic control network. For the first time, PF+ and TP-only patients have been studied as separate groups, and differences in behaviour has been found. The connection of the RH with semantic control has never been explored, and this study provides preliminary evidence that it has some role to play in semantic control.

Theme 2: Modality and domain effects

SA patients have a semantic control deficit across domains, showing equal impairments in word, picture and action tasks (Corbett, Jefferies, Ehsan, et al., 2009; Corbett, et al., 2008; Corbett, Jefferies, & Lambon Ralph, 2009; Jefferies & Lambon Ralph, 2006). These patients show a strong influence of control demands, with higher performance on picture naming with a cue in comparison to no cue, and for strong associations compared to weak association matching. These effects have been found in verbal and non-verbal domains alike (Corbett, et al., 2011; Jefferies, Patterson, et al., 2008). Aphasic patients might be expected to show more substantial semantic deficits for verbal materials, while SD patients show amodal deficits. Of course, it is possible to show deficits for a single modality, if damage occurs to a ‘spoke’ which holds representations of a particular modality (Patterson, et al., 2007). However, the ‘access’ behavioural deficit (e.g., inconsistent performance over a period of time), is qualitatively different semantic deficit to those with a representational deficit, and is specific to the auditory domain (Crutch & Warrington, 2008b; Warrington & Crutch, 2004). However, if SA cases have deficits of semantic control across modalities, they might show ‘access’ impairments also across modalities. This is the hypothesis tested in Chapter 2.

Chapter 2 assesses the performance of SA patients on a picture, spoken word and environmental sounds cyclical tasks. The ‘refractory’ effect has been described as (1) impaired access to semantics following activation (McNeil, et al., 1994; Warrington & Cipolotti, 1996; Warrington & McCarthy, 1983, 1987), (2) increased lexical competition impairing verbal selection (Belke, et al., 2005; Damian, et al., 2001; Schnur, et al., 2006), (3) deficits in neuromodulation, which lead to inattention to new inputs and reduced synaptic depression of distractors which have been targets (Gotts & Plaut, 2002), and (4) deficits in multimodal semantic control mechanisms which produce increased competition between targets and previously relevant distractors, irrespective of the requirement for lexical selection or production (Jefferies, et al., 2007). The main difference between these theories is modality – the first two emphasise the refractory effect in the verbal domain, the neuromodulation theory is potentially applicable across domains, and the semantic control theory proposes an amodal refractory effect. As a group, SA patients show ‘access’ deficits across modalities. Across 3 experiments comparing verbal and non-verbal refractory tasks using 3 methods, there was also inconsistency and variation between patients. Individually, there were some patients who showed the refractory effect only in the verbal domain (e.g., PG, NY), and some that showed it only in the visual domain (e.g., BB), but the majority (e.g., DB, KA, LS) showed refractory effects in more than one modality. Patients that only showed significant refractory effects in one modality showed semantic control deficits across domains in other tasks, and therefore this finding is likely to reflect the fact that not all SA or ‘access’ patients show strong refractory effects (Crutch & Warrington, 2008b). SA patients with single modality refractory effects showed the same pattern in all modalities, but more weakly than classic refractory cases – who might represent the extreme end of a continuum (Jefferies, et al., 2007). Additionally, our patients were greatly influenced by the difficulty of the task – with some (e.g., LS, DB) showing only verbal impairments on an identity matching experiment, however, in further experiments involving association matching, these patients showed the opposite pattern (e.g., stronger refractory effects in non-verbal than verbal judgements).

The refractory effect is described by Warrington and colleagues as a deficit in the verbal system. It is therefore possible that, if systems are separate, multimodal refractory effects of SA patients seen in **Chapter 2** may be because SA patients have deficits to all systems, which remain independent – the visual system, the verbal system and the non-verbal auditory system. To test this, we interleaved the trials, so that on one trial, a picture was presented, followed by a word, then picture and word – or vice versa. We found mixed data from SA patients on this task – there was a significant drop in accuracy in patient DB - who showed the most dramatic refractory effects in the single modality tasks. However, patients were, on the whole, distracted by the change in modality – and did not attend to a spoken word probe after seeing a picture as a probe. This may be related to damage to the dAG, leading to deficits of attention to task related items (Noonan, et al., submitted; Seghier, et al., 2010). It is therefore possible that SA patients have damage to all modality ‘access’ systems. However, it is at least plausible for an amodal refractory effect to exist, given the work by Forde and Humphreys (1997) which suggests spreading activation across verbal and non-verbal domains. It also seems unlikely that a semantic control region could exist which was modality specific – seeing as there is activation across tasks and domains in these control regions (Duncan, 2006, 2010; Duncan & Owen, 2000; Freedman, et al., 2001).

An association task was run in **Chapter 2**, which had strongly related probes (presented as either spoken words or pictures, e.g., forms of transport), but targets and distractors (always presented as pictures) which were not as strongly related (e.g., runway, train tracks, motorway and field). This experiment found a weaker effect of refractoriness, with only marginal significance. This suggests the importance of the relatedness of the targets and distractors – which are pictures in all refractory tasks (Crutch & Warrington, 2008b; Jefferies, et al., 2007; Warrington & Crutch, 2004). This is further evidence for an amodal system – as the refractory effect is stronger with both related picture targets and related picture or word probes.

It has also been noted that picture refractory tasks which involve matching the same item invariably have greater visual overlap than tasks which require matching associated items, leading to a weaker effect in this modality than the verbal modality (Caramazza, Hillis, Rapp, & Romani, 1990; Chertkow, Bub, & Caplan, 1992; Forde & Humphreys, 1997; Riddoch, et al., 1988). The stimuli in the picture task were chosen to be visually dissimilar, but this remained an issue with certain stimuli (e.g. CAMERA), leading to the refractory effect being marginally weaker (but not significantly so) in the picture task in relation to the spoken word task in Experiment 1. This was the reason behind running follow-up experiments, including a refractory task which involved matching associated items with no visual overlap.

In **Chapter 3**, we explored a patient (DNe) with a verbal-only semantic access deficit in detail. He showed refractory effects restricted to the spoken modality – in contrast to case studies AZ and BBB who showed refractory effects extending to non-verbal auditory stimuli (Crutch & Warrington, 2008b), although he was impaired at matching environmental sounds to pictures. However, on more demanding tasks, he showed a semantic control impairment on written and picture tasks (e.g., the synonym judgement task, ambiguity and semantic distance tasks, and association tasks). This profile suggests a profound auditory impairment and mild difficulties in high-control semantic tasks across modalities. An amodal semantic system interacts with modality-specific spokes, and can lead to amodal impairments which are accentuated in a single domain. SA cases have control deficits across modalities, but this suggests that it is possible to have a deficit heightened in one modality. The semantic control network is distributed, and includes the pMTG which is close to the auditory cortex (pSTG). It is perhaps unsurprising to find a patient with an auditory impairment combined with mild semantic control deficits across modalities, given the proximity of pMTG to pSTG. Disruption of auditory input paired with a mild amodal semantic control deficit leads to a control deficit, with noticeably reduced performance in the auditory domain (while still showing the effects of semantic control in this domain). This hypothesis may explain several case studies in the literature that seem to show an 'access' or control deficit in only one modality.

Another explanation for his performance on certain tasks is described by Crutch and Warrington (2011a). They argue that discrepancies between modalities can result from the graded nature of representations, where some neurons are multimodal – but still preferentially process a particular modality. They suggest that deficits in representations which activate to spoken information leads to 'access' like impairments, which are category independent, frequency independent and more significant in multiple than single presentation tasks. It is certainly true that DNe never shows normal performance on spoken word tasks – suggesting the possibility for a representational deficit. Nonetheless, his performance on non-verbal tasks is related to semantic control demands – so for example, he is significantly worse at subordinate than dominant meaning comprehension of an ambiguous homonym. These two conditions of the task uses the same number of items, as well as the same distractors, and holds constant frequency and imageability levels. It is hard to link this data with the suggestion of the representational deficit described above. We would therefore predict that the patient described by Crutch and Warrington (2011a) would show semantic control impairments in non-verbal tasks which were more demanding – like DNe.

In order to fully test the hypothesis that impaired initial processing of a single domain, paired with domain general control impairments, lead to control deficits accentuated in one modality, a test on healthy participants would be useful. In **Chapter 3**, healthy participants show impaired performance in tasks when they have degraded auditory input – but this does not correlate with semantic control demands. In order to test the hypothesis that impairment of both input and control leads to this deficit, a behavioural test could be carried out involving both degraded input and a dual-task (e.g., a semantic task using words embedded in pink noise, paired with an n-back task). This could be extended to degraded visual input stimuli too.

‘Spokes’ support sensory, verbal and motor sources, and are necessary for domain and modality specific representation, whereas the ‘hub’ is necessary for amodal representation (Patterson, et al., 2007). TMS to spokes has been found to influence performance only on tasks which are processed in this region (Pobric, et al., 2010b). In this task, rTMS to ATL generates category-general impairment, whereas rTMS to IPL induces category-specific deficits for man-made objects in relation to living things. Therefore, it is possible that dual rTMS, of both LIFG and a ‘spoke’ (either auditory regions such as the STS or visual areas such as ITL) would lead to a refractory deficit that was greater in this domain. All our PF+ patients in **Chapter 2** had damage to LIFG as well as posterior regions, and this pattern of brain injury might be crucial in producing the effects of interest. We would predict that TMS to a spoke, such as pSTG, may produce modality specific deficits in the task but not a decline in performance over cycles, where TMS of LIFG *and* pSTG may produce refractory effects in a single modality.

Wernicke’s Aphasia (WA) patients have lesions centring pSTG regions, and most show a strong modality effect – having particular difficulties with the spoken domain. It has been shown that this acoustic-phonological deficit extends to semantic processing, producing greater deficits in understanding words than pictures, and auditory stimuli over visual stimuli (Robson, Keidel, Lambon Ralph, & Sage, 2012; Robson, Sage, et al., 2012), possibly due to a lesion extending to pMTG. It is not yet clear, however, if this phonological deficit interacts with refractory effects in a single modality. For example, it may be that LIFG damage causes refractory effects, and when paired with pMTG damage, these effects are multimodal. However, when paired with unimodal regions – such as the pSTG, the refractory effects may remain only in this modality (as seen in our case study). Therefore, analysis of patients’ lesion location, and remaining or damaged connectivity between LIFG and pSTG/ pMTG, may be fruitful in learning how the refractory effect comes about in single modality cases. We would predict that patients with damage to LIFG and pSTG would show refractory effects specific to the verbal domain.

Chapter 3 describes a variety of refractory tasks in single-case DNe. Verbal tasks included using items which were semantically related and unrelated (distractors and targets selected from different categories), and phonologically related or unrelated (items which began with the same letter e.g., WATCH, WHEEL, WELL, and WHIP, or items beginning with different letters, taken from other cycles). DNe showed a decline in performance over cycles in all spoken word versions of this task – including unrelated items. This suggests something different to the pattern seen in SA patients – who show a strong effect of relatedness in this task (Jefferies, et al., 2007). DNe was greatly affected by length of display – with performance on phoneme discrimination being particularly poor, but good performance on pictures displayed indefinitely. His performance radically altered in a go-no go task where SRI was altered a few hundred milliseconds. Therefore, it is possible that DNe's performance is influenced by this – leading to a mild semantic control deficit paired with a general slowing of processing, which invariably affects words over pictures (as spoken words have a limited presentation period). This may mean that given the ability to repeat a spoken word probe, he is able to process this to the same level as a picture. DNe shows fatigue of the representations that continually repeat within each block, but this doesn't spread to semantically related items any more than unrelated items. DNe shows a strong effect of presentation rate, along with a notable decline in accuracy over testing time within a task and over a session (metal fatigue). It may be that this mental fatigue is particularly prominent in the verbal domain as the presentation of each probe is only once and relatively short. To test this, we could assess DNe's performance on novel items in cycle 4, in relation to old items in cycle 4. If there was no difference, it would suggest the deficit goes beyond the semantic domain. Additionally, we could shorted the environmental sounds stimuli (currently, they are around 5 seconds), to see if his performance decreases to the same magnitude as seen in the spoken word task – an auditory deficit similar to 'access' and SA patients (Crutch & Warrington, 2008b; Gardner, et al., 2012).

In **Chapter 4**, TP-only patients show greater impairment for visual items: it was notable that they showed significantly higher performance in comparison to both SD and PF+ patients on the CCT word task (~20%) than tasks involving pictures, such as picture naming, word-picture matching or the CCT picture task (~5%). Some patients may be particularly impaired at visual stimuli processing (e.g., ME), who show strong effects of picture naming cues, low performance on background neuropsychological visual tasks (e.g., VOSP), but high performance on executive tasks without visual demands (e.g., digit span, TEA). This patient, however, shows impairment on semantic control tasks (e.g., being worse at subordinate meanings than dominant meanings of an ambiguous word) where items are both presented in written form and read out. Therefore, there is evidence of TP-only patients showing a semantic control deficit, but with a particular deficit for visual items. This deficit may lead to more consistent performance across tasks (with accuracy maintained over these relatively simple semantic tasks), category effects with word-picture matching (with items from the some categories being more difficult to differentiate), more superordinate naming errors (if the patient is able to decipher an object belongs to a certain category, but nothing more specific about the item).

In **Chapter 5**, we assessed RH patients for semantic control impairments across modalities. In particular, we focused on picture tasks involving faces, and written word tasks involving metaphors (two aspects of semantics which are thought to rely on the RH). We found that patients showed semantic control deficits across modalities, suggesting both LH and RH contribute to semantic cognition across modalities, with a possible division of labour between them.

We also tested RH patients on another refractory task, using face identity matching (spoken word-picture matching, of people who were related according to job, e.g., “Marilyn Monroe” presented with other actresses). When subjects were asked to match a name to a face identity, their performance was at ceiling across cycles. Therefore, the refractory effect is highly dependent on the stimuli. In the task that did find refractory effects, using face emotions of the same identity face, the target and distractors were much harder to visually differentiate, which may have lead to the build up of competition between the target and distractors. RH patients may be particularly sensitive to visual similarity (given their configural processing deficits), and so the refractory task which used visually similar items produced a stronger effect.

However, there was some evidence for a difference in performance according to modality – most notably on the metaphor picture and word tasks. There was also impairment on a relatively simple matching task which used faces (refractory task), which was only seen with words when the task was highly demanding (the summation task). It is possible, therefore, that this RH performance also reflects an interaction of modality-dependent visual ‘spokes’, and executive control mechanisms, leading to accentuated deficits in a single domain (while still present in more challenging tasks in other domains). This would therefore predict a similar pattern in our RH patients to DNe in **Chapter 3**, with the exception that the deficit would be greater for visual than verbal materials. The pattern seen in **Chapter 5** may reflect damage to visual spokes in right temporal and parietal areas (Bartolomeo, et al., 2007; Konen, et al., 2011; Mort, et al., 2003), paired with damage to control regions, which produce higher performance in the verbal compared to visual domain. The same task in two different modalities is required to assess this hypothesis thoroughly.

Concluding remarks

This thesis explores the impact of damage to different areas of the distributed cortical network underpinning semantic cognition, employing tasks which aim to assess the effects of modality and manipulations of semantic control demands. The research builds on previous data to show that semantic control impairment in SA results in multimodal refractory effects when competition builds up within a small set of semantically-related items that are presented repeatedly as both targets and distracters (**Chapter 2**). It explores several controversies in the literature, such as the proposal that there are modality-specific ‘access’ patients: our case study in **Chapter 3** suggests that at least some patients with modality specific ‘access’ impairments have a dual deficit – i.e., input processing problems combined with multimodal control deficits. **Chapters 4 and 5** look in more detail at potential dissociations between stroke cases who have damage to different sites within the distributed network underpinning semantic control. We found that patients with damage to anterior and posterior semantic control regions are broadly similar but show some dissociations (**Chapter 4**). Finally, this thesis provides a preliminary investigation of a novel idea – that semantic deficits following RH stroke may reflect damage to bilateral semantic control processes which are qualitatively similar to those seen in SA cases with left hemisphere damage (**Chapter 5**). The fact that RH cases were found to show effects of several relevant manipulations – such as refractory variables, cueing, strength of association and distractor strength – provides some support for this view. These patient studies explore the neural basis of semantic control to understand the mechanisms which lead to multimodal comprehension under normal circumstances and deficits in this area.

References

Adelman, J. S., Brown, G. D. A., & Quesada, J. F. (2006). Contextual diversity, not word frequency, determines word-naming and lexical decision times. *Psychological Science, 17*, 814-823.

Adlam, A. L. R., Patterson, K., Bozeat, S., & Hodges, J. R. (2010). The Cambridge Semantic Memory Test Battery: Detection of semantic deficits in semantic dementia and Alzheimer's disease. *Neurocase, 16*(3), 193-207.

Adolphs, R. (1999). Social cognitive and the human brain. *Trends in Cognitive Sciences, 3*(12), 469-479.

Adolphs, R., Damasio, H., Tranel, D., Cooper, G., & Damasio, A. R. (2000). A role for somatosensory cortices in the visual recognition of emotion as revealed by three-dimensional lesion mapping. *Journal of Neuroscience, 20*, 2683-2690.

Ahrens, K., Liu, H., Lee, C., Gong, S., Fang, S., & Hsu, Y. Y. (2007). Functional MRI of conventional and anomalous metaphors in Manderin Chinese. *Brain and Language, 100*, 163-171.

Almaghyuli, A., Thompson, H. E., Lambon Ralph, M. A., & Jefferies, E. (2012). Deficits of semantic control produce absent or reverse frequency effects in comprehension: Evidence from neuropsychology and dual task methodology. *Neuropsychologia, 50*(8), 1968-1979.

Anaki, D., Faust, M., & Kravetz, S. (1998). Cerebral hemispheric asymmetries in processing lexical metaphors. [Article]. *Neuropsychologia, 36*(4), 353-362.

