Temporal and Spatial Dynamics of the Semantic Network: Explorations using Transcranial Magnetic Stimulation (TMS) and fMRI

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Rebecca L. Jackson

School of Psychological Sciences

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Abstract

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Rebecca L. Jackson, The University of Manchester

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Convergent findings have elucidated the regions involved in semantic cognition. The anterior temporal lobes (ATL) act as a hub for multimodal semantic processing alongside modality-specific 'spoke' regions. In addition, areas of inferior parietal, posterior temporal and frontal cortex are necessary for semantic cognition. However, many questions remain. Little is known about the timing of the ATL or how distributed regions interact in order to perform semantic processing. In order to gain knowledge of the precise spatial and temporal dynamics of the ATL and semantic cognition network, a series of studies was performed.

Chapter 3 investigated the time at which the ATL is necessary for a semantic judgement using chronometric TMS. The ATL was found to be necessary for semantic cognition from 400ms post-stimuli presentation. This is known to be a critical time for semantic processing. Processing of items presented in different modalities converges around this time. This supports the role of the ATL in multimodal semantic cognition. Chapter 4 used offline repetitive TMS to investigate the role of ATL subregions and posterior temporal cortex in semantic and phonological processing. However, no significant TMS effects were demonstrated.

Chapter 5 employed dual echo fMRI to assess how different types of semantic relationships are instantiated within the brain. Association (spatially and temporally co-occurring concepts) and conceptual similarity (concepts sharing features) were shown to rely on the same cortical regions. This provides evidence against theories suggesting separate representational hubs for these different relationship types. Instead it supports the reliance of both relationship types on the ATL hub. These two kinds of relationship may be more similar than previously thought, with the hub-and-spoke model able to explain both. The semantic network identified here included ATL, posterior temporal, frontal and ventral parietal cortex. This network of semantic regions was shown to be interconnected in Chapter 6 during a semantic task (using a psychophysiological interaction analysis) and during rest (using a seed-based functional connectivity analysis). Differential connectivity was identified between the ventral ATL (to multimodal semantic regions) and the aSTG (to language-related regions). The semantic network overlapped with the default mode network (DMN) and involved regions previously found to constitute the frontoparietal network (FPN).

Emergent questions related to the overlap between previously identified network and the semantic network were addressed with preliminary independent component analyses in Chapter 7. This showed the dynamic connectivity of the ATL in task and rest. The semantic network was found to be distinct from but overlapping with the DMN and FPN. The role of this network in semantic cognition was confirmed, whereas the DMN was not found to relate to semantic processing. The anterior DMN component appeared semantic based on activity alone, suggesting prior results relating the DMN to semantic cognition fail to take the dynamic connectivity of the regions in to account. The left FPN overlapped with semantic control regions but appeared to relate to more general control processes. When assessed with dual echo fMRI, the ATL appears to be highly connected in a dynamic fashion and may be an important region currently under-represented within studies of the connectome. Overall, these studies add to the hub-and-spoke model of semantic cognition, elucidating the types of relationship involved, how regions interact and the precise temporal and spatial dynamics of these areas.

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.

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General Introduction

Chapter 1

Semantic Memory and the Anterior Temporal Lobe

Overview

This thesis has been submitted in alternative thesis format. As such Chapters 3 to 7 are written in the style of journal articles. Chapter 3 details a chronometric TMS investigation of the timecourse of semantic processing within the anterior temporal lobe. Chapter 4 uses offline TMS to assess the spatial dynamics of semantic and phonological processing in anterior and posterior temporal lobe regions. Differences between types of semantic representation are investigated as an organising principle of the semantic network in Chapter 5. Chapters 6 and 7 investigate the functional connectivity of semantic regions during semantic tasks and at rest. Chapter 6 uses seed-based approaches whereas Chapter 7 gives preliminary results on a method to assess dynamic connectivity of these regions. A general discussion of how the aims were addressed and further issues raised is provided in Chapter 8. The remainder of this chapter and the following chapter provide a general introduction to the background literature. The aims of the thesis are introduced and it is outlined how specific chapters address these aims. This chapter addresses the role of the anterior temporal lobes in semantic processing and Chapter 2 extends this research to include areas outside of the anterior temporal lobe that are involved in semantic cognition.

How the brain represents meaning has been debated in philosophy since the Ancient Greeks (e.g., Plato, 360 B.C.) and studied empirically for over a century (see Eggert, 1977). Recent findings from neuropsychology, neuroimaging and neurostimulation have converged to highlight the principal areas involved in semantic memory (Binder & Desai, 2011; Jefferies, 2013; Lambon Ralph, 2014; Price, 1998). Although traditional views suggested a fully distributed account of semantic memory (e.g., the Wernicke-Meynert model, see Eggert, 1977) it is now widely accepted that a multimodal semantic hub exists within the anterior temporal lobe (Lambon Ralph, 2014; Patterson et al., 2007). A further set of regions including inferior frontal gyrus, posterior middle temporal gyrus and angular gyrus are responsible for the controlled manipulation of semantic representations (Jefferies, 2013; Noonan et al., 2013). Despite a growing consensus regarding the regions involved, unanswered questions remain concerning the spatial and temporal dynamics of semantic cognition. Questions regarding the dynamics of the ATL hub (see Chapter 1) and the network responsible for semantic cognition (see Chapter 2) may be investigated using fMRI and transcranial magnetic stimulation (TMS), a relatively new technique with which to study cognitive processes.

1. The ATL as a Semantic Hub

1.1 Semantic Memory

Semantic memory may be defined as the decontextualised knowledge of basic meanings and facts (McClelland et al., 1995). This means that semantic memory consists of conceptual information that is not linked to specific events, such as when the information was learnt. This is considered separate to episodic memory; the memory of personal events with temporal and spatial relations (Tulving, 1972). Until recently, the prevailing view assumed no stable neural correlates of semantic memory exist; instead viewing it as the product of 'universal connectivity' (Fodor, 1983). The idea of universal connectivity is reflected in distributed models in which a large number of different areas are involved in the representation of semantic memory (see Figure 1a), such as the Wernicke-Meynert model (see Eggert, 1977). The Wernicke-Meynert model suggests semantic memory is supported by areas subserving sensory, motor and verbal processing distributed representations. Each of these areas stores modality-specific representations, or 'engrams', the connections between which constitute semantic memory (see Eggert, 1977). Imaging studies provide evidence that the organisation of semantic memory is based on sensory and motor input, including visual, auditory, motor, tactile and gustatory processing areas (Chao et al., 1999; Chao & Martin, 2000; Goldberg et al., 2006; Hauk et al., 2004; Martin et al., 1995). Damage to one of these attribute-specific memory stores would cause impairment of a specific set of properties relating to one sense or to motion (Gainotti, Silveri, Daniele & Giustolisi, 1995; Warrington & Shallice, 1984). However, distributed models of semantic memory cannot account for a global impairment of semantic knowledge without positing damage throughout the brain (Eggert, 1977). The existence of a selective, global semantic impairment in the context of damage to a specific brain region, therefore, is contrary to the predictions of distributed-only frameworks (Lambon Ralph & Patterson, 2008). This kind of global semantic impairment can be observed in semantic dementia.

1.2 Semantic Dementia

Semantic dementia (SD) is the temporal lobe variant of frontotemporal dementia involving a selective and progressive deterioration of multimodal semantic representations (Hodges et al., 1992a; Snowden et al., 1989; Warrington, 1975). This means that a conceptual deficit can be identified regardless of the modality of input or the required output. This occurs despite intact phonological and visual processing, decision making, episodic and short term memory, syntax and spatial skills (Hodges et al., 1992a; Warrington, 1975). Deficits may be seen to affect the representations themselves (a storage deficit) or the ability to correctly select the appropriate representation (an access deficit; Mirman & Britt, 2014; Warrington & Shallice, 1979). Although often presenting with anomia, patients also show a nonverbal impairment highlighting a degradation of the multimodal semantic representations as opposed to an 'access' deficit (Bozeat et al., 2000; Jefferies & Lambon Ralph, 2006; Lambon Ralph et al., 2001). Similarly, when tested on the same concept accessed via different modalities, (such as a picture of a dog, a barking sound or the word 'dog') patients show high levels of consistency and impairment is equal regardless of concept category (Coccia et al., 2004; Lambon Ralph et al., 1999; Lambon Ralph et al., 1998b). SD patients suffer a loss of semantic acuity; the ability to differentiate between conceptual neighbours (Jefferies & Lambon Ralph, 2006; Rogers et al., 2004). As well as severity, SD patient's performance is affected by frequency, familiarity, domain-specific typicality and age of acquisition of the concept name (Lambon Ralph et al., 1998a; Patterson, 2007; Woollams et al., 2008). Errors made often include omissions and typicalisation errors; giving a concept attributes belonging to more typical concepts within a domain and omitting distinguishing features, for instance, colouring a carrot green or drawing a rhinoceros without a horn (Bozeat et al., 2003; Lambon Ralph & Patterson, 2008; Patterson et al., 2006; Rogers et al., 2007). Although different pathology may underpin SD, post mortem examination usually shows neuronal inclusions formed from aggregates of the protein ubiquitin and not the protein tau, suggesting pathology more similar to motor neuron disease than to other forms of fronto-temporal dementia (Davies et al., 2005; Hodges & Patterson, 2007).

SD is characterised by atrophy maximal in anterior, inferior and lateral aspects of the bilateral temporal lobes (Galton et al., 2001; Mummery et al., 2000; Mummery et al., 1999). Although atrophy may be asymmetrical, usually favouring the left anterior temporal lobe (ATL), it is always bilateral and longitudinal studies show bilateral deterioration (Brambati et al., 2009; Nestor et al., 2006; Studholme et al., 2004). It could be argued that the semantic impairment is due to global brain damage, not focal ATL atrophy. However, at least in the early and intermediate stages of SD, both atrophy and hypometabolism have been shown to be confined to rostral temporal areas (Diehl et al., 2004; Nestor et al., 2006). Even in severe SD when atrophy and hypometabolism may spread to the amygdalae, caudate nuclei, fusiform gyri, thalamus and hippocampal and parahippocampal areas, only temporal lobe atrophy relates to semantic performance (Desgranges et al., 2007). Similarly, anterior fusiform hypometabolism was the only variable found to predict semantic impairment in a group of patients with frontotemporal lobar degeneration (Mion et al., 2010). More recent investigation shows the atrophy is dominant in the ATL with some involvement of orbitofrontal lobes and insulae (Rohrer et al., 2010). In comparison, Alzheimer's disease (AD) has a greater spread of damage but is less likely to cause semantic impairment, suggesting that the bilateral ATL are particularly important for semantic cognition (Nestor et al., 2006). One potential criticism of this view is that the impairment is due to white matter tracts underpinning language processing in left hemisphere temporal areas which have been shown to be affected in a number of SD patients (Agosta et al., 2009). In summary, a multimodal semantic deficit is apparent with relatively focal ATL atrophy. Furthermore, this ATL degeneration correlates with the semantic impairment (Levy et al., 2004; Nestor et al., 2006; Patterson et al., 2007). This provided evidence against a purely distributed view of semantic processing and led to the creation of a new model.

1.3 The Hub-and-Spoke Model of Semantic Memory

The hub-and-spoke model incorporates the evidence from SD patients into the Wernicke-Meynert framework. It asserts that modality-specific association cortices are of secondary importance for the storage of semantic representations to a hub located within the ATL (see Fig 1b, Patterson et al., 2007; Pobric et al., 2007). Direct connections between modality-specific areas are considered insufficient to explain higher order generalisation; the ability to understand conceptual relationships regardless of similarities within a single domain (Patterson et al., 2007). Distillation of motor, sensory and verbal information for all concepts over the same set of neurons in a multimodal hub allows encoding of the deep statistical structure of conceptual relationships (Lambon Ralph et al., 2010b). The use of statistics that are not tied to one modality, but instead reflect overall conceptual similarity, allows generalisation to similar concepts (e.g. upon learning that a Himalayan monal is a bird I know it is likely to have wings and feathers, lay eggs, etc.) as well as translation between modalities. Information from more than one modality may be necessary to form sensible semantic categories that are not overly influenced by one modality (e.g., a light bulb and a pear are visually similar but conceptually very different; Rogers et al., 2007). Thus, a multimodal hub is critical for the flexible use of multimodal conceptual knowledge. This concept is similar to the idea of convergence zones, where modality-specific information from distinct modality-specific regions is mapped together in secondary or tertiary association cortex (Damasio et al., 1996). However, only one zone is postulated, allowing the mappings to be semantic representations of the underlying statistical structure as opposed to merely being connections between semantic areas (Lambon Ralph et al., 2010b). The ATLs are an ideal location for a semantic hub due to the high level of connectivity with modality-specific association areas as well as proximity to the medial temporal lobe associated with episodic memory and the limbic system and orbitofrontal cortex associated with reward (Patterson et al., 2007). Input from the ventral visual processing stream as well as somatosensory and auditory processing streams are known to reach anterior aspects of the temporal lobe (Gainotti et al., 1995; Gloor, 1997; Grey & Bannister, 1995; Lambon Ralph et al., 2009).

A computational model of the hub and spoke view has been implemented which demonstrates the nature of the cross-modal mappings and the extraction of a deeper statistical structure. Two different architectures were computationally modelled. In one version modules storing representations of visual and verbal features were connected using a convergent architecture. This meant that a shared pathway connected all the modality-specific modules so that similar patterns of neurons within the semantic hub encoded the statistical structure of the connections between the different types of information (Rogers et al., 2004; see Figure 1b). In contrast the other version employed a gating architecture whereby mappings between the different types of features went through separate modules or neural populations. This comparison supported the hub and spoke model by showing that only the convergent architecture led to crossmodal mappings reflecting conceptual relationships not evident in either modality in isolation (Rogers et al., 2004). The role of the ATL and the validity of the hub-and-spoke model have been assessed further using multiple convergent modalities (see Chapter 1.2). This work was extended outside the ATL due to the discovery that the ATL hub was not the only region in which damage could lead to a general semantic impairment (see Chapter 2).

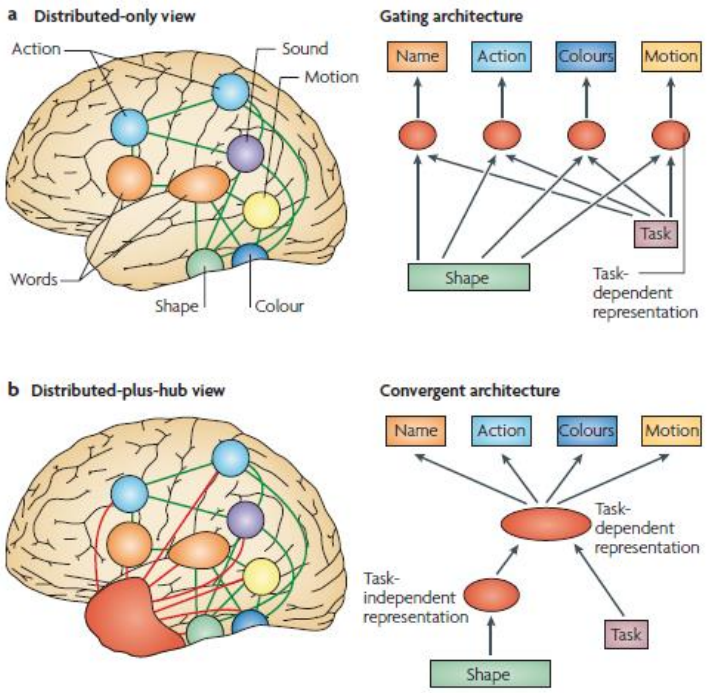

***Figure 1.* The architecture of distributed-only and distributed-plus-hub views of semantic memory (reproduced from Patterson et al., 2007).** a. The traditional distributed-only model of semantic memory consisting of modality-specific representation areas only. This uses a gating architecture to map between each modality separately. b. The distributed-plus-hub view also incorporates a semantic hub through which all intermodal mapping occurs. This is a convergent architecture. Only systems using a convergent architecture have been shown to be able to compare concepts based on similarities not evident in individual modalities.

2. Convergent Evidence of the Role of the ATL for Semantic Cognition

In order to provide evidence for the role of the ATL in multimodal semantic memory a number of different methods with different positive and negative attributes were employed. Despite their individual methodological issues, results from these different methods have converged to show the involvement and necessity of the ATLs in multimodal semantic cognition.

2.1 Neuropsychological Evidence

One line of research assessed other disorders affecting the ATL to determine whether they corroborate the evidence from SD. Although assessment of the deficit caused by cerebrovascular accident (CVA) has been informative for many areas of the brain, this rarely affects the ATL as blood is supplied to the area by both the posterior temporal branch of the middle cerebral artery and the parieto-occipital branch of the posterior cerebral artery (Conn, 2003). As much early work focused on CVA, this led to the ATL being ignored in traditional distributed models of semantic memory, although a more recent study using voxel based lesion symptom mapping has shown that semantic errors are related to anterior to mid MTG damage (Jefferies & Lambon Ralph, 2006; Patterson et al., 2007; Schwartz et al., 2009). More recently the effect of ATL damage has been assessed in Alzheimer's disease (AD), herpes simplex virus encephalitis (HSVE) and unilateral temporal lobe resection after epilepsy.

Although the primary early symptom of AD is an anterograde memory impairment, atypical presentation or disease progression causes a general impairment of multimodal semantic memory, if the ATL are damaged (Galton et al., 2000; Garrard et al., 2005; Hodges et al., 1992b). Similarly patients with HSVE usually have prominent anterograde amnesia. However, a semantic impairment is often present, associated with additional lateral temporal lobe damage (Kapur et al., 1994a; Noppeney et al., 2007). Despite the overlapping damage to the ATL, HSVE has been shown to cause a category-selective deficit (e.g., Warrington & Shallice, 1984) unlike SD (Lambon Ralph et al., 1998b; Lambon Ralph et al., 2003). This relative preservation of inanimate concepts may be explained by the relatively dense distribution of living items in conceptual space (i.e., because living items such as animals are usually more similar to each other within modalities and conceptually than non-living items, for instance, many four-legged animals are a similar shape whilst tools have greatly variable shapes, they may be less resistant to damage). Both a multimodal deficit, characteristic of SD and a category selective deficit, representative of HSVE have been modelled within the hub-and-spoke framework. In order for the model to display SD-like behaviour, the representations are 'dimmed' affecting both dense and sparse conceptual neighbourhoods equally (Rogers et al., 2004). Distorting the representations in the HSVE version led to more category coordinate errors (giving the wrong exemplar from the semantic category e.g., answering 'dog' instead of 'fox') especially in dense conceptual neighbourhoods (Lambon Ralph et al., 2007). The category effect may be removed for both patients and the model if neighbourhood density is controlled for, thus category effects do not necessitate a distributed semantic system (Lambon Ralph et al., 2007).

The importance of the ATL has been questioned due to findings of little or no impairment after unilateral resection of the temporal lobes as a treatment for epilepsy (e.g., Simmons & Martin, 2009), although this has rarely been systematically assessed (e.g., Hermann et al., 1999). Although no case series has been conducted on people with unilateral resection for epilepsy alone, a case series has been conducted including patients with multiple aetiologies leading to unilateral temporal lobe damage including resection for epilepsy, tumour and vascular accident. This study showed little evidence of clinically significant semantic impairment (Lambon Ralph et al., 2010a). There are however a number of explanations why this may occur within the hub-and-spoke view. Firstly, reorganisation could occur before the operation. At a physiological level, changes in the function of GABAergic receptors and the structure of white matter tracts have been shown to occur in epilepsy leading to changes involving increased right hemisphere language function (Huberfeld et al., 2007; Powell et al., 2007). GABA, or gamma-aminobutyric acid, is the main inhibitory neurotransmitter in the human nervous system and drugs affecting the level of GABA in the brain have been shown to affect semantic memory (Hartley et al., 1982; Kälviäinen, 1997; Saenz-Campos et al., 1995). Resection for epilepsy may therefore not be representative of the role of the ATL in a brain with normal functioning. An alternative explanation is that unilateral damage is unlikely to cause a clinically significant impairment due to duplication of representations between the left and right ATL allowing graceful degradation (Lambon Ralph et al., 2010a). Graceful degradation means that, although there is damage to representations within a system, limited functionality remains allowing the representations to still be accessible. In this case a duplicate representation may still have enough information to allow good task performance (Rumelhart, 1998). Although a large enough unilateral lesion could cause a significant deficit (e.g., M.P., see Bub et al., 1988), bilateral damage is argued to be necessary most of the time (Lambon Ralph et al., 2010a). Evidence for this dissociation can be seen in animal research showing bilateral ablation of the temporal lobe is necessary for severe impairment of object recognition, paired-associate learning and auditory recognition (Buckley & Gaffan, 2006; Heffner & Heffner, 1986; Li et al., 1999). The necessity of coordinated processing between the two ATLs is supported by a greater relationship with the comprehension ability of aphasic patients for interhemispheric ATL connectivity and the connection between the ATL and inferior frontal regions, than the activation of the temporal lobes (Warren et al., 2009).

2.2 Neuroimaging Evidence

Despite significant neuropsychological evidence that bilateral ATL damage impairs semantic memory, without convergent evidence it may still be postulated that this is due to damage elsewhere or changes in connectivity (e.g., Hart et al., 2007). Neuroimaging studies are one source of convergent evidence which is important to confirm the significance of the ATL. Despite becoming increasingly popular as a noninvasive method of imaging brain function during task or rest, functional magnetic resonance imaging (fMRI) is not without obstacles. Although often ignored, the signal to noise ratio (the MR signal compared to the background noise of the image) is not consistent across the brain. Signal drop out and distortion caused by inhomogeneities within the magnetic field near air filled cavities, particularly affect the orbitofrontal cortex and inferior, anterior temporal lobes (Devlin et al., 2000; Visser et al., 2010a). For this reason standard gradient echo fMRI studies of semantic memory rarely support the hub-and-spoke view, often lacking ATL activation (Devlin et al., 2000; Garavan et al., 2000). Instead studies show a left lateralised semantic network usually including frontal, posterior temporal, temporo-parietal and parietal areas (Joseph, 2001; Martin, 2007; Moore & Price, 1999; Thompson-Schill, 2003). This inconsistency between the neuropsychological and imaging data had to be addressed in order to further models of semantic memory. A meta-analysis of the literature found that the likelihood of finding bilateral ATL activation during a semantic task was dependent on four factors; imaging technique, size of field of view, level of baseline in control tasks and pre-selection of the ATL as a region of interest (Visser et al., 2010b). All of these factors increase the likelihood of finding activation of an area where signal distortion and drop out make this problematic. Use of a large field of view, PET instead of fMRI and a high baseline for comparison should all help increase the signal to noise ratio and reduce distortion (Visser et al., 2010b). Selecting the ATL as a region of interest based on prior knowledge allows the statistical level at which the activation may be considered significant to be lowered. Using the same task and similar analyses for PET imaging and fMRI, Devlin et al. (2000) found differential activation of the temporal poles (TP). Only with PET could the full extent of temporal lobe activation be observed, showing that the lack of ATL activation in fMRI studies does not prove they are not involved in semantic cognition (Devlin et al., 2000). Development of distortion correction for spin echo EPI allowed the importance of the ATL in semantic tasks to be shown with fMRI as well as PET imaging (Embleton et al., 2010; Visser et al., 2010a). Spin echo EPI is an alternative pulse sequence to gradient echo EPI, which promotes a greater reliance of the contrast on micro field inhomogeneities than macro field inhomogeneities, rendering it less susceptible to distortion and signal loss due to magnetic susceptibility artefacts (in spin echo EPI a 180 pulse is used to refocus the photons prior to the gradient reversal used in gradient echo EPI, a full discussion of this is beyond the scope of this thesis, see Embleton et al., 2010).

The greater spatial resolution of neuroimaging compared to patient studies allowed further assessment of the effect of modality in the ATL, both supporting and elucidating the hub and spoke model. Plaut (2002) has suggested there is a graded specialisation within the semantic system. As the system mediates between different input and output modalities, the areas closest to modality-specific input become somewhat functionally specialised for this type of information in a graded fashion (Plaut, 2002). This suggests that different areas of the ATLs may activate differentially for different stimuli. A meta-analysis found a greater number of peak activations within superior temporal regions for verbal stimuli and in the inferior areas for pictorial stimuli which became increasingly distinctive in the posterior temporal lobe (Visser, Jefferies & Lambon Ralph, 2010). The ATL subregions were not functionally homogenous. Some subregions of the ATL showed greater activation when stimuli were presented in a particular modality, such as superior temporal gyrus for auditory stimuli (spoken words and environmental sounds) and inferior temporal and fusiform gyri for visual stimuli (written words and pictures; Binney et al., 2010; Visser et al., 2012; Visser & Lambon Ralph, 2011). However, key regions of ventral ATL and lateral MTG were found to be involved in multimodal semantic processing (Binney et al., 2010; Visser et al., 2010a; Visser et al., 2012). This organisation is thought to reflect two different gradients reflecting the level of multimodal semantic processing within the temporal lobe, one from posterior areas, considered to be strongly affected by proximity to sensory inputs, to anterior aspects, affected by all modalities and a lateral gradient towards the MTG (Binney et al., 2012; Visser et al., 2012). The core ventral region identified with fMRI also shows the greatest atrophy in SD, showing a high level of convergence between the results of the neuropsychological and neuroimaging techniques (Binney et al., 2010).

An alternative method of imaging areas of high magnetic susceptibility has recently been developed. Dual echo imaging uses standard gradient echo EPI but involves the use of two echoes in parallel (Halai et al., 2014). Shorter echoes (e.g., 12 ms) lead to less signal loss in vulnerable areas, such as the ATL, due to reduced spin dephasing whilst standard long echoes (e.g., 35 ms) maintain signal throughout the brain (Halai et al., 2014; Poser & Norris, 2007; 2009). The results at multiple echoes may be combined via linear summation (Halai et al., 2014; Poser et al., 2006). This dual echo method has been shown to have greater signal in inferior temporal and frontal regions than standard gradient echo and distortion corrected spin echo (Halai et al., 2014).

2.3 Evidence from Neurostimulation

First used by Barker, Jalinous and Freeston (1985), transcranial magnetic stimulation (TMS) relies upon Faraday's principles of electromagnetic induction. A wire coil is placed on a participant's scalp before high amplitude pulses changing in magnitude induce a parallel time-varying magnetic field in the neural tissue (Sack & Linden, 2003). This is thought to affect approximately 600mm^2 of tissue up to 2-3cm deep, around the foci situated under the central point of a figure-of-eight coil (Paus, 1999; Roth et al., 2007; Sandrini et al., 2011). TMS may facilitate or impair cognitive task performance depending on a number of factors including pulse pattern, timing, stimulation intensity, intervals and total stimulation time (Bolognini & Ro, 2010; Silvanto & Muggleton, 2008). Although knowledge of the neural mechanisms of TMS-related changes is limited, increased TMS intensity has been linked to increased activation of the stimulated and connected areas, whilst neural changes remain strongly coupled with haemodynamic changes, suggesting TMS provides a valid model of normal physiology (Allen et al., 2007; Bohning et al., 1997; Sack & Linden, 2003). The magnetic field has been argued to affect cortical axons and subcortical white matter. These effects may be excitatory or inhibitory and could be seen as adding noise (Harris et al., 2008; Ruzzoli et al., 2010; Walsh & Cowey, 2000). There is increasing evidence that an initial burst of activity, during which neurons fire rapidly, is followed by intracortical inhibition due to the release of GABA (Pascual-Leone et al., 2000). This process may last between 20-200ms and a corresponding increase then long decrease in blood flow and blood oxygenation has been identified (Allen et al., 2007; Pascual-Leone et al., 2000; Sandrini et al., 2011). Frequencies below 1Hz have been demonstrated to increase inhibitory effects and frequencies above 1Hz excitatory effects (Miniussi et al., 2000; Sandrini et al., 2011).

Accurate positioning of the TMS coil in an experiment requires coregistration with a high resolution T_1-weighted image. This type of MR scan contrasts different types of tissue based on differences in the time the tissue takes to relax after magnetisation giving a structural image of the participant's brain (Weishaupt, Kochli & Marincek, 2008). A tracking system can then be used to match the participant to their scan using easily identifiable points such as the inion (on the back of the head) and tragus (the top of the nose), marked on the MR with vitamin capsules (Paus, 1999; Sandrini et al., 2011; Weishaupt et al., 2008). The TMS site may be determined anatomically based on prior literature or functionally based on group averaged peaks within the literature or on an individual basis after functional neuroimaging during a relevant task (Bolognini & Ro, 2010). Although a small number of seizures were reported before the current safety guidelines were implemented, TMS is considered to be safe with seizures being a rare occurrence (Sack & Linden, 2003; Sandrini, Umilta & Rusconi, 2010). An individual's level of cortical excitability may be measured as the resting motor threshold of the relaxed abductor pollicis brevis muscle in the hand (Sandrini et al., 2011). Determining stimulation intensity using the individual's cortical excitability, allows increased safety (Sack & Linden, 2003). Control sites and tasks may be used to factor out the contribution of non-specific effects of TMS, such as auditory and somatosensory sensations and non-specific neural effects (Sandrini et al., 2011).

TMS allows experimental assessment of the causal links between function and neural correlates unlike functional neuroimaging (Sack & Linden, 2003; Sandrini et al., 2011; Walsh & Rushworth, 1999). Creating a reversible short term 'virtual lesion' avoids some of the problems of traditional neuropsychology, such as compensatory processing and differences in premorbid ability (Devlin & Watkins, 2007; Walsh & Cowey, 2000). The technique is extremely versatile allowing investigation of hemispheric specialisation, timing, plasticity and functional connectivity as well as the necessity of an area for an aspect of cognition (Sack & Linden, 2003). TMS may be applied offline in a train of low frequency pulses up to 50Hz, the effects of which are extended beyond the period of stimulation, known as repetitive TMS (rTMS) or online with single pulses each around 100μs long, known as single pulse TMS (spTMS; Pascual-Leone et al., 2000; Sandrini et al., 2011).

Like fMRI, TMS has better spatial and temporal resolution than neuropsychological assessments, yet, unlike fMRI, it can assess the necessity of an area for a task. Thus, it can contribute significantly to the exploration of the role of the ATL. Following 10 minutes of left ATL rTMS stimulation at 1Hz, reaction times were slowed for semantic judgements, abstract word comprehension and picture naming (Pobric et al., 2007; Pobric et al., 2009). This finding has been replicated for the right temporal pole for both verbal and non-verbal stimuli with no significant differences found between the effect of left and right ATL rTMS on pictures or words (Lambon Ralph et al., 2009; Pobric et al., 2010a). Thus, rTMS may be used to mimic the general semantic impairment evident in SD, providing convergent evidence of a causal role for bilateral ATL processing in semantic cognition. In contrast, rTMS of the left inferior parietal lobe has been shown to lead to a specific impairment of non-living items that are highly manipulable, mimicking the category-specific impairment of non-living items found after CVA in this area (Pobric et al., 2010b). TMS may therefore be used to show the necessity of both the ATL hub and the distributed spokes, providing convergent evidence for the hub-and-spoke view.