Anderson, J. R., & Bower, G. H. (1972). Configural properties in sentence memory. *Journal of Verbal Learning and Verbal Behavior, 11*(5), 594-605.

Andrews, M., Vigliocco, G., & Vinson, D. (2009). Integrating experimental and distributional data to learn semantic representations. *Psychological Review, 116*(3), 463-498.

Aron, A. R., Fletcher, P., Bullmore, E., Sahakian, B. J., & Robbins, T. W. (2003). Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. *Nature Neuroscience, 6*, 115-116.

Aron, A. R., Robbins, T. W., & Poldrack, R. A. (2004). Inhibition and the right inferior frontal cortex. *Trends in Cognitive Sciences, 8*(4), 170-177.

Aydelott, J., Leech, R., & Crinion, J. (2010). Normal adult aging and the contextual influences affecting speech and meaningful sound perception. *Trends in amplification, 14*(4), 218-232.

Baayen, R. H., Piepenbrock, R., & Van Rijn, H. (1995). The CELEX Lexical Database. Release 2 [CD-ROM]. Philadelphia: University of Pennsylvania.

Badecker, W. (2005). *Speech perception following focal brain injury*. Maldin, MA: Blackwell Publishing.

Badre, D., & D'Esposito, M. (2007). Functional magnetic resonance imaging evidence for a hierarchical organization of the prefrontal cortex. *Journal of Cognitive Neuroscience, 19*, 2082-2099.

Badre, D., Hoffman, J., Cooney, J. W., & D'Esposito, M. (2009). Hierarchical cognitive control deficits following damage to human frontal lobe. *Nature Neuroscience, 12*, 515-522.

Badre, D., Poldrack, R. A., Paré-Blagoev, E. J., Insler, R. Z., & Wagner, A. D. (2005). Dissociable controlled retrieval and generalized selection mechanisms in ventrolateral prefrontal cortex. *Neuron, 47*(6), 907-918.

Badre, D., & Wagner, A. D. (2002). Semantic retrieval, mnemonic control, and prefrontal cortex. *Behavioral and Cognitive Neuroscience Reviews, 1*(3), 206-218.

Badre, D., & Wagner, A. D. (2007). Left ventrolateral prefrontal cortex and the cognitive control of memory. *Neuropsychologia, 45*(13), 2883-2901.

Baldo, J. V., Bunge, S. A., Wilson, S. M., & Dronkers, N. F. (2010). Is relational reasoning dependent on language? A voxel-based lesion symptom mapping study. *Brain and Language, 113*(2), 59-64.

Baldo, J. V., Dronkers, N. F., Wilkins, D., Ludy, C., Raskin, P., & Kim, J. (2005). Is problem solving dependent on language? *Brain and Language, 92*(3), 240-250.

Baldo, J. V., Schwartz, S., Wilkins, D. P., & Dronkers, N. F. (2006). Role of frontal versus temporal cortex in verbal fluency as revealed by voxel-based lesion symptom mapping. *Journal of International Neuropsychological Society, 12*(6), 896-900.

Bambati, S. M., Rankin, K. P., Narvid, J., Seeley, W. W., Dean, D., Rosen, H. J., Miller, B. L., Ashburner, J., & Gorno-Tempini, M. L. (2009). Atrophy progression in semantic dementia with asymmetric temporal involvement: a tensor-based morphometry study. *Neurobiology of Aging, 30*(1), 103-111.

Bartolomeo, P., Thiebaut de Schotten, M., & Doricchi, F. (2007). Left unilateral neglect as a disconnection syndrome. *Cereb. Cortex, 45*, 3127-3148.

Bates, E., Wilson, S. M., Saygin, A. P., Dick, F., Sereno, M. I., Knight, R. T., & Dronkers, N. F. (2003). Voxel-based lesion−symptom mapping. *Nature Neuroscience, 6*, 448-450.

Beauchamp, M. S., Lee, K. E., Haxby, J. V., & Martin, A. (2002). Parallel visual motion processing streams for manipulable objects and human movements. *Neuron, 34*, 149-159.

Bedny, M., Hulbert, J. C., & Thompson-Schill, S. L. (2007). Understanding words in context: The role of Broca's area in word comprehension. *Brain Research, 1146*, 101-114.

Bedny, M., McGill, M., & Thompson-Schill, S. L. (2008). Semantic adaptation and competition during word comprehension. *Cerebral Cortex, 5*(11), 2574-2585.

Beeman, M. (1998). *Coarse semantic coding and discourse comprehension*. Mahwah, NJ: Lawrence Erlbaum Associates Inc.

Beeman, M., Friedman, R. B., Grafman, J., Perez, E., Diamond, S., & Beadle Lindsay, M. (1994). Summation priming and coarse semantic coding in the right hemisphere. *Journal of Cognitive Neuroscience, 6*(1), 26-45.

Behrns, I., Wengelin, A., Broberg, M., & Hartelius, L. (2009). A comparison between written and spoken narratives in aphasia. *Clinical linguistics & Phonetics, 23*(7), 507-528.

Belke, E., Meyer, A. S., & Damian, M. F. (2005). Refractory effects in picture naming as assessed in a semantic blocking paradigm. *The Quarterly Journal of Experimental Psychology Section A: Human Experimental Psychology, 58*(4), 667 - 692.

Benson, D. F. (1979). *Neurologic correlates of anomia* (Vol. 4). New York: Academic Press.

Benson, D. F. (1988). *Classical syndromes in aphasia* (Vol. 1). Amsterdam: Elsevier Science Publishers, BV.

Benson, R. R., Whalen, D. H., Richardson, M., Swainson, B., Clark, V. P., Lai, S., & Liberman, A. M. (2001). Parametrically Dissociating Speech and Nonspeech Perception in the Brain Using fMRI. *Brain and Language, 78*, 364-396.

Berthier, M. L. (2001). Unexpected brain-language relationships in aphasia: Evidence from transcortical sensory aphasia associated with frontal lobe lesions. *Aphasiology, 15*(2), 99 - 130

Binder, J. R., Desai, R. H., Graves, W. W., & Conant, L. L. (2009). Where Is the Semantic System? A Critical Review and Meta-Analysis of 120 Functional Neuroimaging Studies. *Cerebral Cortex, 19*(12), 2767-2796.

Binder, J. R., Frost, J. A., Hammeke, T. A., Bellgowan, P. S. F., Rao, S. M., & Cox, R. W. (1999). Conceptual processing during the conscious resting state: A functional MRI study. *Journal of Cognitive Neuroscience, 11*, 80-93.

Binder, J. R., Frost, J. A., Hammeke, T. A., Bellgowan, P. S. F., Springer, J. A., Kaufman, J. N., & Possing, E. T. (2000). Human temporal lobe activation by speech and nonspeech sounds. *Cereb. Cortex, 10*(5), 512-528.

Binder, J. R., Rao, S. M., Hammeke, T. A., Yetkin, Y. Z., Jesmanowicz, A., Bandettini, P. A., Wong, E. C., Estkowski, L. D., Goldstein, M. D., Haughton, V. M., & Hyde, J. S. (1994). Functional magnetic resonance imaging of human auditory cortex. *Annals of Neurology, 35*, 662-672.

Binney, R. J., Embleton, K. V., Jefferies, E., Parker, G. J. M., & Lambon Ralph, M. A. (2010). The ventral and inferolateral aspects of the anterior temporal lobe are crucial in semantic memory: Evidence from a novel direct comparison of distortion-corrected fMRI, rTMS, and semantic dementia. *Cerebral Cortex, 20*(11), 2728-2738.

Binney, R. J., Parker, G. J. M., & Lambon Ralph, M. A. (2012). Convergent connectivity and graded specialization in the rostral human temporal lobe as revealed by diffusion-weighted imaging probabilistic tractography. *Journal of Cognitive Neuroscience*.

Bird, H., Lambon Ralph, M. A., Patterson, K., & Hodges, J. R. (2000). The rise and fall of frequency and imageability: Noun and verb production in semantic dementia. *Brain and Language, 73*(1), 17-49.

Blair, R. J., & Cipolotti, L. (2000). Impaired social response reversal. A case of "acquired sociopathy". *Brain, 123*, 1122-1141.

Blair, R. J., Morris, J. S., Frith, C. D., Perrett, D. I., & Dolan, R. J. (1999). Dissociable neural responses to facial expressions of sadness and anger. *Brain, 122*, 883-893.

Blonder, L. X., Bowers, D., & Heilman, K. M. (1991). The role of the right hemisphere in emotional communication. *Brain, 114*(3), 1115-1127.

Blumstein, S. E., Milberg, W., & Shrier, R. (1982). Semantic processing in aphasia: Evidence from an auditory lexical decision task. *Brain and Language, 17*(2), 301-315.

Blumstein, S. E., Myers, E. B., & Rissman, J. (2005). The perception of voice onset time: An fMRI investigation of phonetic category structure. *Journal of Cognitive Neuroscience, 17*(9), 1353-1366.

Boatman, D., Gordon, B., Hart, J., Selnes, O., Miglioretti, D., & Lenz, F. (2000). Transcortical sensory aphasia: Revisited and revised. *Brain, 123*, 1634-1642.

Bogen, J. E. (1997). Does cognition in the disconnected right hemisphere require right hemisphere possession of language? *Brain and Language, 57*, 12-21.

Booth, J. R., Burman, D. D., Meyer, J. R., Gitelman, D. R., Parrish, T. B., & Mesulam, M. M. (2002). Modality independence of word comprehension. *Human Brain Mapping, 16*, 251-261.

Borden, N. M. (2006). *3D Angiographic Atlas of Neurovascular Anatomy and Pathology*. Cambridge Cambridge University Press.

Borgo, F., & Shallice, T. (2001). When living things and other "sensory-quality" categories behave in the same fashion: A novel category-specific effect. *Neurocase, 7*, 201-220.

Borod, J. C. (2000). *The neuropychology of emotion*. New York: Oxford University Press.

Bottini, G., Corcoran, R., Sterzi, R., Paulesu, E., Schenone, P., Scarpa, P., Frackowiak, R. S. J., & Frith, C. D. (1994). The role of the right hemisphere in the interpretation of figurative aspects of language. A positron emission tomography activation study. *Brain, 117*(6), 1241-1253.

Bowers, D., & Bauer, R. M. (1985). Processing of faces by patients with unilateral hemisphere lesions: I. Dissociation between judgements of facial affect and facial identity. *Brain and Cognition, 4*(3), 258-272.

Bowers, D., Blonder, L. X., Feinberg, T., & Heilman, K. M. (1991). Differential impact of right and left hemisphere lesions on facial emotion and object imagery. *Brain, 114*(6), 2593-2609.

Bozeat, S., Lambon Ralph, M. A., Graham, K. S., Patterson, K., Wilkin, H., Rowland, J., Rogers, T. T., & Hodges, J. R. (2003). A duck with four legs: Investigating the structure of conceptual knowledge using picture drawing in semantic dementia. *Cognitive Neuropsychology, 20*(1), 27 - 47.

Bozeat, S., Lambon Ralph, M. A., Patterson, K., Garrard, P., & Hodges, J. R. (2000). Non-verbal semantic impairment in semantic dementia. *Neuropsychologia, 38*(9), 1207-1215.

Bozeat, S., Lambon Ralph, M. A., Patterson, K., & Hodges, J. R. (2002). When objects lose their meaning: What happens to their use? *Cognitive, Affective, & Behavioral Neuroscience, 2*(3), 236-251.

Brieter, H. C., Etcoff, N. L., Whalen, P. J., Kennedy, W. A., Rauch, S. L., Buckner, R. L., Strauss, M. M., Hyman, S. E., & Rosen, B. R. (1996). Response and habituation of the human amygdala during visual processing of facial expression. *Neuron, 17*, 875-887.

Bright, P., Moss, H., & Tyler, L. K. (2004). Unitary vs multiple semantics: PET studies of word and picture processing. *Brain and Language, 89*(3), 417-432.

Brownell, H. H., Simpson, T. L., Bihrle, A. M., Potter, H. H., & Gardner, H. (1990). Appreciation of metaphoric alternative word meanings by left and right brain-damaged patients. *Neuropsychologia, 28*, 375-383.

Bruyer, R. (2011). Configural face processing: A meta-analytic survey. *Perception, 40*, 1478-1490.

Bryan, K. L. (1995). *The Right Hemisphere Language Battery* (Second ed.). London: Whurr.

Bukach, C. M., Gauthier, I., & Tarr, M. J. (2006). Beyond faces and modularity: The power of an expertise framework. *Trends in Cognitive Sciences, 10*(4), 159-166.

Bull, R., Phillips, L. H., & Conway, C. A. (2008). The role of control functions in metanlizing: Dual-task studies of Theory of Mind and executive function. *Cognition, 107*(2), 663-672.

Burgess, P. W., & Shallice, T. (1997). *The Hayling and Brixton Tests*. Bury St Edmunds: Thames Valley Test Company.

Burle, B., Vidal, F., Tandonnet, C., & Hasbroucq, T. (2004). Physiological evidence for response inhibition in choice reaction time tasks. *Brain and Cognition, 56*, 153-164.

Cacciari, C., Reati, F., Colombo, M. R., Padovani, R., Rizzo, S., & Papagno, C. (2006). The comprehension of ambiguous idioms in aphasic patients. *Neuropsychologia, 44*, 1305-1314.

Cambier, J., Elghozi, D., Signoret, J. L., & Henin, D. (1983). Contribution de l'hemisphere droit au langage des aphasiques. Disparition de ce langage apres lesion droite. *Rev. Neurol., 139*, 55-63.

Campanella, F., Crescentini, C., Mussoni, A., & Skrap, M. (2012). Refractory semantic access dysphasia resulting from resection of a left frontal glioma. *Neurocase*, 1-9.

Campanella, F., Mondani, M., Skrap, M., & Shallice, T. (2009). Semantic access dysphasia resulting from left temporal lobe tumours. *Brain, 132*(1), 87-102.

Cao, Y., Vikingstad, E. M., George, K. P., Johnson, A. F., & Welch, K. M. A. (1999). Cortical language activation in stroke patients recovering from aphasia with functional MRI. *Stroke, 30*, 2331-2340.

Capitani, E., Laiacona, M., Mahon, B. Z., & Caramazza, A. (2003). What are the facts of semantic category-specific deficits? A critical review of the clinical evidence. *Cognitive Neuropsychology, 20*(3/4/5/6), 213-261.

Caramazza, A., Hillis, A. E., Rapp, B. C., & Romani, C. (1990). The multiple semantics hypothesis: Multiple confusions? *Cognitive Neuropsychology, 7*(3), 161 - 189.

Caramazza, A., & Mahon, B. Z. (2003). The organization of conceptual knowledge: the evidence from category-specific semantic deficits. *Trends in Cognitive Sciences, 7*(8), 354-361.

Caramazza, A., & Shelton, R. (1998). Domain-specific knowledge systems in the brain: The animate-inanimate distinction. *Journal of Cognitive Neuroscience, 10*, 1-34.

Catani, M., & Ffytche, D. H. (2005). The rises and falls of disconnection syndromes. *Brain, 128*(10), 2224-2239.

Catani, M., & Mesulam, M. M. (2008). The arcuate fasciculus and the disconnection theme in language and aphasia: History and current state. *Cortex, 44*(8), 953-961.

Champagne-Lavau, M., & Joanette, Y. (2009). Pragmatics, theory of mind and executive functions after a right-hemisphere lesion: Different patterns of deficits. *Journal of Neurolinguistics, 22*, 413-426.

Chao, L. L., Haxby, J. V., & Martin, A. (1999). Attribute-based neural substrates in temporal cortex for perceiving and knowing about objects. *Nature Neuroscience, 2*, 913-919.

Charpentier, F. (1986). Pitch detection using the short-term phase spectrum. *Acoustics, Speech, and Signal Processing, IEEE International, 11*, 113-116.

Chen, E., Widick, P., & Chatterjee, A. (2008). Functional-anatomical organization of predicate metaphor processing. *Brain and Language, 107*, 194-202.

Chertkow, H., Bub, D., & Caplan, D. (1992). Constraining theories of semantic memory processing: Evidence from dementia. *Cognitive Neuropsychology, 9*(4), 327-365.

Chertkow, H., Bub, D., Deaudon, C., & Whitehead, V. (1997). On the status of object concepts in aphasia. *Brain and Language, 58*(2), 203-232.

Chikazoe, J., Konishi, S., Asari, T., Jimura, K., & Miyashita, Y. (2007). Activation of right inferior frontal gyrus during response inhibition across response modalities. *Journal of Cognitive Neuroscience, 19*(1), 69-80.

Coccia, M., Bartolini, M., Luzzi, S., Provinciali, L., & Lambon Ralph, M. A. (2004). Semantic memory is an amodal, dynamic system: Evidence from the interaction of naming and object use in semantic dementia. *Cognitive Neuropsychology, 21*(5), 513 - 527.

Cohen, L., & Dehaene, S. (2004). Specialization within the ventral stream: The case for the visual word form area. *NeuroImage, 22*(1), 466-476.

Collette, F., Hogge, M., Salmon, E., & Van der Linden, M. (2006). Exploration of the neural substrates of executive functioning by functional neuroimaging. *Neuroscience, 139*(1), 209-221.

Collins, A. M., & Loftus, E. F. (1975). Spreading activation theory of semantic processing. *Psychological Review, 82*, 407-428.

Conn, P. M. (2003). *Neuroscience in medicine* (Second Edition ed.): Humana Press.

Conroy, P., Sage, K., & Lambon Ralph, M. A. (2009). A comparison of word versus sentence cues as therapy for verb naming in aphasia. *Aphasiology, 23*(4), 462-482.