2.4 Other Roles of the ATL

Although considered to be critical, the precise role of the ATL has been interpreted in a number of other ways, with different authors positing a role in processing specific types of items or in specific aspects of processing. It has been suggested that the ATLs are only important for understanding unique, concrete concepts (Tranel, 2009), for processing social concepts (often argued to be right lateralised; Olson et al., 2007; Ross & Olson, 2010; Zahn et al., 2009; Zahn et al., 2007) or for sentence-level processing, where single words are combined to gain information not contained in any of the words in isolation (e.g., Hickok & Poeppel, 2007). However, none of these explanations fit all the available data including the imaging of a range of multimodal single item stimuli at different levels of specificity and the general semantic impairment without agrammatism in SD (Devlin et al., 2000; Hodges et al., 1992a; Snowden et al., 1989; Tranel, 2009; Visser et al., 2012; Visser & Lambon Ralph, 2011). It is therefore likely that these results reflect graded differences within the hub relating to difficulty (more specific items are harder, processing more items in combination is harder) or to an increased importance of certain input modalities, such as affective content, leading to greater dependence on subregions of the ATL (Binney et al., 2012; Rogers et al., 2004; Rosch et al., 1976; Zahn et al., 2009).

3. Further Exploration of the Spatial and Temporal Dynamics of the ATL Hub using TMS

Convergent evidence supports the role of the ATL in semantic cognition. However, many aspects of its function have not been elucidated. The high spatial and temporal specificity of TMS allows for more specific exploration of (a) the time at which the ATL is necessary and (b) the role of distinct subregions.

3.1 When is the ATL Hub Critical for Semantic Processing?

One way to further the understanding of the ATL's role within the semantic network is to investigate the time at which it is necessary for semantic processing. The high temporal resolution of spTMS allows assessment of the precise time points at which an area is necessary for a given process (Sandrini et al., 2011). This online 'chronometry' gives an enhanced understanding of the flow of information between cortical areas which may contribute differentially to processing. Word production has, for instance, been shown to require left MTG around 225ms followed by Broca's area at 300ms then Wernicke's area and further left MTG processing at 400ms (Schuhmann et al., 2012).

With regard to the timing of semantic processing in the ATL, one prediction would be that the key processing time would occur around 400ms after stimulus onset, at which point a negative event-related potential is regularly and reliably observed in ERP studies. The N400 is a negative peak between 250-550ms first identified with experiments which included syntactically-correct but semantically-odd sentences, but since shown to occur regardless of expectations or modality (Kutas & Federmeier, 2007; Kutas & Hillyard, 1980a; Pulvermuller, 2007; Sitnikova et al., 2003; Van Petten & Rheinfelder, 1995; West & Holcomb, 2002a). It has been shown to vary depending on frequency, imageability and semantic or lexical category (Federmeier et al., 2000; Kounios & Holcomb, 1994; Van Petten & Rheinfelder, 1995; West & Holcomb, 2002b). Although the spatial origin of the N400 varies, possibly as it is the sum of a number of different processes occurring at the same time, it has been found to involve much of the temporal lobe (see Van Petten & Luka, 2006 for review). This suggests that the N400 may reflect semantic processing occurring around this time. This idea is supported by MEG data, which show activity converging in the ATL and inferior prefrontal cortex (PFC) around 400ms (Marinkovic et al., 2003). Although the N400 is often argued to be left lateralised, this may be due to the use of verbal stimuli which is likely to have a left lateralised input to the ATL (Lambon Ralph et al., 2010b). Alternatively, the ATL may be critical at an earlier stage. A phase-locking analysis of MEG data showed greater synchronisation of signals from the ATL and left fusiform gyrus during recognition of basic items between 120-220ms, thought to reflect increased recurrent interactions between storage and access areas with greater semantic demands (Clarke et al., 2011). Words with high and low numbers of semantic associates induce distinguishable electrophysiological responses around 100ms, followed later by differences based on grammatical class, suggesting early semantic effects (Pulvermuller, 2001). In order to provide an independent source of evidence about the timing characteristics of the ATL, spTMS was applied to the ATL at a range of time points during a synonym judgement task to ascertain at what time this region is necessary for semantic judgements (see Chapter 3).

3.2 The Role of ATL Subregions and Posterior Temporal Cortex in Semantic and Phonological Processing

The anterior – posterior gradient within the temporal lobe relates the anterior portion to semantics and more posterior regions to other processes including phonology (Binney et al., 2012). However, activation is apparent in phonological tasks along the full length of the superior temporal gyrus (Vigneau et al., 2006). A lateral gradient across the temporal lobe relates to the modality of input (auditory vs. visual). We assessed the necessity of these regions of temporal cortex for semantic and phonological processing, hypothesising a double dissociation between ventral ATL and posterior STG. The ventral ATL is hypothesised to be the most important subregion for multimodal processing yet so far TMS studies of the ATL have targeted the middle temporal gyrus (MTG). The role of the anterior superior temporal gyrus (aSTG) is less clear and may vary by modality (auditory>visual) as well as stimulus type (verbal>non-verbal). It may have a role in phonology or semantics. The roles of these different subregions and the separability of semantic and phonological processing were investigated using offline rTMS (see Chapter 4). This also addressed the methodological question of where to TMS in order to simulate SD.

Chapter 2

A Semantic Cognition Network

The ATL is not the only region involved in multimodal semantic processing. A number of other regions are thought to be responsible for different aspects of semantic cognition. The roles of other areas within the semantic network are discussed. One dimension on which these may be separated is semantic representation vs. semantic control. Unlike the ATL, where semantic representations are stored, other regions are responsible for the controlled access and manipulation of representations stored elsewhere (Jefferies, 2013). Others have suggested a different organising principle whereby some regions are differentially involved based on type of semantic relationship (Schwartz et al., 2011). How different types of semantic relationships are stored is a long standing debate in philosophy, psychology and linguistics (see for example, Crutch & Warrington, 2005; Goldstein, 1948; Landauer & Dumais, 1997). Although these underlying principles of organisation allow some degree of separation of an individual area's roles, the regions do not work independently but form a network responsible for semantic cognition. An understanding of how regions work together is critical. The subject matter of cognitive neuroscience has shifted from describing the function of an area to assessing the connectivity of a network, sometimes considered to be a revolution of paradigms (Friston, 1994; 2011; van den Heuvel & Pol, 2010). These interactions may depend on the current state (e.g., task vs. rest) and may vary over time (Breakspear, 2004; Deco et al., 2008; Friston, 1997). fMRI may be used to measure functional connectivity as well as changes in activity (for review see Friston, 1994; 2011; van den Heuvel & Pol, 2010). The importance and methodology of a network approach is laid out. New directions are discussed including investigations of the network of functional connections with and without a semantic task. Preliminary work on the spatiotemporal dynamics of the semantic network is introduced.

1. The Semantic Network and Control

The ATLs are not thought to be the sole contributor to semantic cognition but instead to work in conjunction with prefrontal cortex (PFC), posterior MTG (pMTG) and ventral parietal cortex (Jefferies, 2013; Jefferies & Lambon Ralph, 2006; Lambon Ralph, 2014). Unlike the ATL, these areas have been highlighted in neuroimaging studies of semantic memory (Binder & Desai, 2011;

Chou et al., 2009; Devlin et al., 2003; Kapur et al., 1994b; Petersen et al., 1988; Price, 1998; Price, 2010; Roskies et al., 1996; Thompson-Schill et al., 1997). Meta-analyses have highlighted specific frontal regions (including dorsomedial PFC, ventromedial PFC and the inferior frontal gyrus; IFG) and temporoparietal areas (including pMTG and the angular gyrus) in semantic cognition (Binder et al., 2009; Noonan et al., 2013). These regions are thought to be critical for the controlled manipulation of semantic knowledge based on context and task demands, not areas responsible for the storage of representations (Jefferies, 2013; Jefferies & Lambon Ralph, 2006). This distinction between control and representation may be seen by contrasting SD patients with semantic aphasia (SA) patients.

Patients with cerebrovascular accident affecting left hemisphere TPC and PFC are referred to as semantic aphasia (SA) patients as they appear to have a problem with semantic access, unlike those with SD (Jefferies, 2013; Jefferies et al., 2007; Jefferies & Lambon Ralph, 2006; Warrington & Cipolotti, 1996; Warrington & McCarthy, 1983). SA patients show inconsistent performance between tasks with different demands, and performance may be dramatically improved through phonemic cueing (Jefferies & Lambon Ralph, 2006; Jefferies et al., 2009; Randolph et al., 1993; Robinson et al., 1998). Compared to SD patients they are less affected by specificity and word frequency, and more affected by how related the foils are to the target (Jefferies & Lambon Ralph, 2006). Similarly, 'pre-semantic' tasks and naturalistic object use are impaired in a qualitatively different way to SD, with decreased influence of familiarity and typicality, and a higher rate of perseverative, associative semantic and unrelated errors (Corbett et al., 2009a; Corbett et al., 2009b; Jefferies et al., 2010).

fMRI studies have supported a control-based interpretation of these regions, in particular the PFC. Activation of the IFG, has been shown to increase with task difficulty, automatically activate when primed and reduce with repeated semantic judgements (Copland et al., 2003; Demb et al., 1995; Galati et al., 2008). Indirectly related words and increased competition have also been shown to lead to an increased BOLD effect in IFG (Bedny et al., 2008; Kuperberg et al., 2007). The role of the left IFG has been concluded to be the task-sensitive executive control of semantic retrieval, possibly specifically the control of selection processes (Cohen & Servanschreiber, 1992; Shallice, 1988; Thompson-Schill et al., 1997; Wagner et al., 1997). There has been much debate as to whether this PFC-based processing supports semantic, phonological or syntactic processing. However, the PFC does have cytoarchitecturally and functionally distinct areas with evidence of semantic executive control in ventral inferior areas and phonological executive control in posterior areas, so there is no reason to believe the PFC must be specialised for only one of these processes (Barde & Thompson-Schill, 2002; Buckner et al., 1995; Devlin et al., 2003; Fiez, 1997; Gold & Buckner, 2002; Roskies et al., 1996). Activation of angular gyrus and pMTG have also been shown to relate to the difficulty of semantic tasks (Noonan et al., 2013). Some of these regions may be domain general and may be part of a multiple demand network for executive processing (Baldo et al., 2005; Duncan, 2010; Wiener et al., 2004). This is in accordance with the general executive problem found in some semantic aphasia patients (Jefferies, 2013). The angular gyrus is involved in many domains including episodic memory, attention, number processing, phonology and the default mode network (e.g., Binder et al., 2009; Buckner et al., 2008; Dehaene et al., 2003; Vigneau et al., 2006; Wagner et al., 2005; Walsh, 2003). This region may be responsible for a different aspect of knowledge such as statistics varying over time and space or concept integration (Binder & Desai, 2011; Humphreys & Lambon Ralph, in press). The roles of the ventromedial and dorsomedial PFC in semantic memory have not been elucidated but may relate to affective content, reward, planning or working memory processes (e.g., Binder et al., 2009; Chadick et al., 2014; Jefferies, 2013; Noonan et al., 2013; Tusche et al., in press).

Distinguishing separable roles of different semantic control regions has proved difficult. Few differences have been identified between PFC and TPJ lesions and rTMS of both the inferior frontal gyrus and the posterior middle temporal cortex has been shown to affect the processing of non-automatic semantic judgements (Whitney et al., 2011; 2012). Jefferies and Lambon Ralph (2006) suggested that these two regions may work in conjunction to control semantic activation in accordance with task demands, an idea supported by the evidence of white matter pathways linking them (Berthier, 2001; Chertkow et al., 1997; Glasser & Rilling, 2008; Noonan et al., 2013; Parker et al., 2005; Saur et al., 2008). rTMS to ventral and inferior areas of the PFC have been shown to affect semantic decisions and abstract word comprehension (Devlin et al., 2003; Hoffman et al., 2010; Knecht et al., 2002). spTMS has shown the necessity of the left anterior inferior PFC on a semantic task at 250ms (Devlin et al., 2003).

2. The Semantic Network and Conceptual Relationship Type

An alternative view of the separation of labour between semantic regions suggests that both the TPC and ATL are responsible for the storage of semantic representations but that there is different information stored in each. A critical distinction has been made between those semantic relationships based on the similarity between concepts, known as taxonomic or conceptual similarity, and those based on the temporal and spatial co-occurrence of the concepts often contributing to the same act or event, known as thematic or associative relations (e.g., Crutch & Warrington, 2005; Estes et al., 2011; Kalénine et al., 2012a). Most theories of the development of semantic organisation tend to focus on categorisation by conceptual similarity, arising from the presence of shared features. During the development of conceptual representations children show increasing differentiation of concepts resulting in a hierarchical taxonomic structure (e.g., Mandler et al., 1991; Mandler & McDonough, 1996). However, much evidence highlights the importance of the co-occurrence of concepts within the environment and language in the structure of conceptual representations (Albright, 2012; Landauer & Dumais, 1997). Associations have been shown to be important in category sorting, category verification and inductive reasoning tasks (Lin & Murphy, 2001). Measures of semantic relatedness based on the occurrence of two words in the same or similar texts, such as latent semantic analysis, have been shown to reflect aspects of meaning and are considered vital for the inductive reasoning that allows the development of language and semantics (Landauer & Dumais, 1997). This knowledge of associative relationships is integral for related processes, such as the top down influence of context on visual object recognition (Albright, 2012; Bar et al., 2006).

A voxel based lesion symptom mapping study of stroke patients related semantic errors based on these two relationship types to the TPC and ATL. Semantic errors involve substituting an intended word for a different semantically related word (e.g., Goldstein, 1948; Hodgson & Lambon Ralph, 2008; Luria, 1966). The related word may be connected to the intended word by sharing features and often therefore, category membership, or less commonly, the error and the intended word may be related through association (Butterworth et al., 1984; Dell & Reich, 1981; Hodgson & Lambon Ralph, 2008; Jefferies & Lambon Ralph, 2006; Schwartz et al., 2011). Thus, semantic errors may be based on conceptual similarity or association. The likelihood of these two error types being produced during aphasic patients' picture naming was predicted by lesions in different areas (Schwartz et al., 2011). Lesions to the anterior temporal lobe (ATL) were predictive of taxonomic errors, whilst associative/thematic errors were predicted by lesioned voxels in temporoparietal cortex (TPC; Schwartz et al., 2011). The authors concluded there was evidence for a dissociation of similarity based and associative relations with a separate semantic hub for each, referred to as the dual hub model. Similarity is argued to depend on knowledge stored in the ATL and association on parietal and posterior temporal regions (Kalénine et al., 2012b).

The two relationship types may depend on different methods of acquisition leading to separate frameworks of semantic knowledge and neural underpinnings. Cluster analysis of a computational implementation of the hub and spoke model showed an emergent semantic organisation based on similarity (Rogers et al., 2004). The hub and spoke model readily explains the acquisition and organisation of feature based similarity but it is less clear whether associative relations can be explained by this model. There have also been attempts to explain the process by which associative relationships are acquired. Models using co-occurrence to learn associations, such as latent semantic analysis and Hyperspace Analogue to Language demonstrate how meaning can be derived from the structure of language (Burgess, 1998; Landauer & Dumais, 1997). Viewing two objects in spatial and temporal proximity is argued to lead to a strengthening of the neural connections between their representations due to co-activation (Albright, 2012). The activation of the sensory representation of one then becomes predictive of the likely activation of the other. These models are not well integrated with models of similarity or of the neural underpinnings of semantic memory. A key step in assessing how associative relations can fit within standard models of the acquisition and representation of semantic memory, such as the hub-and-spoke model of semantic memory, is to assess whether associative relations rely on the same areas of the brain as similarity-based relationships.

The evidence for the dual hub model is not clear cut. Separating similarity and association in behavioural studies has proven difficult. Despite different potential methods of acquisition a strong correlation exists between the two dimensions of similarity and association. This may be seen through classic examples of conceptually similar concepts such as 'cat' and 'dog'. As well as sharing a number of features (e.g., four legged, furry, whiskers) they are also found in similar contexts (such as within the home as pets, at the vets, in relation to pet food) and the words themselves co-occur and occur in conjunction with many of the same words (e.g., basket, food, treats, stroke). This complicates the interpretation of much of the evidence assessing the organisation of concepts in patients and healthy participants where this correlation has often not been adequately addressed. The presence and strength of a priming effect for different kinds of related stimuli has been argued to directly show the organisation of the semantic network (Collins & Loftus, 1975). Semantic priming has been demonstrated for both associative and conceptual similarity-based relations and attempts to separate these different effects have led to conflicting results (Cree et al., 1999; Hare et al., 2009; Hutchison, 2003; Lucas, 2000; McRae & Boisvert, 1998; Shelton & Martin, 1992). As with priming experiments, participant ratings and choices between associative and conceptual similarity based relations may reflect the difficulty in separating associative and similarity based relations and can depend on the specific wording of the instructions (Hutchison, 2003).

Previous fMRI studies comparing types of semantic relationships have found different results: ranging from no difference between relationship types to large scale differences over both hemispheres (Kalénine et al., 2009; Kotz et al., 2002; Sass et al., 2009). This may be because they often lack appropriate stimuli for comparison, for instance, having taxonomic related words that are also associated (e.g., Kotz et al., 2002; Sachs et al., 2008b) or having pictures which may encourage participants to focus on lower level perceptual similarities (e.g., Kalénine et al., 2009). Most have focused on implicit processing of the relationship using priming which may have been confounded by the strength of the priming effect (e.g., Sachs et al., 2008b; Sass et al., 2009). Susceptibility artefacts caused by nearby air-tissue boundaries also means that signal from the inferior temporal lobes is likely to be lost in these studies meaning that differences within the ATL could have been missed (Embleton et al., 2010).

The dual model leads to clear predictions about patients with selective damage to the ATL or TPC. Both groups of patients should have a semantic representation problem. However, damage to the TPC in SA should cause a specific problem with association and damage to the ATL in SD should lead to a greater problem with conceptual similarity. Semantic dementia patients make a large number of superordinate and taxonomic errors and rarely make associative errors (Jefferies & Lambon Ralph, 2006). CVA patients with damage to the TPC make both similarity-based and associative errors (Jefferies & Lambon Ralph, 2006). Although patients with SD make less associative errors than semantic control participants, both show high numbers of similarity based errors. Errors may be produced for a variety of reasons and may reflect other processes such as the patient's remaining level of semantic control (Jefferies, 2013). Although association and similarity have not often been carefully separated, the patient's remaining ability in semantic tasks does not support the conclusions based on error type. Both semantic dementia and semantic aphasia patients are severely impaired at tasks requiring knowledge of associative relationships, such as the Camel and Cactus Test and the Pyramid and Palm Trees Test (Bozeat et al., 2000; Butler et al., 2009; Jefferies & Lambon Ralph, 2006). A direct comparison showed semantic dementia patients were actually worse at identifying an associatively related than a conceptually similar concept (Hoffman et al., 2013).

The neuropsychological data does not give a clear picture of whether association and similarity have the same neural underpinning. The strong version of the dual model of semantic memory hypothesises separate stores for association although a weaker version of this theory could be postulated with differences in the relative reliance on different areas in the semantic network. Alternatively, association could depend on a region outside the TPC. Other regions of the parietal lobe, have been suggested to be responsible for processes requiring the integration of concepts interacting in time and space creating an 'event ' and could be sensitive to the statistical likelihood of the co-occurrence of concepts (Binder & Desai, 2011; Mirman & Graziano, 2012a; Walsh, 2003). The IPL has been suggested as an ideal area for an 'event hub' due to its proximity to areas responsible for processing action, motion, time and space and its involvement in processing stories and assigning grammatical roles (Binder & Desai, 2011; Mirman & Graziano, 2012a). However, the ventral parietal cortex is complex and has been shown to be involved in a number of domains outside of semantics (e.g., Binder et al., 2009; Buckner et al., 2008; Dehaene et al., 2003; Vigneau et al., 2006; Wagner et al., 2005; Walsh, 2003). Association and conceptual similarity may also show differential dependence on sensory-specific spoke regions or areas involved in contextual top down processing of visual object recognition, such as parahippocampal, retrosplenial and medial prefrontal cortices (Kveraga et al., 2011).

The neural correlates of semantic relation type were investigated alongside semantic control using dual echo fMRI in order to establish the core organising factors within the semantic network and how association and conceptual similarity can fit in to models of semantic memory such as the hub-and-spoke model (see Chapter 5).

3. Connectivity within the Semantic Network

Connectomics, the study of the connections within the brain, has become an increasing focus for neuroscience in the last decade (Catani et al., 2013; van den Heuvel & Pol, 2010; Van Essen et al., 2013). This change from localist to distributed explanations of brain function has largely been brought about by advances in the methodology available for investigating both structural and functional connectivity (Pan et al., 2011; van den Heuvel & Pol, 2010). Diffusion tensor imaging assesses the preferred direction of water diffusion allowing in vivo imaging assessment of white matter pathways (bundles of axons), a major advance from post mortem dissection (Mori & Zhang, 2006; van den Heuvel & Pol, 2010). As well as assessing activity, fMRI enables the measurement of functional connectivity between brain regions, the temporal correlation between spatially-distinct brain regions measured with or without a task (Friston, 1994; Friston et al., 1993).

Psychophysiological interaction (PPI) is a method for assessing functional connectivity within a task (Friston et al., 1997). Signal is extracted from a chosen seed region and deconvolved with a haemodynamic response function. A regression analysis is performed to assess which areas show a significant interaction between the physiology and psychological contrast (Friston et al., 1997). This controls for areas that are coactivated within a condition but not causally related and, as such, is a moderate form of effective connectivity (Fornito et al., 2012; Friston, 2011). When participants do not switch between conditions during a scan, for instance when there is no explicit task, correlations between areas can be used as a measure of functional connectivity (Fox & Raichle, 2007; van den Heuvel & Pol, 2010). The discovery of low frequency oscillations (0.01-0.1 Hz) in scans without an explicit task, known as resting state fMRI, has generated a large amount of interest (Biswal et al., 1995; Cordes et al., 2001; Cordes et al., 2000; Lowe et al., 1998; Xiong et al., 1999). Contributing factors include physiological noise related to respiration and cardiac function and movement related artefacts (Birn et al., 2006; Glover et al., 2000; Lund et al., 2006; Wise et al., 2004). However, procedures have been developed to control for these factors and an underlying neural basis remains (Anderson et al., 2011; Fox & Raichle, 2007; Fox et al., 2005; Power et al., 2014; van den Heuvel & Pol, 2010; Van Dijk et al., 2012; Yan et al., 2013). Further research has consistently identified complex dynamic neural networks reflecting ongoing cognition, including visual, auditory, sensorimotor and higher order cognitive networks (e.g., Beckmann et al., 2005; Calhoun et al., 2008; Duncan, 2010; Fox et al., 2005; Mueller et al., 2013; Vincent et al., 2008). In addition a 'default mode network' (DMN) was discovered, named after the observation of decreased activation during performance of most tasks (Buckner et al., 2008; Cabeza & Nyberg, 2000; Raichle et al., 2001; Shulman et al., 1997). This network has been suggested to include medial prefrontal cortex, posterior cingulate, precuneus, lateral ATL, angular gyrus and medial temporal lobe (Andrews-Hanna et al., 2010b; Buckner et al., 2008; Greicius et al., 2003; Greicius et al., 2009; Utevsky et al., 2014). More recent findings indicate that these regions do not deactivate or deactivate relatively less for a number of tasks involving processes likely to be engaged strongly during spontaneous cognition, including episodic and semantic memory, mentalising, retrospection, prospection, theory of mind, spatial navigation and maintaining a narrative (Andrews-Hanna et al., 2014; Binder et al., 1999; Buckner et al., 2008; Buckner & Carroll, 2007; Shapira-Lichter et al., 2013; Spreng, 2012; Wirth et al., 2011). A frontoparietal control network has been postulated to be responsible for general controlled processing and includes the frontal and parietal regions linked to semantic control (Spreng et al., 2010; Vincent et al., 2008). How this connects to areas responsible for semantic representation and whether a separate semantic control network exists is not known. Resting state functional connectivity measures correlate strongly with structural connectivity (Damoiseaux & Greicius, 2009; Greicius et al., 2009; Honey et al., 2009; Tewarie et al., 2014).

A number of white matter tracts underlie conceptual processing. The uncinate fasciculus connects temporopolar and frontal cortex and is critical for semantic cognition (Binney et al., 2012; Catani et al., 2002; Grossman et al., 2004; Han et al., 2013; Harvey et al., 2013; Lu et al., 2002; Von Der Heide et al., 2013). A number of other structural connections may be relevant to semantic cognition, including the arcuate fasciculus connecting posterior temporal and parietal regions, the inferior longitudinal fasciculus running from the occipital lobe towards the temporal pole (Binney et al., 2012; Borroni et al., 2007; Catani & Ffytche, 2005; Catani et al., 2003; Catani & Mesulam, 2008). Less is known about the functional connectivity of the semantic network although connections have been demonstrated between some semantic areas in a range of tasks (Abrams et al., 2013; Assmus et al., 2007; Husain et al., 2006; Snijders et al., 2010; Stamatakis et al., 2005; Tyler & Marslen-Wilson, 2008; Vitali et al., 2005; Yang et al., 2011). Connections have been shown to differ between pSTS and pMTG areas responsible for social and tool comprehension during rest (Simmons & Martin, 2012; Simmons et al., 2010). Connectivity within the superior ATL has been identified and compared to the damage in SD (Seeley et al., 2009), yet the core multimodal semantic region of inferior ATL region is missing from resting state networks due to lack of signal (Wig et al., 2014; Zuo et al., 2012). Thus, the connectivity of the ATL and its contribution to resting state networks is not known. Networks relating to semantics may overlap with the DMN or frontoparietal control networks (Binder et al., 1999; Cole et al., 2013; Duncan, 2010; Greicius & Menon, 2004; Leech et al., 2011; Spreng et al., 2010; Vincent et al., 2008). The connectivity of the ATL and semantic regions may be studied with seed based functional connectivity analyses during rest and PPI during a semantic task. This allows an understanding of the connectivity of semantic regions and the dependency of this on different states (see Chapter 6).

Functional connectivity is dynamic; not only do changes occur over hours and minutes due to learning and task state but at the millisecond level due to intrinsic flexibility (Breakspear, 2004; Deco et al., 2008; Friston, 1997; Hutchison et al., 2013). Although seed based functional connectivity analyses show where a region is connected to they do not give information about the spatiotemporal dynamics of these connections, for instance, subsets of regions may be connected at different times representing different networks with different functional significance. One approach that takes temporal information in to account is Independent Components Analysis (ICA) which allows the separation of spatially or temporally independent sources without the need for a model (Calhoun et al., 2001; Cichocki & Amari, 2003; McKeown & Sejnowski, 1998). ICA has been applied to resting state data successfully and can identify key networks (e.g., Beckmann et al., 2005; Calhoun et al., 2008; Smith et al., 2009). This may help assess the separation between the semantic network and other previously identified networks such as the DMN (for preliminary discussion see Chapter 7).

Research Objectives

Despite the newly acquired knowledge of the areas critical for semantic cognition, many questions remain regarding the spatial and temporal dynamics of the semantic system. Methodological advances allow spatial and temporal resolution not previously available in the study of semantic cognition. Elucidating these dynamics and clarifying how regions and subregions contribute to semantic cognition was the main goal of this thesis. One approach taken was to use TMS to assess when the ATL was necessary in semantic cognition allowing a better understanding of its role within the network (see Chapter 3). Previously very little was known about the timing of the ATL in semantic processing. Advantage was also taken of the spatial precision of TMS in order to clarify results from the neuroimaging literature regarding the critical subregions of the ATL and the organisation of the ATL hub and posterior temporal lobe. An offline TMS study was performed investigating the role of the ventral ATL, aSTG and pSTG in semantic and phonological processing (see Chapter 4).

The organisation of the semantic network across the whole brain was investigated using fMRI to assess the importance of semantic control and type of semantic relationship (see Chapter 5). Despite knowledge of these organising principles the functional connections between these semantic regions have not been investigated using adequate methods for assessing the ATL. The connectivity of the ATL was investigated during the semantic task and during rest in order to discover how these regions work together in different states (see Chapter 6). The spatiotemporal dynamics of these connections may be complex and knowing which regions work with each other at different times may allow a more precise understanding of how the network processes meaning. Preliminary investigations to assess this using ICA are discussed in Chapter 7.

Chapter 3

The Timing of Anterior Temporal Lobe Involvement in Semantic Processing

Rebecca L. JACKSON, Matthew A. LAMBON RALPH* and Gorana POBRIC*.

Neuroscience and Aphasia Research Unit (NARU)

School of Psychological Sciences (Zochonis Building)

University of Manchester

* Correspondence to:
Dr. Gorana Pobric or
Prof. Matthew A. Lambon Ralph
Neuroscience and Aphasia Research Unit (NARU)
School of Psychological Sciences (Zochonis Building)
University of Manchester
Brunswick Street
Manchester
M13 9PL

Email: gorana.pobric@manchester.ac.uk
Or: matt.lambon-ralph@manchester.ac.uk

Tel: +44 (0) 161 275 2551
Fax: +44 (0) 161 275 2683

Running head: Timing of Semantic Processing in the ATL

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1. Abstract

Despite the growing consensus that regions within the anterior temporal lobe (ATL) make a crucial contribution to pan-modal semantic representation, to date there have been no investigations of when during semantic processing the ATL plays a necessary role. To test the timing of the ATL involvement in semantic processing, we studied the effect of double-pulse transcranial magnetic stimulation (TMS) on behavioural responses in semantic and difficulty-matched control tasks. Chronometric TMS (cTMS) was delivered over the left ATL (10 mm from the tip of the temporal pole along the middle temporal gyrus). During each trial, two pulses of TMS (40 msec apart) were delivered either at baseline (before stimulus presentation) or at one of the experimental time points 100, 250, 400 and 800 msec post stimulus onset. A significant disruption to performance was identified from 400 msec on the semantic task but not on the control assessment. Our results not only reinforce the key role of the ATL in semantic representation but also indicate that its contribution is especially important around 400 msec post stimulus onset. Together these facts suggest that the ATL may be one of the neural sources of the N400 ERP component.

Key words: chronometric TMS; anterior temporal lobes: conceptual knowledge; semantic memory, N400.

2. Introduction

The anterior temporal lobe (ATL) is known to be a critical substrate for pan-modal semantic representation (Lambon Ralph, 2014; Lambon Ralph et al., 2010b; Patterson et al., 2007) but little is known about the timing within this area. Neuropsychology, functional neuroimaging and repetitive transcranial magnetic stimulation (TMS) experiments have identified a three-part network responsible for multimodal semantic representation and control, including the prefrontal cortex (PFC), temporoparietal regions and bilateral ATL (Binder et al., 2009; Binney et al., 2010; Hoffman et al., 2010; Jefferies & Lambon Ralph, 2006; Noonan et al., 2013; Pobric et al., 2007; Visser et al., 2012; Visser & Lambon Ralph, 2011; Wagner et al., 2001b; Whitney et al., 2011). In contrast, the temporal dynamics of processing within the ATL have not been studied comprehensively. The temporal resolution of fMRI studies is poor and although electrophysiological techniques have good temporal resolution, spatial resolution is sacrificed (Walsh & Cowey, 2000). A long history of EEG and MEG studies have related semantic processing across a variety of modalities to a negative event-related potential, the N400, found 250 - 550 msec after stimulus onset (Kutas & Federmeier, 2011). Although somewhat inconsistent, attempts to localise the N400 have identified a number of sources within the semantic network, including areas in the temporal lobe (Helenius et al., 1998; Kutas & Federmeier, 2011; McCarthy et al., 1995). Beyond N400-focussed studies, one MEG investigation showed converging auditory- and visually-related activity for a semantic judgement task within the ATL around 400 msec (Marinkovic et al., 2003). However, other studies have suggested much earlier semantic influences in reading and visual object recognition (Bar et al., 2006; Halgren et al., 2002; Liu et al., 2009; Pulvermuller et al., 2009). Finally, a recent MEG investigation found that these differential timing effects may be related to the precision of semantic activation required, with earlier (120 msec) synchronisation between anterior and posterior temporal regions for domain-level picture-name verification and later (260 msec) for basic level decisions (Clarke et al., 2011).

In contrast to electrophysiological approaches (where data are correlational and therefore could be epiphenomenal), chronometric TMS (cTMS) assesses *when* neural activity within a specific brain area is *necessary* for a task, with a temporal resolution within tens of milliseconds (Sandrini et al., 2011; Silvanto & Pascual-Leone, 2012). Thus, the time at which there is a causal relation between the activity of a specific region and a particular behaviour may be identified (Duncan et al., 2010; Silvanto & Pascual-Leone, 2012). The present study investigated the timing of ATL involvement in semantic processing by applying TMS in a chronometric fashion. Double-pulse TMS was applied to the left ATL during a synonym judgement task and a non-semantic control task (to assess for any non-specific effects of ATL cTMS and to test if the cTMS effect is specific to semantic processing). This allowed identification of the time at which the ATL is necessary for semantic processing, hypothesised to be around 400 msec from stimulus onset. The ATL may also be active at other time points, for instance by contributing to early top down processing, but it is unclear whether this activation is necessary for semantic processing.

3. Method

3.1 Participants

Fifteen healthy, native English-speaking volunteers with normal or corrected-to-normal vision (7 female; mean age 24.39 years, SD = 5.98) completed the experiment, which was approved by the local ethics board.

3.2 Materials

The synonym judgement task was adapted from previous ATL offline-rTMS, neuropsychological and fMRI studies (Binney et al., 2010; Jefferies et al., 2009; Lambon Ralph et al., 2012; Pobric et al., 2007). This paradigm has proved to be a sensitive probe of semantic processing and has generated convergent cross-methodology evidence for the selective role of the ATL in semantic processing. These studies have not provided information, however, about the time course of this ATL semantic computation (the aim of the current study). Each task contained 200 experimental and 55 practice trials. We selected low imageability [target words mean imageability = 265.95, standard deviation 59.30 using Bird et al.'s (2001) ratings] and low frequency (target words mean CELEX frequency = 9.85, standard deviation 5.35) words because they are more sensitive to ATL rTMS and to the mild semantic impairment in patients with unilateral ATL resection and lead to poorer performance in SD patients (Hoffman et al., 2013; Hoffman & Lambon Ralph, 2011; Jefferies et al., 2009; Lambon Ralph et al., 2012; Lambon Ralph et al., 2009; Pobric et al., 2009).

3.2.1. Semantic Task

In each semantic trial, participants were presented with three words: a probe (e.g., RHYTHM), a target synonym (e.g., CADENCE) and an unrelated foil (e.g., NETWORK). Participants were asked to select which word was most related in meaning to the probe. The two options were matched within trials for frequency (foil mean 10.01, standard deviation 11.15, t(199)=-0.22, p>.05), imageability (foil mean 268.78, standard deviation 58.00, t(199)=-1.51, p>.05) and part of speech. The reaction time and accuracy was examined in a pilot study (mean RT = 1265.4 msec, mean accuracy = 94.4%).

3.2.2 Inter- and intra-task controls

The number judgement task was designed to match the synonym test in overall difficulty (reaction times and accuracy: pilot study - mean RT=1295.38, mean accuracy=96.2%). Participants were asked to choose which three-digit number was closest to the probe in terms of numerical value (e.g., probe - 391; target – 379; foil - 377). This inter-task comparison provides, therefore, an important assessment for the selectivity of semantic processing in the ATL and also for any non-specific effects of ATL cTMS. Following previous rTMS examinations of ATL function (e.g., Chiou et al., 2013; Pobric et al., 2007), we expected a slowing of semantic decision times but no effect on the control task – which would rule out any alternative explanation of the semantic data in terms of non-specific effects of ATL cTMS. In addition, a further potential advantage of chronometric TMS over offline rTMS is that cTMS can provide an "intra-task control" if decision times are slowed at some but not all of the probed time-points (e.g., Duncan et al., 2010). As noted above, we hypothesised that cTMS might have its greatest effect on the semantic task around 400 msec post stimulus presentation but not at its onset. If this timing pattern was coupled with no effect of TMS on the control task at any time point then the inter- and intra-task data would provide evidence for both task- and time-selectivity of semantic processing in the ATL.

3.3 Procedure

A PC running ePrime (Psychology Software Tools Inc., Pittsburgh, USA) was used to present the items and record participants' responses. The participants completed two sessions (one for each task) at least one week apart. The order of sessions was counterbalanced across participants.

The order of trials was randomised. At the start of every trial a fixation point was presented in the middle of the screen for 500 msec. Then the target and foil choices appeared at the top of the screen and remained for 2500 msec. These items were replaced by a fixation cross at the bottom of the screen which remained for 200 msec before the probe item appeared in its place. The target and foil item returned at the same time. All three items remained on screen for 2500 msec or until the participant's button-press response (see Figure 2). They were instructed to respond as quickly and accurately as possible. Displaying the foil and target before the probe allowed us to measure reaction time and to compute stimulation times against a single stimulus event (presentation of the probe item) rather than the complexities involved in timing from dual presentation of the target and foil items.

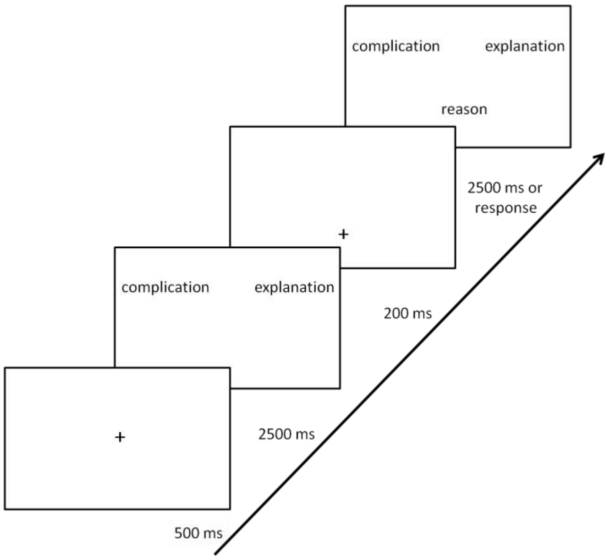

Figure 2. **The structure and timing of a semantic trial.** In both tasks a target and a foil item appeared after a fixation cross. Participants had time to read these items before presentation of the probe item in place of a fixation cross. The participants were then required to indicate which item was closer numerically or semantically.

3.4 Design

The experiment employed a 2×5 repeated-measures design with task (semantic vs. control) and TMS time (0 msec vs. 100 msec vs. 250 msec vs. 400 msec vs. 800 msec) as the within-participant factors. The 0 msec time point was employed as a baseline. This is superior to comparison against a no-TMS condition because TMS can produce generalised alerting effects (Dräger et al., 2004; Pobric et al., 2007). Interleaving trials without TMS stimulation has also been shown to affect the online TMS results and our own pilot study found slowing in the trials immediately after no TMS trials, perhaps reflecting increased attention to the stimulation following its absence (Kapoula et al., 2005). Accordingly, we adopted two types of control/baseline: (a) comparison to stimulation at 0 msec when semantic processing of the probe item had not yet started and (b) an RT-matched non-semantic control task used to detect potential non-semantic variation of decision times after stimulation at different SOAs. In both sessions participants completed a practice of 55 trials. They then completed 200 trials with TMS delivered at five different time points. These trials were split into blocks of 40 allowing participants to take a break in between.

3.4.1 Stimulation Parameters

TMS was delivered using a Magstim Rapid2 stimulator (Magstim Co., Whitland, UK) and a figure-of-eight coil with a diameter of 50 mm. Stimulation was performed at 100% of the individual's motor threshold, measured before the start of each session. The resting motor threshold of the relaxed contralateral abductor pollicis brevis muscle was measured as the lowest stimulation intensity able to cause a visible twitch in the muscle five out of ten times (Sandrini et al., 2011). Motor thresholds ranged from 40% to 66% of stimulator output (mean = 57.2, standard deviation = 7.06). Maximum stimulator output is approximately 2 Tesla (Magstim Co., Whitland, UK).

Double-pulse TMS was used as the effects of two pulses summate whilst maintaining temporal specificity (O'Shea et al., 2007). This inhibitory effect has been demonstrated in a variety of domains including language processing (Duncan et al., 2010; Juan & Walsh, 2003; O'Shea et al., 2007; Pitcher et al., 2007; Sliwinska et al., 2012). Two TMS pulses were delivered 40 msec apart in each trial. The two pulses were applied at -40 msec and 0 msec, 100 and 140 msec, 250 and 290 msec, 400 and 440 msec, and 800 and 840 msec following presentation of the probe number/word. Participants received stimulation in every trial but the stimulation time was randomised. These stimulation times were designed to sample a full range of potentially important times at which crucial semantic processing might occur in the ATL, including the hypothesised time of 400 msec as well as earlier and later time points.

3.4.2 Selection of TMS Site

A Phillips MR Achieva scanner (Phillips Electronics, The Netherlands) was used to acquire high resolution T1-weighted anatomical images of each participant. The scan had an in-plane resolution of 1mm with a slice thickness of 1.8mm. The acquisition matrix was 256 x 256 voxels. Full head coverage was maintained causing the number of slices acquired to vary depending on head size.

An Ascension Minibird magnetic tracking system (Ascension Technology Co, Burlington, Vermont, USA) was used to co-register the participant's scalp and T1-weighted MRI scan on MRIreg (www.MRIcro.com/mrireg.html). The individual's ATL coordinates were determined by measuring 10 mm posterior along the middle temporal gyrus from the tip of the left temporal pole. The average MNI coordinates were [-50, 12, -29].

Every effort was taken to minimize the potential discomfort of stimulating the ATL. Following the procedures developed in our previous studies (Pobric et al., 2007; 2010a), coil orientation was manipulated for maximum comfort and stimulus intensity was reduced if the participant considered the stimulation unpleasant. As noted above, non-specific effects of online TMS (such as muscle twitches) on reaction times were evaluated using the difficulty-matched non-semantic control task as well as intra-task comparisons (different time points during the semantic task).

3.5 Analyses

A composite RT-accuracy measure was used as the primary indicator of overall performance because it allows for variation in speed-accuracy trade-off across participants. The measure is commonly used in experimental psychology for this reason, and is also useful in TMS studies where, across participants, the effects of TMS can be found in reaction times, errors or both (Cattaneo et al., 2009; Chambers et al., 2004; Townsend & Ashby, 1983). Following the standard method, the composite measure was computed as RT/accuracy (Townsend and Ashby, 1983). As this was an updated version of the synonym and number judgement tests, performance for each item was screened. Seventeen items in the synonym judgement task and 23 in the control judgement task had a mean accuracy below 75%. These items were removed from the analyses causing a loss of 7.7 % of the semantic items and 10.5 % of the control items. For each participant and each time point, trials with reaction times more than 2 standard deviations from the mean were considered outliers and removed causing a loss of 4.42% of the remaining semantic and 4.4% of the control trials.

The effects of double-pulse TMS at different time points on the composite performance were assessed using a 2×5 within-subjects ANOVA with the repeated measures factors, task (synonym judgement, number judgement) and TMS time (0, 100, 250, 400, 800 msec). In order to assess the time points at which there was a greater effect of TMS on the semantic task, the ANOVA was repeated for two subsets of time points. The change in performance caused by TMS at time points implicated in these ANOVAs was computed by subtracting the individual's mean composite score at these time points from their mean composite score at the baseline time point on the each task. This allowed comparison of the effect of TMS at each time point on the two different tasks.

4. Results

The results for the two tasks at each time point are shown in Figure 3, with a clear effect of cTMS arising for the semantic task but no effect at any time point for the control task. A 2 (task; control vs. semantic) × 5 (stimulation time point; 0 vs. 100 vs. 250 vs. 400 vs. 800 msec) repeated-measures ANOVA found no significant main effects but, crucially, there was an interaction of task and TMS time point (F(4, 56) = 2.6, p=.046, partial η^2= .156). The nature of this TMS interaction was confirmed in the following way. As expected, given the pilot data and careful RT matching of the tasks for general difficulty, performance was not significantly different between the two tasks at the 0 msec baseline time point (t(14) = -.632, p=.538, two-tailed) and thus this time point provided a suitable baseline reference to compare changes in performance across the other time points. Accordingly, the relative effect of cTMS at each time point was extracted by subtracting the baseline (0 msec) composite score from the composite score at each experimental time point. The two tasks were then compared directly by computing direction-specific, one-tailed t-tests as we expected ATL TMS to slow semantic decision times, as found in numerous previous ATL offline rTMS studies (e.g., Chiou et al., 2013; Pobric et al., 2007). As is clear from Figure 3, this analysis confirmed that there was significant slowing of the semantic over control task at 400 ms (t(14) = -2.101, p=.027) and 800 ms (t(14) = -2.038, p=.030). There were no significant effects at any of the other time points (p>.05).

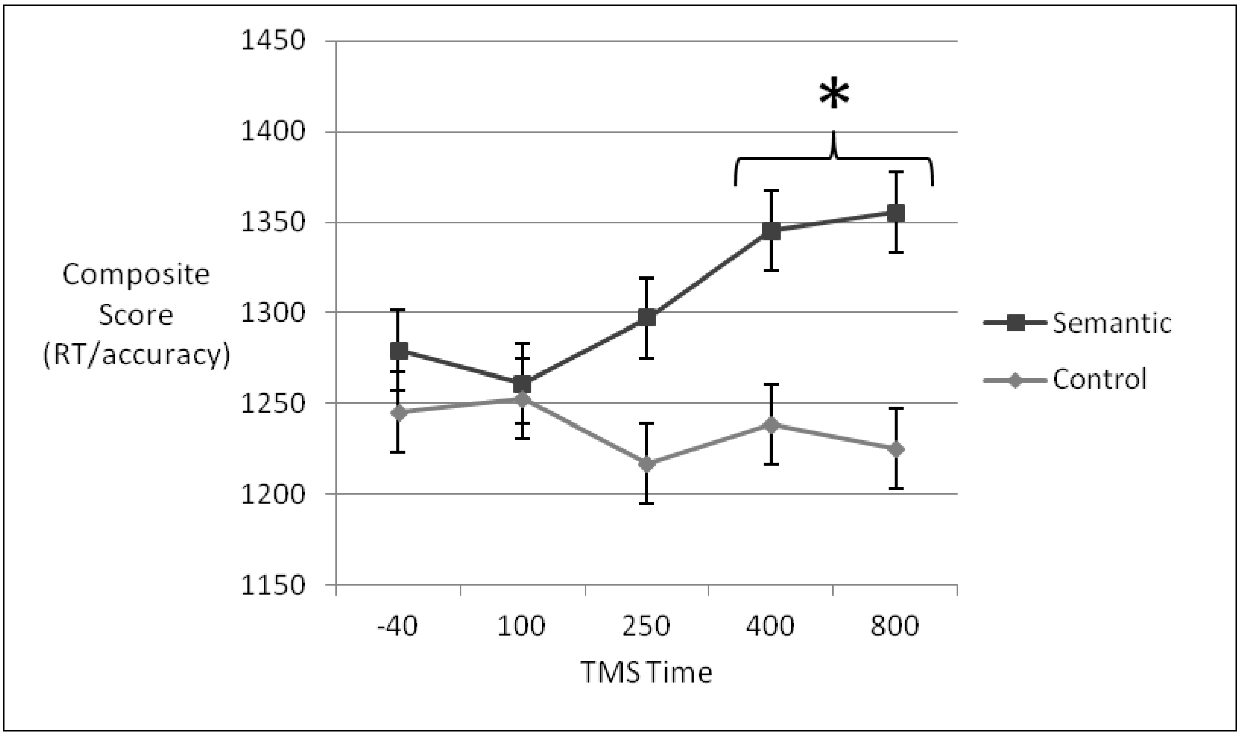

Figure 3. **Composite score (RT/accuracy) for the semantic and control tasks at each different TMS time point.** Error bars = standard error of the mean, corrected for a within participant design (Loftus & Masson, 1994). A significant TMS effect was found for the later time points (denoted by the asterisk).

A second additional analysis confirmed these same results. We used an interaction contrast to confirm the significant effects of cTMS at 400ms and 800ms on the semantic task alone. Specifically, we averaged the data across these two time points for each task and contrasted them against the combined data for the earlier time points. Again, following the pattern shown in Figure 3, there was no change in performance on the control task between the earlier and later time points (t(14)=.224, p=.826), whereas there was a significant slowing for the semantic task (t(14)= 9.536, p<.001). We also formally compared the early-to-late changes in performance across the two tasks and confirmed that the early-to-late slowing on the semantic task was significantly greater than the null effect on the control task, (t(14)=4.891, p<.001).

Accuracy and reaction time scores were also analysed separately (see Table 1). Accuracy was relatively stable across conditions and tasks. The ANOVA on these data demonstrated no significant results, although numerically the greatest TMS effects were apparent at the 400 and 800 msec time points in the semantic task. Reaction time changes mirrored those in the composite score and the ANOVA on these data confirmed the same interaction between task and TMS time (F(4, 56)= 2.556, p=.049, partial η^2= .154). We explored this interaction in exactly the same way as described above for the composite score. The same pattern emerged, with a significant slowing in the semantic compared to control task at 400 msec (t(14)= -2.694, p=.009) and 800 msec (t(14) = -2.109, p= .026). As before, the TMS effect at these time points was not significantly different to the 0 msec baseline for the control task (t(14)=-.127,p=.901) but was for the semantic task (t(14)=-2.50,p=.025). Again, this difference between the two tasks was significant (t(14)=2.528,p=.024).

Table 1. Mean reaction time (msec) and accuracy per TMS time point.

	Semantic Task		Control Task	
TMS Time (msec)	RT (SD)	Accuracy (SD)	RT (SD)	Accuracy (SD)
-40	1177.31 (231.58)	.924 (.06)	1149.58 (297.16)	.922 (.05)
100	1150.57 (261.07)	.919 (.08)	1141.11 (288.99)	.911 (.05
250	1178.56 (310.07)	.907 (.04)	1108.46 (292.72)	.906 (.06)
400	1206.56 (291.9)	.895 (.08)	1125.34 (327.71)	.912 (.08)
800	1234.15 (310.09)	.917 (.05)	1145.72 (303.90)	.939 (.04)

5. Discussion

Chronometric TMS was used to elucidate the time at which the ATL is necessary for semantic processing. TMS had a significant effect on semantic performance at 400 and 800 msec post stimulus onset. No significant effects of TMS were observed at earlier time points or at any point during the control task. Due to the a priori expectation of worse performance during the semantic task with TMS, the t-tests assessing the effect at each time point were one-tailed and uncorrected for multiple comparisons. This means there may be an increased chance of a type I error. As such, further assessments of the necessity of the ATL at different times may be needed to verify this finding. These results add to the convergent evidence for the necessity of the ATL in semantic processing (from neuropsychological, offline TMS and neuroimaging studies: Binney et al., 2010; Patterson et al., 2007; Pobric et al., 2007; Visser et al., 2012; Visser & Lambon Ralph, 2011) and reveal the temporal dynamics of this processing for the first time.

MEG studies demonstrate two stages of processing in semantic tasks: early processing within sensory areas and then a large degree of interactivity between higher-order pan-modal areas (Dale et al., 2000; Halgren et al., 2002; Marinkovic et al., 2003). A translational phase between modality-specific and pan-modal processing is thought to start around 230 msec post stimulus presentation (Marinkovic et al., 2003). ATL involvement has been identified within the second pan-modal stage, peaking around 400 msec (Halgren et al., 2002; Marinkovic et al., 2003). The current study not only provides convergent evidence for these hypotheses but goes further to demonstrate that ATL activity at this time point is *necessary* for semantic processing, which neuroimaging studies alone cannot establish. Although this necessity has only been demonstrated here in a single modality using visually-presented abstract words, the evidence of a more general necessity from rTMS and the demonstration of a multimodal processing stage support the likelihood that this necessity occurs at a similar time for different modalities. Theories that limit the role of the ATL to social entities (e.g., Moll et al., 2005; Olson et al., 2007; Ross & Olson, 2010), unique entities (e.g. Tranel, 2009) or combinatorial processes (Hickok & Poeppel, 2007; Lau et al., 2008) cannot easily explain the current and prior rTMS studies which used a range of stimuli including single basic-level, non-social concepts and found significant effects of TMS in all cases (see Lambon Ralph, 2014 for a more detailed review and discussion).

Our results indicate that the ATL is necessary for semantic processing 400 msec after stimulus presentation. This fits the timing of the N400 in electrophysiological studies, suggesting the ATL as one potential source. Source localisation of the EEG signal in previous studies has generated conflicting results about the N400 source, although a number of studies have implicated a distributed fronto-temporal network (Kutas & Federmeier, 2011; Lau et al., 2008; Van Petten & Luka, 2006). In addition, intracortical recordings have localised an N400-like ERP to areas including anterior fusiform gyrus and the temporal pole (Halgren et al., 1994; Kotz et al., 2007; McCarthy et al., 1995; Nobre et al., 1994; Nobre & McCarthy, 1995) and MEG studies indicate a pan-modal role for the ATL at this time point as well (Halgren et al., 2002; Maess et al., 2006; Marinkovic et al., 2003). Finally, damage to left or right ATL can result in a loss of the N400 (Kotz et al., 2007).

One interpretation of the N400 is that it reflects semantic access regardless of input modality (Kutas & Federmeier, 2000; 2011). This implies that the areas involved are responsible for pan-modal processing (Holcomb & Anderson, 1993; Kutas & Federmeier, 2011). Within the hub-and-spoke semantic model, the ATL hub is responsible for pan-modal representation whereas the 'spokes' represent modality-specific information (Patterson et al., 2007; Pobric et al., 2010b). Thus the modality-invariant processing within the ATL could be reflected in the N400, a notion consistent with the current cTMS findings.

Instead of viewing the N400 as representing semantic processing per se, some researchers have suggested that it is an index of violations of expectation, reflecting a process whereby words or other constituent parts are integrated in to a context (Brown & Hagoort, 1993; Kutas & Hillyard, 1980b). This violation requires semantic and lexical access, however, and so it is unclear that these explanations are mutually exclusive. The ATL may be a source of the N400 or it may be necessary in parallel with the source(s) of the N400, responsible for access to and integration of the necessary pan-modal semantic representations. In order to assess whether the ATL is a source of the N400, future studies could assess the effect of ATL TMS in eradicating the N400 component.

Finally we note that, although this cTMS study only found evidence for necessary semantic processing at 400 and 800 msec, some neuroimaging studies have implicated earlier time points. Superordinate semantic differences have been shown in the phase-locking of the ATL from 120 msec and in activity level from 170 msec (Clarke et al., 2011). Similarly, intracortical electrode recordings have shown category-sensitive responses in inferior anterior temporal areas less than 200 msec post stimulus presentation (Liu et al., 2009). There are at least three possible explanations. First, electrophysiological data reflect changes in activity level whereas TMS elucidates the time at which an area becomes necessary (Walsh & Cowey, 2000). Thus, it may be that the ATL starts to become involved before 200 msec but does not start to become crucial until around 400 msec. This activity may be epiphenomenal or may just have a minor effect on the resulting decision due to the relatively greater importance of the later processing. A second possibility is that the early activity may be critical in certain conditions, such as more general semantic (domain/category) distinctions than those probed in this cTMS study (Clarke et al., 2011) or in tasks using impoverished stimuli which may promote greater top-down processing (e.g., Bar et al., 2006). Finally, an alternative possibility is that there is an earlier necessary phase of ATL involvement but that this is much smaller and transient in nature, making it much harder to detect with cTMS.

Chapter 4

A TMS Investigation of Semantic and Phonological Processing in the Left Temporal Lobe

Rebecca L. JACKSON, Gorana POBRIC* and Matthew A. LAMBON RALPH*.

Neuroscience and Aphasia Research Unit (NARU)

School of Psychological Sciences (Zochonis Building)

University of Manchester

* Correspondence to:
Dr. Gorana Pobric or
Prof. Matthew A. Lambon Ralph
Neuroscience and Aphasia Research Unit (NARU)
School of Psychological Sciences (Zochonis Building)
University of Manchester
Brunswick Street
Manchester
M13 9PL

Email: gorana.pobric@manchester.ac.uk
Or: matt.lambon-ralph@manchester.ac.uk

Tel: +44 (0) 161 275 2551
Fax: +44 (0) 161 275 2683

Running head: Timing of Semantic Processing in the ATL

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Semantic and phonological processing occurs in ventral and dorsal language routes, respectively. Within the ventral route, the anterior temporal lobe is a key region for multimodal semantics. Although the ventral ATL subregion has been shown to be core for semantics in neuroimaging and neuropsychological studies, prior TMS studies have focused on the lateral anterior MTG. A further subregion, the aSTG has been suggested to have a role in both semantics and phonology, the precise nature of which is unclear. This study investigated the role of these two regions, a third region thought to be responsible for phonology (the pSTG) and a control site (the occipital pole). Fifteen minutes of 1 Hz TMS was delivered offline before and after semantic, phonological and control tasks. None of the areas that received TMS showed significantly different changes in performance on any of the tasks compared to the control site. Methodological and theoretical considerations of why this may be are discussed. TMS delivered to the ventral ATL site may have been unsuccessful despite a critical role of the subregion due to practical issues, such as the depth of the target site. Future studies of the ATL as a whole may wish to continue using the lateral site. The role of the aSTG subregion remains to be further elucidated.

1. Introduction

Imaging studies and meta-analyses comparing semantic and phonological processing have highlighted separable networks of regions involved in language processing. Areas of activation commonly associated with phonological processing include frontal cortex, supramarginal gyrus (SMG) and superior temporal gyrus (STG; Price, 1998; Price et al., 2005; Price et al., 1997; Vigneau et al., 2006). Areas responsible for multimodal semantic processing include regions of the anterior temporal lobe (ATL) as well as posterior temporal and inferior frontal cortex (Price, 1998; Price et al., 2005; Price et al., 1997; Vigneau et al., 2006). These areas constitute the dorsal and ventral language routes hypothesised to be responsible for mapping sound to articulation and meaning, respectively (Hickok & Poeppel, 2004; Parker et al., 2005; Saur et al., 2008). Posterior STG (pSTG) is argued to encode acoustic-phonetic speech codes providing the input to both routes (Hickok & Poeppel, 2004). The dorsal route connects pSTG to the supramarginal gyrus and frontal regions via the arcuate and superior longitudinal fasciculi (Makris et al., 2005; Parker et al., 2005; Saur et al., 2008). This pathway supports repetition and may be damaged in conduction aphasia (Fridriksson et al., 2010). The ventral route allows auditory comprehension by connecting the pSTG to more anterior temporal areas, which may include middle and inferior temporal gyri, as well as a ventral region sometimes referred to as the basal temporal language area (Hickok & Poeppel, 2004; Parker et al., 2005; Saur et al., 2008). The ventral route may include white matter tracts such as the inferior longitudinal fasciculus, uncinate fasciculus and inferior fronto-occipital fasciculus (Parker et al., 2005; Saur et al., 2008). A computational implementation of the ventral and dorsal routes, the Lichtheim 2 model, has shown the high explanatory power of the dual-route theory to explain language processes and classic disorders, including conduction aphasia and semantic dementia (Ueno et al., 2011). The performance of the model in naming, repetition and comprehension of multisyllabic Japanese words was comparable to developing children and adults. Damaging the model at different locations within the ventral pathway simulated semantic dementia and Wernicke's aphasia, whilst dorsal damage led to behavioural patterns consistent with transcortical motor and conduction aphasias.

Despite differing origins the processing routes for spoken and written language converge at an early level, allowing meaning to be extracted in common ventral route areas (Spitsyna et al., 2006). As well as converting auditory input to phonology, the pSTG has been shown to be active during reading (Moore & Price, 1999; Simos et al., 2000; Spitsyna et al., 2006). This may reflect grapheme-phoneme conversion suggesting phonological information may be accessed automatically within the STG whether the verbal input is written or spoken (Dijkstra et al., 1993; Moore & Price, 1999; Simos et al., 2000; Spitsyna et al., 2006; Visser et al., 2012). This suggests these areas are responsible for phonological processing whether accessed from the auditory or visual domain.

Multimodal convergence of semantic processing occurs in a posterior-anterior gradient along the temporal lobe resulting in differing roles for posterior and anterior temporal regions (Binney et al., 2012). The ATL area, part of the ventral route thought to be integral for multimodal semantics, is affected in semantic dementia (SD). SD patients show a gradual loss of multimodal conceptual knowledge with atrophy and hypometabolism greatest in the ventral ATL (Nestor et al., 2006; Patterson et al., 2007). Imaging studies support the importance of the ATL as a high level convergence zone by showing a convergence of processing from different input modalities (Binney et al., 2010; Marinkovic et al., 2003; Spitsyna et al., 2006; Visser et al., 2012; Visser & Lambon Ralph, 2011). Although patient studies are not circumscribed enough to allow differentiation of function within subregions of the ATL (due to large lesions or diffuse atrophy), imaging and intracortical electrode studies show the core role of a ventral ATL region for this convergence of processing from different input modalities including verbal and nonverbal stimuli (Binney et al., 2010; Matsumoto et al., 2004; Visser et al., 2012; Visser & Lambon Ralph, 2011). A further lateral ATL region has also been highlighted as an area supporting multimodal semantic processing (Visser et al., 2012). As well as a posterior-anterior gradient of convergence, processing within the temporal lobe displays a second gradient of convergence progressing laterally towards aMTG (Visser et al., 2012). Due to differences in connectivity, the relative importance of the different temporal gyri varies by modality with auditory stimuli primarily engaging STG and higher order visual processing reliant upon inferior and fusiform gyri (Binney et al., 2012). Transcranial magnetic stimulation (TMS) studies have confirmed the necessity of the ATL in semantic processing using a variety of tasks and input modalities but have yet to elucidate further the roles of the subregions (Lambon Ralph et al., 2009; Pobric et al., 2007; 2010a). These studies have targeted an anterior MTG site likely to stimulate the lateral ATL site shown to activate during semantic tasks in fMRI studies although this stimulation could be affecting inferior, middle and superior temporal gyri (Lambon Ralph et al., 2009; Pobric et al., 2007; 2010a; Pobric et al., 2009). TMS to the ventral region will help assess the role of this area both in comparison to the other regions investigated in this study and in comparison to the standard aMTG site.