Copland, D. A., de Zubicaray, G. I., McMahon, K. L., & Eastburn, M. (2007). Neural correlates of semantic priming for ambiguous words: An event-related fMRI study. *Brain Research, 1131*, 163-172.

Copland, D. A., de Zubicaray, G. I., McMahon, K. L., Wilson, S. J., Eastburn, M., & Chenery, H. J. (2003). Brain activity during automatic semantic priming revealed by event-related functional magnetic resonance imaging. *NeuroImage, 20*, 302-310.

Corbett, F., Jefferies, E., Ehsan, S., & Lambon Ralph, M. A. (2009). Different impairments of semantic cognition in semantic dementia and semantic aphasia: evidence from the non-verbal domain. *Brain, 132*(9), 2593-2608.

Corbett, F., Jefferies, E., & Lambon Ralph, M. A. (2008). The use of cueing to alleviate recurrent verbal perseverations: Evidence from transcortical sensory aphasia. *Aphasiology, 22*, 362-382.

Corbett, F., Jefferies, E., & Lambon Ralph, M. A. (2009). Exploring multimodal semantic control impairments in semantic aphasia: Evidence from naturalistic object use *Neuropsychologia, 47*(13), 2721-2731.

Corbett, F., Jefferies, E., & Lambon Ralph, M. A. (2011). Deregulated semantic cognition follows prefrontal and temporoparietal damage: Evidence from the impact of task constraint on non-verbal object use. *Journal of Cognitive Neuroscience, 23*(5), 1125-1135.

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci, 3*(3), 201-215.

Coull, J. T., Frackowiak, R. S. J., & Frith, C. D. (1998). Monitoring for target objects: Activation of right frontal and parietal cortices with increasing time on task. *Neuropsychologia, 36*, 1325-1334.

Coull, J. T., Frith, C. D., Frackowiak, R. S. J., & Grasby, P. M. (1996). A fronto-parietal network for rapid visual information processing: A PET study of sustained attention and working memory. *Neuropsychologia, 34*, 1085-1095.

Crawford, J. R., & Garthwaite, P. H. (2002). Investigation of the single case in neuropsychology: Confidence limits on the abnormality of test scores and test score differences. *Neuropsychologia, 40*(8), 1196-1208.

Crinion, J., Lambon Ralph, M. A., Warburton, E. A., Howard, D., & Wise, R. (2003). Temporal lobe regions engaged during normal speech comprehension. *Brain, 126*, 1193-1201.

Crinion, J., & Leff, A. P. (2007). Recovery and treatment of aphasia after stroke: functional imaging studies. *Current opinion in Neurology, 20*(6), 667-673.

Cristescu, T. C., Devlin, J. T., & Nobre, A. C. (2006). Orienting attention to semantic categories. *NeuroImage, 33*, 1178-1187.

Cristescu, T. C., & Nobre, A. C. (2008). Differential modulation of word recognition by semantic and spatial orienting of attention. *Journal of Cognitive Neuroscience, 20*(5), 787-801.

Crutch, S. J., Ridha, B. H., & Warrington, E. K. (2006). The different frameworks underlying abstract and concrete knowledge: Evidence from a bilingual patient with a semantic refractory access dysphasia. *Neurocase, 12*(3), 151-163.

Crutch, S. J., & Warrington, E. K. (2003a). The organisation of semantic memory: Evidence from semantic refractory access dysphasia. *Brain and Language, 87*(1), 81-82.

Crutch, S. J., & Warrington, E. K. (2003b). The selective impairment of fruit and vegetable knowledge: A multiple processing channels account of fine-grain category specificity. *Cognitive Neuropsychology, 20*(3-6), 355-372.

Crutch, S. J., & Warrington, E. K. (2003c). Spatial coding of semantic information: knowledge of country and city names depends on their geographical proximity. *Brain, 126*(8), 1821-1829.

Crutch, S. J., & Warrington, E. K. (2004). The semantic organisation of proper nouns: the case of people and brand names. *Neuropsychologia, 42*(5), 584-596.

Crutch, S. J., & Warrington, E. K. (2005a). Abstract and concrete concepts have structurally different representational frameworks. *Brain, 128*(3), 615-627.

Crutch, S. J., & Warrington, E. K. (2005b). Gradients of semantic relatedness and their contrasting explanations in refractory access and storage semantic impairments. *Cognitive Neuropsychology, 22*(7), 851-876.

Crutch, S. J., & Warrington, E. K. (2007). The Semantic Organisation of Mass Nouns: Evidence from Semantic Refractory Access Dysphasia. *Cortex, 43*(8), 1057-1067.

Crutch, S. J., & Warrington, E. K. (2008a). Contrasting patterns of comprehension for superordinate, basic-level, and subordinate names in semantic dementia and aphasic stroke patients. *Cognitive Neuropsychology, 25*(4), 582-600.

Crutch, S. J., & Warrington, E. K. (2008b). The influence of refractoriness upon comprehension of non-verbal auditory stimuli. *Neurocase, 14*(6), 494 - 507

Crutch, S. J., & Warrington, E. K. (2010a). The differential dependence of abstract and concrete words upon associative and similarity-based information: Complementary semantic interference and facilitation effects. *Cognitive Neuropsychology, 27*(1), 46-71.

Crutch, S. J., & Warrington, E. K. (2010b). Spatially coded semantic information about geographical terms. *Neuropsychologia, 48*(7), 2120-2129.

Crutch, S. J., & Warrington, E. K. (2011a). Different patterns of spoken and written word comprehension deficit in aphasic stroke patients. *Cognitive Neuropsychology, 28*(6), 414-434.

Crutch, S. J., & Warrington, E. K. (2011b). Taxonomic and thematic organisation of proper name conceptual knowledge. *Behavioural Neurology, 24*(4), 265-276.

Damasio, A. R. (1989a). The brain binds entities and events by multiregional activation from convergence zones. *Neural Computation, 1*, 123-132.

Damasio, A. R. (1989b). Time-locked multiregional retroactivation: a systems-level proposal for the neural substrates of recall and recognition. *Cognition, 33*, 25-62.

Damasio, H., & Damasio, A. R. (1989). *Lesion analysis in neuropsychology*. New York: Oxford University Press.

Damasio, H., Grabowski, T. J., Tranel, D., Hichwa, R., & Damasio, A. R. (1996). A neural basis for lexical retrieval. *Nature, 380*, 498-504.

Damian, M. F., Vigliocco, G., & Levelt, W. J. M. (2001). Effects of semantic context in the naming of pictures and words. *Cognition, 81*(3), B77-B86.

Davey, J., & Jefferies, E. (in prep). Semantic control and representation in the pMTG; the effects of manipulating both control and tool knowledge.

Davis, A. (1995). *Hearing in Adults*. London: Whurr Publishers Ltd.

Davis, M. H., & Johnsrude, I. S. (2003). Hierarchical Processing in Spoken Language Comprehension. *The Journal of Neuroscience, 23*(8), 3423-3431.

de Renzi, E., & Lucchelli, F. (1994). Are semantic systems separately represented in the brain? The case of living category impairment. *Cortex, 30*, 3-25.

de Zubicaray, G. I., Andrew, C., Zelaya, F. O., Williams, S. C., & Dumanoir, C. (2000). Motor response suppression and the prepotent tendency to respond: a parametric fMRI study. *Neuropsychologia, 38*(9), 1280-1291.

de Zubicaray, G. I., Rose, S. E., & McMahon, K. L. (2011). The structure and connectivity of semantic memory in the healthy older adult brain. *NeuroImage, 54*, 1488-1494.

Degroot, A. M. B. (1989). Representational aspects of word imageability and word frequency as assessed through word association. *Journal of Experimental Psychology: Learning, Memory and Cognition, 15*, 824-845.

DeLeon, J., Gottesman, R. F., Kleinman, J. T., Newhart, M., Davis, C., Heidler-Gary, J., Lee, A., & Hillis, A. E. (2007). Neural regions essential for distinct cognitive processes underlying picture naming. *Brain, 130*, 1408-1422.

Dell, G. S. (1989). *The retrieval of phonological forms in production: Tests of predictions from a connectionist model*. Cambridge, MA: MIT Press.

Dell, G. S., & O'Seaghdha, P. G. (1992). Stages of lexical access in language production. *Cognition, 42*, 287-314.

Dell, G. S., Schwartz, M. F., Martin, N., Saffran, E. M., & Gagnon, D. A. (1997). Lexical access in aphasic and nonaphasic speakers. *Psychological Review, 104*, 801-838.

Demb, J. B., Desmond, J. E., Wagner, A. D., Vaidya, C. J., Glover, G. H., & Gabrieli, J. D. (1995). Semantic encoding and retrieval in the left inferior prefrontal cortex: a functional MRI study of task difficulty and process specificity. *J. Neurosci., 15*(9), 5870-5878.

Demonet, J. F., Chollet, F., Ramsay, S., Cardebat, D., Nespoulous, J. L., Wise, R., Rascol, A., & Frackowiak, R. S. J. (1992). The anatomy of phonological and semantic processing in normal subjects. *Brain, 115*(6), 1753-1768.

Demonet, J. F., Price, C. J., Wise, R., & Frackowiak, R. S. J. (1994). Differential activation of right and left posterior sylvian regions by semantic and phonological tasks: A positron emission tomography study in normal human subjects. *Neuroscience Letters, 182*, 25-28.

Desai, R. H., Conant, L. L., Waldron, E., & Binder, J. R. (2006). fMRI of Past Tense Processing: The Effects of Phonological Complexity and Task Difficulty. *Journal of Cognitive Neuroscience, 18*(2), 278-297.

Desgranges, B., Matuszewski, V., Piolino, P., Chetelat, G., Mezenge, F., Landeau, B., de la Sayette, V., Belliard, S., & Eustache, F. (2007). Anatomical and functional alterations in semantic dementia: A voxel-based MRI and PET study. *Neurobiology of Aging, 28*(12), 1904-1913.

Devlin, J. T., Gonnerman, L., Andersen, E., & Seidenberg, M. (1998). Category specific semantic deficits in focal and widespread brain damage: A computational account. *Journal of Cognitive Neuroscience, 10*, 77-94.

Devlin, J. T., Matthews, P. M., & Rushworth, M. F. S. (2003). Semantic Processing in the Left Inferior Prefrontal Cortex: A Combined Functional Magnetic Resonance Imaging and Transcranial Magnetic Stimulation Study. *Journal of Cognitive Neuroscience, 15*(1), 71-84.

Devlin, J. T., Moore, C. J., Mummery, C. J., Gorno-Tempini, M. L., Phillips, J., Noppeney, U. T. A., Frackowiak, R. S. J., Friston, K., & Price, C. J. (2002). Anatomical constraints on cognitive theories of category specificity. *NeuroImage, 15*(3), 675-685.

Devlin, J. T., Russell, R. P., Davis, M. H., Price, C. J., Moss, H., Fadili, M. J., & Tyler, L. K. (2002). Is there an anatomical basis for category-specificity? Semantic memory studies in PET and fMRI. *Neuropsychologia, 40*, 54-75.

Dien, J. (2009). A tale of two recognition systems: Implications of the fusiform face area and the visual word form area for lateralized object recognition models. *Neuropsychologia, 47*, 1-16.

Dolan, R. J., Fletcher, P., Morris, J. S., Kapur, N., Deakin, J. F., & Frith, C. D. (1996). Neural activation during covert processing of positive emotional facial expressions. *NeuroImage, 4*, 194-200.

Dosenbach, N. U. F., Fair, D. A., Cohen, A. L., Schlagger, B. L., & Petersen, S. E. (2008). A dual-networks architecture of top-down control. *Trends in Cognitive Sciences, 12*, 99-105.

Douglas, J. M. (2010). Relation of executive functioning to pragmatic outcome following severe traumatic brain injury. *Journal of Speech Language and Hearing Research, 53*(2), 365-382.

Dove, A., Pollmann, S., Schubert, T., Wiggins, C. J., & Yves von Cramon, D. (2000). Prefrontal cortex activation in task switching: an event-related fMRI study. *Cognitive Brain Research, 9*(1), 103-109.

Dronkers, N. F., Ludy, C., & Redfern, B. B. (1998). Pragmatics in the absence of verbal language: Descriptions of a severe aphasic and a language-deprived adult. *Journal of Neurolinguistics, 11*, 179-190.

Dronkers, N. F., Wilkins, D. P., Van Valin, R. D., Redfern, B. B., & Jaeger, J. J. (2004). Lesion analysis of the brain areas involved in language comprehension. *Cognition, 92*(1-2), 145-177.

Duffau, H. (2008). The anatomo-functional connectivity of language revisited: New insights provided by electrostimulation and tractography. *Neuropsychologia, 46*(4), 927-934.

Dumontheil, I., Thompson, R., & Duncan, J. (2011). Assembly and Use of New Task Rules in Fronto-parietal Cortex. *Journal of Cognitive Neuroscience, 23*(1), 168-182.

Duncan, J. (2006). EPS Mid-Career Award 2004: Brain mechanisms of attention. *The Quarterly Journal of Experimental Psychology, 59*(1), 2-27.

Duncan, J. (2010). The multiple-demand (MD) system of the primate brain: mental programs for intelligent behaviour. *Trends in Cognitive Sciences, 14*(4), 172-179.

Duncan, J., & Owen, A. M. (2000). Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends in Neurosciences, 23*(10), 475-483.

Eggert, G. H. (1977). *Wernicke's work on aphasia: A sourcebook and review*. The Hague: Mouton Publishers.

Ekstrom, R., French, J. W., & Harman, H. H. (1976). *Manual for Kit of Factor-referenced Cognitive Tests*. Princeton, NJ: Educational Testing Service.

Ellis, H. D., Ellis, D. M., Fraser, W., & Deb, S. (1994). A preliminary study of right hemisphere cognitive deficits and impaired social judgments among young people with Asperger syndrome. *European child & adolescent psychiatry, 3*(4), 255-266.

Farah, M. J., McMullen, P. A., & Meyer, M. (1991). Can recognition of living things be selectively impaired? *Neuropsychologia, 29*, 185-193.

Farah, M. J., Wilson, K. D., Drain, M., & Tanaka, J. (1998). What is 'special' about face perception? *Psychological Review, 105*, 482-498.

Fassbender, C., Simoes-Franklin, C., Murphy, K., Hester, R., Meaney, J., Robertson, I. H., & Garavan, H. (2006). The role of a right fronto-parietal network in cognitive control. *Journal of Psychophysiology, 20*(4), 286-296.

Faust, M., & Mashal, N. (2007). The role of the right cerebral hemisphere in processing novel metaphoric expressions taken from poetry: A divided visual field study. [Review]. *Neuropsychologia, 45*(4), 860-870.

Faust, M., & Weisper, S. (2000). Understanding metaphoric sentences in the two cerebral hemispheres. [Proceedings Paper]. *Brain and Cognition, 43*(1-3), 186-191.

Fersti, E. C., Neumann, J., Bogler, C., & Yves von Cramon, D. (2008). The extended language network: A meta-analysis of neuroimaging studies on text comprehension. *Human Brain Mapping, 29*(5), 581-593.

Fiebach, C. J., Rissman, J., & D'Esposito, M. (2006). Modulation of inferotemporal cortex activation during verbal working memory maintenance. *Neuron, 51*(2), 251-261.

Finger, S., Buckner, R. L., & Buckingham, H. (2003). Does the right hemisphere take over after damage to Broca's area? The Barlow case of 1877 and its history. *Brain and Language, 85*, 385-395.

Fink, G. R., Manjaly, Z. M., Stephan, K. E., Gurd, J. M., Zilles, K., Amunts, K., & Marshall, J. C. (2006). A role for Broca’s area beyond language processing: evidence from neuropsychology and fMRI. In K. Amunts & Y. Grodzinsky (Eds.), *Broca’s area*. Oxford: University Press.

Foldi, N. S., Cicone, M., & Gardner, H. (1983). *Pragmatic aspects of communications in brain damaged patients*. New York: Academic Press.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini-Mental State: a practical method of grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*, 189-198.

Forde, E. M. E., & Humphreys, G. W. (1995). Refractory semantics in global aphasia - on semantic organisation and the access-storage distinction in neuropsychology. *Memory, 3*(3-4), 265-307.

Forde, E. M. E., & Humphreys, G. W. (1997). A Semantic Locus for Refractory Behaviour: Implications for Access Storage Distinctions and the Nature of Semantic Memory. *Cognitive Neuropsychology, 14*(3), 367-402.

Foundas, A. L., Daniels, S. K., & Vasterling, J. J. (1998). Anomia: Case studies with lesion localization. *Neurocase, 4*, 35-43.

Freedman, D. J., Riesenhuber, M., Poggio, T., & Miller, E. K. (2001). Categorical representation of visual stimuli in the primate prefrontal cortex. *Science, 291*(5502), 312-316.

Fridriksson, J., Bonilha, L., Baker, J. M., Moser, D., & Rorden, C. (2010). Activity in preserved left hemisphere regions predicts anomia severity in aphasia. *Cerebral Cortex, 20*, 1013-1019.

Friederici, A. D. (2009). Pathways to language: Fiber tracts in the human brain. *Trends in Cognitive Sciences, 13*, 175-181.

Frith, U. (1989). *Autism: Explaining the Enigma*. Oxford: Blackwell.

Funnell, E. (1995). Objects and properties: A study of the breakdown of semantic memory. *Memory, 3*, 497-518.

Gagnon, L., Goulet, P., Giroux, F., & Joanette, Y. (2003). Processing of metaphoric and non-metaphoric alternative meanings of words after right- and left-hemispheric lesion. *Brain and Language, 87*(2), 217-226.

Gainotti, G. (2000). What the locus of brain lesion tells us about the nature of the cognitive defect underlying category-specific disorders: A review. *Cortex, 36*(4), 539-559.

Gainotti, G., Silveri, M. C., Villa, G., & Miceli, G. (1986). Anomia with and without lexical comprehension disorders. *Brain and Language, 29*, 18-33.

Galton, C. J., Patterson, K., Graham, K. S., & Lambon Ralph, M. A. (2001). Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. *Neurology, 57*, 216-225.

Garavan, H., Ross, T. J., & Stein, E. A. (1999). Right hemispheric dominance of inhibitory control: An event-related functional MRI study. *Proceedings of the National Academy of Sciences, 96*(14), 8301-8306.

Gardner, H. E., Lambon Ralph, M. A., Dodds, N., Jones, T., Eshan, S., & Jefferies, E. (2012). The differential contributions of pFC and temporoparietal cortices to multimodal semantic control: Exploring refractory effects in semantic aphasia. *Journal of Cognitive Neuroscience, 24*(4), 778-793.

Garrard, P., & Carroll, E. (2006). Lost in semantic space: a multi-modal, non-verbal assessment of feature knowledge in semantic dementia. *Brain, 129*(5), 1152-1163.

Garrard, P., Lambon Ralph, M. A., Hodges, J. R., & Patterson, K. (2001). Prototypicality, distinctiveness and intercorrelation: Analysis of the semantic attributes of living and nonliving concepts. *Cognitive Neuropsychology, 18*(2), 125-174.

Gauthier, I., & Palmeri, T. J. (2002). Visual neurons: Categorization-based selectivity. *Current Biology, 12*(8), R282-R284.

Gauthier, I., Skudlarski, P., Gore, J. C., & Anderson, A. W. (2000). Expertise for cars and birds recruits brain areas involved in face recognition. *Nature Neuroscience, 3*(2), 191-197.

Gazzaniga, M. (1983). Right hemisphere language following brain bisection. A 20-year perspective. *American Psychologist, 38*, 525-537.

Gazzaniga, M. (2000). Cerebral specialization and interhemispheric communication - does the corpus callosum enable the human condition? *Brain, 123*, 1293-1326.

Gazzaniga, M., Smylie, C. S., & Baynes, K. (1984). Profiles of right hemisphere language and speech following brain bisection. *Brain and Language, 22*, 206-220.

Gennari, S. P., MacDonald, M. C., Postle, B. R., & Seidenberg, M. S. (2007). Context-dependent interpretation of words: Evidence for interactive neural processes. *NeuroImage, 35*(3), 1278-1286.

George, E. L., Zekveld, A. A., Kramer, S. E., Goverts, S. T., Festen, J. M., & Houtgast, T. (2007). Auditory and nonauditory factors affecting speech reception in noise by older listeners. *Journal of the Acoustical Society of America, 121*, 2362-2375.

George, M. S., Ketter, T. A., Gill, D. S., Haxby, J. V., Ungerleider, L. G., Herscovitch, P., & Post, R. M. (1993). Brain regions involved in recognizing facial emotion or identity: An oxygen-15 PET study. *Journal of Neuropsychiatry and Clinical Neuroscience, 5*, 384-394.

George, M. S., Parekh, P. I., Rosinsky, N., Ketter, T. A., Kimbrell, T. A., Heilman, K. M., Herscovitch, P., & Post, R. M. (1996). Understanding emotional prosody activates right hemisphere regions. *Archives of Neurology, 53*(7), 665-670.

Gerlach, C., Law, I., Gade, A., & Paulson, O. B. (2000). Categorization and category effects in normal object recognition - A PET study. *Neuropsychologia, 38*, 1693-1703.

Gernsbacher, M. A. (1990). *Language comprehension as structure building*. Hillsdale, NJ: Lawrence Erlbaum Associates Inc.

Geschwind, N. (1965). Disconnection syndromes in animals and man. *Brain, 88*, 237-294.

Giora, R. (1997). Understanding figurative and literal language: The graded salience hypothesis. *Cognitive Linguistics, 8*(3), 183-206.

Giora, R. (1999). On the priority of salient meanings: Studies of literal and figurative language. *Journal of Pragmatics, 31*(7), 919-929.

Giora, R. (2007). Is metaphor special? *Brain and Language, 100*(2), 111-114.

Giora, R. (2009). Understanding figurative and literal language: The graded salience hypothesis. *Cognitive Linguistics, 8*(3), 183-206.

Giora, R., Zaidel, E., Soroker, N., Batori, G., & Kasher, A. (2000). Differential Effects of Right- and Left-Hemisphere Damage on Understanding Sarcasm and Metaphor. *Metaphor and Symbol, 15*(1), 63 - 83.

Glasser, M. F., & Rilling, J. K. (2008). DTI tractography of the human brain's language pathways. *Cerebral Cortex, 18*(11), 2471-2482.

Gold, B. T., Balota, D. A., Jones, S. J., Powell, D. K., Smith, C. D., & Andersen, A. H. (2006). Dissociation of automatic and strategic lexical-semantics: functional magnetic resonance imaging evidence for differing roles of multiple frontotemporal regions. *Journal of Neuroscience, 26*, 6523-6532.

Gold, B. T., & Buckner, R. L. (2002). Common Prefrontal Regions Coactivate with Dissociable Posterior Regions during Controlled Semantic and Phonological Tasks. *Neuron, 35*(4), 803-812.

Gold, R., & Faust, M. (2010). Right hemisphere dysfunction and metaphor comprehension in young adults with asperger syndrome. *Journal of Autism and Developmental Disorders, 40*(7), 800-811.

Gold, R., Faust, M., & Ben-Artzi, E. (2011). Metaphors and verbal creativity: The role of the right hemisphere. *Laterality, iFirst*, 1-13.

Goldberg, G., & Spatt, S. (2009). The neural basis of tool use. *Brain, 132*, 1645-1655.

Goldstein, K. (1948). *Language and language disturbances*. New York: Grune & Stratton.

Goodglass, H., & Kaplan, E. (1983). *The assessment of aphasia and related disorders (2nd Edition)*. Philadelphia: Lea & Febiger.

Goodglass, H., Kaplan, E., & Barresi, B. (2001). *The assessment of aphasia and related disorders (3rd ed.)*. Baltimore: Lippincott Williams & Wilkins. (BDAE).

Gorno-Tempini, M. L., Dronkers, N. F., Rankin, K. P., Ogar, J. M., Phengrasamy, L., Rosen, H. J., Johnson, J. K., Weiner, M. W., & Miller, B. L. (2004). Cognition and anatomy in three variants of primary progressive aphasia. *Annals of Neurology, 55*(3), 335-346.

Gotts, S. J., & Plaut, D. C. (2002). The impact of synaptic depression following brain damage: A connectionist account of "access/refractory" and "degraded-store" semantic impairments. *Cognitive Affective & Behavioral Neuroscience, 2*(3), 187-213.

Gough, P. M., Nobre, A. C., & Devlin, J. T. (2005). Dissociating linguistic processes in the left inferior frontal cortex with transcranial magnetic stimulation. *Journal of Neuroscience, 25*(35), 8010-8016.

Griffiths, T. D. (2002). Central auditory processing disorders. *Current opinion in Neurology, 15*(31-33).

Grindrod, C. M., Bilenko, N. Y., Myers, E. B., & Blumstein, S. E. (2008). The role of the left inferior frontal gyrus in implicit semantic competition and selection: An event-related fMRI study. *Brain Research, 1229*, 167-178.

Grison, S., Paul, M. A., Kessler, K., & Tipper, S. P. (2005). Inhibition of object identity in inhibition of return: Implications for encoding and retrieving inhibitory processes. *Psychonomic Bulletin & Review, 12*, 553-558.

Hagoort, P. (1997). Semantic priming in Broca's aphasic at short SOA: No support for an automatic access deficit. *Brain and Language, 56*, 287-300.

Hagoort, P. (2005). On Broca, brain, and binding: a new framework. *Trends in Cognitive Sciences, 9*(9), 416-423.

Halgren, E., Wang, C. M., Schomer, D. L., Knake, S., Marinkovic, K., Wu, J. L., & Ulbert, I. (2006). Processing stages underlying word recognition in the anteroventral temporal lobe. *NeuroImage, 30*(4), 1401-1413.

Hamilton, A. C., & Coslett, H. B. (2008). Refractory access disorders and the organisation of concrete and abstract semantics: Do they differ? *Neurocase, 14*(2), 131-140.

Hampshire, A., Chamberlain, S. R., Monti, M. M., Duncan, J., & Owen, A. M. (2010). The role of the right inferior frontal gyrus: inhibition and attentional control. *NeuroImage, 50*(3), 1313-1319.

Hampshire, A., Thompson, R., Duncan, J., & Owen, A. M. (2008). The Target Selective Neural Response — Similarity, Ambiguity, and Learning Effects. *PLoS ONE, 3*(6), 1-11.

Hampshire, A., Thompson, R., Duncan, J., & Owen, A. M. (2009). Selective tuning of the right inferior frontal gyrus during target detection. *Cognitive, Affective, & Behavioral Neuroscience, 9*(1), 103-112.

Hamsher, K. (1991). *Intelligence and aphasia* (2nd ed.). San Diego: Academic Press.

Hamzei, F., Rijntjes, M., Dettmers, C., Glauche, V., Weiller, C., & Büchel, C. (2003). The human action recognition system and its relationship to Broca's area: an fMRI study. *NeuroImage, 19*(3), 637-644.

Happe, F., Brownell, H. H., & Winner, E. (1999). Acquired 'theory of mind' impairments following stroke. *Cognition, 70*(3), 211-240.

Harciarek, M., & Heilman, K. M. (2009). The contribution of anterior and posterior regions of the right hemisphere to the recognition of emotional faces. *Journal of Clinical and Experimental Neuropsychology, 31*(3), 322-330.

Hart, J., & Gordon, B. (1990). Delineation of single-word semantic comprehension deficits in aphasia, with anatomical correlation. *Annals of Neurology, 27*(3), 226-231.

Hart, J., & Gordon, B. (1992). Neural subsystems for object knowledge. *Nature, 359*, 60-64.

Haxby, J. V., Hoffman, E. A., & Gobbini, M. I. (2000). The distributed human neural system for face perception. *Trends in Cognitive Sciences, 4*, 223-233.

Hazeltine, E., Bunge, S. A., Scanlon, M. D., & Gabrieli, J. D. E. (2003). Material-dependent and material-independent selection processes in the frontal and parietal lobes: an event-related fMRI investigation of response competition. *Neuropsychologia, 41*(9), 1208-1217.

Heiss, W. D., Kessler, J., Karbe, H., Fink, G. R., & Pawlik, G. (1993). Cerebral glucose metabolism as a predictor of recovery from aphasia in ischemic stroke. *Archives of Neurology, 50*, 958-964.

Hermer-Vazquez, L., Spelke, E. S., & Katsnelson, A. S. (1999). Sources of flexibility in human cognition: Dual task studies of space and language. *Cognitive Psychology, 39*, 3-36.

Hickok, G., & Poeppel, D. (2004). Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language. *Cognition, 92*(1-2), 67-99.

Hickok, G., & Poeppel, D. (2007). The cortical organization of speech processing. *Nature Reviews Neuroscience, 8*(5), 393-402.

Hillis, A. E., & Caramazza, A. (1991). Category-specific naming and comprehension impairment: A double dissociation. *Brain, 114*(5), 2081-2094.

Hillis, A. E., Newhart, M., Heidler, J., Barker, P. B., Herskovits, E., & Degaonkar, M. (2005). The roles of the "visual word form area" in reading. *NeuroImage, 24*, 548-559.

Hillis, A. E., Tuffiash, E., Wityk, R. J., & Barker, P. B. (2002). Regions of neural dysfunction associated with impaired naming of actions and objects in acute stroke. *Cognitive Neuropsychology, 19*, 523-534.

Hirano, S., Naito, Y., Okazawa, H., Kojima, H., Honjo, I., Ishizu, K., Yenokura, Y., Nagahama, Y., Fukuyama, H., & Konishi, J. (1997). Cortical activation by monaural speech sound stimulation demonstrated by positron emission tomography. *Experimental Brain Research, 113*, 75-80.

Hirshorn, E. A., & Thompson-Schill, S. L. (2006). Role of the left inferior frontal gyrus in covert word retrieval: Neural correlates of switching during verbal fluency. *Neuropsychologia, 44*, 2547-2557.

Hodges, J. R., Patterson, K., Oxbury, S., & Funnell, E. (1992a). Progressive fluent aphasia with temporal lobe atrorphy. *Brain, 115*, 1783-1806.

Hodges, J. R., Patterson, K., Oxbury, S., & Funnell, E. (1992b). Semantic Dementia - progressive fluent aphasia with temporal-lobe atrophy. *Brain, 115*(6), 1783-1806.

Hoenig, K., & Scheef, L. (2009). Neural correlates of semantic ambiguity processing during context verification. *NeuroImage, 45*(3), 1009-1019.

Hoffman, P., Jefferies, E., & Lambon Ralph, M. A. (2010). Ventrolateral prefrontal cortex plays an executive regulation role in comprehension of abstract words: Convergent neuropsychological and repetitive TMS evidence. *The Journal of Neuroscience, 30*(46), 15450-15456.

Hoffman, P., Jefferies, E., & Lambon Ralph, M. A. (2011). Remembering ‘zeal’ but not ‘thing’: Reverse frequency effects as a consequence of deregulated semantic processing. *Neuropsychologia, 49*, 580-584.

Hoffman, P., & Lambon Ralph, M. A. (2011). Reverse Concreteness Effects Are Not a Typical Feature of Semantic Dementia: Evidence for the Hub-and-Spoke Model of Conceptual Representation. *Cerebral Cortex, 21*, 2103-2112.

Hoffman, P., Pobric, G., Drakesmith, M., & Lambon Ralph, M. A. (2011). Posterior middle temporal gyrus is involved in verbal and non-verbal semantic cognition: Evidence from rTMS. *Aphasiology*, 1-12.

Hoffman, P., Rogers, T. T., & Lambon Ralph, M. A. (2011). Semantic diversity accounts for the “missing” word frequency effect in stroke aphasia: Insights using a novel method to quantify contextual variability in meaning. *Journal of Cognitive Neuroscience, 23*, 2432-2446.

Hon, N., Epstein, R. A., Owen, A. M., & Duncan, J. (2006). Frontoparietal Activity with Minimal Decision and Control. *The Journal of Neuroscience, 26*(38), 9805-9809.

Howard, D., & Gatehouse, C. (2006). Distinguishing semantic and lexical word retrieval deficits in people with aphasia. *Aphasiology, 20*(9-11), 921-950.

Howard, D., & Patterson, K. (1992). *Pyramid and palm trees: a test of semantic accessfrom pictures and words.* Bury Saint Edmunds: Thames Valley Test Company.

Howard, D., Patterson, K., Wise, R., Brown, W. D., Friston, K., Weiller, C., & Frackowiak, R. S. J. (1992). The cortical localization of the lexicons: Positron Emission Tomography evidence. *Brain, 115*(6), 1769-1782.

Huberle, E., & Karnath, H. O. (2012). The role of temporo-parietal junction (TPJ) in global Gestalt perception. *Brain Structure and Function, 217*(3), 735-746.

Hubner, R., & Studer, T. (2009). Functional hemispheric differences for the categorization of global and local information in naturalistic stimuli. *Brain and Cognition, 69*(1), 11-18.

Humphreys, G. W., & Forde, E. M. E. (2001). Heirarchies, similarity, and interactivity in object recognition: "Category-specific" neuropsychological deficits. *Behavioural and Brain Sciences, 24*, 453-509.

Humphreys, G. W., & Forde, E. M. E. (2005). Naming a giraffe but not an animal: Base-level but not superordinate naming in a patient with impaired semantics. *Cognitive Neuropsychology, 22*, 539-558.

Humphreys, G. W., & Riddoch, M. J. (2003). A case series analysis of "category-specific" deficits of living things: The hit account. *Cognitive Neuropsychology, 20*(3), 262-306.

Humphreys, G. W., Riddoch, M. J., & Quinlan, P. T. (1988). Cascade processes in picture identification. *Cognitive Neuropsychology, 5*, 67-103.

Indefrey, P., & Levelt, W. J. M. (2004). The spatial and temporal signatures of word production components. *Cognition, 92*(1-2), 101-144.

James, T. W., Culham, J., Humphrey, G. K., Milner, A. D., & Goodale, M. A. (2003). Ventral occipital lesions impair object recognition but not object-directed grasping: An fMRI study. *Brain, 126*, 2463-2475.

Jefferies, E. (in press). The neural basis of semantic cognition: Converging evidence from neuropsychology, neuroimaging and TMS. *Cortex*.

Jefferies, E., Baker, S. S., Doran, M., & Lambon Ralph, M. A. (2007). Refractory effects in stroke aphasia: A consequence of poor semantic control. *Neuropsychologia, 45*(5), 1065-1079

Jefferies, E., Hoffman, P., Jones, R. W., & Lambon Ralph, M. A. (2008). The impact of semantic impairment on verbal short-term memory in stroke aphasia and semantic dementia: A comparative study. *Journal of Memory and Language, 58*(1), 66-87.

Jefferies, E., & Lambon Ralph, M. A. (2006). Semantic impairment in stroke aphasia versus semantic dementia: a case-series comparison. *Brain, 129*(8), 2132-2147.

Jefferies, E., Patterson, K., Jones, R. W., & Lambon Ralph, M. A. (2009). Comprehension of concrete and abstract words in semantic dementia. *Neuropsychology, 23*(4), 492-499.

Jefferies, E., Patterson, K., & Lambon Ralph, M. A. (2008). Deficits of knowledge versus executive control in semantic cognition: Insights from cued naming. *Neuropsychologia, 46*(2), 649-658.

Jefferies, E., Rogers, T. T., & Lambon Ralph, M. A. (2011). Premorbid expertise produces category-specific impairment in a domain-general semantic disorder. *Neuropsychologia, 49*, 3213-3223.