The comparison of intelligible and unintelligible speech suggests a posterior-anterior gradation along the temporal lobe from phonology to semantics. Contrasting intelligible and unintelligible speech shows regions related to processing meaning in speech. This intelligibility contrast activates the anterior superior temporal gyrus (aSTG; Crinion et al., 2003; Scott et al., 2000). This shift was also found in the computational Lichtheim 2 model where the aSTG connected the ventral ATL area to the frontal and posterior temporal regions (Ueno et al., 2011). Representations in the anterior regions were found to be preferentially organised by semantics whilst more posterior representations were organised by phonology (Ueno et al., 2011). Activation of the aSTG has also been found for nonverbal auditory stimuli such as environmental sounds (Price et al., 2003; Visser & Lambon Ralph, 2011). The aSTG is disproportionately involved in processing auditory stimuli although it is not clear whether this reflects semantics alone or whether it may still have some role in phonology (Visser & Lambon Ralph, 2011). A meta-analysis suggests both anterior and posterior STG are involved in phonological processing (Vigneau et al., 2006). Although part of the ATL, the aSTG acts differently to lateral and ventral ATL and may be more modality-dependent. Alternatively, the aSTG may have a more complex function due to its pivotal role in connecting the ventral ATL with inferior frontal gyrus regions thought to be involved in the executive regulation of semantic knowledge (Binney et al., 2012). The Lichtheim 2 model shows the region is necessary for speech/naming and auditory comprehension (Ueno et al., 2011). This may explain the association between damage to this area and speech errors, found using voxel-symptom lesion mapping (Schwartz et al., 2009). This may suggest a role for the aSTG in the coordination of temporal and inferior frontal regions.

The organisation of the temporal lobe is complex and the contribution of various temporal regions to semantic and phonological processing has not been fully established. In the current study, semantic, phonological and control tasks were completed before and after repetitive TMS was delivered to three temporal regions which may have key roles in processing semantics and phonology. This includes the ventral ATL as the core semantic region in the ventral route, previously shown to be activated during the semantic task (Binney et al., 2010). In addition, stimulation was delivered to the pSTG, thought to be critical for phonological processing, and the aSTG which may be involved in semantics or phonology. An occipital region was also used as a control site as it is not considered necessary for semantic or phonological processing. Due to the convergence of visual and auditory routes for semantics and phonology and the evidence of multimodal semantic processing, written words could be used to probe these processes whilst avoiding the potential effects of stimulation to primary auditory regions (Patterson et al., 2007; Spitsyna et al., 2006). To avoid any potential contribution of semantic processing regions to the phonological task (Simos et al., 2000), we used nonwords in the phonological task. This experiment aimed to assess the role of the ventral ATL, aSTG and pSTG. In addition, by qualitatively comparing the effect of TMS at the ventral ATL site in this study with prior studies using the lateral ATL region, we aimed to further elucidate the role of the subregions and inform the methodology of future TMS studies aiming to investigate the ATL. A more general question which can also be considered is to what extent are semantic and phonological processes neurally separable.

2. Method

2.1 Participants

Sixteen healthy, native English-speaking volunteers (8 female; mean age 25.86 years, SD = 5.97) with normal or corrected-to-normal vision completed the experiment. The local ethics board approved the study.

2.2 Materials

Semantic, phonological and control tasks were employed. Each task included 192 trials split into 4 lists with a further 40 trials used as a practice at the start of each session. Visually-presented verbal stimuli were employed to necessitate effortful phonological processing by accessing phonology from the orthography, rather than auditory speech sounds. This also eliminated the need for acoustic input processing, which could have been disrupted by stimulation near the primary auditory cortex.

2.2.1 Semantic Task

The synonym judgement task was adapted from previous single pulse and rTMS investigations of the ATL as well as neuropsychological and fMRI studies (e.g. Chapter 3; Binney et al., 2010; Jefferies et al., 2009; Pobric et al., 2007). 192 trials were selected involving low imageability (mean target imageability = 290.13 using Bird et al.'s (2001) ratings), low frequency (mean target CELEX frequency = 12.54) nouns and adjectives, shown to be sensitive to TMS and vulnerable in SD (Jefferies et al., 2009; Lambon Ralph et al., 2009; Pobric et al., 2010a).

Each trial involved the presentation of a probe (e.g., rhythm), semantically-related target (e.g., cadence) and unrelated foil (e.g., network). Participants chose the word most related to the probe in terms of meaning. Targets and foils were matched within the trial for frequency and imageability ($p>.05$). The probe items were matched to the targets and foils on frequency ($p>.05$). The trials were split in to four lists matched on probe frequency and length and target and foil frequency, length and imageability as well as the RT and accuracy in a pilot of 4 participants (mean RT = 1908.97(397.18) ms, mean accuracy = .851 (.108), all ANOVAs $p<.5$).

2.2.2 Phonological Task

The phonological task was created using nonwords from the MCWord orthographic wordform database (Medler & Binder, 2005). Nonwords were 1 or 2 syllables and 5 or 6 letters long with legal trigrams (each combination of three letters had to be possible in English words at that position in a word that length) allowing pronunciation. Pseudohomophones were not used. Trials consisted of a target, probe and foil nonword. Participants chose the nonword that had the same number of syllables as the probe (e.g. storgy has the same number of syllables as womer unlike plasp). Half the one syllable and half the two syllable probes, targets and foils were 5 letters long and half were 6 letters long so that the number of syllables could not be determined by the number of letters. Target and foil nonwords were matched within trial to the probes on the number (probe average = 2.81(2.45)) and frequency (probe average = 64.12(214.99)) of orthographic neighbours, frequency of the constrained trigrams (probe average = 313.23(398.26)) and the number of words containing the constrained trigrams (probe average = 10.35(9.00), p<.05). Trials were separated in to 4 lists matched on the same variables as well as the average RT (mean= 2217.76(326.65)) and accuracy (mean= .887(.061)) in a pilot of 3 people (all ANOVAs p<.4).

2.2.3 Control Task

A number judgement task was employed as in prior TMS and fMRI studies of semantics as it has been shown to be unaffected by ATL stimulation (Binney et al., 2010; Pobric et al., 2007; Pobric et al., 2009). Participants were presented with triads of 3 digit numbers and chose which was closest to the probe in terms of numerical value (e.g. 716 is closer to 724 than 716). This was designed to be as difficult as the harder phonological task to control for effects of difficulty on the TMS effect. A pilot of 3 people had a mean RT of 2013.85 (37.77) and a mean accuracy of .922 (.036).

2.3 Procedure

Presentation of items and recording responses was completed using a PC running ePrime (Psychology Software Tools Inc., Pittsburgh, USA). Participants completed 4 sessions, approximately one week apart. Each of the 4 lists was presented to each participant twice, once before and once after TMS in non-consecutive sessions. Thus, the first list presented before the TMS in session 1 was presented again in the third session after TMS. List order was held constant whilst stimulation site was counterbalanced between participants in order to make sure stimulation site order did not relate to list order or session. The trials presented before and after TMS were split into halves allowing presentation of the 3 tasks in a balanced order of ABCCBA each including 24 trials. This meant that the time after TMS was approximately equal on average between the 3 tasks. The order of tasks within this was randomised each time (i.e. each participant's session, before and after). Within these sections the order of the trials was randomised. In each trial a fixation cross was presented centrally for 500 ms before presentation of the probe, target and foil for 3500 ms or until a response is made. Participants responded by pressing a button on the left if the left-hand item was a synonym in the semantic task, had the same number of syllables in the phonological task or was the closest numerically in the control task (see Figure 4).

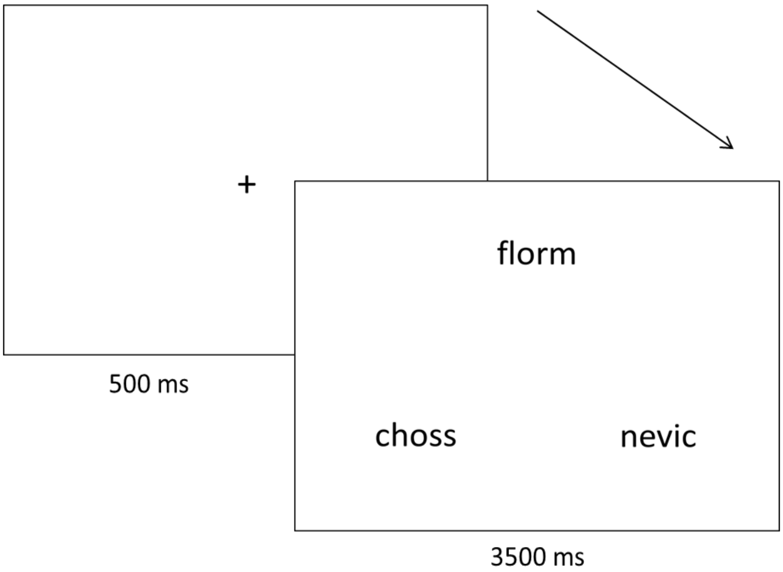

Figure 4. **Procedure within a trial.** Participants view a fixation cross for 500 ms before presentation of the probe, target and foil. During this time the participants respond by indicating whether the target is on the left or right. The example shown is from the phonological task. The correct response is 'choss' as it has the same number of syllables as 'florm'.

2.4 Design

A 4 (TMS site; vATL, pSTG, aSTG, OP) x 3 (task; semantics, phonology, control) within subjects design was employed including both a control site (occipital pole) and a control task (number judgement). Including a control site not thought to relate to language processing provides a better baseline than areas that may be specialised to one aspect of language but may not be completely independent of others. Including a control task controls for discomfort and non-specific TMS effects specific to the area. Each session involved completion of 40 practice trials for each task then 48 trials of each task. Participants then had TMS for 15 minutes in one of the 4 stimulation sites before immediately completing another 48 trials per task. TMS site order was counterbalanced between participants.

2.4.1 Stimulation Parameters

Individual's motor thresholds were determined as the lowest stimulation intensity able to cause a visible twitch in the relaxed contralateral abductor pollicis brevis muscle five out of ten times (Sandrini et al., 2011). Stimulation was performed at 110% of motor threshold up to a maximum of 70% of the machine's output (mean = 63.62, standard deviation = 7.58, range=48-70% machine output). Stimulation was delivered for 15 minutes at 1Hz using a Magstim Rapid2 stimulator (Magstim Co., Whitland, UK) and a figure-of-eight coil with a diameter of 70 mm.

Maximum stimulator output is approximately 2 Tesla (Magstim Co., Whitland, UK). This has previously been shown to slow performance of semantic judgement when applied 10 mm along the MTG from the temporal pole (Lambon Ralph et al., 2009; Pobric et al., 2007; 2010a; Pobric et al., 2009).

2.4.2 Selection of TMS Site

TMS was delivered to 3 experimental sites (vATL, aSTG and pSTG) and one control site (occipital pole). The ventral ATL coordinates (-36 -15 -30) were taken from Binney et al. (2010) where fMRI showed activation of this basal region during completion of a synonym judgement task. This area is thought to be a key multimodal region towards which information regarding different modalities converges and is highly overlapping with the peak areas found in a number of other imaging and intracortical electrode studies as well as being affected in SD (Liu et al., 2009; Nestor et al., 2006; Sharp et al., 2004; Visser et al., 2012; Visser & Lambon Ralph, 2011). Although the exact coordinate is quite deep and the effect of TMS at this depth may not be strong, the TMS will be closer to the wider area involved in the multimodal semantic processing, including more lateral aspects of the inferior temporal gyrus. The posterior STG coordinate (-50 -38 12) was the most posterior peak in Vigneau et al.'s (2006) highly-cited meta-analysis of phonological processing. This pSTG area may be the start of the dorsal route of language and is close to Okada and Hickok's (2006) Spt region. The anterior STG coordinates (-54 6 -16) were taken from Scott et al.'s (2000) intelligibility analysis showing the importance of the area in auditory semantic processing. This same area is used to assess whether it is also involved in semantic and phonological judgements involving visual presentation. All of these areas are separated by more than the sufficient distance apart to be functionally dissociable using TMS with a figure-of-eight coil, shown to be 5-10 mm (Brasil-Neto et al., 1992). The occipital pole is located at POz in the 10-20 electrode system which was determined anatomically as 1/10 of the distance from the inion towards the nasion. This area is not thought to be involved in processing semantics, phonology or numbers.

Localisation of the three main sites was performed using a Brainsight Neuronavigation system (Rogue Resolutions, Cardiff). The MNI coordinates were transformed in to each individual's space and used as targets. Secondary targets for coil placement on the skin were chosen to have the shortest route to the target whilst angled approximately parallel to the coronal plane in order to avoid targeting other temporal gyri. The TMS was monitored online using BrainSight and the distance from the area where the pulse was delivered to the target area on the skin was recorded for 52 of the 64 sessions. The average error was less than 1 mm and was not significantly different between TMS areas (F(1.352, 6.760)=.502, p=.557, Greenhouse-Geisser corrected).

2.5 Analyses

The main comparisons were performed on median reaction time as this minimises the effect of outliers and has been shown to be a robust measure of the effect of TMS (e.g. Gough et al., 2005; Stoeckel et al., 2009). Planned analyses included a 3 (task; semantic vs. phonology vs. control) x 4 (area; vATL vs. pSTG vs. aSTG vs. OP) within-subjects ANOVA on the TMS-induced change in median RT to assess whether TMS to the chosen areas differentially affected the tasks. The TMS-induced change was calculated for each session (and therefore TMS area) and task as median RT after stimulation minus median RT before stimulation. Positive numbers therefore reflect TMS-induced slowing whereas negative numbers reflect TMS-induced speeding up caused by the TMS or practice effects. Whether the TMS effect was significantly greater than for the control site was assessed for each of the main areas with a 3 (task; semantic vs. phonology vs. control) x 2 (area; e.g. vATL vs. OP) within-subjects ANOVA. T-tests could then be employed to compare the TMS effect on the semantic and phonological tasks over the control task within areas showing significant TMS effects in order to identify the source of the differences. The same analyses were performed on the accuracy data to confirm the conclusions and assess whether the RT differences could relate to a speed-accuracy trade off.

3. Results

Two participants were replaced due to accuracy below .75 on the phonological task allowing the counterbalancing to remain unaffected. Although the semantic and phonological tasks were not matched for difficulty (t(15)=-3.37, p<.05) the control task was matched to the harder phonological task (t(15)=-1.08, p>.05) as planned to ensure that TMS was not merely having a generic effect on difficult tasks. Median RT and mean accuracy before and after TMS to each area are shown in Table 2.

Table 2. Median RT and mean accuracy before and after TMS to each area per task.

		Semantics		Phonology		Control	
		Before	After	Before	After	Before	After
RT	vATL	1454.84 (360.39)	1499.97 (356.03)	1702.60 (524.97)	1677.25 (518.05)	1835.50 (308.21)	1699.47 (254.24)
	pSTG	1419.06 (317.63)	1439.06 (322.90)	1720.47 (516.54)	1737.5 (477.96)	1848.31 (327.10)	1748.34 (324.69)
	aSTG	1434.28 (319.94)	1430.34 (294.00)	1705.59 (537.99)	1624.72 (535.26)	1819.78 (298.70)	1751.81 (343.46)
	OP	1420.75 (341.18)	1415.05 (327.94)	1744.78 (521.04)	1692.97 (530.31)	1817.66 (307.83)	1742.50 (343.58)
Accuracy	vATL	.953 (.034)	.946 (.050)	.897 (.069)	.913 (.051)	.900 (.054)	.911 (.053)
	pSTG	.932 (.057)	.931 (.040)	.913 (.070)	.901 (.082)	.899 (.054)	.901 (.061)
	aSTG	.944 (.045)	.933 (.053)	.878 (.082)	.900 (.061)	.893 (.051)	.906 (.046)
	OP	.946 (.036)	.929 (.048)	.924 (.075)	.928 (.050)	.900 (.073)	.900 (.064)

Standard deviations shown in brackets.

The TMS effect (median RT after stimulation minus median RT before stimulation) is shown in Figure 5 per area and task. The assumption of sphericity has been checked for using Mauchly's W and where violated a Greenhouse-Geisser has been used and noted within the text. A 3 (task; semantic vs. phonology vs. control) x 4 (area; vATL vs. pSTG vs. aSTG vs. OP) within-subjects ANOVA performed on the TMS change scores found a significant effect of task (F(2, 90)=10.62,

$p<.05$) but no effect of area ($F(3, 90)=.37$, $p=.773$) or interaction effect ($F(6, 90)=1.45$, $p=.204$). This meant there was no evidence of differential effects of TMS to the different areas on the different tasks. Direct comparisons of each main area to the control area, OP, were made as a further verification that no areas showed significantly different patterns of change to baseline. None of these 3 (task; semantic vs. phonology vs. control) x 2 (area; vATL/pSTG/aSTG vs. OP) within-subjects ANOVA showed a significant interaction effect (vATL; $F(2, 30)=1.74$, $p=.203$, pSTG; $F(2, 30)=.91$, $p=.414$, aSTG; $F(1.475, 22.128)=.28$ $p=.759$ Greenhouse-Geisser corrected) although the vATL ($F(2, 30)=9.04$, $p<.05$) and pSTG ($F(2, 30)=5.00$, $p<.05$) showed significant main effects of task.

In order to directly test the prediction that the pSTG and vATL would result in a different pattern of slowing across the tasks a 3 (task; semantic vs. phonology vs. control) x 2 (area; vATL vs. pSTG) within-subjects ANOVA was performed. A significant effect of task ($F(2, 30)=10.45$, $p<.05$) was found but no interaction effect ($F(2, 30)=.76$, $p=.475$). As no significant interaction between TMS area and task was found, no evidence could be found for the necessity of any of these areas in phonological or semantic processing. Thus, no further investigations of the data were performed.

In order to verify that there were no effects on the accuracy, the accuracy after stimulation minus accuracy before stimulation was computed to get the accuracy TMS effect[1]. A 3 (task; semantic vs. phonology vs. control) x 4 (area; vATL vs. pSTG vs. aSTG vs. OP) within-subjects ANOVA found no significant effects of task ($F(2, 90)=2.87$, $p=.072$) or area ($F(3, 90)=.18$, $p=.906$) or an interaction effect ($F(6, 90)=.31$, $p=.932$). No significant interaction effects were found when comparing each area to the control site directly (vATL; $F(2, 30)=.03$, $p=.969$, pSTG; $F(2, 30)=.39$, $p=.684$, aSTG; $F(2, 30)=.05$ $p=.950$) or by comparing the pSTG and vATL ($F(2, 30)=.27$, $p=.769$).

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[1] Similarly, computing an efficiency measure able to take in to account changes in RT and accuracy regardless of differences in response bias (calculated as accuracy/mean reaction time), did not substantially change the results.

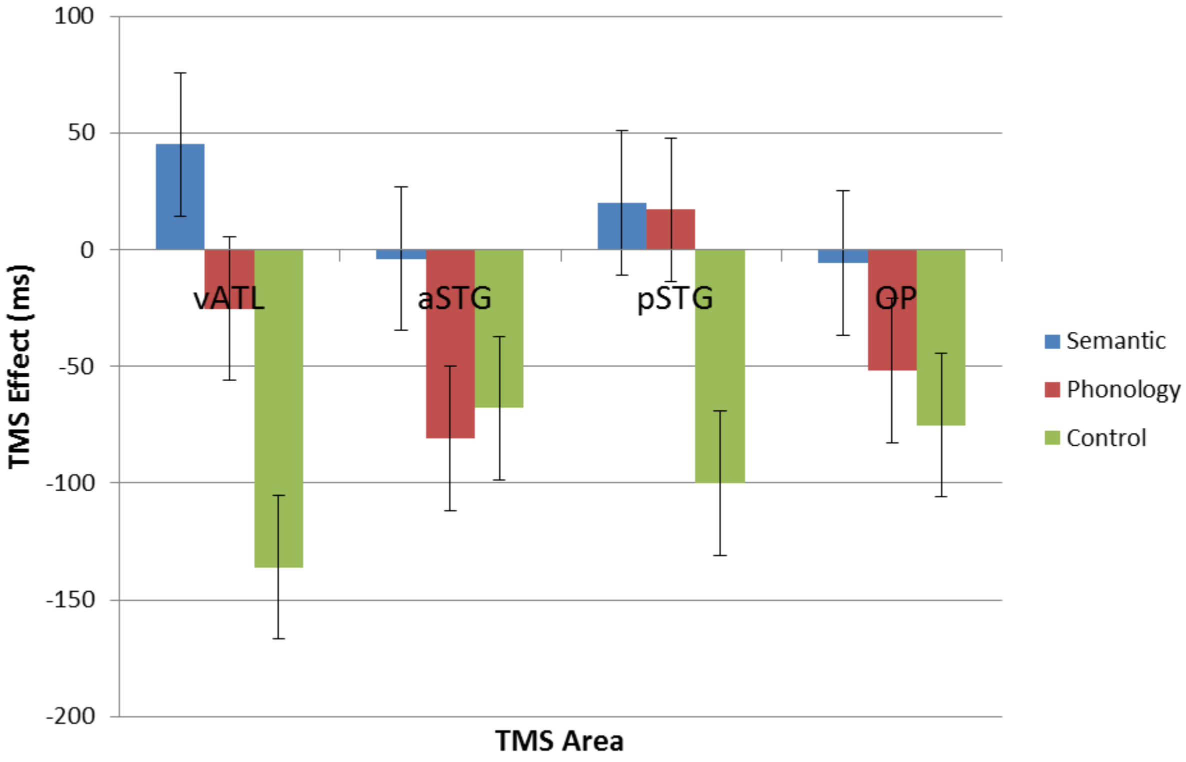

Figure 5. **Change in median RT after TMS to each area on the 3 tasks.** Change is calculated as median RT after stimulation minus median RT before stimulation and measured in ms. Positive numbers indicate slowing and negative numbers speeding. Error bars show standard error of the mean, corrected for a within participant design (Loftus & Masson, 1994).

4. Discussion

TMS delivered to the temporal regions did not result in significant changes in reaction time on either the semantic or phonological tasks compared to the occipital control site TMS. This gives no support to the theory that the pSTG is involved in phonological processing and the ventral ATL in semantic processing. Nor does it show a role for the aSTG in either semantic or phonological tasks. However, null results are hard to interpret in TMS studies and may be due to various methodological reasons as well as the role of the areas are involved. Some potential explanations are considered below.

The TMS effect could have been too weak due to some general methodological problem. However, there are few differences between the design of this study and prior TMS studies of the ATL. One potential problem could be a non-specific effect of the TMS speeding task responses, a rarely documented but common effect (Dräger et al., 2004; Pobric et al., 2007).

Here significant speeding is found for the control task at the vATL, pSTG and OP sites and the phonological task at aSTG and OP (p>.05). There may also be more complex changes in performance over time, such as practice effects, not well modelled within the ANOVAs. This may have been a particular problem for the phonology task which was harder and less naturalistic than the semantic task (counting syllables in nonwords vs. comparing the similarity in meaning of words). An alternate paradigm that controls for practice effects would be to use online TMS which has been employed successfully to assess phonological processing within the supramarginal gyrus (Sliwinska et al., 2012) and semantic processing at the lateral ATL site (see Chapter 3).

A large body of research links the pSTG to phonological processing although the precise aspect of phonology performed here may be less well established. The pSTG has been proposed to map sound to meaning and articulation, a role it is well suited for due to its connections to both ventral and dorsal routes (Hickok & Poeppel, 2004; Saygin et al., 2003). The lack of an effect of stimulating the pSTG may mean this area is not critical for phonological manipulation of written words, for instance, only being required for auditory-phonological mapping. Although pSTG has been shown to be activated during phonological judgements of written stimuli (Moore & Price, 1999; Simos et al., 2000; Spitsyna et al., 2006) this finding is not consistent (Price et al., 1997; Scott & Wise, 2003). Activation does not prove necessity and instead may be epiphenomenal (Silvanto & Pascual-Leone, 2012). Alternatively, if the role of the pSTG is in mapping sound to meaning it may be that the use of nonwords without semantic representation meant that the pSTG was not required but areas responsible for the phonology itself were. Attempts to access semantic knowledge relevant to the nonwords may in fact slow performance in this task. This would fit with the role of the pSTG in other phonological tasks which can be supported with semantic processing and the rapid convergence shown for processing real words regardless of modality. If either of these explanations are true it may be that processing phonology within this task recruited different areas, such as the supramarginal gyrus, and potentially the employment of different strategies. Online TMS has shown the necessity of the SMG at an early stage in phonological processing lending support to this possibility (Sliwinska et al., 2012).

Prior convergent evidence from neuropsychology, imaging and TMS shows the importance and necessity of the ATL for semantics and for the synonym judgement task (Binney et al., 2010; Jefferies et al., 2009; Lambon Ralph et al., 2009; Patterson et al., 2007; Pobric et al., 2009). Prior experiments with the same design, stimulation frequency, synonym judgement task and control task have shown an effect of TMS delivered to the ATL (Lambon Ralph et al., 2009; Pobric et al., 2009). Although stimulation was delivered at 110% of motor threshold instead of 120%, TMS was delivered for 50% longer. This suggests the null result here is likely to be due to targeting a different subregion of the ATL. Instead of identifying lateral MTG anatomically, this study used a group level peak from a prior imaging study to identify the ventral ATL thought to be a centre of convergence within the ATL. The lack of effect on the semantic task may mean this is not a core area for semantic representation, although this does not fit well with the evidence from semantic dementia and imaging studies. An alternate explanation is that the ventral ATL is a core region of equal or greater importance than the lateral aspect of the aMTG but that it is too deep to be strongly affected by the TMS. Due to the thickness of the bone at this height, even the stimulation of the most lateral ITG may be weak compared to stimulation of the MTG. This would fit better with the work suggesting the central role of the aMTG and vATL over other ATL subregions (Visser et al., 2012). Although this was considered as a possibility it was considered that the effect on the anterior ITG would make up for this subtle effect. However, the ITG may not be a core multimodal subregion and the TMS may be affecting a smaller area overall. This ventral region may also be hard to localise, possibly varying greatly between individuals. All these possibilities could result in the failure to detect the subtle TMS effect. The direction of the effect for the vATL was in the correct direction although it failed to reach significance. Future studies wanting to investigate the ATL region overall may find it best to target the original lateral aMTG location or to test more participants.

The aSTG shows a non-significant speeding up on all tasks, the same pattern as the control task. The results do not provide any support for the necessity of the aSTG in phonological or semantic processing of written words. It may be that the aSTG is only necessary for processing auditory stimuli and is not strongly multimodal. This fits the evidence that it is disproportionately engaged in semantic processing based on an auditory input (Visser & Lambon Ralph, 2011). Whether the aSTG is involved in phonological processing without semantic content is less clear. Although the aSTG is more active for meaningful words it has been shown to be active during phonological processing of meaningless auditory stimuli (Vigneau et al., 2006). The results cannot further elucidate other possible factors determining when the aSTG is necessary, such as a role in semantic control. Semantic and phonological processing were not successfully separated. This distinction may not be clear-cut as areas may be processing phonology and semantics in conjunction.

Chapter 5

The Nature and Neural Correlates of Semantic Association vs. Conceptual Similarity

Rebecca L. JACKSON, Paul HOFFMAN, Gorana POBRIC, & Matthew A. LAMBON RALPH*
Neuroscience and Aphasia Research Unit (NARU)
School of Psychological Sciences (Zochonis Building)
University of Manchester

* Correspondence to:
Prof. Matthew A. Lambon Ralph
Neuroscience and Aphasia Research Unit (NARU)
School of Psychological Sciences (Zochonis Building)
University of Manchester
Brunswick Street
Manchester
M13 9PL
Email: matt.lambon-ralph@manchester.ac.uk
Tel: +44 (0) 161 275 2551
Fax: +44 (0) 161 275 2683

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This chapter has been submitted for review at Cerebral Cortex.

1. Abstract

The ability to represent concepts and the relationships between them is critical to human cognition. How does the brain code relationships between items that share basic conceptual properties (e.g., dog and wolf) while simultaneously representing associative links between dissimilar items that co-occur in particular contexts (e.g., dog and bone)? To clarify the neural bases of these semantic components in neurologically-intact participants, both types of semantic relationship were investigated in an fMRI study optimised for anterior temporal lobe (ATL) coverage. The clear principal finding was that the same core semantic network (ATL, superior temporal sulcus, ventral prefrontal cortex) was equivalently engaged when participants made semantic judgements on the basis of association or conceptual similarity. Direct comparisons revealed small, weaker differences for conceptual similarity>associative decisions (e.g., inferior prefrontal cortex) and associative>conceptual similarity (e.g., ventral parietal cortex) which appear to reflect graded differences in task difficulty. Thus, the same prefrontal region was found in a parallel manipulation of executive semantic demands (hard>easy). Conversely, as a part of the default mode network (DMN), the VPC region was deactivated by the semantic and baseline tasks (in comparison to rest). Indeed, once reaction time was entered as a covariate into the analysis, no associative vs. category differences remained. The paper concludes with a discussion of how categorical/feature-based and associative relationships might be represented within a single, unified semantic system.

2. Significance Statement

Conceptual knowledge is critical to human cognition. Over many years, various disciplines have considered how we represent the meaning of objects, words, etc. Considerable separate research efforts have been focussed on understanding two different kinds of knowledge – how to represent similarity between concepts (e.g., dog and wolf) or to encode associative links between concepts (e.g., dog and bone) – yet very few studies have considered how the brain encodes both types of information. Using optimised fMRI, this study found that the *same* network of brain regions is implicated in both types of semantic information. With reference to recent computational models of semantic memory, we consider how both defining characteristics of conceptual knowledge can arise from a single neurocomputational mechanism.

3. Introduction

Investigating the nature of semantic representation has been a core pursuit in many different disciplines including philosophy, linguistics, cognitive science and neuroscience. The focus of the current study was on the comparison between, and neural basis of, two key forms of information that are extracted from semantic memory: associations and conceptual similarities (Crutch & Warrington, 2005; Estes et al., 2011; Kalénine et al., 2012b). The central question addressed in this study was: do semantic association and conceptual similarity arise from neuroanatomically separable components of semantic memory or are they the result of a single conceptualisation process?

Although there are lively and long-standing debates about the underpinning mechanisms, most researchers agree that concepts are formed from, and reflect a distillation of, our verbal and nonverbal experience (Barsalou, 1999; Eggert, 1977; Lambon Ralph et al., 2010b; Rogers et al., 2004; Smith & Medin, 1981; Wittgenstein, 1953). Thus, for example, we know many things about the concept <CROISSANT> including features of its taste, smell, texture, visual form, knowledge of how it is made and served, etc. Semantic memory is, however, more than an exhaustive list of multimodal features. Crucially, we are able to extract higher-order structures that code the relationships between concepts. First, *associative (or thematic) relationships* reflect the temporal and spatial co-occurrence of concepts, often contributing to the same acts or events. Thus, for example, croissants are associated with coffee and jam, despite these concepts having different appearances, tastes, smells and functions. Secondly, we can generalise properties across concepts based on a sophisticated coding of *conceptual similarity*. For instance, we can correctly ascribe similar properties and actions to croissants, scones, crumpets and naan bread, despite them having very different physical forms and occurring in different contexts. Many researchers have proposed different hypotheses on how coherent, generalisable concepts are formed and thus this key dimension of semantic memory is given various theory-specific labels: family resemblances (Wittgenstein, 1953); taxonomical/categorical similarity (Quillian, 1968); prototypicality (Rosch, 1975); feature-similarity (McRae & Cree, 2002; Smith & Medin, 1981). For the sake of brevity, the theory-neutral term ‘conceptual similarity’ will be used hence forth.