Jiang, Y., Haxby, J. V., Martin, A., Ungerleider, L. G., & Parasuraman, R. (2000). Complementary neural mechanisms for tracking items in human working memory. *Science, 287*(5453), 643-646.

Johnson-Frey, S. H. (2004). The neural bases of complex tool use in humans. *Trends in Cognitive Sciences, 8*(2), 71-78.

Jung-Beeman, M. (2005). Bilateral brain processes for comprehending natural language. *Trends in Cognitive Sciences, 9*(11), 512-518.

Jung-Beeman, M., Bowden, E. M., & Gernsbacher, M. A. (2000). Right and left hemisphere cooperation for drawing predictive and coherence inferences during normal story comprehension. *Brain and Language, 71*(2), 310-336.

Kable, J. W., Kan, I. P., Wilson, A., Thompson-Schill, S. L., & Chatterjee, A. (2005). Conceptual representations of action in the lateral temporal cortex. *Journal of Cognitive Neuroscience, 17*, 1855-1870.

Kable, J. W., Lease-Spellmeyer, J., & Chatterjee, A. (2002). Neural substrates of action event knowledge. *Journal of Cognitive Neuroscience, 14*(5), 795-805.

Kacinik, N. A., & Chiarello, C. (2007). Understanding metaphoric language: is the right hemisphere uniquely involved? *Brain and Language, 100*, 188-207.

Kalenine, S., Buxbaum, L. J., & Coslett, H. B. (2010). Critical brain regions for action recognition: Lesion symptom mapping in left hemisphere stroke. *Brain, 133*, 3269-3280.

Kanwisher, N., McDermott, J., & Chun, M. M. (1997). The fusiform face area: A module in human extrastriate cortex speicalized for face perception. *Journal of Neuroscience, 17*, 4302-4311.

Kaplan, E., Goodglass, H., & Weintraub, S. (1983). *Boston Naming Test*. Philadelphia: Lea & Febiger.

Karnath, H. O., Ruter, J., Mandler, A., & Himmelbach, M. (2009). The anatomy of object recognition-visual form agnosia caused by medial occipitotemporal stroke. *Journal of Neuroscience, 29*, 5854-5862.

Katz, R. B., & Goodglass, H. (1990). Deep dysphasia: Analysis of a rare form of repetition disorder. *Brain and Language, 39*, 153-185.

Kawashima, R., Kazunori, S., Hiroshi, I., Shuichi, O., Shozo, F., Ryoui, G., Masamichi, K., Seiro, Y., Tsuneo, T., Kunihisa, T., Toru, Y., & Hiroshi, F. (1996). Functional anatomy of go/no-go discrimination and response selection — a PET study in man. *Brain Research, 728*(1), 79-89.

Kay, J., Lesser, R., & Coltheart, M. (1992). *Psycholinguistic assessments of language processing in aphasia (PALPA)*. Hove, UK: Lawrence Erlbaum Associates.

Kellenbach, M. L., Brett, M., & Patterson, K. (2003). Actions speak louder than functions: The importance of manipulability and action in tool representation. *Journal of Cognitive Neuroscience, 15*(1), 30-46.

Kintsch, W. (1998). *Comprehension: A paradigm for cognition*. Cambridge, UK: Cambridge University Press.

Kircher, T. T. J., Brammer, M. J., Tous, A. N., Williams, S. C., & McGuire, P. K. (2001). Engagement of right temporal cortex during processing of linguistic context. *Neuropsychologia, 39*, 798-809.

Kircher, T. T. J., Rapp, A. M., Grodd, W., Buchkremer, G., Weiskopf, N., Lutzenberger, W., Ackermann, H., & Mathiak, K. (2004). Mismatch negativity responses in schizophrenia: A combined fMRI and whole-head MEG study. *American Journal of Psychiatry, 161*, 294-304.

Kiss, G. R., Armstrong, C., Milroy, R., & Piper, J. (1973). *An associative thesaurus of English and its computer analysis*. Edinburgh: University Press.

Klepousniotou, E. (2002). The processing of lexical ambiguity: Homonymy and polysemy in the mental lexicon. *Brain and Language, 81*(1-3), 205-223.

Klepousniotou, E., & Baum, S. R. (2005a). Processing homonym and polysemy: Effects of sentential context and time-course following unilateral brain damage. *Brain and Language, 95*(3), 365-382.

Klepousniotou, E., & Baum, S. R. (2005b). Unilateral brain damage effects on processing homonymous and polysemous words. *Brain and Language, 93*(3), 308-326.

Knight, R. T., Scabini, D., Woods, D. L., & Clayworth, C. C. (1989). Contributions of temporal-parietal junction to the human auditory P3. *Brain Research, 502*(1), 109-116.

Kolb, B., & Taylor, L. (2000). *Facial expression, emotion and hemispheric organization*. Oxford: Oxford University Press.

Konen, C. S., Behrmann, M., Nishimura, M., & Kastner, S. (2011). The functional neuroanatomy of object agnosia: A case study. *Neuron, 71*(1), 49-60.

Konishi, S., Nakajima, K., Uchida, I., Kikyo, H., Kameyama, M., & Miyashita, Y. (1999). Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. *Brain, 122*, 981-991.

Krieger-Redwood, K. (2012). *Exploring the nature of the semantic control network.* University of York, York.

Krieger-Redwood, K., & Jefferies, E. (in prep.). The role of LIFG in picture naming: A refractory paradigm.

Kriegeskorte, N., Formisano, E., Sorger, B., & Goebel, R. (2007). Individual faces elicit distinct response patterns in human anterior temporal cortex. *Proceedings of the National Academy of Sciences, 104*(51), 20600-20605.

Kucharska-Pietura, K., Phillips, M. L., Gernand, W., & David, A. S. (2003). Perception of emotions from faces and voices following unilateral brain damage. *Neuropsychologia, 41*, 1082-1090.

Lambon Ralph, M. A. (1998). Distributed versus localist representations: Evidence from a study of item consistency in a case of classical anomia. *Brain and Language, 64*, 339-360.

Lambon Ralph, M. A., Cipolotti, L., Manes, F., & Patterson, K. (2010). Taking both sides: do unilateral anterior temporal lobe lesions disrupt semantic memory? *Brain, 133*, 3243-3255.

Lambon Ralph, M. A., Ehsan, S., Baker, G. A., & Rogers, T. T. (2012). Semantic memory is impaired in patients with unilateral anterior temporal lobe resection for temporal lobe epilepsy. *Brain, 135*, 242-258.

Lambon Ralph, M. A., Graham, K. S., Ellis, A. W., & Hodges, J. R. (1998). Naming in semantic dementia - What matters? *Neuropsychologia, 36*, 775-784.

Lambon Ralph, M. A., Graham, K. S., Patterson, K., & Hodges, J. R. (1999). Is a picture worth a thousand words? evidence from concept definitions by patients with semantic dementia. *Brain and Language, 70*(3), 309-335.

Lambon Ralph, M. A., McClelland, J. L., Patterson, K., Galton, C. J., & Hodges, J. R. (2001). No Right to Speak? The Relationship between Object Naming and Semantic Impairment: Neuropsychological Evidence and a Computational Model. *Journal of Cognitive Neuroscience, 13*(3), 341-356.

Lambon Ralph, M. A., Moriarty, L., & Sage, K. (2002). Anomia is simply a reflection of semantic and phonological impairments: Evidence from a case-series study. *Aphasiology, 16*(1-2), 56-82.

Lambon Ralph, M. A., & Patterson, K. (2003). Gogi aphasia or semantic dementia? Neuropsychological evidence for an amodal, dynamic semantic system. *Brain and Language, 87*(1), 83-83.

Lambon Ralph, M. A., & Patterson, K. (2008). Generalization and differentiation in semantic memory: insights from semantic dementia. *Annals of the New York Academy of Science, 1124*, 61-76.

Lambon Ralph, M. A., Pobric, G., & Jefferies, E. (2009a). Conceptual Knowledge Is Underpinned by the Temporal Pole Bilaterally: Convergent Evidence from rTMS. *Cereb. Cortex, 19*(4), 832-838.

Lambon Ralph, M. A., Pobric, G., & Jefferies, E. (2009b). Conceptual knowledge is underpinned by the temporal pole bilaterally: Convergent evidence from rTMS. *Cerebral Cortex, 19*(4), 832-838.

Lambon Ralph, M. A., Sage, K., Jones, R. W., & Mayberry, E. J. (2010). Coherent concepts are computed in the anterior temporal lobes. *Proceedings of the National Academy of Sciences, 107*(6), 2717-2722.

Lambon Ralph, M. A., Sage, K., & Roberts, J. (2000). Classical anomia: A neuropsychological perspective on speech production. *Neuropsychologia, 38*(2), 186-202.

Langner, O., Dotsch, R., Bijstra, G., Wigboldus, D. H. J., Hawk, S. T., & van Knippenberg, A. (2010). Presentation and validation of the Radboud Faces Database. *Cognition & Emotion, 24*(8), 1377-1388.

Larsby, B., Mathias, H., Bjorn, L., & Stig, A. (2005). Cognitive performance and perceived effort in speech processing tasks: Effects of different noise backgrounds in normal-hearing and hearing-impaired subjects. *International Journal of Audiology, 44*(3), 131-143.

Leder, H., & Carbon, C. C. (2006). Face-specific configural processing of relational information. *British Journal of Psychology, 97*(1), 19-29.

Lee, S. S., & Dapretto, M. (2006). Metaphorical vs. literal word meanings: fMRI evidence against a selective role of the right hemisphere. *NeuroImage, 29*(2), 536-544.

Lenartowicz, A., Verbruggen, F., Logan, G. D., & Poldrack, R. A. (2011). Inhibition-related activation in the right inferior frontal gyrus in the absence of inhibitory cues. *Journal of Cognitive Neuroscience, 23*(11), 3388-3399.

Lerner, Y., Honey, C. J., Silbert, L. J., & Hasson, U. (2011). Topographic mapping of a hierachy of temporal receptive windows using a narrated story. *The Journal of Neuroscience, 31*, 2906-2915.

Leslie, A. M., Friedman, O., & German, T. P. (2004). Core mechanisms in "theory of mind". *Trends in Cognitive Sciences, 8*, 528-533.

Leslie, A. M., German, T. P., & Pollizi, P. (2005). Belief-desire reasoning as a process of selection. *Cognitive Psychology, 50*, 40-85.

Levelt, W. J. M. (2001). Spoken word production: A theory of lexical access. *Proceedings of the National Academy of Sciences, 98*(23), 13464-13471.

Levy-Agresti, J., & Sperry, R. W. (1968). Differential perceptual capacities in the major and the minor hemispheres. *Proceedings of the National Academy of Sciences, 61*, 1151.

Lewis, J. W. (2006). Cortical networks related to human use of tools. *Neuroscientist, 12*(3), 211-231.

Lewis, J. W., Wightman, F. L., Brefczynski, J. A., Phinney, R. E., Binder, J. R., & DeYoe, E. A. (2004). Human Brain Regions Involved in Recognizing Environmental Sounds. *Cereb. Cortex, 14*(9), 1008-1021.

Li, K. Z. H., & Lindenberger, U. (2002). Relations between aging sensory/sensorimotor and cognitive functions. *Neuroscience & Biobehavioral Reviews, 26*(7), 777-783.

Liu, W., Miller, B. L., Kramer, J. H., Rankin, K. P., Wyss-Coray, C., Gearhart, R., Phengrasamy, L., Weiner, M. W., & Rosen, H. J. (2004). Behavioral disorders in the frontal and temporal variants of frontotemporal dementia. *Neurology, 62*(5), 742-748.

Manly, T., Owen, A. M., McAvinue, L., Datta, A., Lewis, G. H., Scott, S. K., Rorden, C., Pickard, J., & Robertson, I. H. (2003). Enhancing the sensitivity of a sustained attention task to frontal damage: Convergent clinical and functional imaging evidence. *Neurocase, 9*(4), 340-349.

Marek, T., Fafrowicz, M., Golonka, K., Mojsa-Kaja, J., Oginska, H., Tucholska, K., Urbanik, A., Beldzik, E., & Domagalik, A. (2010). Diurnal patterns of activity of the orienting and executive attention neuronal networks in subjects performing a stroop-like task: A functional magnetic resonance imaging study. *Chronobiology International, 27*(5), 945-958.

Marinkovic, K., Baldwin, S., Courtney, M. G., Witzel, T., Dale, A. M., & Halgren, E. (2011). Right hemisphere has the last laugh: neural dynamics of joke appreciation. *Cognitive, Affective, & Behavioral Neuroscience, 11*(1), 113-130.

Marinkovic, K., Dhond, R. P., Dale, A. M., Glessner, M., Carr, V., & Halgren, E. (2003). Spatiotemporal Dynamics of Modality-Specific and Supramodal Word Processing. *Neuron, 38*(3), 487-497.

Marshall, J. C., Pring, T., Chiat, S., & Robson, J. (2001). When ottoman is easier than chair: An inverse frequency effect in jargon aphasia. *Cortex, 37*, 33-53.

Martin, A. (2007). The Representation of Object Concepts in the Brain. *Annual Review of Psychology, 58*(1), 25-45.

Martin, A., & Chao, L. L. (2001). Semantic memory and the brain: structure and processes. *Current Opinion in Neurobiology, 11*(2), 194-201.

Martin, A., Haxby, J. V., Lalonde, F. M., Wiggs, C. L., & Ungerleider, L. G. (1995). Discrete cortical regions associated with knowledge of color and knowledge of action. *Science, 270*(5233), 102-105.

Martin, A., Ungerleider, L. G., & Haxby, J. V. (2000). *Category specificity and the brain: The sensory/ motor model of semantic representations of objects*. Cambridge, MA: MIT Press.

Martin, A., Wiggs, C. L., Ungerleider, L. G., & Haxby, J. V. (1996). Neural correlates of category-specific knowledge. *Nature, 379*, 649-652.

Martin, I., & McDonald, S. (2003). Weak coherence, no theory of mind, or executive dysfunction? Solving the puzzle of pragmatic language disorders. *Brain and Language, 85*, 451-466.

Martin, R. C., & Byrne, M. D. (2006). Why opening a door is as easy as eating an apple: A reply to Thompson-Schill and Botvinick (2006). *Psychonomic Bulletin & Review, 13*(3), 409-411.

Martin, R. C., & Cheng, Y. (2006). Selection demands versus association strength in the verb generation task. *Psychonomic Bulletin & Review, 13*(3), 396-401.

Martinez, A., Moses, P., Frank, L., Buxton, R., Wong, E. C., & Stiles, J. (1997). Hemispheric asymmetries in global and local processes: Evidence from fMRI. *NeuroReport, 8*(7), 1685-1689.

Mashal, N., & Faust, M. (2008). Right hemisphere sensitivity to novel metaphoric relations: Application of the signal detection theory. *Brain and Language, 104*(2), 103-112.

Mashal, N., & Faust, M. (2009). Conventionalisation of novel metaphors: A shift in hemispheric asymmetry. *Laterality: Asymmetries of Body, Brain and Cognition, 14*(6), 573 - 589.

Mashal, N., & Faust, M. (2010). The effects of metaphoricity and presentation style on brain activation during text comprehension. *Metaphor and Symbol, 25*(1), 19-33.

Mashal, N., Faust, M., Hendler, T., & Jung-Beeman, M. (2009). An fMRI study of processing novel metaphoric sentences. *Laterality: Asymmetries of Body, Brain and Cognition, 14*(1), 30 - 54.

Mason, R. A., Williams, D. L., Kana, R. K., Minshew, N., & Just, M. A. (2008). Theory of mind disruption and recruitment of the right hemisphere during narrative comprehension in autism. *Neuropsychologia, 46*(1), 269-280.

Masson, M. (1991). *A distributed memory model of context effects in word identification*. Hilldale, NJ: Lawrence Erlbaum Associates.

Matsumoto, R., Nair, D. R., LaPresto, E., Najm, I., & Bingaman, W. (2004). Functional connectivity in the human language system: a cortico-cortical evoked potential study. *Brain, 127*(10), 2316-2330.

Maurer, D., Le Grand, R., & Mondloch, C. J. (2002). The many faces of configural processing. *Trends in Cognitive Sciences, 6*(6), 255-260.

Mayberry, E. J., Sage, K., Ehsan, S., & Lambon Ralph, M. A. (2011). Relearning in semantic dementia reflects contributions from both medial temporal lobe episodic and degraded neocortical semantic systems: Evidence in support of the complementary learning systems theory. *Neuropsychologia, 49*, 3591-3598.

McCarthy, G., Luby, M., Gore, J. C., & Goldman-Rakic, P. (1997). Infrequent events transiently activate human prefrontal and parietal cortex as measured by functional MRI. *Journal of Neurophysiology, 77*(3), 1630-1634.

McCarthy, R. A., & Warrington, E. K. (1985). Category specificity in an agrammatic patient: The relative impairment of verb retrieval and comprehension. *Neuropsychologia, 23*, 709-727.

McClelland, J. L., & Rogers, T. T. (2003). The parallel distributed processing approach to semantic cognition. *Nat Rev Neurosci, 4*(4), 310-322.

McDonald, S. (1993). Pragmatic language skills after closed head injury: Ability to meet the informational needs of the listener. *Brain and Language, 44*, 28-46.

McDonald, S., & Pearce, S. (1996). Clinical insights into pragmatic theory: Frontal lobe deficits and sarcasm. *Brain and Language*, 81-104.

McKinnon, M. C., & Moscovitch, M. (2007). Domain-general contributions to social reasoning: Theory of Mind and deontic reasoning re-explored. *Cognition, 102*, 179-218.

McNeil, J. E., Cipolotti, L., & Warrington, E. K. (1994). The accessibility of proper names. *Neuropsychologia, 32*(2), 193-208.