The literature contains at least three types of inconclusive empirical comparisons of conceptual similarity vs. associative relationships. Neuropsychological investigations potentially offer definitive information on the separability of these two forms of knowledge, if a double dissociation between associative and conceptual similarity could be established. Goldstein (1936;

1948) was perhaps the first to suggest a single dissociation in patients with semantic aphasia (Head, 1926; Jefferies & Lambon Ralph, 2006). Although not formally tested, Goldstein noted that these patients were able to detect and, perhaps were overly influenced by, strong associations. In addition, he noted that they found it difficult to consider the more abstract notion of categorically-related items (a part of his broader notion of a loss of 'abstract thinking' in semantic aphasia). A potentially related contrast was reported by Jefferies and Lambon Ralph (2006). One of a range of qualitative differences between semantic dementia (a neurodegenerative condition leading to atrophy focussed on the anterior temporal lobe) and semantic aphasia (a subtype of aphasia associated with prefrontal or temporoparietal lesions) is a difference in picture naming errors; SA patients make a mixture of associative and category-related errors whereas SD patients almost never produce associative semantic errors. In an innovative study of aphasic picture naming, Schwartz et al. (2011) used voxel-based symptom-lesion mapping to relate the likelihood of each error type to lesion distribution. When focussed on the relative rates of each error type, a higher rate of taxonomic errors was associated with voxel integrity in the anterior temporal lobe (ATL) whereas more associative/thematic errors were predicted by lesions in temporoparietal cortex (TPC). Schwartz et al. (2011) concluded that there are separate stores for conceptual similarity (ATL) and associative relationships (TPC), a position that we refer to here as the *dual-hub model* (see also, Kalénine et al., 2012b). At least three neuropsychological phenomena do not seem to fit easily with this conclusion, however. First, all stroke-related aphasic patients make a mixture of category- and associatively-related errors and thus there is no absolute double dissociation within this group (Jefferies & Lambon Ralph, 2006). Secondly, direct assessment has established that both semantic dementia and semantic aphasia patients are impaired at tasks requiring knowledge of associative relationships, such as the Camel and Cactus Test and the Pyramid and Palm Trees Test (Bozeat et al., 2000; Jefferies & Lambon Ralph, 2006). Indeed, a direct comparison showed that semantic dementia patients were actually worse at identifying associative than conceptual similarity-based relationships, which appears incompatible with the notion that the ATL exclusively codes conceptual similarity-based relationships (Hoffman et al., 2013). Finally, previous investigations have suggested that the ATL and TPC regions may underpin different components of semantic cognition rather than different types of semantic representation (Jefferies, 2013). Whilst ATL regions appear to play a crucial role in semantic representation and extraction of conceptual knowledge (Lambon Ralph et al., 2010b; Patterson et al., 2007), semantic aphasia patients with damage to the TPC or prefrontal cortex exhibit poorly controlled retrieval and manipulation of semantic memory rather than impaired representation per se (Jefferies & Lambon Ralph, 2006). We refer to these executive functions as *semantic control.* This hypothesis is supported by evidence from fMRI and TMS studies suggesting that PFC, pMTG and IPS may form a distributed control network (Duncan, 2010; Jefferies, 2013; Lambon Ralph; Noonan et al., 2013; Whitney et al., 2011).

To clarify these issues, we used fMRI to contrast associative relationships and conceptual similarity directly, and also manipulated the level of semantic control. A second key novelty in this study was methodological, namely a strict separation and direct probing of associative vs. conceptual knowledge. This is an important step in that many concepts are related in both ways (e.g., <cat> and <mouse>) and previous comparative investigations have been dogged by this issue. Within experimental psychology, semantic priming has been demonstrated for both associative and conceptual similarity-based relations and attempts to separate these different effects have led to conflicting results (Cree et al., 1999; Hare et al., 2009; Hutchison, 2003; Lucas, 2000; McRae & Boisvert, 1998; Shelton & Martin, 1992). Likewise, previous fMRI studies comparing the two types of semantic relationship have found different results, ranging from no difference to large scale differences over both hemispheres (Kalénine et al., 2009; Kotz et al., 2002; Sass et al., 2009). This may be because the studies lacked appropriate stimuli for comparison, for instance adopting taxonomically-related words that are also associated with each other (e.g., Kotz et al., 2002; Sachs et al., 2008b) or using picture stimuli, which may encourage participants to focus on lower level perceptual similarities (e.g., Kalénine et al., 2009). Furthermore, most studies have not probed knowledge of conceptual similarity vs. associative relationships but have relied upon implicit processing of these relationships via priming which requires the neuroimaging method to detect a small subtle behavioural effect (e.g., Sachs et al., 2008b; Sass et al., 2009).

In order to explore these key theoretical questions and alternative hypotheses, this study was designed in the following manner. First, there was a direct manipulation of two factors: type of semantic relationship (associative vs. conceptual similarity) and semantic control (hard vs. easy decisions; see Table 3 for example stimuli). Secondly, knowledge of each type of relationship was directly probed in the same semantic decision task rather than relying on secondary, implicit activation. Finally, the fMRI data were acquired in a way that allows full coverage of the entire semantic network including the ventral aspects of the ATL. Various methodological issues in previous investigations have led to inconsistent coverage and sensitivity to activation in this region (Embleton et al., 2010). Accordingly, the present study utilised a dual-echo gradient EPI paradigm to ensure ATL coverage (Halai et al., 2014).

Table 3. Example stimuli for each condition in the three tasks.

	Probe	Target	Foil
Semantic judgement task			
Association	vase	tulip	elephant
Conceptual similarity	vase	bucket	platform
Baseline (letter matching) task			
Low control demands	##HΨz##	bqwcHΨz	ctkdLXQ
High control demands	##HΨz##	bqwcHΨz	cHΨdLXQ
Task to vary semantic control demands			
Low control demands	mountain	pyramid	doe
High control demands	mountain	pyramid	arch

Type of semantic relationship was varied in the main semantic judgement task and the necessary level of control was manipulated in the baseline letter matching task and separate similarity-based semantic task. In the two semantic tasks participants chose the word most related to the probe word and in the baseline task participants chose the item with the most letters from the probe.

4. Results

4.1 Behavioural Data

A semantic judgement task employing trials based on either association or conceptual similarity was employed along with a letter matching task designed to provide a high level baseline. A manipulation of semantic control was included in a separate set of conceptual similarity judgements. A manipulation of non-semantic control was incorporated within the letter matching task. The conceptual similarity judgements (mean RT=1783.69, SD=277.44) had significantly longer reaction times than the associative trials (mean RT=1653.68, SD=286.48; t(23)=-4.58, p<.05). As designed, the letter matching task was harder than both the conceptual similarity (mean RT=2076.16, SD=265.49; t(23)=7.33, p<.05) and association-related trials (t(23)=10.9, p<.05), thereby providing an appropriate high-level control condition. The manipulations of control in both the semantic and letter matching tasks successfully led to significant differences in RT as expected (high semantic control (mean RT=1939.16, SD=273.71), low semantic control (mean RT=1809.55, SD=299.24); t(23)=4.22, p<.05, high non-semantic control (mean RT=2158.85, SD=500.35), low non-semantic control (mean RT=1993.48, SD=493.77); t(23)=4.79, p<.05)).

4.2 Whole Brain Analyses

Average signal-to-noise ratio of the EPI data is displayed in Figure 6. This shows the high signal found with dual-echo EPI throughout the brain including in key inferior temporal and frontal regions.

4.2.1 Semantic Task > Letter Matching Task

All whole brain analyses reported employ an FWE-correction at the cluster level with a critical cluster level of .05 as well as significance at the voxel level of .001 and are reported in MNI space. Activation was first compared between the semantic and letter matching tasks. Areas of peak activation for the semantic task are summarised in Table 4. Both left and right temporal clusters extended across a large region to include the temporal pole, Heschl's gyrus, STG, MTG, ITG, fusiform gyrus, hippocampus, parahippocampal gyrus, amygdala, insula, rolandic operculum and cerebellum. Both clusters also extended posteriorly to mid-occipital cortex with activity in the angular gyrus on the left only. In addition, the cluster on the left included inferior frontal gyrus and mid-orbital frontal cortex. The activity centred round right STG also extended superiorly into the right pre- and post-central gyri. Left pre- and postcentral gyri activation can be seen in a third cluster. Activation within the mid cingulum was bilateral and extended superiorly in to left and right supplementary motor area. The clusters within the cuneus and medial orbitofrontal cortex were also bilateral with activity extending from the frontal region inferiorly to the left rectus. Subtracting the semantic task from the letter matching task gave a large area of activation throughout bilateral occipital, parietal and frontal lobes as well as the thalamic nuclei, right putamen, right insula and bilateral posterior fusiform gyrus (see Table 5).

Table 4. Significant activation clusters for the contrast semantic task > letter matching task.

Region of Activation	Cluster extent (voxels)	Max z value	P value (FWE corrected)	Peak region	Peak MNI Coordinate		
					X	Y	Z
R temporal	3436	7.02	<.001	R STG	60	3	-3
				R STG	45	-3	-15
				R calcarine	27	-48	9
L temporal	5630	7	<.001	L PHG	-21	-21	-21
				L MTG	-45	-15	-12
				L ITG	-45	-15	-27
L precentral gyrus	233	5.87	<.001	L precentral	-45	-18	63
				L precentral	-33	-21	72
Cerebellum	369	5.65	<.001	R cerebellum	21	-84	-36
L medial frontal	388	5.14	<.001	L superior MFL	-9	48	39
				L superior MFL	-9	54	30
				L superior MFL	-9	57	18
Cingulate	166	4.78	.003	R mid cingulum	12	-3	45
				R mid cingulum	3	3	39
				R mid cingulum	0	-12	48
L OFC	192	4.71	.002	L medial OFC	-3	54	-12
				L anterior cingulum	-15	42	-3
Cuneus	160	4.4	.004	R cuneus	9	-84	27
				L cuneus	-3	-84	27

Clusters significant at .05 after FWE correction. Up to 3 largest peaks listed per cluster L = left. R = right. STG = superior temporal gyrus. PHG = parahippocampal gyrus. MTG = middle temporal gyrus. ITG = inferior temporal gyrus. MFL = medial frontal lobe. OFC = orbitofrontal cortex.

Table 5. Significant activation clusters for the contrast letter matching task > semantic task.

Region of Activation	Cluster extent (voxels)	Max z value	P value (FWE corrected)	Peak region	Peak MNI Coordinate		
					X	Y	Z
L occipito-parietal cortex	12659	7.76	>.001	L inferior occipital	-30	-75	-9
				L IPL	-42	-39	42
				L posterior FG	-39	-66	-12
L inferior frontal	3975	7.06	>.001	L precentral	-30	-3	45
				L IFG	51	9	27
				L IFG	42	9	30
L mid frontal	636	5.91	>.001	L MFG	-39	54	15
				L MFG	-51	36	30
				L MFG	-45	39	24
R thalamus	461	5.26	>.001	R thalamus	9	-15	9
				R thalamus	21	-30	6
				R thalamus	6	-27	-6
R insula	121	5.07	0.015	R insula	30	21	0

Clusters significant at .05 after FWE correction. Up to 3 largest peaks listed per cluster. L = left. R = right. STG = superior temporal gyrus. PHG = parahippocampal gyrus. MTG = middle temporal gyrus. ITG = inferior temporal gyrus. MFL = medial frontal lobe. OFC = orbitofrontal cortex.

4.2.2 Association > Conceptual Similarity

Semantic trials were split into those based on associative relationships vs. conceptual similarity to assess to what extent they share neuronal bases. Significant activation maps for each type of judgement over the letter matching (baseline) task are shown in Figure 6. The principal finding is clear – both judgement types resulted in a large common area of activity. In order to assess whether any areas responded differentially, a direct comparison of the two types of semantic relationship was performed, highlighting small differences generally outside of the large shared cluster for semantic judgements (see Figures 7 & 8). Greater activation was found for associative>conceptual similarity in left supramarginal gyrus extending inferiorly to include superior temporal gyrus and posteriorly to include the angular gyrus (see Figure 7 & Table 6) and in the right inferior temporal gyrus extending to middle temporal gyrus. The opposite (conceptual similarity>associative) contrast revealed a difference in the left inferior frontal gyrus, extending into precentral gyrus, and in a cluster comprising bilateral supplementary motor area, left superior medial frontal cortex and right mid cingulum (see Figure 8 & Table 6).

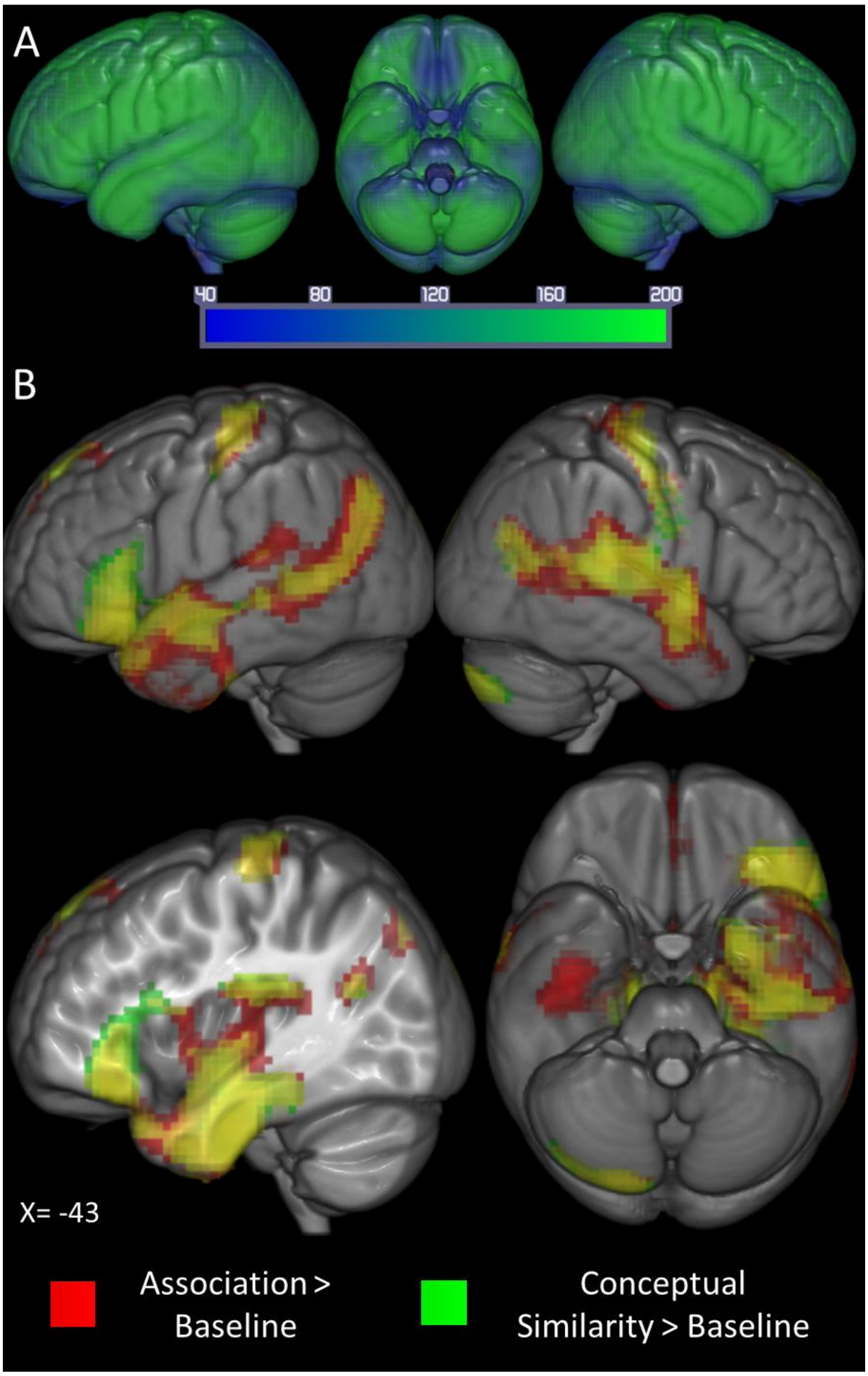

Figure 6. **Temporal signal-to-noise ratio (A) and comparisons of association and conceptual similarity (B).** A. Average temporal signal-to-noise ratio for the smoothed group EPI data in MNI space. The map is set at a threshold of 40, considered to be the minimum TSNR required to reliably detect differences in signal (Murphy et al., 2007; Simmons et al., 2010; Wang et al., 2013) and is displayed as a range from 40 (dark blue) to 200 (bright green). Use of the dual-echo technique meant signal reached the minimum threshold throughout the ATL and inferior frontal regions with some subregions far exceeding this with values above 200. B. Significant activation for the contrasts association judgements> letter matching (red) and conceptual similarity judgements>letter matching (green); yellow = overlap. Voxels significant at .05 with an FWE-correction at the cluster level with a critical cluster level of .05.

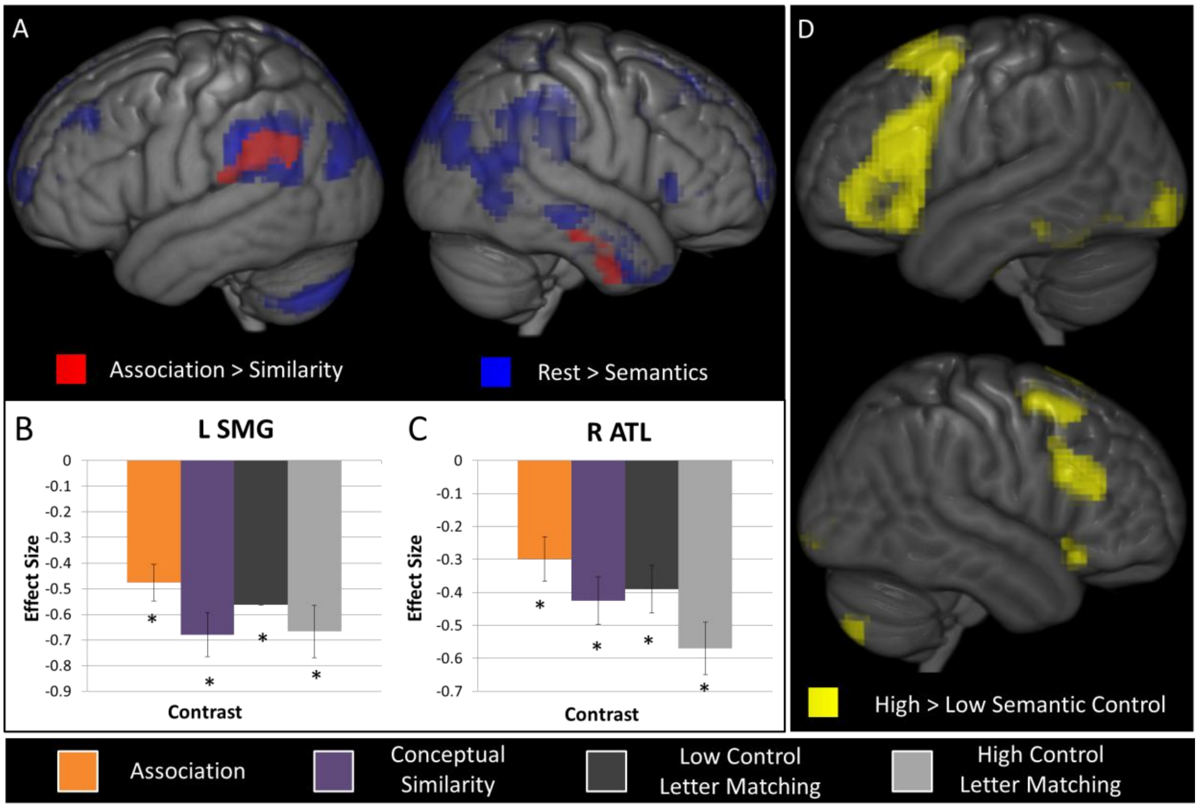

Figure 7. **Assessment of the areas found for the association > conceptual similarity contrast without RT included in the model.** A. Areas with significantly greater activation for the contrast association > similarity (red) shown over the significant regions for the contrast rest > semantic (blue). B: Effect sizes for a 10mm spherical ROI centred around the peak of activity in the left supramarginal gyrus within the contrast association > conceptual similarity for the conditions associative (orange), conceptual similarity (purple), low control letter matching (dark grey) and high control letter matching (light grey) over rest. C. Effect sizes for a 10mm spherical ROI centred around the peak of activity in the right anterior temporal lobe within the contrast association > conceptual similarity for the conditions associative (orange), similarity (purple), low control letter matching (dark grey) and high control letter matching (light grey) over rest. Asterisks denote significant contrasts at $p < .05$ after application of a Bonferroni correction for multiple comparisons. Both ROIs show deactivation from rest for both forms of semantic relationship and the letter matching task (easy vs. hard conditions). Thus, the association>conceptual similarity contrast is due to differences in deactivation. No differences are significant if RT is included in the model (see text). D: Significant activation for the contrast high semantic control > low semantic control (yellow). Voxels significant at .001 with an FWE-correction at the cluster level with a critical cluster level of .05.

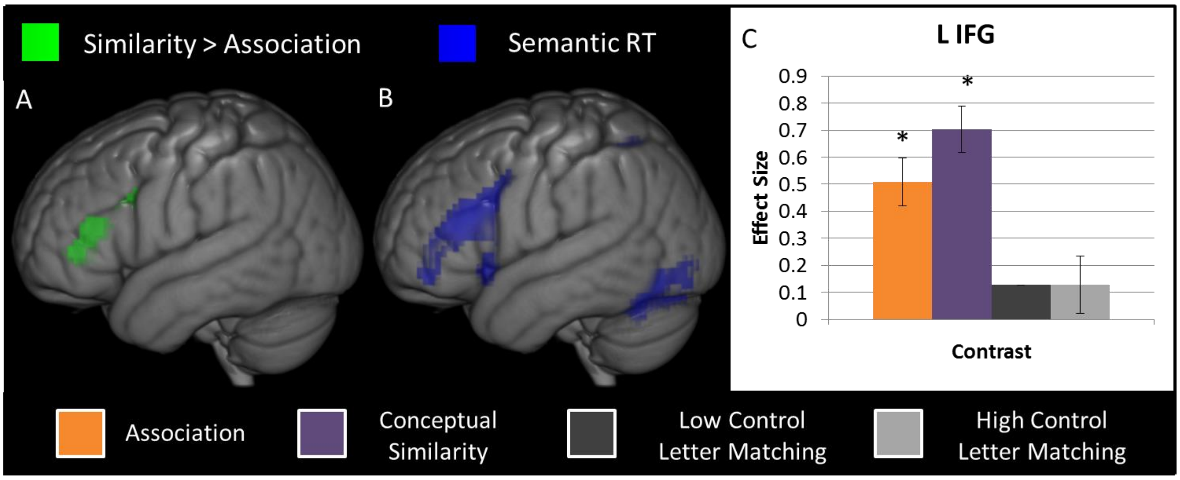

Figure 8. **Assessment of the areas found for the conceptual similarity > association contrast without RT included in the model.** A. Significant activation for the contrast conceptual similarity > association. B. Areas responding more to trials with long reaction times in the semantic task. Voxels significant at .001 with an FWE-correction at the cluster level with a critical cluster level of .05. No differences between association and conceptual similarity are significant if RT is included in the model. C. Effect sizes for a 10mm spherical ROI centred around the peak of activity in the left inferior frontal gyrus within the contrast conceptual similarity > association for the conditions association (orange), conceptual similarity (purple), low control letter matching (dark grey) and high control letter matching (light grey) over rest. Asterisks denote significant contrasts (p < .05) after application of a Bonferroni correction for multiple comparisons.

Table 6. Significant activation clusters for the direct comparison of association and conceptual similarity.

Contrast	Region of Activation	Cluster extent (voxels)	Max z value	P value (FWE corrected)	Peak MNI Coordinate		
					X	Y	Z
Association > conceptual similarity	R inferior temporal gyrus	131	4.17	.038	54	-9	-27
Association > conceptual similarity	L supramarginal & angular gyrus	161	3.76	.018	-63	-45	36
Conceptual similarity > association	L inferior frontal gyrus	728	5.38	<.001	-42	30	6
Conceptual similarity > association	L supplementary motor area	150	3.92	.024	-6	12	54

Clusters significant at .05 after FWE correction. Largest peak listed per cluster. L = left. R = right.

Further analyses were conducted at the whole brain level to assess whether these differences could be explained in terms of two key performance factors: the required level of semantic control and generic difficulty (as measured by RT). Prefrontal regions (and other areas) have been implicated in the executive-regulation of semantic processing (Badre et al., 2005; Noonan et al., 2013; Thompson-Schill et al., 1997) and thus exhibit heightened activation for more difficult semantic judgements or tasks. In line with these many previous studies, the contrast of high>low control semantic judgments revealed large areas of the frontal and occipital lobes as well as the inferior and superior parietal lobes and fusiform gyrus extending to inferior temporal and parahippocampal gyri (see Fig. 2D and Table 7). This indicates that the significantly greater activity for conceptual similarity > associative judgements observed in inferior frontal and supplementary motor areas can be explained in terms of the greater executive demands of these more difficult semantic judgements. No overlap was found between semantic control regions and those revealed by the associative>conceptual similarity contrast. Thus, differences in semantic control cannot explain these effects.

Table 7. Significant activation clusters for the semantic control manipulation (high control conceptual similarity > low control conceptual similarity).

Region of Activation	Max z value	P value (FWE corrected)	Peak MNI Coordinate		
			X	Y	Z
L inferior frontal gyrus	6	<.001	-51	15	27
L calcarine sulcus	4.93	<.001	-9	-96	-9
R inferior frontal gyrus	4.9	<.001	48	18	27
R mid frontal gyrus	4.76	.001	36	21	54
L fusiform gyrus	4.63	.004	-39	-21	-24
R inferior orbitofrontal cortex	4.63	.016	30	24	-6
R calcarine sulcus	4.11	.011	18	-93	-3
L inferior parietal cortex	4.11	.006	-30	-69	45

Clusters significant at .05 after FWE correction. Largest peak listed per cluster. L = left. R = right.

Next, as the associative and conceptual similarity conditions differed in average reaction time (see above), an analysis was run to assess which areas differ according to semantic task RT (i.e., task difficulty) vs. which regions differed by condition regardless of RT (indicating a true effect of the type of semantic relationship). Figure 8 shows the areas where activation is correlated positively with RT alongside the areas found to have higher activation for conceptual similarity judgements (the condition with the longer average RT, see behavioural results and Appendix 2 for the coordinates of peak activation). The results of these contrasts overlapped within the IFG, supporting the idea that conceptual similarity judgements activated this area to a greater extent simply because they were more demanding.

Finally, we considered areas that were deactivated by the semantic task, relative to rest. Both the left supramarginal gyrus and right ATL clusters identified in the associative> conceptual similarity contrast overlapped with a broader set of regions which showed significant deactivation from rest regardless of task (see Figure 7A & Appendix 1). As shown in Figure 7B, the difference between the associative and conceptual similarity-based trials in these areas reflected a differential deactivation. Various previous studies, across different cognitive domains, have demonstrated that the deactivation, commonly observed in ventral parietal cortex (a part of the default mode network), is anti-correlated with task difficulty (Buckner et al., 2008; Fox et al., 2005; Gilbert et al., 2012; Harrison et al., 2011; Humphreys & Lambon Ralph, in press). Indeed, the differential deactivation for associative vs. conceptual trials observed in VPC was no longer significant when reaction time was included as a parametric regressor.

4.3 Region of Interest Analyses

Region of interest analyses were conducted to test the dual-hub model's predictions that ATL is involved specifically in coding conceptual similarity-based relationships and TPC in associative relationships. One ATL ROI located within anterior STS was taken from Schwartz et al. (2011), who had identified this region as a potential representational hub for conceptual similarity (with respect to speech production). Another, from the ventral ATL, was taken from Binney et al.'s (2010) distortion-corrected fMRI study of synonym judgements, which has been proposed as the centrepoint of a transmodal general semantic hub (Lambon Ralph, 2014; Lambon Ralph et al., 2010b). This vATL area has been found in multiple imaging studies across tasks and modalities (Marinkovic et al., 2003; Sharp et al., 2004; Spitsyna et al., 2006; Visser et al., 2012; Visser & Lambon Ralph, 2011) and is an area of maximal atrophy and hypometabolism in semantic dementia, which directly correlates with their degree of semantic impairment (Butler et al., 2009; Galton et al., 2001; Mion et al., 2010). The coordinates of the TPJ ROI was taken from Schwartz et al. (2011) in order to assess the claim that this region reflects the site of a hub for associative semantics. The TPC peak was located at the junction of Brodmann areas 21, 22, 39, 40, 41, 42, 48 (see Figure 9).

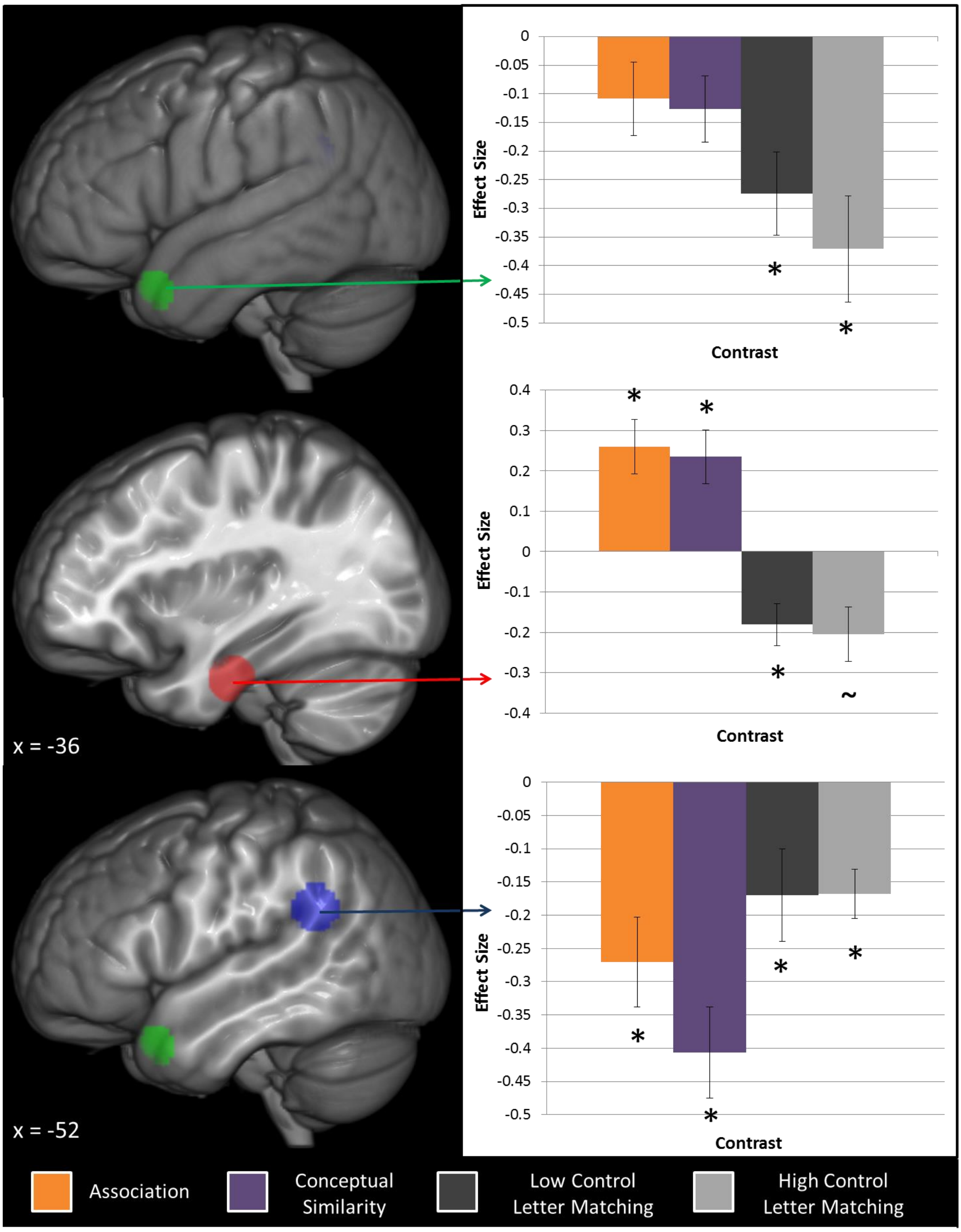

Figure 9. **Location and effect sizes of the three ROIs.** Schwartz et al.'s (2011) aSTS region is shown in green (MNI coordinates = -53 18 -30) with the ventral ATL ROI from Binney et al. (2010) in red (MNI coordinates = -36 -15 -30). Schwartz et al.'s (2011) TPJ ROI is displayed in blue (MNI coordinates = -52 -49 27). The effect sizes of each condition against rest are displayed for each ROI for the conditions associative (red), similarity (green), low control letter matching (light blue) and high control letter matching (dark blue) over rest. Asterisks denote significant contrasts after application of a Bonferroni correction for multiple comparisons ($p < .05$). ~denotes a trend towards significance ($p < .1$).

The results of the ROI analyses for each contrast are listed in Table 8 and summarised in Figure 9. Neither ATL ROI showed a significant difference between association and conceptual similarity judgements (see Table 8), with the vATL ROI showing the strongest activations for both semantic conditions over the letter matching baseline. The superior ATL ROI also showed significantly greater yet equivalent activation for the semantic judgements over the active baseline (which was deactivated with respect to rest). Indeed, these results underline previous observations that ATL semantic activations are much more likely to be detected when an active baseline is used (see Visser et al., 2010; Visser et al., 2010b). In line with the whole-brain analyses, these ROI findings underline the conclusion that the ATL is implicated in general semantic representation regardless of relationship type (see Figure 9). In contrast to the ATL ROIs, all conditions showed significant deactivation from rest within the TPJ ROI. Neither conceptual similarity nor association conditions were significantly more de-activated than the letter matching task, or each other. Deactivation did not relate to reaction time or semantic control. Thus, counter to the dual-hub hypothesis, this study found no evidence in favour of this region supporting associative semantics.

Table 8. Independent ROI analyses.

ROI	Contrast	Effect Size	T value	Bonferroni corrected p value
ATL (Schwartz)	Association > Rest	-0.11	-1.69	.937
	Conceptual Similarity > Rest	-0.13	-2.19	.347
	Low Control Letter Matching > Rest	-0.27	-3.77	<.05
	High Control Letter Matching > Rest	-0.37	-4.00	<.05
	Association > Letter Matching	0.43	3.90	<.05
	Conceptual Similarity > Letter Matching	0.39	3.50	<.05
	Association > Conceptual Similarity	0.02	0.47	1
	High > Low Semantic Control	0.00	0.01	1
	High > Low Non-semantic Control	-0.10	-1.84	.703
ATL (Binney)	Association > Rest	0.26	3.87	<.05
	Conceptual Similarity > Rest	0.23	3.53	<.05
	Low Control Letter Matching > Rest	-0.18	-3.47	<.05
	High Control Letter Matching > Rest	-0.20	-3.02	.055
	Association > Letter Matching	0.90	9.07	<.001
	Conceptual Similarity > Letter Matching	0.85	8.69	<.001
	Association > Conceptual Similarity	0.03	1.05	1
	High > Low Semantic Control	0.06	4.85	<.001
	High > Low Non-semantic Control	-0.02	-0.47	1
L TPC (Schwartz)	Association > Rest	-0.27	-4.02	<.05
	Conceptual Similarity > Rest	-0.41	-5.93	<.001
	Low Control Letter Matching > Rest	-0.28	-4.03	<.05
	High Control Letter Matching > Rest	-0.39	-4.81	<.001
	Association > Letter Matching	0.13	1.29	1
	Conceptual Similarity > Letter Matching	-0.15	-1.51	1
	Association > Conceptual Similarity	0.14	2.75	.104
	High > Low Semantic Control	0.00	0.12	1
	High > Low Non-semantic Control	-0.11	-1.98	.541

5. Discussion

The clear, principal finding from this study was that semantic judgements based on either associative relationships or conceptual similarity engaged the same neural network, including bilateral ATL, posterior temporal regions and left IFG. These areas fit well with previous neuroimaging and neuropsychological findings regarding their roles in general, multimodal semantic cognition (Binney et al., 2010; Jefferies & Lambon Ralph, 2006; Noonan et al., 2013; Patterson et al., 2007; Visser et al., 2012) and suggest that both forms of semantic knowledge arise from a single network (see below). In contrast, we found little evidence for differential activation in the regions hypothesised, under the dual-hub proposal, to represent associative and conceptual similarity separately. The ATL was strongly and significantly activated by semantic judgements regardless of relationship type, consistent with both its proposed role as a graded, transmodal, pan-category representational hub (Lambon Ralph, 2014; Lambon Ralph et al., 2010b; Patterson et al., 2007), and the poor performance on both types of judgement exhibited by patients with semantic dementia (in the context of ATL-centred atrophy: Butler et al., 2009; Hoffman et al., 2013; Jefferies & Lambon Ralph, 2006). The role of the TPC was less clear as both types of semantic relationship showed deactivation from rest, as did the letter matching baseline task and no significant differences were found between association and conceptual similarity. This suggests it is not a hub representing associative relationships as hypothesised in the dual-hub model (24, 37, 61) and does not support a role for this TPC region in semantic processing. This pattern of deactivation was not found for the TPC alone but spread across the ventral parietal cortex (VPC). This is in keeping with a recent meta-analysis showing deactivation of the angular gyrus for semantic tasks with automatic access (62) as well as the involvement of the VPC in the default mode network (40, 63). This cannot be merely due to the high level of semantic processing involved in free thought during rest, as suggested by Binder (58) for the AG and shown here for the ATL, as the deactivation is similar for the semantic and control tasks. This provides evidence against theories postulating a specific role for these areas within the TPC and VPC in semantics (e.g. 24, 35, 64). Beyond these two regions, the only areas to be identified as more active for conceptual similarity than associative semantic judgements were the inferior prefrontal cortex and supplementary motor area. This result reflected differential semantic difficulty (highlighted by the overlap of conceptual similarity>associative and hard>easy semantic judgement contrasts) and is consistent with IPFC's role on controlled semantic processing as demonstrated by previous neuroimaging, neuropsychological and TMS studies (Badre et al., 2005; Hoffman et al., 2010; Jefferies & Lambon Ralph, 2006; Noonan et al., 2013; Thompson-Schill et al., 1997). Indeed, after accounting for the differences in reaction time between the two conditions, no areas were found to exhibit differences between the two types of semantic judgement.

A secondary tested hypothesis was that TPC, rather than representing a particular type of semantic knowledge, was involved in semantic control processes. This hypothesis arose from earlier work on semantic aphasia, namely that SA patients with temporoparietal damage, like those with prefrontal lesions, exhibit impaired semantic control (Head, 1926; Jefferies & Lambon Ralph, 2006). Counter to this hypothesis, at least in its undifferentiated neuroanatomically-general form, we found no effect of semantic control in the TPC ROI (again, alongside the non-semantic baseline task, it was equally deactivated with respect to rest). The posterior SA patients' lesions are large, however, covering the watershed territory from pMTG through ventral parietal cortex to IPS (Berthier, 1999; Jefferies & Lambon Ralph, 2006; Robson et al., 2012) and cutting potentially important white matter pathways such as the middle longitudinal fasciculus (Makris et al., 2009) and parietal branches of the inferior frontal-occipital fasciculus (IFOF: Martino et al., 2010) and inferior longitudinal fasciculus (ILF: Schmahmann et al., 2007). The present fMRI study adds to the growing evidence for differentiation of function across the temporoparietal region frequently damaged in patients. A recent large fMRI meta-analysis and targeted rTMS studies have identified pMTG and IPS as the most important subregions in controlled semantic processing (Noonan et al., 2013; Whitney et al., 2011; 2012). In contrast, much of ventral parietal cortex is part of the default mode network and may be involved in a variety of different cognitive functions, including automatic bottom-up attention and episodic recollection (Buckner et al., 2008; Cabeza et al., 2012; Cabeza et al., 2008). These contrasting functions across the region (IPS-pMTG vs. ventral parietal cortex) may well arise from their different patterns of connectivity (Uddin et al., 2010). The pMTG may not have been identified here due to a lack of power when splitting this task as the region was involved in semantics over the letter matching task. The whole brain analysis of high over low semantic control confirmed the role of the IFG and IPS. Alternatively, the IFG may be responsible for the aspects of semantic control relevant here unlike the pMTG causing these regions to be differentially affected by the manipulation. It may be that varying the relation between the probe and the foil affected selection processes which are dependent on IFG, whereas other aspects, such as semantic working memory or buffering, may depend on pMTG. This would fit with previous work on selection (67, 70, 71).

The finding of greater deactivation in parietal and temporal regions for the easier condition before RT was accounted for fits the deactivation shown within these areas and can be explained by their involvement in the default mode network and attention. The greater frontal activation in this model and its relation to RT can be explained by the importance of this area in semantic control. These negative and positive loadings on difficulty could explain many of the previous findings of prior fMRI examinations of association and conceptual similarity. Many include differences in difficulty, especially those employing priming. These differences relate to areas similar to those found here as well as areas thought to relate to effortful processing. For instance, Kalénine et al. (2009) found greater activity in left IPL and MTG for their easier associated condition and Sass et al. (2009) found left STS activation for their more effective associative primes. It is not possible to tell from the direct contrasts shown whether these differences would reflect differential deactivation when compared to rest. Sachs et al. (2008b) found that the conceptual similarity condition, exhibiting less priming, activated the right precuneus more and Kotz et al. (2002) found greater activity in the right precuneus, isthmus gyrus cinguli and cuneus for their harder conceptual similarity condition which they explained as requiring more effortful processing. Interference from conceptual similarity and facilitation from association in a picture-word interference task was related to greater activation of the left posterior MTG and AG respectively (de Zubicaray et al., 2013). Thus, the previous fMRI studies may be highlighting areas affected by semantic difficulty and not areas differentially involved in association and conceptual similarity per se.

5.1 Relationship to Previous Neuropsychological Findings

If association and conceptual similarity rely on the same multimodal semantic network, why are different semantic error types linked to different regions after brain damage? Semantic aphasic patients make a mixture of associative, categorical and superordinate semantic errors, whereas semantic dementia patients rarely, if ever, produce associative semantic errors (Jefferies & Lambon Ralph, 2006). Although generating fewer errors overall, neurologically-intact participants generate the same ratio of semantic error types as that observed in semantic aphasia (Schwartz et al., 2011). The naming errors in SD are consistent with the progressive collapse and degradation of the underpinning semantic representations (Lambon Ralph et al., 2001). The characteristic of this semantic impairment is that it is increasingly difficult for the semantic system (a) to separate conceptually-similar items (leading to category and superordinate errors) and (b) to generate specific information linked to each concept, including its name (the most common error type in SD is an omission error), specific features and associations (Lambon Ralph et al., 2001; Warrington, 1975). The inability to generate detailed information about each concept will mean that associative naming errors are very unlikely. Indeed, Jefferies and Lambon Ralph (Jefferies & Lambon Ralph, 2006) noted that the presence of conceptually-specific associative errors in SA (e.g., SQUIRREL → "nuts") probably implies a very good underlying semantic database. These factors probably explain, at least in part, the innovative voxel-based lesion-symptom mapping (VLSM) results reported by Schwartz and colleagues. As lesions encroach upon ATL regions, category-related errors will tend to increase and associative errors decrease (as per SD patients). The second effect to account for in the Schwartz et al. (2011) study is the *relative* increase in associative over categorical errors linked to TPC lesions. Perhaps the most obvious possibility follows from the fact that speech production is complex and involves multiple stages (Dell & Reich, 1981). Associative errors may arise from a non-semantic stage linked to TPC or a nearby area. For instance, the angular gyrus has been shown to activate for sentence-level and syntactical processing (Petersson et al., 2012; Zhu et al., 2012). It is entirely possible that these mechanisms may partially activate lexically-associated words (a natural outcome of their role in connected-speech and sentence construction) and, under damage or poor control, these alternatives are incorrectly produced by the patients during picture naming tasks. A second possibility is statistical. Given that Schwartz et al. (2011) reported *partial* correlations (categorical|associative vs. associative|categorical), it is possible that the presence of patients with ATL lesions and less associative errors within the entire dataset will automatically generate a mirror-image partial correlation for the remaining patients with non-ATL MCA lesions. This is consistent with the fact that, in the patient data overall, the ratio of different semantic error types was the same that observed in neurologically-intact participants. If this explanation is correct then there is, in effect, only a single dissociation present in those results (ATL lesions decreasing the rate of associative errors). If, however, there was an absolute increase in associative errors in the TPC subgroup (i.e., significantly more than that observed in general aphasic and control groups, overall) then an alternative explanation is required.

5.2 How Could Association and Conceptual Similarity Arise out of one Representational System?

The primary result of this study was that processing of semantic associations and conceptual similarity rely upon the same semantic neural network. What does this imply for theories of semantic representation? First and foremost, it would seem to suggest that these two important forms of semantic knowledge are coded within a single neurocomputational system. Below, we consider how this might be achieved within a neuroanatomically-inspired, computationally-implemented framework such as the hub-and-spoke model (Lambon Ralph, 2014; Lambon Ralph et al., 2010b; Patterson et al., 2007; Rogers et al., 2004). The key ideas are as follows. Concepts are built from, and reflect the characteristics of, our multi-modal experiences which are acquired, typically, over a long period of time. Registration of the information arising in each input/output modality ('engrams' in the classical neurological accounts of conceptualisation; Eggert, 1977) is achieved within secondary association cortices (the spokes within the hub-and-spoke framework). According to one implemented computational model (Rogers et al., 2004), these different sources of information are drawn together by interaction with a transmodally-connected representational hub (centred on the ventrolateral ATL; Binney et al., 2012) which integrates over time, contexts and modalities to extract generalisable, coherent conceptual representations and computes the many non-linear relationships between each concept and its linked elements or 'features' of knowledge (Lambon Ralph, 2014; Lambon Ralph et al., 2010b). Graded conceptual similarity is an emergent property of this computational framework and reflects the deeper statistical structures present in our multimodal experience (Lambon Ralph et al., 2010b; Rogers et al., 2004). Indeed, the model captured not only hierarchical, taxonomic-like structure, where it exists (e.g., within natural categories) but also strong and weak similarities amongst other types of (non-taxonomic) concept. Although not considered explicitly in the original computational exploration, it is possible that the same framework would code associations between concepts in the same way as the link between any concept and its 'features'. Indeed, it is possible that 'features' and 'associations' are one and the same thing – i.e., the smorgasbord of information that is linked to a concept. Specifically, the model learns to map between a concept and all of its associated/linked information (as described in the Introduction for CROISSANT). The verbal and nonverbal 'features' of croissants (e.g., the name 'croissant', <crescent shaped>, <edible> etc.) are simply elements of experience that reliably co-occur in time and context and therefore coalesce to form an integrated concept of the object. From this perspective, 'associations' (e.g., <coffee>) can be thought of as additional elements of experience that are also often present and thus become integrated into the concept. In other words, there is no strong distinction between an item's 'associations' and its 'features'. They are all simply aspects of the environment that are experienced together when the item is encountered.

The information that is linked to each concept (whether 'features' or 'associations') varies along at least three different dimensions: (a) which sensory-verbal modalities through which it is experienced; (b) the range of concepts to which each piece of information/feature is linked (i.e., shared vs. distinctive features: Garrard et al., 2005; Tyler et al., 2013); and (c) its experiential frequency (i.e., how often each piece of information is experienced alongside the concept – e.g., <buttery taste> and CROISSANT are very commonly paired but <chocolate filling> is a less frequent feature). Both 'features' and 'associates' can vary in their specificity (applicable to individual or collections of concept) and can be extracted from verbal or nonverbal experience. Even a distinction between internal (e.g., parts of the object) vs. external (i.e., present in the environment outside of that object) information does not necessarily distinguish between 'features' and 'associations' given that, like associations, many 'features' are external to the object (e.g., <buttery smell>, <flaky texture>, etc.). We should note here that 'associates' have the key characteristic of co-occurring in time or place, verbally (e.g., lexical associates "French croissants") or nonverbally (e.g., seeing croissants and coffee next to each other). Our working hypothesis does not reject this fact but rather observes that this is true to varying degrees (i.e., experiential frequency) for all information/'features' linked with a concept. Secondly, if different cognitive and neural systems code conceptual similarity vs. 'association' structures then a potential homunculus problem arises in terms of which sub-system should code the information (e.g., are <warmed in the oven>, <made from a yeast dough>, features or associations?). In summary, according to this hypothesis, each concept is linked or associated with a range of verbal and non-verbal experiential information, and conceptual similarity reflects the deeper statistical structure extracted across these concept-to-associations/features structures.

This working hypothesis does not deny that there are systems for coding temporal or spatial statistical structures. Rather it seems likely that these structures are orthogonal to the semantically-related statistical structures and are coded in different neural regions (e.g. frontoparietal 'dorsal' vs. 'ventral' temporal lobe pathways: Bornkessel-Schlesewsky & Schlesewsky, 2013; Ueno et al., 2011). Indeed, the ventral parietal cortex seems to be responsible for processing syntax, numbers and space (Petersson et al., 2012; Walsh, 2003; Zhu et al., 2012). The antithetical nature of these two types of orthogonal statistical reductions (i.e., time-/context-invariant semantics vs. time/spatially-variant representations) is consistent with well-established neuropsychological dissociations: for example, even late into their progressive neurodegenerative disease, semantic dementia patients (with ATL-focussed atrophy) are able to process syntax and number quantities despite profoundly degraded conceptual knowledge (Bozeat et al., 2002; Cappelletti et al., 2001; Hodges et al., 1999; Jefferies et al., 2004; Schwartz et al., 1979).

6. Materials

6.1 Participants

Twenty five healthy native-English speakers took part in the experiment (16 females, age range 20-42 years, mean age 25.48, SD 6.49). One was excluded due to low overall performance suggesting inattention/non-compliance (overall performance for this participant 65%, overall performance for other 24 participants 90%; participants mean overall accuracy was more than 2 SD lower than average). All participants were strongly right handed, with a laterality quotient above 70 on the Edinburgh Handedness Inventory (Oldfield, 1971) and had normal or corrected-to-normal vision. All participants gave informed consent and the study was approved by the local ethics board.

6.2 Stimuli

An example trial from each condition in each task is displayed in Table 3.

6.2.1 Semantic Judgement Task

Participants were presented with triads of concrete nouns and asked to judge which of the two options was more related to the probe word (for full list see Appendix 3). The probe-target relationship was based on either conceptual similarity or association. Semantic associative strength was quantified using latent semantic analysis, a technique that represents relationships between words based on the degree to which they are used in similar linguistic contexts. Hoffman et al. (2013) performed LSA on the British National Corpus using the standard approach described by Landauer & Dumais (1997). This corpus includes more than 87 million words from 3125 different sources. A matrix was generated coding frequency of occurrence for each word in each context and single-value decomposition was applied to these data, yielding LSA representations for words based on their contextual similarity. Pairs of words with a relationship higher than .2 in the resultant LSA measure were considered associated and lower than .2 were not. In order to separate the two semantic measures, associative targets had to have very low levels of conceptual similarity, most commonly selected to be in a different domain (e.g., living vs. artefacts) or, if this was not possible, in a different superordinate category with a low number of shared features (e.g., tools vs. clothing). Conversely, conceptually-similar targets were selected from the same semantic category but had very low associative strength (LSA scores below .2). There was a large, significant difference between the probe-target LSA values for the associative (average = .474, SD=.182) vs. conceptually-similar trials (average = .045, SD=.076; t=20.334, p<.001).The associated and conceptually-similar targets were matched on CELEX frequency (associative mean = 28.91, SD = 44.82; conceptually-similar mean = 29.53, SD = 54.50; t(95)=-.084, p<.5), Bristol/MRC imageability norms (associative mean =567.69 , SD = 62.82; conceptually-similar mean =569.08, SD =63.95; t(95)=-.155, p<.5) and letter length (associative mean = 5.44, SD = 1.72; conceptually-similar mean =5.54, SD =1.72; t(95)=-.473, p<.5) and syllable length (associative mean = 1.7, SD = 0.7; conceptually-similar mean =1.68, SD =.76; t(95)=.222, p<.5) taken from the NWatch program (Davis, 2005).

Two trials were derived for each probe, an associative vs. a conceptually-similar trial, though individual participants only saw one version in the experiment (counter-balanced across participants). The targets for the associative trials were used as foils for the similar trials and vice versa, ensuring that the overall set of words was identical for the two conditions, reducing potential confounds. All foils had an LSA value lower than .2 with their respective probe and target items, and were from the same domain as the target. Foils in the conceptually-similar trials were in a different superordinate category making them less conceptually-similar than the targets. The LSA values for the probe – associative foils (mean = -.007, SD = .059) were matched to those for the probe – conceptually-similar foils (mean = .002, SD = .061; t(95)=-1.223, p>.05). This meant that the foils in the associative condition were less associated to the probe than the target (t(95)=-23.348, p<.001) but both were conceptually-dissimilar.

96 associative and 96 conceptual similarity trials were created. The greater relatedness of the targets than foils to the probe item was confirmed via (a) similarity ratings on a 7 point scale from 'not at all similar' to 'highly similar' by 11 participants who did not take part in the fMRI study (t(95)=29.983, p<.001) and (b) a behavioural pilot of 9 participants (9 female, mean age 19.33, SD 1.0) which confirmed high accuracy on the task in both conditions (association – accuracy=.903, RT=1248.25; conceptual similarity – accuracy=.887, RT=1396.52).

6.2.2 Task to Vary Semantic Control Demand

A further 96 probe-target conceptually-similar pairs were created in the same manner as the main task. Two different foils were combined with each target-probe pair. One foil was selected from an unrelated domain to the probe item in order to minimise the level of control necessary to reject the foil and select the target (e.g., BARREL – BOX, combined with the foil, PLUM). The other foil was selected from the same domain and a related category to the target and probe (e.g., BARREL – BOX, paired with the foil, SEAT), and thus greater control was needed in these trials (for full list, see S5). Targets were matched to related and unrelated foils on frequency (high; t(95)=, p>.5, low; t(95)=, p>.5), imageability (high; t(95)=, p>.5, low; t(95)=, p>.5), LSA value with probe (high; t(95)=.086, p>.5, low; t(95)=.009, p>.5), letter length (high; t(95)=-.216, p>.5, low; t(95)=.309, p>.5) and syllable length (high; t(95)=.291, p>.5, low; t(95)=-.212, p>.5). Each participant completed the high control version for half of the trials and the low control version for the other half (counterbalanced across participants). Using the same rating system described above, participants confirmed greater semantic relatedness of probe-target than probe-foil in both high control (t(95)=17.294, p<.001) and low control conditions (t(95)=13.284, p<.001).

6.2.3 Baseline (Letter Matching) Task

The goal of this task was to provide a non-semantic but challenging visual-matching baseline activity against which the semantic neuroimaging data could be compared. Participants were asked to indicate which of two mixed letter-symbol strings contained more letters in common with the probe string (for full list see Appendix 4). Probes included a Greek letter, dissimilar to those found in the English alphabet, flanked by two English letters. Hash symbols were then placed either side to make the string 7 characters long. The target included the same Greek letter and one or both of the English letters found in the probe in the same order but at any position in a 7 letter string. As in the semantic control-varying task, each probe-target pair had two different foils to alter task difficulty and thus allow assessment of non-semantic executive control. Low control foils did not include any of the same letters as the probe. High control foils included the Greek letter and one or two of the English letters from the probe. Each participant received half of the high and half of the low control foils (counterbalanced across participants). The behavioural pilot confirmed that participants were able to perform the task and that it was as challenging, in terms of RT and accuracy, as the main semantic tasks (accuracy=.856, RT=1693.29). RT for the high control condition (average 2158.85, SD 500.35) was significantly longer than the low control condition (average 1993.48, SD 493.77, t(23)=4.793, p<.001).

6.3 Procedure

Participants practiced 20 trials of each task outside the scanner. Nine trials from each task were then repeated in intermixed mini-blocks to simulate the presentation during scanning. A further 9 were repeated inside the scanner. Mini-blocks lasted 15 seconds and contained 3 trials from one condition. All tasks started with a central fixation cross presented for 1000ms. In the first trial of each mini-block a cue was presented above fixation to allow participants to prepare for the correct task reducing task-switching effects. For both semantic tasks the cue was 'WORDS', for the letter matching task it was 'LETTERS'. The stimuli were then presented for 4000ms in Times New Roman at size 24. The probe was displayed in the top centre with the two options on the left and right at the bottom of the screen. During this time participants responded by pressing one of two buttons representing the left and right options.

There were 4 runs each lasting 10 minutes. Three contained the main task, letter matching (baseline) task and rest. One contained the semantic control-varying task and rest. The order of these was counterbalanced. A pseudo-randomised order of mini-blocks was employed. Presentation of individual trials was randomised within mini-blocks. There were 32 mini-blocks, each, for the semantic control task, letter matching task, rest, and the associative vs. conceptually-similar versions of the main task. The letter matching and semantic control-varying tasks included 16 high and 16 low control mini-blocks.

6.3.1 Imaging and Data Analysis

Scanning was performed with a Phillips Achieva 3.0T TX series system with 32 channel SENSE coil with a SENSE factor of 2.5. Within the scanner, participants wore noise-cancelling Mk II+ headphones (MR Confon, Magdeburg, Germany). A structural reference was obtained with an in-plane resolution of .938 and slice thickness of 1.173.

Two echoes were used in parallel. A short echo at 12ms allows for reduced spin dephasing leading to less signal loss in areas of high magnetic susceptibility whilst a standard long echo at 35ms maintains high contrast sensitivity throughout the brain. The use of multiple echoes has been shown to reduce signal dropout, particularly in inferior temporal and frontal regions (Halai et al., 2014; Poser & Norris, 2007; 2009). Combining the echoes through linear summation has been shown to be optimal (Halai et al., 2014; Poser et al., 2006). Each run included 211 functional scans covering the whole brain with a field of view of 240x240mm, resolution matrix of 80x80, TR of 2.8, flip angle of 85°, reconstructed voxel size of 3mm and slice thickness of 4mm. The field of view was tilted up to 45° off the AC-PC line to reduce ghosting of the temporal pole.

Analysis was carried out using statistical parametric mapping (SPM8) software (Wellcome Trust Centre for Neuroimaging). Functional images were realigned to the individual's first image using a rigid body transform in order to correct for motion artefacts. The functional images were then coregistered to the individual's anatomical scan. Spatial normalisation to the Montreal Neurological Institute template was achieved using the DARTEL toolbox (Ashburner, 2007) by group wise registration of individual's grey and white matter to a template brain created from the group mean. This increases the registration between individuals from the standard SPM normalisation allowing more accurate localisation and greater sensitivity. Smoothing was performed using an 8mm full-width half maximum (FWHM) Gaussian kernel. A general linear model was created with all conditions modelled as box car functions convolved with a canonical HRF (rest was modelled implicitly). A high pass filter with a cut off of 128 seconds was used. The semantic condition in the main semantic judgement task was contrasted with the letter matching task to reveal the areas involved in general semantic processing. Association and conceptual similarity trials were contrasted with the letter matching task as well as compared directly. Effects of semantic control demands were assessed by contrasting the high vs. low conditions in the semantic control task. Non-semantic control demands were assessed by contrasting high and low control trials in the baseline letter task. Whole-brain analyses were subjected to FWE-correction at the cluster level with a critical cluster level of .05. A second model was created to assess the effect of reaction time on neural activity. This model included letter matching and semantic conditions, with semantic trials modulated by (a) RT and (b) association vs. conceptual similarity. The RT and relationship type regressors were treated as equal to assess the unique variance of each factor (not using serial orthogonalisation). Finally, ROIs were created based on peak co-ordinates from previous studies (see Results) and analysed in the MarsBar toolbox (Brett et al., 2002). ROIs were spheres with a diameter of 10mm. Statistics were conducted on the mean activation of the voxels within the ROI.

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Chapter 6

The semantic network at work and rest

Rebecca L. Jackson, Paul Hoffman, Gorana Pobric & Matthew A. Lambon Ralph*
Neuroscience and Aphasia Research Unit (NARU)
School of Psychological Sciences (Zochonis Building)
University of Manchester

* Correspondence to:
Prof. Matthew A. Lambon Ralph
Neuroscience and Aphasia Research Unit (NARU)
School of Psychological Sciences (Zochonis Building)
University of Manchester
Brunswick Street
Manchester
M13 9PL
Email: matt.lambon-ralph@manchester.ac.uk
Tel: +44 (0) 161 275 2551
Fax: +44 (0) 161 275 2683

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1. Abstract

Although there is increasing consensus on the regions involved in multimodal semantic cognition, the functional connectivity of the semantic network has not been elucidated. The functional connectivity of the semantic network was investigated with and without an active task (semantic similarity decisions vs. resting-state activation). A dual-echo gradient EPI paradigm was employed to ensure signal throughout the anterior temporal lobe (ATL). The ventral ATL was connected to core semantic regions, including bilateral ATL, inferior frontal gyrus, medial prefrontal cortex (mPFC), angular gyrus, posterior middle temporal gyrus and medial temporal lobes, regardless of the task or rest state. The left ATL was not one homogenous unit, however. Superior ATL regions connected to an auditory sensorimotor network likely to be critical for language, whereas the ventral region connected to a multimodal semantic network. This distinction varied in a graded manner in interim ATL regions, although the connectivity of the aMTG had greater resemblance to the ventral region. A PPI analysis of the semantic task identified additional engagement of occipital and frontal areas, which overlap with regions found to be sensitive to executively-demanding, controlled semantic processing. The semantic network overlapped with the default mode network in core regions including the ventral ATL, medial temporal lobes and mPFC. This supports theories suggesting the necessity for semantic cognition during internal processes, such as planning and remembering.

2. Introduction

Although neuropsychology and neuroimaging have consistently highlighted a core set of regions involved in semantic cognition, relatively little research has elucidated the functional connectivity of these areas (Duffau et al., 2004). Neural processing is dynamic and may be best understood via the interactions between multiple areas (Bressler & Menon, 2010; McIntosh, 1999; Meehan & Bressler, 2012; Mesulam, 1990). Here we investigated the functional connectivity of the semantic network with and without an explicit task.