Menon, V., Adleman, N. E., White, C., Glover, G., & Reiss, A. (2001). Error-related brain activation during a Go/NoGo response inhibition task. *Human Brain Mapping, 12*(3), 131-143.

Merrill, E. C., Sperber, R. D., & McCauley, C. (1981). Differences in semantic encoding as a function of reading comprehension skill. *Memory & Cognition, 9*(6), 618-624.

Metzler, C. (2001). Effects of Left Frontal Lesions on the Selection of Context-Appropriate Meanings. *Neuropsychology, 15*(3), 315-328.

Meyer, M., Steinhauer, K., Alter, K., Friederici, A. D., & Von Cramon, D. Y. (2004). Brain activity varies with modulation of dynamic pitch variance in sentence melody. *Brain and Language, 89*, 277-289.

Milham, M. P., Banich, M. T., Webb, A., Barad, V., Cohen, N. J., Wszalek, T., & Kramer, A. F. (2001). The relative involvement of anterior cingulate and prefrontal cortex in attentional control depends on the nature of the conflict. *Cognitive Brain Research, 12*, 467-473.

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience, 24*, 167-202.

Mion, M., Patterson, K., Acosta-Cabronero, J., Pengas, G., Izquierdo-Garcia, D., Hong, Y. T., Fryer, T. D., Williams, G. B., Hodges, J. R., & Nestor, P. J. (2010). What the left and right anterior fusiform gyri tell us about semantic memory. *Brain, 133*(11), 3256-3268.

Mirman, D. (2011). Effects of near and distant semantic neighbors on word production. *Cognitive, Affective, & Behavioral Neuroscience, 11*(1), 32-43.

Mitchell, R. L., & Crow, T. J. (2005). Right hemisphere language functions and schizophrenia: the forgotten hemisphere? *Brain, 128*, 963-978.

Moll, J., de Oliveira-Souza, R., Bramati, I. E., & Grafman, J. (2002). Functional networks in emotional moral and nonmoral social judgments. *NeuroImage, 16*, 696-703.

Moll, J., Eslinger, P. J., & Oliveira-Souza, R. (2001). Frontopolar and anterior temporal cortex activation in a moral judgment task: Preliminary functional MRI results in normal subjects. *Arquivos de Neuro-Psiquiatria, 59*, 657-664.

Moore, C. J., & Price, C. J. (1999). A functional neuroimaging study of the variables that generate category specific object processing differences. *Brain, 122*, 943-962.

Morris, J. S., Frith, C. D., Perrett, D. I., Rowland, D., Young, A. W., Calder, A. J., & Dolan, R. J. (1996). A differential neural response in the human amygdala to fearful and happy facial expressions. *Nature, 31*, 812-815.

Mort, D. J., Malhotra, P., Mannan, S. K., Rorden, C., Pambakian, A., Kennard, C., & Husain, M. (2003). The anatomy of visual neglect. *Brain, 126*(9), 1986-1997.

Moss, H., Abdallah, S., Fletcher, P., Bright, P., Pilgrim, L., Acres, K., & Tyler, L. K. (2005). Selecting among competing alternatives: selection and retrieval in the left inferior frontal gyrus. *Cereb. Cortex, 15*(11), 1723-1735.

Moss, H., Tyler, L. K., & Jennings, F. (1997). When leopards lose their spots: Knowledge of visual properties in category-specific deficits for living things. *Cognitive Neuropsychology, 14*, 901-950.

Mummery, C. J., Patterson, K., Hodges, J. R., & Price, C. J. (1998). Functional Neuroanatomy of the Semantic System: Divisible by What? *Journal of Cognitive Neuroscience, 10*(6), 766-777.

Mummery, C. J., Patterson, K., Price, C. J., Ashburner, J., Frackowiak, R. S. J., & Hodges, J. R. (2000). A voxel-based morphometry study of semantic dementia: Relationship between temporal lobe atrophy and semantic memory. *Annals of Neurology, 47*(1), 36-45.

Murphy, D. R., Schneider, B. A., Speranza, F., & Moraglia, G. (2006). A comparison of higher order auditory processes in younger and older adults. *Psychology and Aging, 21*(4), 763-773.

Murray, J. E., Yong, E., & Rhodes, G. (2000). Revisiting the perception of upside-down faces. *Psychological Science, 11*, 492-496.

Myers, P. S. (1983). *Right hemisphere communication disorders*. New York: Thieme-Stratton.

Naeser, M. A., Martin, P. I., Nicholas, M., Baker, E. H., Seekins, H., Kobayashi, M., Theoret, H., Fregni, F., Maria-Tormos, J., Kurland, J., Doron, K. W., & Pascual-Leone, A. (2005). Improved picture naming in chronic aphasia after TMS to part of right Broca's area: an open-protocol study. *Brain and Language, 93*, 95-105.

Nagel, I. E., Schumacher, E. H., Goebel, R., & D'Esposito, M. (2008). Functional MRI investigation of verbal selection mechanisms in lateral prefrontal cortex. *NeuroImage, 43*(4), 801-807.

Nakamura, K., Kawashima, R., Ito, K., Sugiura, M., Kato, T., Nakamura, A., Hatano, K., Nagumo, S., Kubota, K., Fukuda, H., & Kojima, S. (1999). Activation of the right inferior frontal cortex during assessment of facial emotion. *Journal of Neurophysiology, 82*, 1610-1614.

Neely, J. (1990). *Semantic priming in visual word recognition: A selective review of current theories and findings*. Hillsdale, NJ: Lawrence Erlbaum Associates.

Nelson, J. K., Reuter-Lorenz, P. A., Persson, J., Sylvester, C. Y. C., & Jonides, J. (2009). Mapping interference resolution across task domains: A shared control process in left inferior frontal gyrus. *Brain Research, 1256*(23), 92-100.

Nestor, P. J., Fryer, T. D., & Hodges, J. R. (2006). Declarative memory impairments in Alzheimer's disease and semantic dementia. *NeuroImage, 30*(3), 1010-1020.

Nickels, L., & Howard, D. (1995). Aphasic naming: What matters? *Neuropsychologia, 33*, 1281-1303.

Nijboer, T. C. W., & Jellema, T. (2012). Unequal impairment in the recognition of positive and negative emotions after right hemisphere lesions: A left hemisphere bias for happy faces. *Journal of Neuropsychology, 6*(1), 79-93.

Noonan, K. A., Jefferies, E., Corbett, F., & Lambon Ralph, M. A. (2010). Elucidating the nature of deregulated semantic cognition in semantic aphasia: Evidence for the roles of prefrontal and temporo-parietal cortices. *Journal of Cognitive Neuroscience, 22*(7), 1597-1613.

Noonan, K. A., Jefferies, E., Visser, M. E. J., & Lambon Ralph, M. A. (submitted). Going beyond inferior prefrontal involvement in semantic control: Evidence for the additional contribution of parietal and posterior middle temporal cortex.

Noppeney, U. T. A., Patterson, K., Tyler, L. K., Moss, H., Stamatakis, E. A., Bright, P., Mummery, C. J., & Price, C. J. (2007). Temporal lobe lesions and semantic impairment: A comparison of herpes simplex virus encephalitis and semantic dementia. *Brain, 130*, 1138-1147.

Noppeney, U. T. A., Phillips, J., & Price, C. J. (2004). The neural areas that control the retrieval and selection of semantics. *Neuropsychologia, 42*, 1269-1280.

Noppeney, U. T. A., & Price, C. J. (2002). Retrieval of visual, auditory, and abstract semantics. *NeuroImage, 15*, 917-926.

Norbury, C. F. (2005). The relationship between theory of mind and metaphor: Evidence from children with language impairment and autistic spectrum disorder. *British Journal of Developmental Psychology, 23*, 383-399.

Novick, J., Kan, I. P., Trueswell, J., & Thompson-Schill, S. L. (2009). A case for conflict across multiple domains: Memory and language impairments following damage to ventrolateral prefrontal cortex. *Cognitive Neuropsychology, 26*, 527-567.

Obleser, J., & Kotz, S. A. (2009). Expectancy Constraints in Degraded Speech Modulate the Language Comprehension Network. *Cerebral Cortex, 20*(3), 633-640.

Ogar, J. M., Baldo, J. V., Wilson, S. M., Brambati, S. M., Miller, B. L., Dronkers, N. F., & Gomo-Tempini, M. L. (2011). Semantic dementia and persisting Wernicke's aphasia: Linguistic and anatomical profiles. *Brain and Language, 117*(1), 28-33.

Oliveira-Souza, R., & Moll, J. (2000). The moral brain: Functional MRI correlates of moral judgment in normal adults. *Neurology, 54*(S3), 252.

Onifer, W., & Swinney, D. A. (1981). Accessing lexical ambiguities during sentence comprehension: effects of frequency of meaning and contextual bias. *Memory & Cognition, 9*(3), 225-236.

Palmeri, T. J., & Gauthier, I. (2004). Visual object understanding. *Nature Reviews Neuroscience, 5*(4), 291-303.

Parker, G. J. M., Luzzi, S., Alexander, D. C., Wheeler-Kingshott, C. A., Ciccarelli, O., & Lambon Ralph, M. A. (2005). Lateralization of ventral and dorsal auditory-language pathways in the human brain. *NeuroImage, 24*(3), 656-666.

Patterson, K., Nestor, P. J., & Rogers, T. T. (2007). Where do you know what you know? The representation of semantic knowledge in the human brain. *Nat Rev Neurosci, 8*(12), 976-987.

Patterson, K., Purell, C., & Morton, J. (1983). *Facilitation of word retrieval in aphasia*. London: Edward Arnold.

Pavio, A. (1986). *Mental representations: A dual-coding approach*. Oxford: Oxford University Press.

Peers, P. V., Ludwig, C. J. H., Rorden, C., Cusack, R., Bonfiglioli, C., Bundesen, C., Driver, J., Antoun, N., & Duncan, J. (2005). Attentional functions of parietal and frontal cortex. *Cerebral Cortex, 15*(10), 1469-1484.

Pelgrims, B., Olivier, E., & Andres, M. (2011). Dissociation between manipulation and conceptual knowledge of object use in the supramarginalis gyrus. *Human Brain Mapping, 32*(11), 1802-1810.

Pelphrey, K. A., Viola, R. J., & McCarthy, G. (2004). When strangers pass: Processing of mutual and averted social gaze in the superior temporal sulcus. *Psychological Science, 15*, 598-603.

Perani, D., Cappa, S. F., Schnur, T. T., Tettamanti, M., Collina, S., Rosa, M., & Fazio, F. (1999). The neural correlates of verb and noun processing: A PET study. *Brain, 122*, 2337-2344.

Perani, D., Cappa, S. F., Tettamanti, M., Rosa, M., Scifo, P., Miozzo, A., Basso, A., & Fazio, F. (2003). A fMRI study of word retrieval in aphasia. *Brain and Language, 85*, 357-368.

Perry, R., Rosen, H. J., Kramer, J., Beer, J., Levenson, R., & Miller, B. L. (2001). Hemispheric dominance for emotions, empathy and social behavior: Evidence from right and left handers with frontotemporal dementia. *Neurocase, 7*, 145-160.

Phan, T. G., Donnan, G. A., Wright, P. M., & Reutens, D. C. (2005). A digital map of middle cerebral artery infarcts associated with middle cerebral artery trunk and branch occlusion. *Stroke, 36*(5), 986-991.

Phan, T. G., Fong, A. C., Donnan, G. A., & Reutens, D. C. (2007). Digital map of posterior cerebral artery infarcts associated with posterior cerebral artery trunk and branch occlusion. *Stroke, 38*(6), 1805-1811.

Phillips, J., Humphreys, G. W., Noppeney, U. T. A., & Price, C. J. (2002). The neural substrates of action retrieval: An examination of semantic and visual routes to action. *Visual Cognition, 9*(4-5), 662-684.

Pichora-Fuller, M. K., Schneider, B. A., & Daneman, M. (1995). How young and old adults listen to and remember speech in noise. *Journal of the Acoustical Society of America, 97*, 593-608.

Pitcher, D., Walsh, V., Yovel, G., & Duchaine, B. (2007). TMS evidence for the involvement of the right occipital face area in early face processing. *Current Biology, 17*, 1568-1573.

Plaut, D. C. (2002). Graded modality-specific specialisation in semantics: A computational account of optic aphasia. *Cognitive Neuropsychology, 19*, 603-639.

Plaut, D. C., & Shallice, T. (1993). Deep dyslexia: A case stud in connectionist neuropsychology. *Cognitive Neuropsychology, 10*, 377-500.

Pobric, G., Jefferies, E., & Lambon Ralph, M. A. (2007). Anterior temporal lobes mediate semantic representation: Mimicking semantic dementia by using rTMS in normal participants. *Proceedings of the National Academy of Sciences, 104*(50), 20137-20141.

Pobric, G., Jefferies, E., & Lambon Ralph, M. A. (2010a). Amodal semantic representations depend on both anterior temporal lobes: Evidence from repetitive transcranial magnetic stimulation. *Neuropsychologia, 48*(5), 1336-1342.

Pobric, G., Jefferies, E., & Lambon Ralph, M. A. (2010b). Category-specific versus category-general semantic impairment induced by transcranial magnetic stimulation. *Current Biology, 20*(10), 964-968.

Pobric, G., Mashal, N., Faust, M., & Lavidor, M. (2008). The Role of the Right Cerebral Hemisphere in Processing Novel Metaphoric Expressions: A Transcranial Magnetic Stimulation Study. *Journal of Cognitive Neuroscience, 20*(1), 170-181.

Poeppel, D. (2001). Pure word deafness and the bilateral processing of the speech code. *Cognitive Science, 25*, 679-693.

Poldrack, R. A., Wagner, A. D., Prull, M. W., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. E. (1999). Functional Specialization for Semantic and Phonological Processing in the Left Inferior Prefrontal Cortex. *NeuroImage, 10*(1), 15-35.

Price, C. J., & Crinion, J. (2005). The latest on functional imaging studies of aphasic stroke. *Current opinion in Neurology, 18*, 429-434.

Price, C. J., & Devlin, J. T. (2003). The myth of the visual word form area. *NeuroImage, 19*(3), 473-481.

Price, C. J., Devlin, J. T., Moore, C. J., Morton, C., & Laird, A. R. (2005). Meta-analyses of object naming: Effect of baseline. *Human Brain Mapping, 25*(1), 70-82.

Price, C. J., & Friston, K. (2002). *What has neuroimaging contributed to category specificity?* . Sussex: Psychology Press.

Price, C. J., Moore, C. J., Humphreys, G. W., & Wise, R. (1997). Segregating Semantic from Phonological Processes during Reading. *Journal of Cognitive Neuroscience, 9*(6), 727-733.

Price, C. J., Wise, R., Warburton, E. A., Moore, C. J., Howard, D., Patterson, K., Frackowiak, R. S. J., & Friston, K. (1996). Hearing and saying. The functional neuro-anatomy of auditory word processing. *Brain, 119*, 919-931.

Raichle, M. E., Fiez, J. A., Videen, T. O., MacLeod, A. K., Pardo, J. V., Fox, P. T., & Petersen, S. E. (1994). Practice-related Changes in Human Brain Functional Anatomy during Nonmotor Learning. *Cereb. Cortex, 4*(1), 8-26.

Rajah, M. N., Ames, B. J., & D'Esposito, M. (2008). Prefrontal contributions to domain-general executive control processes during temporal context retrieval. *Neuropsychologia, 46*(4), 1088-1103.

Rankin, K. P., Gorno-Tempini, M. L., Allison, S. C., Stanley, C. M., Glenn, S., Weiner, M. W., & Miller, B. L. (2006). Structural anatomy of empathy in neurodegenerative disease. *Brain, 129*(22), 2945-2956.

Raposo, A., Mendes, M., & Marques, J. F. (2012). The heirarchical organization of semantic memory: Executive function in the processing of superordinate concepts. *NeuroImage, 59*, 1870-1878.

Rapp, A. M., Erb, M., Grodd, W., Bartels, M., & Markert, K. (2011). Neural correlates of metonymy resolution. *Brain and Language, 119*(3), 195-205.

Rapp, A. M., Leube, D. T., Erb, M., Grodd, W., & Kircher, T. T. J. (2004). Neural correlates of metaphor processing. *Cognitive Brain Research, 20*(3), 395-402.

Rapp, A. M., Leube, D. T., Erb, M., Grodd, W., & Kircher, T. T. J. (2007). Laterality in metaphor processing: Lack of evidence from functional magnetic resonance imaging for the right hemisphere theory. *Brain and Language, 100*(2), 142-149.

Rapp, A. M., Mutschler, D. E., & Erb, M. (2012). Where in the brain is nonliteral language? A coordinate-based meta-analysis of functional magnetic resonance imaging studies. *NeuroImage*.

Rapp, B. C., & Caramazza, A. (1993). On the distinction between deficits of access and deficits of storage: A question of theory. *Cognitive Neuropsychology, 10*(2), 113-141.

Raven, J. C. (1962). *Coloured Progressive Matrices Sets A, AB, B.* London: H. K. Lewis.

Raymer, A. M., Foundas, A. L., Maher, L. M., Greenwald, M. L., Morris, M., Rothi, L. J. G., & Heilman, K. M. (1997). Cognitive neuropsychological analysis and neuroanatomic correlates in a case of acute anomia. *Brain and Language, 58*(1), 137-156.

Rehak, A., Kaplan, J. A., & Gardner, H. (1992). Sensitivity to conversational deviance in right hemisphere damaged patients. *Brain and Language, 42*, 203-217.

Reitan, R. M. (1958). Validity of the Trail Making test as an indicator of organic brain damage. *Perceptual and Motor Skills, 8*, 271-276.

Riddoch, M. J., & Humphreys, G. W. (1987a). A case of integrative visual agnosia. *Brain, 110*, 1431-1462.

Riddoch, M. J., & Humphreys, G. W. (1987b). Visual object processing in optic aphasia: A case of semantic access agnosia. *Cognitive Neuropsychology, 4*(2), 131-185.

Riddoch, M. J., Humphreys, G. W., Coltheart, M., & Funnell, E. (1988). Semantic systems or system? Neuropsychological evidence re-examined. *Cognitive Neuropsychology, 5*(1), 3-25.

Rinaldi, M. C., Marangolo, P., & Baldassarri, F. (2004). Metaphor comprehension in right brain-damaged patients with visuo-verbal and verbal material: A dissociation (re)considered. *Cortex, 40*, 479-490.

Robertson, I. H., Ward, T., Ridgeway, V., & Nimmo-Smith, I. (1994). *The Test of Everyday Attention*. London: : Thames Valley Test Company.

Robertson, L. C., & Lamb, M. R. (1991). Neuropsychological contributions to theories of part/whole organization. *Cognitive Psychology, 23*, 299-330.

Robinson, G., Blair, J., & Cipolotti, L. (1998). Dynamic aphasia: an inability to select between competing verbal responses? *Brain, 121*(1), 77-89.

Robinson, G., Shallice, T., Bozzali, M., & Cipolotti, L. (2010). Conceptual proposition selection and the LIFG: Neuropsychological evidence from a focal frontal group. *Neuropsychologia, 48*(6), 1652-1663

Robinson, G., Shallice, T., & Cipolotti, L. (2005). A failure of high level verbal response selection in progressive dynamic aphasia. *Cognitive Neuropsychology, 22*(6), 661 - 694.

Robinson, G., Shallice, T., & Cipolotti, L. (2010). A failure of high level verbal response selection in progressive dynamic aphasia. *Cognitive Neuropsychology, 22*(6), 661 - 694.

Robson, H., Keidel, J. L., Lambon Ralph, M. A., & Sage, K. (2012). Revealing and quantifying the impaired phonological analysis underpinning impaired comprehension in Wernicke's aphasia. *Neuropsychologia, 50*, 276-288.

Robson, H., Sage, K., & Lambon Ralph, M. A. (2012). Wernicke's aphasia reflects a combination of acoustic-phonological and semantic control deficits: A case-series comparison of Wernicke's aphasia, semantic dementia and semantia aphasia. *Neuropsychologia, 50*, 266-275.

Roca, M., Parr, A., Thompson, R., Woolgar, A., Torralva, T., Antoun, N., Manes, F., & Duncan, J. (2010). Executive function and fluid intelligence after frontal lobe lesions. *Brain, 133*, 234-247.

Rodd, J. M., Davis, M. H., & Johnsrude, I. S. (2005). The neural mechanisms of speech comprehension: fMRI studies of semantic ambiguity. *Cerebral Cortex, 15*(8), 1261-1269.

Rodd, J. M., Gaskell, M. G., & Marslen-Wilson, W. D. (2004). Modelling the effects of semantic ambiguity in word recognition. *Cognitive Science, 28*, 89-104.

Rogers, T. T., Hocking, J., Noppeney, U. T. A., Mechelli, A., Gorno-Tempini, M. L., Patterson, K., & Price, C. J. (2006). Anterior temporal cortex and semantic memory: Reconciling findings from neuropsychology and functional imaging. *Cognitive, Affective, & Behavioral Neuroscience, 6*(3), 201-213.

Rogers, T. T., Lambon Ralph, M. A., Garrard, P., Bozeat, S., McClelland, J. L., Hodges, J. R., & Patterson, K. (2004). Structure and deterioration of semantic memory: a neuropsychological and computational investigation. *Psychological Review, 111*, 205-235.

Rosen, H. J., Petersen, S. E., Linenweber, M. R., Snyder, A. Z., White, D. A., Chapman, L., Dromerick, A. W., Fiez, J. A., & Corbetta, M. (2000). Neural correlates of recovery from aphasia after damage to left inferior frontal cortex. *Neurology, 55*, 1883-1894.

Roskies, A. L., Fiez, J. A., Balota, D. A., Raichle, M. E., & Petersen, S. E. (2001). Task-Dependent Modulation of Regions in the Left Inferior Frontal Cortex during Semantic Processing. *Journal of Cognitive Neuroscience, 13*(6), 829-843.

Ross, L. A., & Olson, I. R. (2010). Social cognition and the anterior temporal lobes. *NeuroImage, 49*(4), 1-22.

Rossion, B., & Gauthier, I. (2002). How does the brain process upright and inverted faces? *Behavioural and Cognitive Neuroscience Reviews, 1*(1), 63-75.

Rounis, E., Stephan, K. E., Lee, L., Siebner, H. R., Pesenti, A., Friston, K., Rothwell, J. C., & Frackowiak, R. S. J. (2006). Acute changes in frontoparietal activity after repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex in a cued reaction time task. *Journal of Neuroscience, 26*(38), 9629-9638.

Ruby, P., & Decety, J. (2003). What you believe versus what you think they believe: A neuroimaging study of conceptual perceptive-taking. *European Journal of Neuroscience, 17*, 2475-2480.

Ruby, P., & Decety, J. (2004). How would you feel versus how do you think she would feel? A neuroimaging study of perspective-taking with social emotions. *Journal of Cognitive Neuroscience, 16*, 988-999.

Rundblad, G., & Annaz, D. (2010). The atypical development of metaphor and metonymy comprehension in children with autism. *Autism, 14*, 29-46.

Sabsevitz, D. S., Medler, D. A., Seidenberg, M., & Binder, J. R. (2005). Modulation of the semantic system by word imageability. *NeuroImage, 27*(1), 188-200.

Sacchett, C., & Humphreys, G. W. (1992). Calling a squirrel and squirrel but a canoe a wigwam: A category-specific deficit for artifactual objects and body parts. *Cognitive Neuropsychology, 9*(1), 73-86.

Saffran, E. M., & Schwartz, M. F. (1994). Of cabbages and things: Semantic memory from a neuropsychological perspective - A tutorial review. *Attention and performance, 25*, 507-536.

Samson, D., Connolly, C., & Humphreys, G. W. (2007). When "happy" means "sad": Neuropsychological evidence for the right prefrontal cortex contribution to executive semantic processing. *Neuropsychologia, 45*, 896-904.

Satori, G., & Job, R. (1988). The oyster with four legs: A neuropsychological study on the interaction of visual and semantic information. *Cognitive Neuropsychology, 5*, 105-132.

Saur, D., Kreher, B. W., Schnell, S., Kummerer, D., Kellmeyer, P., Vry, M., Umarova, R., Musso, M., Glauche, V., Abel, S., Huber, W., Rijntjes, M., Hennig, J., & Weiller, C. (2008). Ventral and dorsal pathways for language. *Proceedings of the National Academy of Sciences, 105*(46), 18035-18040.

Saur, D., Lange, R., Baumgaertner, A., Schraknepper, V., Willmes, K., Rijntjes, M., & Weiller, C. (2006). Dynamics of language reorganization after stroke. *Brain, 129*(6), 1371-1384.

Saygin, A. P., Dick, F., Wilson, S. W., Dronkers, N. F., & Bates, E. (2003). Neural resources for processing language and environmental sounds: Evidence from aphasia. *Brain, 126*(4), 928-945.

Schlosser, J., Hubner, R., & Studer, T. (2009). The effect of element spacing on hemispheric asymmetries for global/local processing. *Experimental Psychology, 56*(5), 321-328.

Schmidt, G. L., DeBuse, C. J., & Seger, C. A. (2007). Right hemisphere metaphor processing? Characterizing the lateralization of semantic processes. *Brain and Language, 100*(2), 127-141.

Schnur, T. T., Lee, E., Coslett, H. B., Schwartz, M. F., & Thompson-Schill, S. L. (2005). When lexical selection gets tough, the LIFG gets going: A lesion analysis study of interference during word production. *Brain and Language, 95*, 12-13.

Schnur, T. T., Schwartz, M. F., Brecher, A., & Hodgson, C. (2006). Semantic interference during blocked-cyclic naming: Evidence from aphasia. *Journal of Memory and Language, 54*(2), 199–227.

Schnur, T. T., Schwartz, M. F., Kimberg, D. Y., Hirshorn, E., Coslett, H. B., & Thompson-Schill, S. L. (2009). Localizing interference during naming: Convergent neuroimaging and neuropsychological evidence for the function of Broca's area. *Proceedings of the National Academy of Sciences, 106*(1), 322-327.

Schwartz, M. F., Dell, G. S., Martin, N., Gahl, S., & Sobel, P. (2006). A case-series test of the interactive two-step model of lexical access: Evidence from picture naming. *Journal of Memory and Language, 54*, 228-264.

Schwartz, M. F., Kimberg, D. Y., Walker, G. M., Brecher, A., Faseyitan, O. K., Dell, G. S., Mirman, D., & Coslett, H. B. (2011). Neuroanatomical dissociation for taxonomic and thematic knowledge in the human brain. *Proceedings of the National Academy of Sciences, 108*(20), 8520-8524.

Schwartz, M. F., Kimberg, D. Y., Walker, G. M., Faseyitan, O., Brecher, A., Dell, G. S., & Coslett, H. B. (2009). Anterior temporal involvement in semantic word retrieval: voxel-based lesion-symptom mapping evidence from aphasia. *Brain, 132*(12), 3411-3427.

Scott, S. K., Blank, S. C., Rosen, S., & Wise, R. (2000). Identification of a pathway for intelligible speech in the left temporal lobe. *Brain, 123*, 2400-2406.

Scott, S. K., & Johnsrude, I. S. (2003). The neuroanatomical and functional organization of speech perception. *Trends in Neurosciences, 26*(2), 100-107.

Seghier, M. L., Fagan, E., & Price, C. J. (2010). Functional Subdivisions in the Left Angular Gyrus Where the Semantic System Meets and Diverges from the Default Network. *The Journal of Neuroscience, 30*(50), 16809-16817.

Semrud-Clikeman, M., Goldenring Fine, J., & Zhu, D. C. (2011). The role of the right hemisphere for processing of social interactions in normal adults using functional magnetic resonance imaging. *Neuropsychobiology, 64*(1), 47-51.

Sergent, J. (1982). The cerebral balance of power: Confrontation or cooperation? . *Journal of Experimental Psychology: Human Perception and Performance, 8*(2), 253-272.

Shallice, T. (1987). *Impairments of Semantic Processing: Multiple Dissociations*. London: Lawrence Erlbaum Associates Ltd.

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

Shallice, T. (1993). Multiple semantics: Whose confusions? *Cognitive Neuropsychology, 10*, 251-261.

Shamay-Tsoory, S. G., Tomer, R., & Aharon-Peretz, J. (2005). The neuroanatomical basis of understanding sarcasm and its relationship to social cognition. *Neuropsychology, 19*(3), 288-300.

Shamay-Tsoory, S. G., Tomer, R., Berger, B. D., & Aharon-Peretz, J. (2003). Characterization of empathy deficits following prefrontal brain damage: The role of the right ventromedial prefrontal cortex. *Cognitive Neuroscience, 15*, 324-337.

Shamay-Tsoory, S. G., Tomer, R., Berger, B. D., Goldsher, D., & Aharon-Peretz, J. (2005). Impaired "affective theory of mind" is associated with right ventromedial prefrontal damage. *Cognitive and Behavioral Neurology, 18*(1), 55-67.

Shamay-Tsoory, S. G., Tomer, R., Goldsher, D., Berger, B. D., & Aharon-Peretz, J. (2004). Impairment in cognitive and affective empathy in patients with brain lesions: Anatomical and cognitive correlates. *Journal of Clinical and Experimental Neuropsychology, 26*(8), 1113-1127.

Sharp, D. J., Awad, M., Warren, J. E., Wise, R., Vigliocco, G., & Scott, S. K. (2010). The neural response to changing semantic perceptual complexity during language processing. *Human Brain Mapping, 31*, 365-377.

Sharp, D. J., Scott, S. K., & Wise, R. (2004). Retreiving meaning after temporal lobe infarction: The role of the basal language area. *Annals of Neurology, 56*, 836-846.

Sheldon, S., Pichora-Fuller, M. K., & Schneider, B. A. (2008). Effect of age, presentation method, and learning on identification of noise-vocoded words. *Journal of the Acoustical Society of America, 123*(1), 476-488.

Shibata, M., Abe, J., Terao, A., & Miyamoto, T. (2007). Neural mechanisms involved in the comprehension of metaphoric and literal sentences: An fMRI study. *Brain Research, 1166*, 92-102.

Silberman, E. K., & Weingartner, H. (1986). Hemispheric lateralization of function related to emotion. *Brain and Cognition, 5*, 322-353.

Simmonds, D. J., & Mostofsky, S. H. (2008). Response inhibition and response selection: Two sides of the same coin. *Journal of Cognitive Neuroscience, 20*(5), 751-761.

Simmons, A., Miller, D., Feinstein, J. S., Goldberg, T. E., & Paulus, M. P. (2005). Left inferior prefrontal cortex activation during a semantic decision-making task predicts the degree of semantic organization. *NeuroImage, 28*(1), 30-38.

Simmons, W. K., & Martin, A. (2009). The anterior temporal lobes and the functional architecture of semantic memory. *Journal of the International Neuropsychological Society, 15*(5), 645-649.

Simpson, G. B. (1985). Lexical ambiguity and its role in models word recognition. *Psychological Bulletin, 96*(2), 316-340.

Simpson, G. B., & Burgess, C. (1984). Activation and selection processes in the recognition of ambigious words. *Journal of Experimental Psychology: Human Perception and Performance, 11*(1), 28-39.

Slevc, L. R., Martin, R. C., Hamilton, A. C., & Joanisse, M. F. (2011). Speech perception, rapid temporal processing, and the left hemisphere: A case study of unilateral pure word deafness. *Neuropsychologia, 49*(2), 216-230.

Snijders, T. M., Vosse, T., Kempen, G., Van Berkum, J. J. A., Petersson, K. M., & Hagoort, P. (2009). Retrieval and unification of syntactic structure in sentence comprehension: An fMRI study using word-category ambiguity. *Cereb. Cortex, 19*, 1493-1503.

Snowden, J., Goulding, P., & Neary, D. (1989). Semantic dementia: a form of circumscribed atrophy. *Behavioural Neurology, 2*, 167-182.

Snowden, J. S., Thompson, J. C., & Neary, D. (2004). Knowledge of famous faces and names in semantic dementia. *Brain, 127*, 860-872.

Snyder, A. C., Shpaner, M., Molholm, S., & Foxe, J. J. (2012). Visual object processing as a function of stimulus energy, retinal eccentricity and gestalt configuration: A high-density electrical mapping study. *Neuroscience, 221*, 1-11.

Snyder, H. R., Banich, M. T., & Munakata, Y. (2011). Choosing our words: Retrieval and selection processes recruit shared neural substrates in left ventrolateral prefrontal cortex. *Journal of Cognitive Neuroscience, 23*(3470-3482).

Snyder, H. R., Feigenson, K., & Thompson-Schill, S. L. (2007). Prefrontal cortical response to conflict during semantic and phonological tasks. *Journal of Cognitive Neuroscience, 19*(5), 761-775.

Snyder, H. R., Hutchison, N., Nyhus, E., Curran, T., Banich, M. T., O'Reilly, R. C., & Munakata, Y. (2010). Neural inhibition enables selection during language processing. *Proceedings of the National Academy of Sciences, 107*(38), 16483-16488.

Snyder, H. R., & Munakata, Y. (2008). So many options, so little time: The roles of association and competition in underdetermined responding. *Psychonomic Bulletin & Review, 15*(6), 1083-1088.

Soni, M., Lambon Ralph, M. A., Noonan, K. A., Ehsan, S., Hodgson, C., & Woollams, A. M. (2009). "L" is for tiger: Effects of phonological (mis)cueing on picture naming in semantic aphasia. *Journal of Neurolinguistics, 22*(6), 538-547.

Soni, M., Lambon Ralph, M. A., & Woollams, A. M. (2011). "W" is for bath: Can associative errors be cued? *Journal of Neurolinguistics, 24*(4), 445-465.

Sperry, R. W. (1982). Some effects of disconnecting the cerebral hemispheres. *Science, 217*, 1223-1226.

Spitsyna, G., Warren, J. E., Scott, S. K., Turkheimer, F. E., & Wise, R. (2006). Converging language streams in the human temporal lobe. *Journal of Neuroscience, 26*, 7328-7336.

Stefanatos, G. A., Gershkoff, A., & Madigan, S. (2005). On pure word deafness, temporal processing, and the left hemisphere. *Journal of International Neuropsychological Society, 11*(4), 456-470.

Stringaris, A., Medford, N., Giora, R., Giampietro, C. V., Brammer, J. M., & David, S. A. (2006). How metaphors influence semantic relatedness judgments: the role of the right frontal cortex. *NeuroImage, 33*, 784-793.

Stuss, D. T. (2007). *New approaches to prefrontal lobe testing* (2nd ed.). New York: The Guildford Press.

Stuss, D. T., & Alexander, M. P. (2000). Executive functions and the frontal lobes: A conceptual view. *Psychological Research, 63*, 289-298.

Stuss, D. T., Levine, B., Alexander, M. P., Hong, J., Palumbo, C., Hamer, L., Murphy, K., & Izukawa, D. (2000). Wisconsin Card Sorting Test performance in patients with focal frontal and posterior brain damage: Effects of lesion location and test structure on separable cognitive processes. *Neuropsychologia, 38*(4), 388-402.

Swick, D., & Knight, R. T. (1996). Is prefrontal cortex involved in cued recall? A neuropsychologicaltest of PET findings. *Neuropsychologia, 34*(10), 1019-1029.