The anterior temporal lobe (ATL) is a core region for semantic cognition. Semantic dementia patients suffer a progressive degradation of multimodal conceptual knowledge in parallel with atrophy and hypometabolism focussed on the polar and ventrolateral aspects of the ATL (Nestor et al., 2006; Patterson et al., 2007). Although the inferior temporal regions are susceptible to signal loss and distortion in standard fMRI studies, the importance of the ATL during semantic tasks has been confirmed using PET, MEG or fMRI with distortion correction of spin echo EPI data or a dual gradient echo EPI technique (see Chapter 5; Binney et al., 2010;

Devlin et al., 2000; Embleton et al., 2010; Halai et al., 2014; Marinkovic et al., 2003; Vandenberghe et al., 2002; Vandenberghe et al., 1996; Visser et al., 2010a). Modality-specific information from 'spoke' regions converges in and interacts with the ATL 'hub' to create transmodal conceptual representations (Patterson et al., 2007; Rogers et al., 2004). Both neuroimaging studies and recordings suggest that the centrepoint of this multimodal region is within the ventral ATL (Binney et al., 2010; Luders et al., 1991; Luders et al., 1986; Visser et al., 2012; Visser & Lambon Ralph, 2011). Alongside temporopolar cortex, this corresponds to the region of maximal atrophy in semantic dementia (Galton et al., 2001) and is most strongly correlated with the patients' degree of semantic impairment (Butler et al., 2009; Mion et al., 2010). There appears to be graded variations of function in the other ATL subregions. The anterior superior temporal gyrus (aSTG) may be particularly involved in processing the meaning of auditory/verbal stimuli (Scott et al., 2000; Spitsyna et al., 2006; Visser et al., 2012; Visser & Lambon Ralph, 2011) presumably reflecting its connectivity to primary auditory regions (Binney et al., 2012; Morán et al., 1987). Alternatively, the structural connection between the aSTG and inferior frontal gyrus (IFG) via white matter connections running through the extreme capsule complex (Duffau et al., 2004; Friederici, 2011) may cause the aSTG to be suited to a different role, perhaps relating to semantic control. The role of lateral ATL regions is less clear but given their intermediate position (between auditory and visual input), their function may be more multimodal in nature like the ventral ATL area (Binney et al., 2010; Morán et al., 1987; Visser et al., 2012).

In addition to the ATL, semantic cognition depends upon the inferior frontal gyrus (IFG), medial prefrontal cortex (mPFC), posterior middle temporal gyrus (pMTG) and lateral parietal regions (Binder et al., 2009; Binney et al., 2010; Noonan et al., 2010; Noonan et al., 2013). Unlike the multimodal ATL and sensory-specific spoke regions hypothesised to represent semantic knowledge, it has been proposed that the IFG and pMTG are responsible for the controlled retrieval and manipulation of concepts (Badre et al., 2005; Badre & Wagner, 2003; Jefferies, 2013; Jefferies & Lambon Ralph, 2006; Noonan et al., 2010; Thompson-Schill, 2003; Thompson-Schill et al., 1999; Wagner et al., 2001a; Whitney et al., 2011; 2012). Although the AG has been implicated in semantic representation by some researchers (Binder & Desai, 2011; Binder et al., 2009; Geschwind, 1972), the AG is also involved in a diverse set of tasks and thus may be related to a more general cognitive process (e.g. Cabeza et al., 2012; Cabeza et al., 2008; Cattaneo et al., 2009; Gobel et al., 2001; Humphreys & Lambon Ralph, in press; Hutchinson et al., 2009). Although rarely discussed, activation of the mPFC is consistently found for semantic tasks

(Binder et al., 2009). Functional connectivity between many of these semantic areas has been shown during comprehension of speech and written language, sound categorisation, accessing action conceptual knowledge and word fluency (Abrams et al., 2013; Assmus et al., 2007; Husain et al., 2006; Snijders et al., 2010; Stamatakis et al., 2005; Tyler & Marslen-Wilson, 2008; Vitali et al., 2005; Yang et al., 2011). However, due to the poor signal in critical inferior prefrontal and temporal regions, the connectivity of these ATL regions during explicit semantic tasks and rest (when no explicit task is presented) remains to be elucidated.

A number of regions implicated in semantic cognition may also overlap with the default mode network (DMN). Although the precise constituent areas are heavily debated, the mPFC is a core region (Andrews-Hanna et al., 2010b; Buckner et al., 2008; Greicius et al., 2009; Utevsky et al., 2014). Involvement of the lateral temporal cortex and angular gyrus is also often reported (e.g. Andrews-Hanna et al., 2010a; Buckner et al., 2008; Greicius et al., 2003; Wirth et al., 2011). Although often referred to as a 'task negative network' (Fox et al., 2005), the DMN does not de-activate equally to all tasks (Spreng, 2012). Less deactivation has been shown to occur during semantic and episodic tasks and, if sufficiently demanding, the contrast rest over semantics may include very few significant areas (Binder et al., 1999; Buckner et al., 2005; Shapira-Lichter et al., 2013; Wirth et al., 2011). Similarly, the DMN may include areas related to episodic memory, in particular, the hippocampal formation (Buckner et al., 2008; Greicius et al., 2003; Greicius et al., 2009; Maillet & Rajah, 2014; Sestieri et al., 2011). The DMN has been hypothesised to include semantic and episodic subsystems dependent on the ATL and hippocampus respectively (Binder et al., 1999; Greicius & Menon, 2004). The key idea is that free thought, such as planning and daydreaming, involves core DMN regions which require access to past events and meaning in these subsystems.

In this study, we investigated the semantic network by probing the connectivity of the ATL. A dual-echo gradient EPI paradigm was employed to ensure full ATL coverage, including the vATL region which appears to be a crucial subregion but is challenging to image successfully (Devlin et al., 2000; Halai et al., 2014; Visser et al., 2010a). This is a key difference from prior functional connectivity studies (including large scale model-free analyses) which are likely to lack the signal to identify the involvement of the ATL in relevant networks (as described in Wig et al., 2014; Zuo et al., 2012). A further methodological consideration was the inclusion of connectivity analyses during both rest (using seed-based functional connectivity analyses) and a task state (using PPI). This novel approach has been adopted in prior studies of the motor network. These studies show similar connectivity between task and rest but commonly report some task-dependent modulations, such as the involvement of fewer areas (Hampson et al., 2004; Jiang et al., 2004; Newton et al., 2007; Rehme et al., 2013). A similar approach involves assessing the similarity between global resting state connectivity and meta-analytic reviews of task-based connectivity or coactivation patterns although the details of specific task-related changes are lost. These analyses have shown a high level of correspondence (Cole et al., in press; Smith et al., 2009). However, more fine grained analyses have identified changes in efficiency and the connectivity of select areas, including inferior temporal regions (Di et al., 2013). Obtaining both rest and task data in this study allowed for the assessment of a core semantic network (based on the convergence between the results) as well as state-dependent dynamics (based on the key differences).

3. Materials and Methods

3.1 Participants

Resting state scans were collected for 78 participants (57 female, age range 18-42, average age 24.71 years, standard deviation 5.49 years), 24 of whom also completed a dual gradient echo fMRI study of semantic decision making reported previously (15 female, age range 20-42, average age 25.63 years, standard deviation 56.36 years, see Chapter 5). Participants were strongly right handed (minimum laterality quotient 50, average 85.85, standard deviation 14.91 on the Edinburgh Handedness Inventory; Oldfield, 1971). Participants' vision was normal or corrected-to-normal. All participants gave informed consent and the study was approved by the local ethics board.

3.2 Resting State

3.2.1 Procedure

Participants were asked to fixate on a cross and lie still (Van Dijk et al., 2012). Scanning was conducted using a Phillips Achieve 3.0T system with 32 channel SENSE coil with a sense factor of 2.5. Noise cancelling Mk II+ headphones were worn inside the scanner (MR Confon, Magdeburg, Germany). A structural reference was obtained with an in-plane resolution of .938 and slice thickness of 1.173. Whole brain coverage was obtained with a field of view of 240x240mm, which was tilted up to 45° off the AC-PC line to reduce the effect of ghosting on the temporal pole. The TR was 2.8 with a flip angle of 85°, resolution matrix of 80x80, reconstructed voxel size of 3mm and slice thickness of 4mm. 130 volumes were collected over 6.25 minutes.

A dual gradient echo technique was employed. This involves parallel acquisition at a short echo (12ms) leading to less signal loss in areas of high magnetic susceptibility and a standard long echo (35ms) to maintain high contrast sensitivity throughout the brain. The results from the 2 echoes were combined using linear summation, previously shown to be optimal (Halai et al., 2014; Poser et al., 2006). The resultant reduction in signal dropout is greatest within inferior temporal and frontal regions including the vATL, an area of key interest in this investigation (Halai et al., 2014; Poser & Norris, 2007; 2009). Mean TSNR is shown in Figure 10A. TSNR exceeded 40 throughout all subregions of the ATL.

3.2.2 ROIs

Peak coordinates were taken from the whole brain univariate analysis in key semantic areas identified from the literature including ventral and superior ATL, posterior MTG, IFG, medial prefrontal cortex and angular gyrus. Within the ATL a ventral region has been shown to be critical (Binney et al., 2010; Visser et al., 2012; Visser & Lambon Ralph, 2011). The role of the aSTG in multimodal semantics is less clear as it may be more important for auditory and verbal stimuli (Spitsyna et al., 2006; Visser et al., 2012; Visser & Lambon Ralph, 2011). A spherical ROI with a 10mm radius was constructed around the peak coordinate in each of these areas from the whole-brain univariate analyses of the active fMRI study (see Chapter 5). Although activation was found within the AG, no peaks were identified. Due to the growing evidence that this region is implicated in a range of cognitive activities including semantic cognition (Cabeza et al., 2012; Cabeza et al., 2008; Chambers et al., 2004; Dehaene et al., 2003; Noonan et al., 2013), an ROI was constructed from the coordinate of peak overlap between all tasks in a recent, large-scale meta-analysis (Humphreys & Lambon Ralph, in press). Thus, the selected ROIs included vATL (-39 -6 39), aSTG (-51 9 -12), IFG (-51 24 12), mPFC (-9 48 39), pMTG (-60 -48 3) and AG (-48 -64 34). A smaller (6mm) ROI was used to seed from the aMTG (-45 3 -27) in order to compare the role of this third intermediate ATL region to the vATL and aSTG (without overlapping with these ROIs). The Euclidean distance between the aMTG and the two other ATL ROIs was approximately equal (vATL - 16.16mm vs. aSTG - 17.23mm). In order to assess the relation between the semantic and default mode networks a 10mm sphere was created around a commonly used DMN coordinate within the medial PFC (-1 47 -4; Fernandez-Espejo et al., 2010; Flodin et al., 2012; Fox et al., 2005; Jang et al., 2011; Mennes et al., 2010; Sadaghiani et al., 2009; Shulman et al., 1997; Takeuchi et al., 2011; Takeuchi et al., 2012; Takeuchi et al., 2013;

Viviani et al., 2011; Whitfield-Gabrieli et al., 2009). ROI creation and analysis was conducted in the MarsBar toolbox (Brett et al., 2002).

3.2.3 Data Analysis

Analysis was performed using statistical parametric mapping (SPM 8) software (Wellcome Trust Center for Neuroimaging) and the Data Processing Assistant for Resting State fMRI (DPARSF Advanced Edition, V2.3) toolbox (Chao-Gan & Yu-Feng, 2010). Distance-dependent increases in correlations due to motion are a concern for resting state functional connectivity analyses (Friston et al., 1996; Power et al., 2014; Van Dijk et al., 2012; Yan et al., 2013). For this reason, four methods shown to reduce these effects were employed: censoring; global signal regression; 24 motion parameter regression; and scrubbing of high motion time points. These methods are in keeping with other resting state studies and have been shown to greatly reduce the effects of motion (Anderson et al., 2011; Power et al., 2014; Van Dijk et al., 2012; Weissenbacher et al., 2009; Yan et al., 2013).

The first two volumes from each run were discarded to allow for magnetic saturation effects. SPM was used for slice timing correction, realignment and coregistration to the individual's structural image. Participants were censored on the basis of a threshold of translation and rotation. Six participants with greater than 3mm translation or 1 degree of rotation were excluded from the analysis. This meant that only low motion participants were included in the analysis. Within DPARSF nuisance covariates were regressed out and the images were normalised using DARTEL (Ashburner, 2007) and smoothed with an 8mm full-width half maximum (FWHM) Gaussian kernel. The results were filtered at .01 - .08 Hz (Satterthwaite et al., 2013). Nuisance covariates included 24 motion parameters calculated from the 6 original motion parameters using Volterra expansion (Friston et al., 1996). These have been shown to be better than the 6 parameters alone at decreasing motion effects (Power et al., 2014; Yan et al., 2013). Time points with a z-score greater than 2.5 from the mean global power or more than 1mm translation were identified as outliers using the ARtifact detection Tools software package (ART; www.nitrc.org/projects/artifact_detect). Each of these was entered as a covariate. White matter, CSF and global tissue signal were covaried out and linear detrending was performed. Although regression of the global signal can cause spurious negative correlations it greatly reduces motion-related artefacts (Anderson et al., 2011; Power et al., 2014; Weissenbacher et al., 2009; Yan et al., 2013). For this reason analyses were restricted to positive correlations. 6 participants were excluded due to motion greater than 3mm of translation or 1° of rotation or having less than 5 minutes of data remaining after scrubbing high motion time points.

Seed-based functional connectivity analyses were performed from the ATL and DMN ROIs using DPARSF (Chao-Gan & Yu-Feng, 2010; Yan et al., 2013). Functional connectivity maps were z-score normalised. One sample t-tests were used to find areas with significant connectivity to the seed region. The resulting images were FWE-corrected at the cluster level with a critical cluster level of .05. Correlations between ROIs were examined to assess the connectivity between the semantically-related ROI regions. Comparisons between networks were conducted using paired t-tests on the z-score normalised functional connectivity map. In addition, the correlation across the group between the seed and each semantic ROI was computed and the average of these values computed per individual. This gave a single statistic for each participant determining the connection of this seed to known semantic areas. This value was compared between seeds using paired t-tests to assess whether they were part of the same network. To be confident that motion was not a factor the correlation between the main ROI results (the vATL to each semantic ROI) and the motion parameters was assessed. For each individual, the absolute sum of each of the 6 motion parameters used for realignment was computed as well as the absolute sum of all three of the translation parameters and all three of the rotation parameters. The correlation between these 8 values per individual and the correlations between the ventral ATL and semantic ROIs were assessed. No significant relationships between motion and connectivity were found ($p>.05$).

3.3 PPI

3.3.1 Task

The PPI analysis was conducted on 3 runs of data presented in Chapter 5 which included a semantic and baseline task. The semantic task involved a triad judgement in which participants were asked to match a probe word (e.g., HEN) to the most semantically-related of two choices. The target was either strongly associated (e.g., CAGE) or conceptually-similar (e.g., ROBIN) to the probe. Foils were unrelated to probes and targets. Formal whole-brain analysis showed no significant differences between the regions involved in these two conditions and no further distinction is made here. In the control task, participants were asked to decide which of two letter strings (containing Greek and English letters) overlapped the most with the probe string. The control task was designed to act as a high level baseline and therefore needed to be at least as challenging as the semantic task, which proved to be the case (control task: mean RT = 2076 msec (SD=265); semantic task: mean RT = 1719 msec (SD=273); t(23)=9.74, p<.05). Stimuli were presented in mini-blocks of 15 seconds each containing 3 trials. Both tasks started with a central fixation cross presented for 1000ms followed by presentation of the stimuli for 4000ms. During this time participants responded by pressing one of two buttons. The contrast of interest was semantic > control task.

To test an emergent hypothesis (see below) that the PPI analysis highlights areas of the network implicated in demanding processing, a separate contrastive set of trials were selected which provided a manipulation of semantic control. In the low control condition, foils were from a domain unrelated to the probe item whereas, in the high control condition, foils were from the same category (e.g., BARREL – BOX, combined with the foil PLUM or SEAT). These trials were not included in the PPI analysis (see Chapter 5).

3.3.2 Procedure

The imaging parameters were identical to those used to collected the resting state data. Run length was 10 minutes and 211 volumes were collected. Three runs were analysed for each participant.

3.3.3 Data Analysis

Analysis was performed using statistical parametric mapping (SPM 8) software (Wellcome Trust Center for Neuroimaging). A 6mm vATL ROI was created for use as a seed using the same coordinates as the resting state analyses, a size consistent with prior PPI analyses (e.g., Ge & Han, 2008; Green et al., 2010; Veit et al., 2012). The same semantic regions in the IFG, mPFC, AG and pMTG were used as 10mm ROIs. PPI analysis is based on the extraction of signal at the seed region and deconvolution with the haemodynamic response function. Areas with a significant amount of variance relating to the interaction between the physiological and the psychological contrast are identified (Friston, 2011; Green et al., 2010). The whole-brain results were FWE-corrected at the cluster level with a critical cluster level of .05.

4. Results

4.1 Connectivity of Semantic Areas Within the RS Data

The ventral ATL seed showed functional connectivity during a resting state with a network of areas linked to semantic cognition (see Figure 10, Table 9). Significant regions are found within bilateral ATL, MTL, pMTG, AG, frontal cortex and insula. Further significant connectivity was found within bilateral mid and posterior cingulate and precuneus as well as the right pre- and postcentral gyri, and the cerebellum. Figure 10C shows the overlap between this vATL-seeded RS network and the areas identified in the active semantic task. ROI analyses of the resting state data showed that the vATL was functionally connected to all regions associated with multimodal semantic processing (IFG, t(70)=4.152, p<.001; mPFC, t(70)=7.746, p<.001; pMTG, t(70)=7.255, p<.05; AG, t(70)=7.885, p<.001). Furthermore, all of these regions were functionally connected to each other (p<.001).

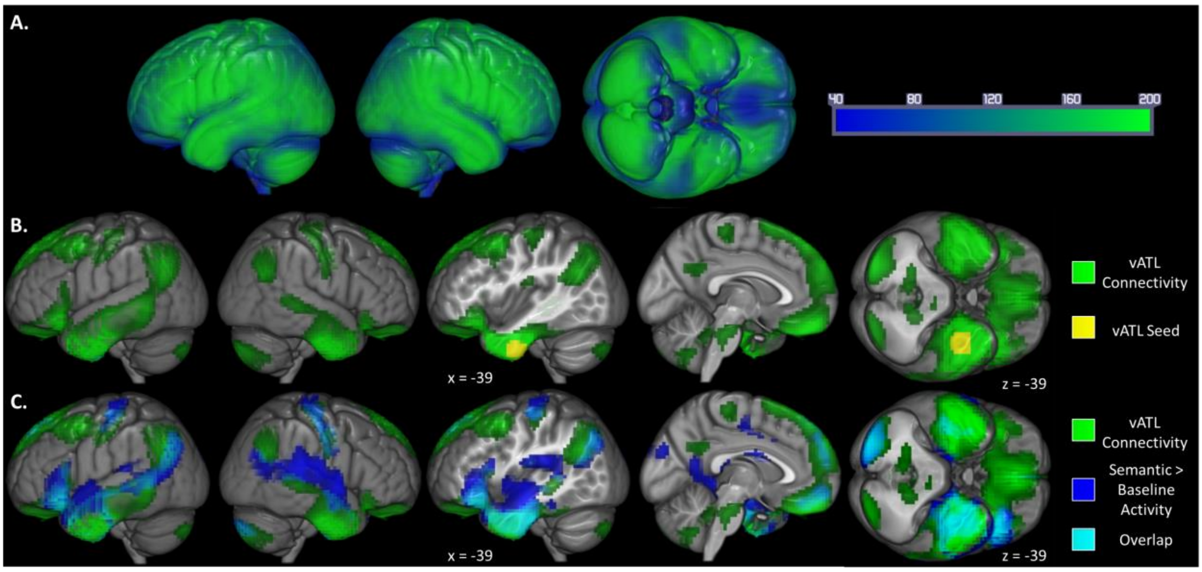

Figure 10. **TSNR map & the functional connectivity of the vATL during resting state.** A. Average temporal signal-to-noise ratio for the smoothed group EPI data in MNI space. The map is set at a threshold of 40, considered to be the minimum TSNR required to reliably detect differences in signal (Murphy et al., 2007; Simmons et al., 2010; Wang et al., 2013) and is displayed as a range from 40 (dark blue) to 200 (bright green). Use of the dual-echo technique meant signal reached the minimum threshold throughout the ATL and inferior frontal regions with some subregions far exceeding this with values above 200. This meant we had adequate signal to assess the functional connectivity of the areas commonly suffering from signal loss. B. Resting state functional connectivity of the ventral ATL. Voxels displaying significant functional connectivity with the vATL are shown in green. The image was thresholded at .001 at the voxel level and an FWE-correction was performed at the cluster level with a critical cluster level of .05. The vATL seed is overlaid in yellow. C. The functional connectivity (green) of the ventral ATL is shown with the activity from a univariate contrast of semantics over baseline (dark blue, see Chapter 5). Overlap is shown in cyan. Both the connectivity and activity maps are thresholded at .001 at the voxel level and FWE-corrected at the cluster level. During rest a network connects the ventral ATL and other regions critical for semantic processing.

Table 9. Significant clusters of functional connectivity during resting state with subregions of the ATL

Seed	Cluster Region	Cluster extent (voxels)	Max z value	P value (FWE corrected)	Peak MNI Coordinate		
					X	Y	Z
vATL	Bilateral fronto-temporal cortex, L AG & insula	11067	Inf	<.001	-39	-9	-39
					51	-9	-39
					39	-12	-42
	Cerebellum	157	6.71	.005	-21	-87	-42
	R AG	191	6.41	.002	60	-60	30
	R pre- & postCG	296	6.13	<.001	60	-6	45
					51	-18	60
					57	-15	54
	Bilateral PCC	174	5.18	.003	3	-27	63
	R MCC				12	-9	48
	L PCC & precuneus	98	4.99	.036	21	-39	21
					12	-12	27
					24	-42	12
aSTG	Bilateral STG, posterior temporal & occipital cortex, IFG, pre & post CG, SMA & insula	15437	Inf	<.001	-48	12	-12
					54	6	-12
					-39	-6	-12
	L MFG	231	7.02	.001	-30	48	24
	L PhG	288	5.3	<.001	6	-12	-27
					-6	-12	-30
					-18	-24	-24
	R MFG	94	4.97	.043	30	48	24
aMTG	Bilateral fronto-temporal cortex, thalamus & insula	8897	Inf	<.001	-45	3	-24
					51	6	-21
					30	-3	-27
	L AG	500	6.73	<.001	-51	-66	24
					-48	-69	45
	Cerebellum	190	6.46	.002	24	-78	-33
					45	-78	-39
	Bilateral PCC & precuneus	452	6.22	<.001	-3	-51	33
	R AG	219	5.93	.001	60	-57	30
					54	-69	36
					45	-54	27
	Cerebellum	110	5.89	.021	-27	-81	-36
	Bilateral PCC	218	4.93	<.001	-6	-30	63
					6	-27	63
					15	-33	69

Clusters significant at .001 after FWE correction. Largest 3 peaks listed per cluster. L = left. R = right. SMA = supplementary motor area, MTL = medial temporal lobe, PhG = parahippocampal gyrus, MFG = middle frontal gyrus, PCC = posterior cingulate cortex, MCC = mid cingulate cortex, CG = central gyrus, STG = superior temporal gyrus.

The aSTG seed shows a functional connectivity pattern that differs greatly to the vATL (see Figure 11, Table 9). Significant connectivity is found along the superior aspects of the temporal lobes bilaterally and in posterior temporal cortex. Bilateral inferior and middle frontal gyri, pre- and postcentral gyri, SMA, insula and occipital cortex and left PhG are also significantly connected. Significant positive correlations were found between the aSTG and the IFG (t(70)=2.925, p<.05) and pMTG (t(70)=5.293, p<.001) ROIs only. In order to assess whether these results reflect two separate networks, paired t-tests were performed, thus identifying voxels with significantly greater functional connectivity to the vATL than the aSTG or vice versa (see Figure 11B&C). These distinct subcomponents included bilateral ATL, AG and frontal cortex for the vATL seed vs. aSTG, IFG, pre- and postcentral gyri for the aSTG seed vs. vATL (see Appendix 6). The distinct nature of the vATL and aSTG networks was confirmed with a paired t-test comparing the correlation between the aSTG and all other ROIs to the vATL and all other ROIs (t(70)=7.254, p<.001). In summary, unlike the vATL, the aSTG does not appear to be a core part of the semantic network in the resting state data. Instead it forms a network with areas implicated in language and auditory processing.

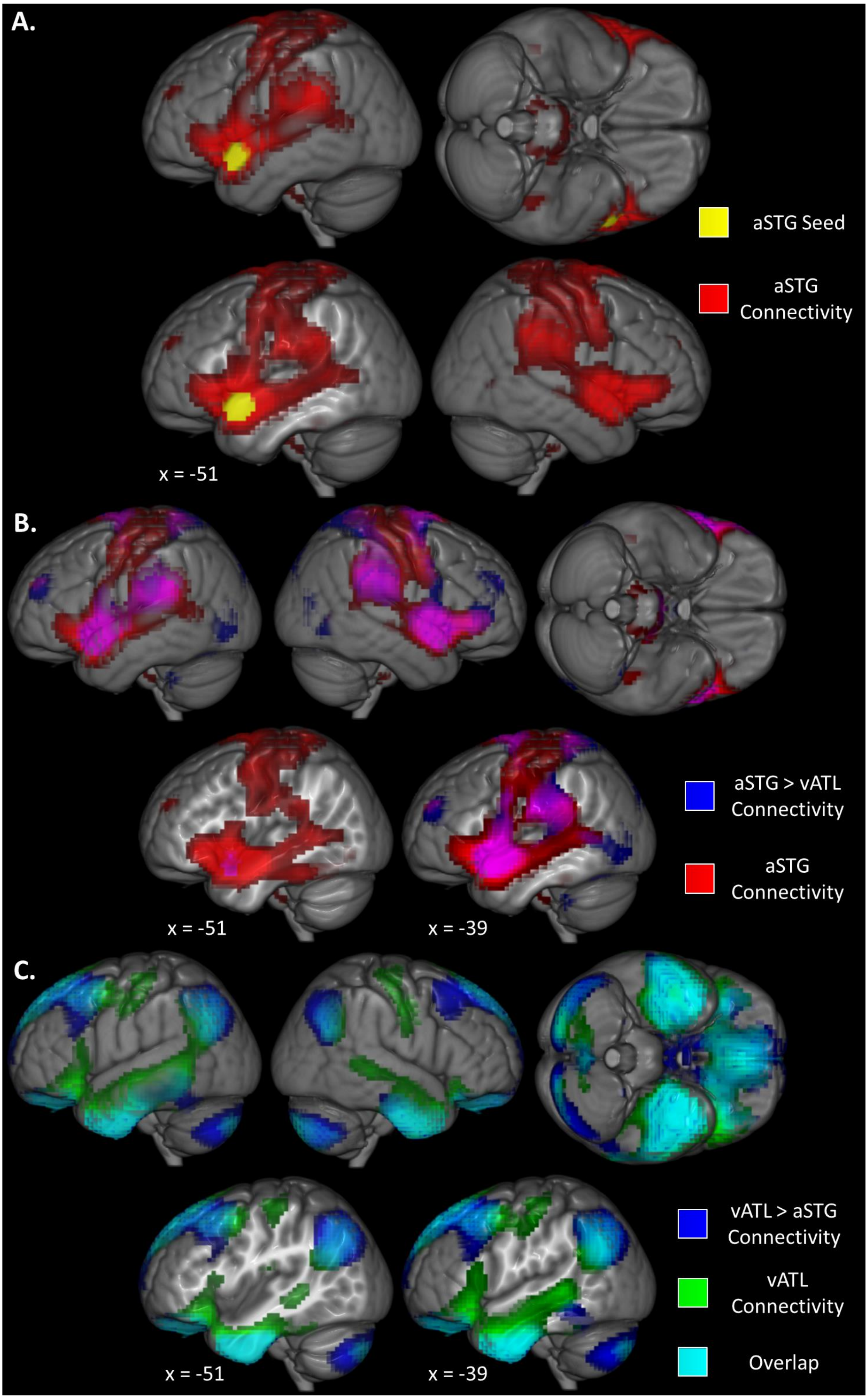
A.
aSTG Seed
aSTG Connectivity
x = -51
B.
aSTG > vATL Connectivity
aSTG Connectivity
x = -51
x = -39
C.
vATL > aSTG Connectivity
vATL Connectivity
Overlap
x = -51
x = -39

Figure 11. **Functional connectivity of the aSTG during the resting state.** A. Resting state connectivity of the aSTG. Voxels displaying significant functional connectivity with the vATL are shown in red. The image was thresholded at .001 at the voxel level and an FWE-correction was performed at the cluster level with a critical cluster level of .05. The aSTG seed is overlaid in yellow. B & C. Comparison of the functional connectivity of the vATL and aSTG. B. Areas with significantly greater functional connectivity with the aSTG (blue) are shown on top of the areas connected to the aSTG (red). The image was thresholded at .001 at the voxel level and an FWE-correction was performed at the cluster level with a critical cluster level of .05. Pink areas represent the regions of the aSTG network that show significantly greater connectivity to the aSTG than the vATL. C. Areas with significantly greater functional connectivity with the vATL (dark blue) are shown on top of the areas connected to the vATL (green). The image was thresholded at .001 at the voxel level and an FWE-correction was performed at the cluster level with a critical cluster level of .05. Light blue areas represent the regions of the vATL network that show significantly greater connectivity to the vATL than the aSTG.

The functional connectivity of the aMTG is shown in Figure 12A (see Table 9). Of the *a priori* ROIs, there was significant connectivity between the aMTG and the AG (t(70)=5.304, p<.001) and mPFC (t(70)=6.262, p<.001) only. Paired t-tests comparing the correlations with the semantic ROIs between the aMTG and the vATL (t(70)= -6.216, p<.001) and aSTG (t(70)= 3.764, p<.001) showed significant differences which could suggest that all three seeds connect to different networks. However, this may instead reflect a gradation between superior and inferior aspects of the ATL. In order to assess whether the aMTG was part of a distinct network areas with significantly greater connectivity to the aMTG than the aSTG or vATL and vice versa were identified (see Figures 12B & 12C). The areas in the aMTG-seeded network included those in the vATL-seeded network at a lower strength (but higher than in the aSTG seed). The regions specific to the aSTG-seeded network did not appear greater in the aMTG-seeded than vATL-seeded network except within the aMTG. This suggests that the aMTG shows similar but weaker connectivity to the vATL but not the aSTG. These results were replicated with a larger aMTG seed showing that this was not merely a difference in power relating to the use of a smaller seed for the aMTG.