Tanaka, Y., Yamadori, A., & Mori, E. (1987). Pure word deafness following bilateral lesions: A psychophysical analysis. *Brain, 110*, 381-403.

Tarr, M. J., & Gauthier, I. (2000). FFA: A flexible fusiform area for subordinate-level visual processing automatized by expertise. *Nature Neuroscience, 3*(8), 764-769.

Thiel, A., Habedank, B., Winhuisen, L., Herholz, K., Kessler, J., Haupt, W. F., & Heiss, W. D. (2005). Essential language function of the right hemisphere in brain tumor patients. *Annals of Neurology, 57*, 128-131.

Thompson-Schill, S. L. (2003). Neuroimaging studies of semantic memory: inferring "how" from "where". *Neuropsychologia, 41*(3), 280-292.

Thompson-Schill, S. L. (2005). *Dissecting the language organ: A new look at the role of Broca's area in language processing*. Hillsdale, NJ: Lawrence Erlbaum Associates.

Thompson-Schill, S. L., D'Esposito, M., Aguirre, G. K., & Farah, M. J. (1997). Role of left inferior prefrontal cortex in retrieval of semantic knowledge: A reevaluation. *Proceedings of the National Academy of Sciences of the United States of America, 94*(26), 14792-14797.

Thompson-Schill, S. L., D'Esposito, M., & Kan, I. P. (1999). Effects of repetition and competition on activity in left prefrontal cortex during word generation. *Neuron, 23*(3), 513-522.

Thompson-Schill, S. L., Swick, D., Farah, M. J., D'Esposito, M., Kan, I. P., & Knight, R. T. (1998). Verb generation in patients with focal frontal lesions: A neuropsychological test of neuroimaging findings. *Proceedings of the National Academy of Sciences of the United States of America, 95*(26), 15855-15860.

Thompson, P. (1980). Margaret Thatcher: A new illusion. *Perception, 9*(4), 483-484.

Thulborn, K. R., Carpenter, P. A., & Just, M. A. (1999). Plasticity of language related brain function during recovery from stroke. *Stroke, 30*, 749-754.

Tompkins, C. A., Fassbinder, W., Scharp, V. L., & Meigh, K. M. (2008). Activation and maintenance of peripheral semantic features of unambiguous words after right hemisphere brain damage in adults. *Aphasiology, 22*, 119-138.

Tranel, D., Martin, C., Damasio, H., Grabowski, T. J., & Hichwa, R. (2005). Effects of noun-verb homonymy on the neural correlates of naming concrete entities and actions. *Brain and Language, 92*(3), 288-299.

Troyer, A. K., Moscovitch, M., & Winocur, G. (1997). Clustering and switching as two components of verbal fluency: Evidence from younger and older healthy adults. *Neuropsychology, 11*(1), 138-146.

Troyer, A. K., Moscovitch, M., Winocur, G., Alexander, M. P., & Stuss, D. T. (1998). Clustering and switching on verbal fluency: The effects of focal frontal and temporal lobe lesions. *Neuropsychologia, 36*, 499-504.

Troyer, A. K., Moscovitch, M., Winocur, G., Leach, L., & Freedman, M. (1998). Clustering and switching on verbal fluency tests in Alzheimer's and Parkinson's disease. *Journal of the International Neuropsychological Society, 4*(2), 137-143.

Turken, A. U., & Dronkers, N. F. (2011). The neural architecture of the language comprehension network: Converging evidence from lesion and connectivity analysis. *Frontiers in Systems Neuroscience, 5*(1), 1-20.

Turken, A. U., Whitfield-Gabrieli, S., Bammer, R., Baldo, J. V., Dronkers, N. F., & Gabrieli, J. D. (2008). Cognitive processing speed and the structure of white matter pathways: Convergent evidence from normal variation and lesion studies. *NeuroImage, 42*(2), 1032-1044.

Tyler, L. K., Dick, E., Tavares, P., Pilgrim, L., Bright, P., Moss, H., & Fletcher, P. (2003). Do semantic categories activate distinct cortical regions? Evidence for a distributed neural semantic system. *Cognitive Neuropsychology, 20*(3-6), 541-559.

Tyler, L. K., Moss, H., Durrant-Peatfield, M. R., & Levy, J. P. (2000). Conceptual structure and the structure of concepts: A distributed account of category-specific deficits. *Brain and Language, 75*, 195-231.

Tyler, L. K., Stamatakis, E. A., Bright, P., Acres, K., Abdallah, S., Rodd, J. M., & Moss, H. (2004). Processing objects at different levels of specificity. *Journal of Cognitive Neuroscience, 16*, 351-362.

Ullsperger, M., & von Cramon, D. Y. (2001). Subprocesses of Performance Monitoring: A Dissociation of Error Processing and Response Competition Revealed by Event-Related fMRI and ERPs. *NeuroImage, 14*(6), 1387-1401.

Van Kleeck, M. H. (1989). Hemispheric differences in global versus local processing of hierarchical visual stimuli by normal subjects: New data and a meta-analysis of previous studies. *Neuropsychologia, 27*(9), 1165-1178.

van Oers, C. A., Vink, M., van Zandvoort, M. J. E., van der Worp, H. B., De Haan, E. H. F., Kappelle, L. J., Ramsey, N. F., & Dijkhuizen, R. M. (2010). Contribution of the left and right inferior frontal gyrus in recovery of aphasia. A functional MRI study in stroke patients with preserved hemodynamic responsiveness. *NeuroImage, 49*, 885-893.

Vandenberghe, R., Price, C. J., Wise, R., Josephs, O., & Frackowiak, R. S. J. (1996). Functional anatomy of a common semantic system for words and pictures. *Nature, 383*(6597), 254-256.

Vanhalle, C., Lemieux, S., Joubert, S., Goulet, P., Ska, B., & Joanette, Y. (2000). Processing of speech acts by right hemisphere brain-damaged patients: An ecological approach. *Aphasiology, 14*, 1127-1142.

Verte, S., Guerts, H., Roeyers, J., Ooosterlaan, J., & Sergeant, J. (2006). Executive functioning in children with an autism spectrum disorder: Can we differentiate within the spectrum? *Journal of Autism and Developmental Disorders, 36*, 351-372.

Vigneau, M., Beaucousin, V., Herve, P. Y., Duffau, H., Crivello, F., Houde, O., Mazoyer, B., & Tzourio-Mazoyer, N. (2006). Meta-analyzing left hemisphere language areas: phonology, semantics and sentence processing. *NeuroImage, 49*, 1414-1432.

Vigneau, M., Beaucousin, V., Herve, P. Y., Jobard, G., Petit, L., Crivello, F., Mellet, E., Zago, L., Mazoyer, B., & Tzourio-Mazoyer, N. (2011). What is right hemisphere contribution to phonological, lexico-semantic, and sentence processing? Insights from a meta-analysis. *NeuroImage, 54*(1), 577-593.

Vingerhoets, G., Van Borsel, J., Tesink, C., van den, N. M., Deblaere, K., Seurinck, R., Vandemaele, P., & Achten, E. (2003). Multilingualism: an fRMI study. *NeuroImage, 20*, 2181-2196.

Visser, M. E. J., Embleton, K. V., Jefferies, E., Parker, G. J. M., & Lambon Ralph, M. A. (2010). The inferior, anterior temporal lobes and semantic memory clarified: Novel evidence from distortion-corrected fMRI. *Neuropsychologia, 48*(6), 1689-1696.

Visser, M. E. J., Embleton, K. V., & Lambon Ralph, M. A. (2012). Evidence for a caudo-rostral gradient of information convergence in the temporal lobes: An fMRI study of verbal and non-verbal semantic processing. *Journal of Cognitive Neuroscience*.

Visser, M. E. J., Jefferies, E., Embleton, K. V., & Lambon Ralph, M. A. (2012). Both the Middle Temporal Gyrus and the Ventral Anterior Temporal Area Are Crucial for Multimodal Semantic Processing: Distortion-corrected fMRI Evidence for a Double Gradient of Information Convergence in the Temporal Lobes. *Journal of Cognitive Neuroscience, 24*(8), 1766-1778.

Visser, M. E. J., Jefferies, E., & Lambon Ralph, M. A. (2010). Semantic processing in the anterior temporal lobes: A meta-analysis of the functional neuroimaging literature. *Journal of Cognitive Neuroscience, 22*(6), 1083-1094.

Visser, M. E. J., & Lambon Ralph, M. A. (2011). Differential contributions of bilateral ventral anterior temporal lobe and left anterior superior temporal gyrus to semantic processes. *Journal of Cognitive Neuroscience, 23*(10), 3121-3131.

Vuilleumier, P., Armony, J. L., Driver, J., & Dolan, R. J. (2001). Effects of attention and emotion on face processing in the human brain: An event-related fMRI study. *Neuron, 30*(3), 829-841.

Wager, T. D. (2004). Neuroimaging studies of shifting attention: a meta-analysis. *Neuroimage, 22*, 1679-1693.

Wagner, A. D., Maril, A., Bjork, R. A., & Schacter, D. L. (2001). Prefrontal Contributions to Executive Control: fMRI Evidence for Functional Distinctions within Lateral Prefrontal Cortex. *NeuroImage, 14*(6), 1337-1347.

Wagner, A. D., Paré-Blagoev, E. J., Clark, J., & Poldrack, R. A. (2001). Recovering meaning: Left prefrontal cortex guides controlled semantic retrieval. *Neuron, 31*(2), 329-338.

Wambaugh, J. (2003). A comparison of the relative effects of phonologic and semantic cueing treatments. *Aphasiology, 17*(5), 433-441.

Warburton, E. A., Price, C. J., Swinburn, K., & Wise, R. (1999). Mechanisms of recovery from aphasia: Evidence from positron emission tomography studies. *Journal of Neurology, Neurosurgery and Psychiatry, 66*, 155-161.

Warrington, E. K. (1975). Selective impairment of semantic memory. *Quarterly Journal of Experimental Psychology, 27*(4), 635-657.

Warrington, E. K. (1981). Neuropsychological Studies of Verbal Semantic Systems. *Philosophical Transactions of the Royal Society of London. B, Biological Sciences, 295*(1077), 411-423.

Warrington, E. K., & Cipolotti, L. (1996). Word comprehension - The distinction between refractory and storage impairments. *Brain, 119*(2), 611-625.

Warrington, E. K., & Crutch, S. J. (2004). A circumscribed refractory access disorder: A verbal semantic impairment sparing visual semantics. *Cognitive Neuropsychology, 21*(2-4), 299 - 315

Warrington, E. K., & James, M. (1991). *The Visual Object and Space Perception Battery.* Bury St Edmunds: Thames Valley Test Company.

Warrington, E. K., & Leff, A. P. (2000). Jargon dyslexia: A single case study of intact reading comprehension in a jargon dysphasic. *Neurocase, 6*, 499-507.

Warrington, E. K., & McCarthy, R. A. (1983). Category specific access dysphasia. *Brain, 106*(4), 859-878.

Warrington, E. K., & McCarthy, R. A. (1987). Categories of knowledge - further fractionations and an attempted integration. *Brain, 110*(5), 1273-1296.

Warrington, E. K., & McCarthy, R. A. (1994). Multiple meanings in the brain - a case for visual semantics. *Neuropsychologia, 32*(12), 1465-1473.

Warrington, E. K., & Shallice, T. (1979). Semantic access dyslexia. *Brain, 102*(1), 43-63.

Warrington, E. K., & Shallice, T. (1984). Category specific semantic impairments. *Brain, 107*, 829-854.

Warrington, E. K., & Weiskrantz, L. (1982). Amnesia: A disconnection syndrome? *Neuropsychologia, 20*(3), 233-248.

Wasserstein, J., Zappulla, R., Rosen, J., & Gerstman, L. (1987). In search of closure: Subjective contour illusions, gestalt completion tests, and implications. *Brain and Cognition, 6*, 1-14.

Wechsler, D. (1987). *Wechsler Memory Scale - Revised (WMS-R)*. New York: Psychological Corporation.

Weed, E. (2008). Theory of mind impairment in right hemisphere damage: A review of the evidence. *International Journal of Speech - Language Pathology, 10*(6), 1-11.

Weed, E., McGregor, W., Nielsen, J. F., Roepstorff, A., & Frith, U. (2010). Theory of mind in adults with right hemisphere damage: What's the story? *Brain and Language, 113*(2), 65-72.

Weiller, C., Isensee, C., Rijintjes, M., Huber, W., Muller, S., Bier, D., Dutschka, K., Woods, R. P., Noth, J., & Diener, H. C. (1995). Recovery from Wernicke's aphasia: a positron emission tomographic study. *Annals of Neurology, 37*, 103-118.

Weiner, D. A., Connor, L. T., & Obler, L. K. (2004). Inhibition and auditory comprehension in Wernicke's aphasia. *Aphasiology, 18*, 599-609.

Whitney, C., Grossman, M., & Kircher, T. T. J. (2009). The influence of multiple primes on bottom-up and top-down regulation during meaning retrieval: Evidence for two distinct neural networks. *Cerebral Cortex, 19*(11), 2548-2560.

Whitney, C., Hymers, M., Gouws, A., & Jefferies, E. (submitted). Charting the effects of TMS with fMRI: Changes in cortical recruitment and effective connectivity within the semantic control network.

Whitney, C., Jefferies, E., & Kircher, T. T. J. (2011). Heterogeneity of the left temporal lobe in semantic representation and control: Priming multiple vs. single meanings of ambiguous words. *Cerebral Cortex, 21*, 831-844.

Whitney, C., Kirk, M., O'Sullivan, J., Lambon Ralph, M. A., & Jefferies, E. (2011). The neural organization of semantic control: TMS evidence for a distributed network in left inferior frontal and posterior middle temporal gyrus. *Cereb. Cortex, 21*(5), 1066-1075.

Whitney, C., Kirk, M., O'Sullivan, J., Lambon Ralph, M. A., & Jefferies, E. (2012). Executive semantic Processing Is Underpinned by a Large-scale Neural Network: Revealing the Contribution of Left Prefrontal, Posterior Temporal, and Parietal Cortex to Controlled Retrieval and Selection Using TMS. *Journal of Cognitive Neuroscience, 24*(1), 133-147.

Wilkinson, D., Ko, P., Wiriadjaja, A., Kilduff, P., McGlinchey, R., & Milberg, W. (2009). Unilateral damage to the right cerebral hemisphere disrupts the apprehension of whole faces and their component parts. *Neuropsychologia, 47*, 1701-1711.

Williams, G. B., Nestor, P. J., & Hodges, J. R. (2005). Neural correlates of semantic and behavioural deficits in frontotemporal dementia. *NeuroImage, 24*(4), 1042-1051.

Wilson, M. D. (1988). The MRC Psycholinguistic Database: Machine Readable Dictionary, Version 2. *Behavioural Research Methods, Instruments and Computers, 20*(1), 6-11.

Winhuisen, L., Thiel, A., Schumacher, B., Kessler, J., Rudolf, J., Haupt, W. F., & Heiss, W. D. (2005). Role of the Contralateral Inferior Frontal Gyrus in Recovery of Language Function in Poststroke Aphasia. *Stroke, 36*, 1759-1763.

Winner, E., & Gardner, H. (1977). Comprehension of metaphor in brain-damaged patients. *Brain, 100*, 717-729.

Wise, R., Chollet, F., Hadar, U. R. I., Friston, K., Hoffner, E., & Frackowiak, R. S. J. (1991). Distribution of cortical neural networks involved in word comprehension and word retrieval. *Brain, 114*(4), 1803-1817.

Wise, R., Scott, S. K., Blank, S. C., Mummery, C. J., Murphy, K., & Warburton, E. A. (2001). Separate neural subsystems within 'Wernicke's area'. *Brain, 124*, 83-95.

Woolgar, A., Hampshire, A., Thompson, R., & Duncan, J. (2011). Adaptive coding of task-relevant information in human fronto-parietal cortex. *The Journal of Neuroscience, 31*, 14592-14599.

Yang, F. G., Edens, J., Simpson, C., & Krawczyk, D. C. (2009). Differences in task demands influence the hemispheric lateralization and neural correlates of metaphor. [Article]. *Brain and Language, 111*(2), 114-124.

Zahn, R., Drews, E., Specht, K., Kemeny, S., Reith, W., Willmes, K., Schwarz, M., & Huber, W. (2004). Recovery of semantic word processing in global aphasia: A functional MRI study. *Cognitive Brain Research, 18*, 322-336.

Zahn, R., Huber, W., Drews, E., Specht, K., Kemeny, S., Reith, W., Willmes, K., & Schwarz, M. (2002). Recovery of semantic word processing in transcortical sensory aphasia: A functional magnetic resonance imaging study. *Neurocase, 8*, 376-386.

Zahn, R., Moll, J., Krueger, F., Huey, E. D., Garrido, G., & Grafman, J. (2007). Social concepts are represented in the superior anterior temporal cortex. *Proceedings of the National Academy of Sciences, 104*(15), 6430-6435.

Zaidel, E., Kasher, A., Soroker, N., & Batori, G. (2002). Effects of Right and Left Hemisphere Damage on Performance of the "Right Hemisphere Communication Battery". *Brain and Language, 80*(3), 510-535.

Zekveld, A. A., Heslenfeld, D. J., Festen, J. M., & Schoonhoven, R. (2006). Top-down and bottom-up processes in speech comprehension. *NeuroImage, 32*(4), 1826-1836.

Zempleni, M. Z., Renken, R., Hoeks, J. C., Hoogduin, J. M., & Stowe, L. A. (2007). Semantic ambiguity processing in sentence context: Evidence from event-related fMRI. *NeuroImage, 34*, 1270-1279.

Zgaljardic, D. J., Borod, J. C., & Sliwinski, M. (2002). Emotional perception in unilateral stroke patients: Recovery, test stability, and interchannel relationships. *Applied Neuropsychology: Adult, 9*(3), 159-172.