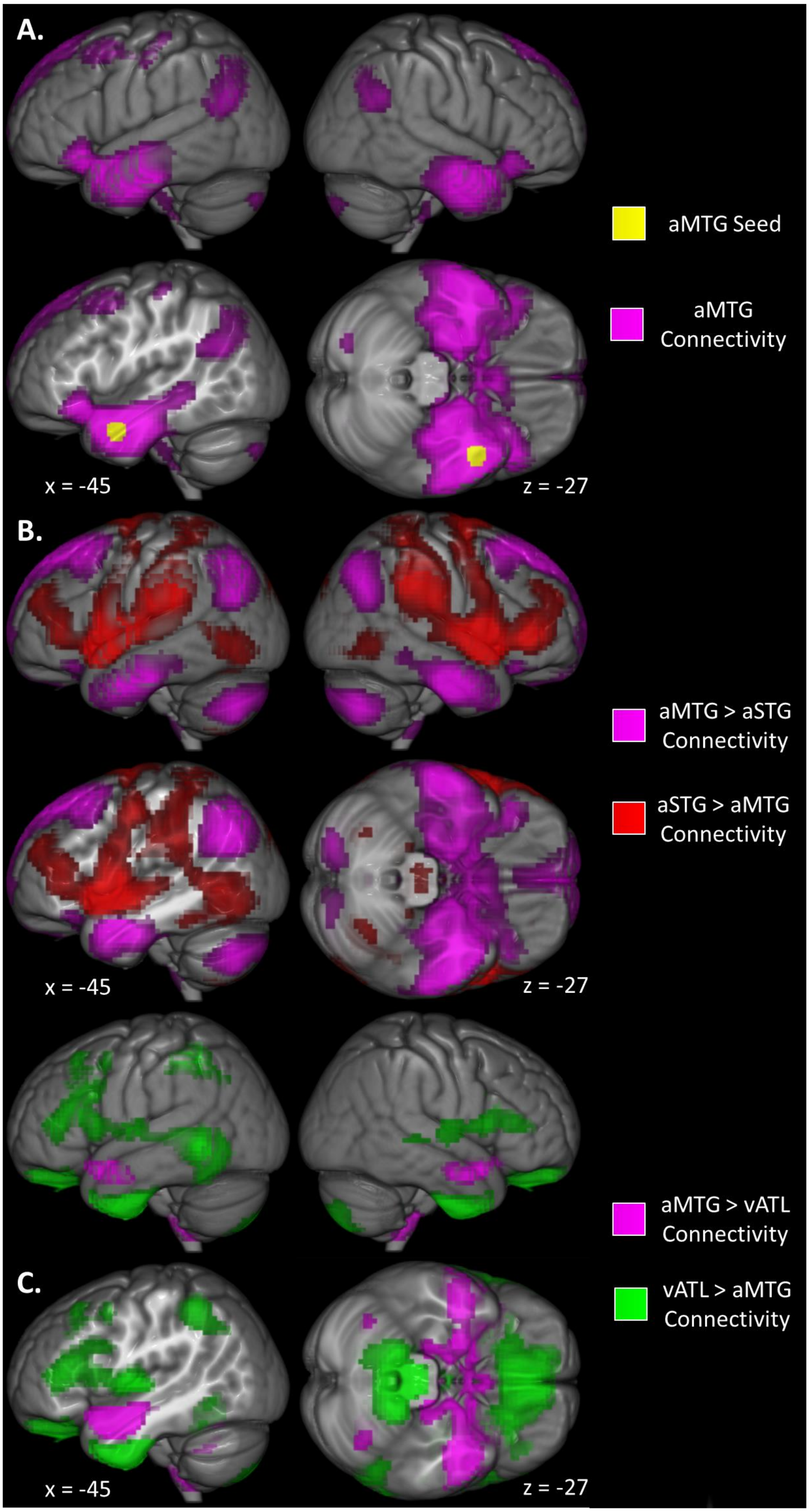
A.
aMTG Seed
aMTG Connectivity
x = -45
z = -27
B.
aMTG > aSTG Connectivity
aSTG > aMTG Connectivity
x = -45
z = -27
aMTG > vATL Connectivity
vATL > aMTG Connectivity
C.
x = -45
z = -27

Figure 12. **The functional connectivity of the aMTG during rest.** A. Areas significantly connected to the aMTG (violet). The aMTG seed is shown in yellow. The image was thresholded at .001 at the voxel level and an FWE-correction was performed at the cluster level with a critical cluster level of .05. B. Comparing the aMTG and aSTG. Areas with significantly greater connectivity to the aMTG then the aSTG are shown in violet and areas with significantly greater connectivity to the aSTG then the aMTG are shown in red. C. Comparing the aMTG and vATL. Areas with significantly greater connectivity to the aMTG then the vATL are shown in violet and areas with significantly greater connectivity to the vATL then the aMTG are shown in green.

4.2 Task-related Semantic Network

The functional connectivity of the vATL during explicit semantic judgements was determined using a PPI analysis. Figure 13 shows the results (see Table 10). Greater connectivity with the vATL was found during a semantic than baseline task for regions including anterior and posterior temporal cortex, angular gyrus, IFG, mPFC and occipital cortex. The PPI results show both similarities and differences to the RS results. The PPI highlights areas known to be important in semantic processing that were also in the semantic network found during rest, including vATL, IFG, OFC, pMTG, AG and mPFC. The PPI analysis showed significant connectivity between the vATL and all the semantic ROIs (AG, t(70)=3.952, p<.001, IFG, t(70)=5.871, p<.001, pMTG, t(70)=3.927, p<.001, mPFC, t(70)=4.273, p<.001). However, the networks were not identical; the PPI identified large areas of occipital and frontal cortex not found in the resting state functional connectivity analysis. This may be due to the recruitment of these areas during hard semantic processing that requires high level of control over semantic cognition (involving frontal regions) and longer strong interaction of semantic regions with lower order visual regions (in the occipital lobe). In order to assess this potential explanation the PPI results were compared to a comparison of trials requiring high and low level semantic control based on the relation between the probe and the foil (see Chapter 5). The contrast high > low semantic control did indeed activate similar occipital and frontal regions suggesting these areas are recruited for more difficult semantic processing requiring more control (see Figure 13B). Control processes may be more critical for task-based processing than semantic cognition during rest, for instance, due to the requirements to reject a foil and make an explicit choice.

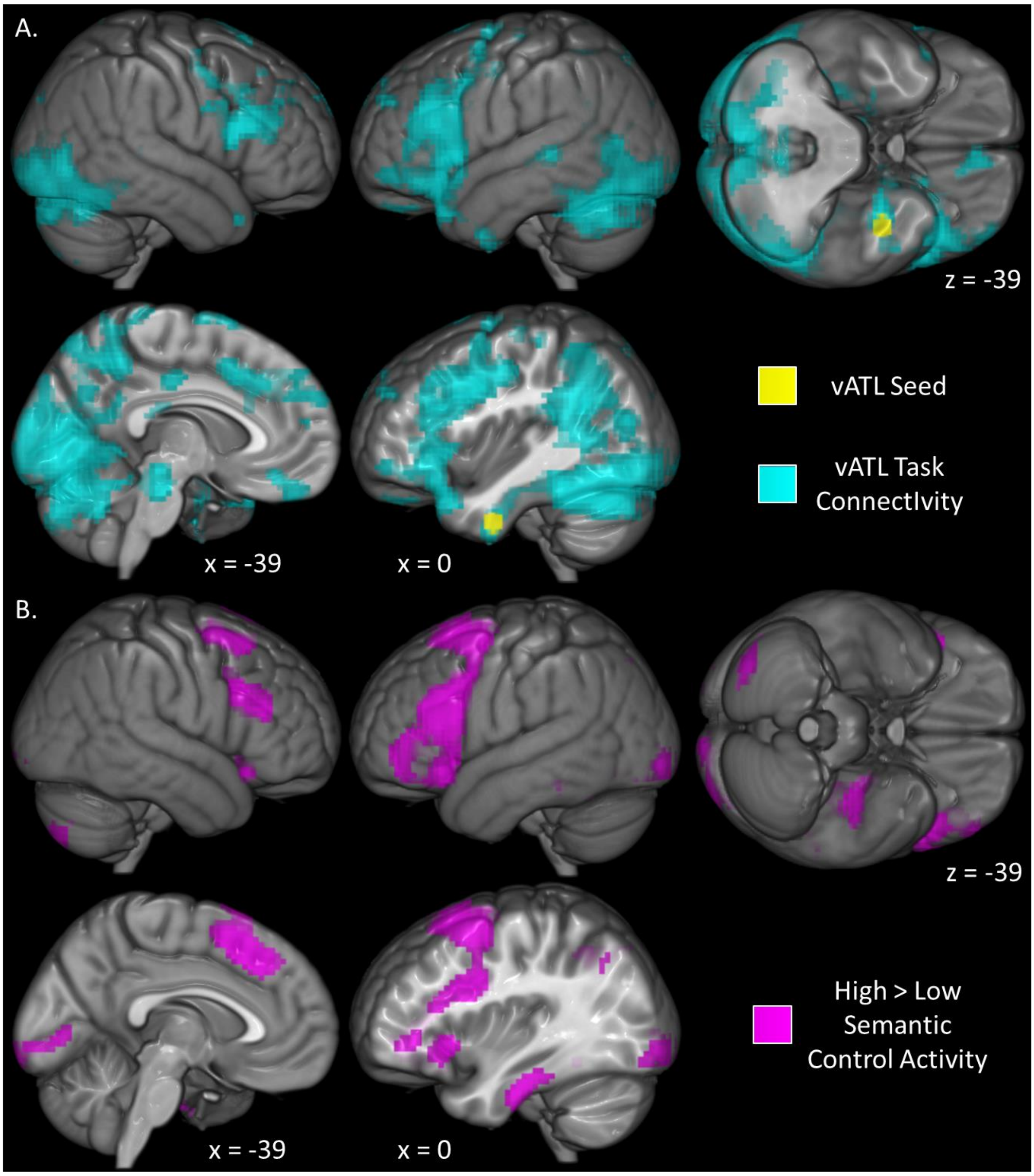

Figure 13. **Functional connectivity of the vATL during performance of a semantic task.** A. Results of the PPI analysis for semantic judgements > letter matching. Voxels that have a significantly greater connection with the vATL during the semantic than the baseline task are shown in cyan. The vATL ROI is shown in yellow. Results are thresholded at .001 at the voxel level and FWE-corrected at the cluster level with a critical cluster level of .05. B. Results of the contrast high semantic control > low semantic control on the activity (violet). Results are thresholded at .001 at the voxel level and FWE-corrected at the cluster level with a critical cluster level of .05.

Table 10. Peak areas of the PPI analyses showing significant functional connectivity with the vATL seed during semantic judgements > letter matching.

Seed region	Region	Cluster extent (voxels)	Max z value	P value	Peak region	Peak MNI Coordinate		
						X	Y	Z
vATL	L frontal & aSTS	11005	5.48	<.001	L pFG	-36	-51	-21
	Bilateral occipital, temporal & parietal & R frontal	3193	4.92	<.001	R iOFC	30	39	-24
	Midbrain	203	4.53	<.001	Midbrain	-6	-24	-18
	R frontal	345	4.09	<.001	R IFG	51	27	27

Clusters significant at .001 after FWE correction. Largest peak listed per cluster. L = left. R = right, a = anterior, i = inferior. STS = superior temporal sulcus. IFG = inferior frontal gyrus. OFC = orbitofrontal cortex. FG= fusiform gyrus.

4.3 Default Mode Network & Semantics

The default mode network was elicited by seeding from one of its core regions, the mPFC, as has been done previously (Fernandez-Espejo et al., 2010; Flodin et al., 2012; Fox et al., 2005; Jang et al., 2011; Mennes et al., 2010; Sadaghiani et al., 2009; Shulman et al., 1997; Takeuchi et al., 2011; Takeuchi et al., 2012; Takeuchi et al., 2013; Viviani et al., 2011; Whitfield-Gabrieli et al., 2009). Areas showing significant functional connectivity with the mPFC can be seen in Figure 14A & Table 11. These regions include mPFC, precuneus, mid and posterior cingulate cortex, AG, cerebellum, medial temporal lobe and ventral and lateral aspects of the anterior temporal lobe. This is in keeping with prior investigations of the DMN but shows the inferior ATL more clearly than most studies due to the higher level of signal (Andrews-Hanna et al., 2010a; Andrews-Hanna et al., 2010b; Buckner et al., 2008; Fox et al., 2005; Greicius et al., 2003; Greicius et al., 2009). T-tests assessing the difference in the correlation values between the semantic *a priori* ROIs for these two seeds confirm that there are 2 networks (t(70)=-0.324, p<.001). High overlap between these default mode regions and the semantic network can be seen in Figure 14B. Overlap was found in the ventral and lateral regions of the ATL, MTL, AG and ventral and dorsal regions of mPFC as well as a small region of the precuneus. Thus, overlap was found in key functional hubs of the semantic and DMNs. Not all regions of the DMN are part of the semantic network, as shown in Figure 14C. The DMN is shown without the regions that show significant connectivity with the vATL. This shows areas of the DMN that do not overlap, which primarily includes those on the medial surface. This suggests that the role of some medial regions may not relate to core semantic cognition, at least for single words.

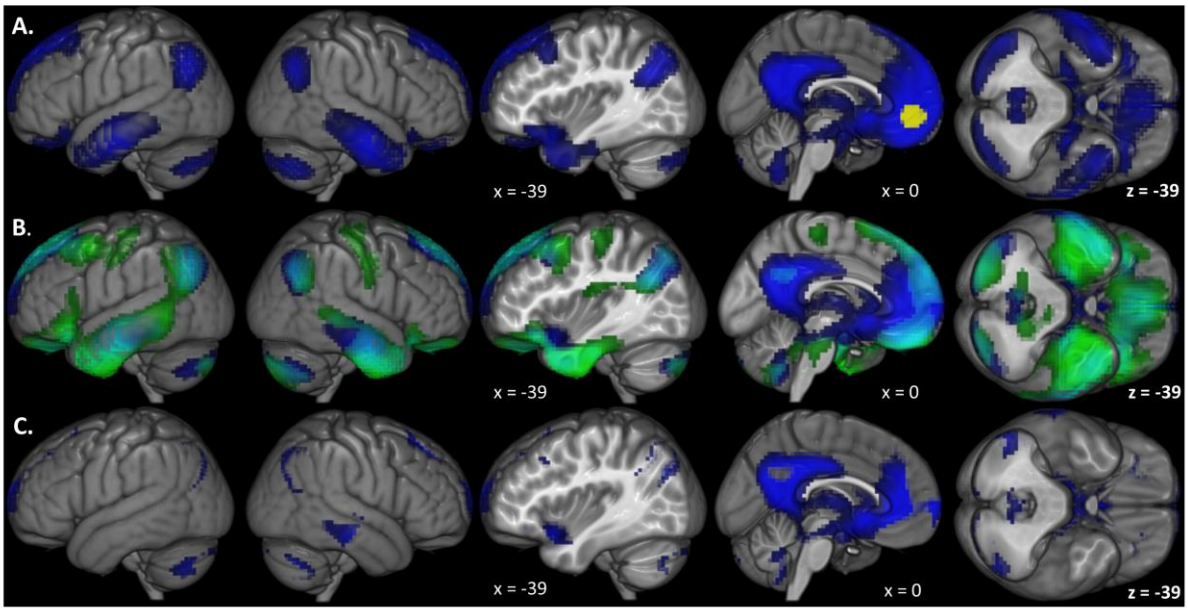

Figure 14. **A comparison of the semantic and default mode networks.** A. The functional connectivity of the DMN seed (blue). The seed is located within the medial prefrontal cortex (yellow). B. The overlap between regions significantly connected to the vATL (green) and the mPFC (dark blue). The main overlap (cyan) can be seen in bilateral ATL, MTL, AG and mPFC. The image was thresholded at .001 at the voxel level and an FWE-correction was performed at the cluster level with a critical cluster level of .05. C. A visualisation of DMN areas not relating to the semantic network. The areas with significant default mode connectivity are masked in a binary fashion by the semantic network (so as to only include regions outside this network). This loses most of the lateral and ventral regions but not those on the medial surface.

Table 11. Significant clusters of functional connectivity with the mPFC DMN ROI during rest.

Cluster Region	Cluster extent (voxels)	Max z value	P value (FWE corrected)	Peak MNI Coordinate		
				X	Y	Z
mPFC, precuneus, MCC, PCC, MTL, lateral & ventral ATL	14825	Inf	<.001	0	48	-6
				6	45	0
				-6	-57	21
L AG	646	Inf	<.001	-48	-69	36
R AG	453	Inf	<.001	51	-63	33
Cerebellum	414	Inf	<.001	48	-66	-42
				27	-81	-33
				21	-90	-39
Cerebellum	311	7.61	<.001	6	-57	-45
				-6	-57	-42
Cerebellum	235	6.92	<.001	-30	-81	-36
				-45	-75	-42
				-18	-90	-39

Clusters significant at .001 after FWE correction. Largest 3 peaks listed per cluster. L = left. R = right. MTL = medial temporal lobe, PCC = posterior cingulate cortex, MCC = mid cingulate cortex, CG = central gyrus.

5. Discussion

The functional connectivity of the vATL region critical for semantic processing was explored. This region was connected to a network of regions implicated in semantic processing including the bilateral ATL, IFG, mPFC, AG, pMTG. Connectivity was not identical throughout the ATL. The aSTG showed differential connectivity to the vATL, with connections to superior and posterior temporal cortex, frontal cortex, SMA and pre- and postcentral gyri. These regions are involved in aspects of language processing including phonology and speech production (Hickok, 2009; Price, 2010; 2012; Vigneau et al., 2006). This is consistent with the idea that the aSTG may be particularly critical for processing auditory and verbal stimuli, whereas the vATL may be responsible for multimodal semantic processing (Binney et al., 2010; Butler et al., 2009; Galton et al., 2001; Mion et al., 2010; Scott et al., 2000; Spitsyna et al., 2006; Visser et al., 2010a; Visser & Lambon Ralph, 2011). The difference between the connectivity of superior and inferior ATL regions appeared to be graded with the aMTG showing an intermediate pattern more similar to the vATL. This is consistent with its hypothesised role as a multimodal region of the ATL (Visser et al., 2012). The vATL was also shown to connect to the same semantic regions during the performance of a semantic judgement task, including bilateral ATL, IFG, mPFC, AG, pMTG. Additional frontal and occipital regions were connected, potentially reflecting areas involved during controlled semantic cognition. The DMN overlapped with the vATL-seeded network in ventral and lateral regions of the ATL, MTL, AG and ventral and dorsal regions of mPFC as well as a small region of the precuneus. Other regions of mPFC and precuneus as well as the PCC were unique to the DMN.

The major finding was of a single semantic network apparent during rest and a semantic task. The network included regions implicated in semantic processing, such as the bilateral ATL, IFG, mPFC, AG, pMTG as well as the medial temporal lobes involved in episodic memory. This may be interpreted as a multimodal semantic network, responsible for the representation and control of meaning. The ATL hub interacts with modality-specific regions to represent coherent concepts, yet the controlled retrieval and use of concepts is supported by frontal and parietal cortices (Jefferies, 2013; Lambon Ralph, 2014; Noonan et al., 2010; Noonan et al., 2013; Patterson et al., 2007; Thompson-Schill et al., 1999; Wagner et al., 2001b). Whilst bilateral ATLs are known to be involved in semantic processing (based on evidence from semantic dementia, fMRI, TMS and computational modelling), the contribution of the right hemisphere in other regions implicated in semantic cognition has not been well established (Binney et al., 2010; Lambon Ralph, 2014; Lambon Ralph et al., 2001; Lambon Ralph et al., 2009; Mion et al., 2010; Patterson et al., 2007; Pobric et al., 2010a; Schapiro et al., 2013; Visser et al., 2010a). The semantic network identified here is clearly bilateral, consistent with a role for both hemispheres in semantic processing.

The medial temporal lobes were connected to the vATL despite having been traditionally associated with episodic memory (Milner et al., 1968; Squire et al., 2004). However, attempts to separate semantic and episodic memory have not shown a clear division in the recruitment of the hippocampal formation (e.g. Maguire & Mummery, 1999; Manns et al., 2003; Ryan et al., 2008). Hippocampal regions are often engaged during tasks involving access to stored conceptual knowledge and have been shown to be functionally connected to semantic regions (Binder et al., 2009; Burianova & Grady, 2007; Ranganath et al., 2005; Ritchey et al., 2014; Ryan et al., 2008). Anterior and posterior regions of the hippocampus have been shown to have differential connectivity to anterior temporal and parietal modules (Ranganath et al., 2005; Ritchey et al., 2014). Both modules overlap with regions identified here and are very similar to the damage within semantic dementia and Alzheimer's disease. The spread of damage within different disorders has been shown to reflect resting state connectivity in healthy participants (Seeley et al., 2009). The connectivity of areas affected in semantic and Alzheimer's dementia overlapped in the hippocampus although the same anterior-posterior shift was found. Both disease-related networks included regions identified as part of the semantic network and DMN (La Joie et al., 2014). The network identified here may involve separable semantic and episodic components, reflecting the differential networks identified in these studies. Seed-based analyses are unable to separate components that both show connectivity with the seed region.

It is possible that some of the areas within the network (e.g., IFG, AG, mPFC) fulfil more general roles, for instance, in selection, retrieval, attention, working memory or the processing of time-varying statistics (Humphreys & Lambon Ralph, in press; Nyberg et al., 2003; Owen et al., 1990; Petrides & Milner, 1982; Thompson-Schill et al., 1997). A multi-demand network of frontal and parietal areas has been hypothesised to show adaptive coding, allowing the constituent areas to perform similar control processes in a wide array of domains (Duncan, 2001; 2006). A meta-analysis of control processes showed partial overlap between semantic and non-semantic control regions. PFC and IPS were found to be domain general whereas anterior IFG and pMTG were selective for semantics (Noonan et al., 2013). A similar overlap may be seen between the semantic network found here and the domain general frontoparietal control network identified previously (Leech et al., 2011; Spreng et al., 2010; Vincent et al., 2008). Although these areas may be involved in other non-semantic processes as well, they commonly activate during semantic processing and as such function as part of this network.

5.1 Differential Connectivity of Subregions of the ATL

There was a clear separation of connectivity patterns within the ATL. Areas critical for semantic cognition were functionally connected to the ventral ATL seed. This is consistent with the core role of this region in multimodal semantic processing (Binney et al., 2010; Galton et al., 2001; Jefferies, 2013; Patterson et al., 2007; Visser et al., 2010a; Visser et al., 2012). In sharp contrast, the aSTG was predominantly connected to bilateral STG, pre- & postcentral gyri, supplementary motor area, supramarginal gyrus, posterior temporal cortex and inferior and middle frontal gyri. These regions constitute a distinct network responsible for motor, tactile and auditory processing (Price, 2010; 2012; Rauschecker & Scott, 2009). These areas are crucial for receptive and expressive language, including phonology and articulation, and are consistently included in traditional and modern models of language (Berker et al., 1986; Eggert, 1977; Hartwigsen et al., 2010; Hickok, 2009; Hickok & Poeppel, 2004; Hickok & Poeppel, 2007; Indefrey & Levelt, 2004;

Price, 2010; 2012; Vigneau et al., 2006). Functional connectivity has been shown between IFG, posterior STG and premotor cortex during passive listening to stories (Hampson et al., 2002). A similar network, argued to relate to language processing, has been demonstrated when seeding from IFG (particularly pars opercularis) although little ATL connectivity was identified (Xiang et al., 2010). Thus, the network appears critical for auditory and sensorimotor processing including language processing.

Connectivity to regions linked to auditory and language processing fits well with proposed roles of the aSTG. The aSTG is activated during extraction of meaning from environmental sounds and intelligible speech suggesting a role in accessing meaning from auditory inputs (Scott et al., 2000; Spitsyna et al., 2006; Visser & Lambon Ralph, 2011). In addition, visually presented language can activate the aSTG (Ross & Olson, 2010; Skipper et al., 2011; Spitsyna et al., 2006). This may be due to the visual language system commandeering the evolutionarily earlier auditory system and automatic conversion of orthography to phonology (Spitsyna et al., 2006). Alternatively, both may involve a related process. Within the Lichtheim 2 computational model of the ventral and dorsal language routes, the aSTG connected the ventral ATL area to frontal and posterior temporal regions (Ueno et al., 2011). Within the aSTG units, sequential input was collapsed on to non-sequential meaning (Ueno et al., 2011). This could be necessary for all meaningful time-variant inputs such as auditory and verbal stimuli and may relate to the idea of 'combinatorial semantics' whereby areas may be involved in constructing a new concept from a set of base concepts, such as a sentence, story or phrase (Hickok & Poeppel, 2004; Vandenberghe et al., 2002).

The functional connectivity of the aMTG appears more similar to that of the ventral ATL than the aSTG. This suggests a role in multimodal semantic processing. There may be a graded difference in how divorced from a specific modality the two areas are with the aMTG responsible for the initial connection between the auditory and visual streams. The vATL may relate less to the modality and maintain greater functional connectivity with areas involved in multimodal semantic processing, such as those responsible for semantic control. The connectivity results indicate graded differences between the MTG and ITG, yet a sharp contrast between MTG and STG. This difference is mirrored by the cytoarchitecture as noted by Brodmann (2006). This distinct connectivity of ventral and superior aspects of the ATL may be maintained in the rostral temporal pole where Pascual (2013) showed a similar 'somatosensory auditory network' when seeding from more superior regions (area TA) and a network of semantic regions when seeding from more ventral regions (areas TE and TG).

5.2 Functional Connectivity Within the Task State

PPI analyses revealed similar vATL connectivity during the semantic task to that of the resting state, as well as additional connectivity to occipital and frontal regions. These differences are secondary compared to the finding of core semantic regions functionally connected in both task and rest states. The differences are likely due to real connectivity changes during task processing, as well as the nature of PPI analyses. The use of visual stimuli here probably explains the increased connectivity between core semantic and occipital regions during the task than rest. Similarly, active tasks are likely to demand greater cognitive control and therefore, heightened connectivity to executively-related frontal regions (on the assumption that harder, more focused semantic processing is less likely to occur during free thought). In addition, the nature of PPI is such that main effects of condition are regressed out and the results reflect the remaining interaction between the condition and physiological time series (Friston, 2011; Friston et al., 1997; O'Reilly et al., 2012). Thus, the PPI analysis may have greater power to detect variation between semantic trials that is less apparent in the simple semantic > control contrast. Both of these explanations fit the finding that the PPI results showed greater connectivity of regions engaged in harder, more controlled semantic processing. In summary, the PPI results seem to reflect the core semantic network plus greater connectivity to the sensory input modality (occipital cortex) and control-related (frontal) regions. This high correspondence between the two datasets plus subtler differences is consistent with prior investigations of the connectivity during task and rest states (Cole et al., in press; Di et al., 2013; Hampson et al., 2004; Jiang et al., 2004; Smith et al., 2009).

5.3 Underlying Structural Connectivity

A strong correlation exists between functional connectivity and structural connectivity, although many functional connections are not based on underlying direct structural connections (Greicius et al., 2009; Hagmann et al., 2008; Honey et al., 2007; Honey et al., 2009; Koch et al., 2002; van den Heuvel et al., 2009). Several of the connections between core regions of the semantic network show clear relations to known structural connections. Temporopolar regions connect to orbital cortex via the uncinate fasciculus, a tract previously linked to semantic cognition (Binney et al., 2012; Catani et al., 2002; Grossman et al., 2004; Han et al., 2013; Lu et al., 2002; Von Der Heide et al., 2013). The structural integrity of the uncinate and the functional connectivity of the aSTG and IFG have been shown to correlate negatively with performance of aphasic patients in tasks requiring semantic control (Harvey et al., 2013). An absence of direct connections from the ventral aspects of the ATL to extra-temporal regions was identified in a probabilistic tractography investigation of the ATL (Binney et al., 2012). Although pars orbitalis connected to the ATL, pars triangularis, pars opercularis and the angular gyrus connected to posterior middle and inferior temporal gyri only. Thus it seems likely that many of the functional connections between the ventral ATL and other core semantic regions are indirect, for instance, via posterior temporal regions. A cortico-cortical evoked potential study showed fast transmission between the ATL and ventral IFG and pMTG suggesting there may be direct connections from these regions to the vATL (Matsumoto et al., 2004).

The functional connections from the ATL to the AG in the semantic network, and the supramarginal gyrus in the auditory sensorimotor network, may depend on indirect connections via pMTG and posterior STS, respectively (Binney et al., 2012; Catani & Mesulam, 2008). Connections along the temporal lobe depend on the inferior and middle longitudinal fasciculi and may be affected in semantic dementia (Acosta-Cabronero et al., 2011; Borroni et al., 2007; Catani et al., 2003). The connections from pMTG and posterior STG to angular and supramarginal gyri have been shown to depend on the arcuate fasciculus (Binney et al., 2012; Catani & Ffytche, 2005; Catani & Mesulam, 2008). The arcuate fasciculus is part of the dorsal route for language whereas the uncinate and inferior-frontal occipital fasciculi (IFOF) are part of the ventral route (Duffau et al., 2009; Hickok & Poeppel, 2004; Parker et al., 2005; Rolheiser et al., 2011; Saur et al., 2008). The connectivity to occipital cortex during the semantic task is likely to depend on the inferior longitudinal fascicule allowing fast transmission of visual information to the ATL for semantic processing (Catani et al., 2003; Catani & Mesulam, 2008).

5.4 Semantics & the Default Mode Network

The default mode and semantic networks were separate but highly overlapping. Using data with good ATL coverage, the DMN was shown to include ventral as well as lateral ATL. The DMN overlapped with core regions of the semantic network including bilateral ATL, MTL, IFG, AG, and mPFC. Regions of the DMN that did not overlap with the semantic network were apparent on the medial surface, including much of the anterior and posterior cingulate cortices, medial superior frontal gyrus and precuneus. Although clearly separate networks, the semantic and default mode networks have large overlapping components. The DMN and overlapping regions are consistent with previous studies with the addition of the inferior ATL, likely due to improved coverage of this region (Andrews-Hanna et al., 2010a; Andrews-Hanna et al., 2010b; Buckner et al., 2008; Fox et al., 2005; Greicius et al., 2003; Greicius et al., 2009). Ventral temporal regions have been shown to deactivate during non-semantic tasks using PET imaging (Shulman et al., 1997). A prior investigation of the AG showed separable regions related to semantics and the DMN, whereas here both included large, highly overlapping proportions of the region (Seghier et al., 2010). This is likely due to differences in how the networks are defined; the activation pattern in a range of tasks may be more useful for highlighting specific differences, whereas standard functional connectivity analyses may give a better idea of all areas the region is connected to.

Many of the overlapping areas may be domain general and as such could be seen to reflect the same process engaged in different domains. For instance, mPFC regions have been associated with working memory and IFG with selection (Nyberg et al., 2003; Ranganath et al., 2004; Thompson-Schill et al., 1997). However, the ventral ATL and hippocampal formation are domain-specific, therefore their involvement strongly suggests components of the DMN are involved in episodic and semantic processing during rest. This may be underpinned by the structural connection between the medial temporal lobe and the retrosplenial cortex of the DMN, as well as tracts known to relate to semantic cognition (Greicius et al., 2009). The DMN has been implicated in spontaneous cognition such as imagining and planning the future and understanding the mental states of others (Andrews-Hanna et al., 2014; Buckner et al., 2008; Moran et al., 2009; Saxe & Kanwisher, 2003). This often involves high affective content and may relate to a stream of consciousness (Kucyi et al., 2014; McKiernan et al., 2006; Tusche et al., in press). These internally mediated processes, supported by the DMN, require access to episodic and semantic representations (Buckner et al., 2008; Buckner & Carroll, 2007; Greicius et al., 2003; Greicius et al., 2009; Shapira-Lichter et al., 2013). Thus, episodic and semantic areas form part of the DMN, either as distinct subcomponents or in an integrated fashion (Binder et al., 1999; Buckner et al., 2008; Buckner & Carroll, 2007; Greicius & Menon, 2004; Maillet & Rajah, 2014; Sestieri et al., 2011; Wirth et al., 2011). The DMN has been shown to be heterogeneous and may be fractionated in to distinct subcomponents. However, the exact nature of these subcomponents is still highly debated (Andrews-Hanna et al., 2010b; Assaf et al., 2010; Buckner et al., 2008; Calhoun et al., 2008; Jafri et al., 2008; Leech et al., 2011; Sestieri et al., 2011; Uddin et al., 2009). More work is needed to uncover the factors determining these separations and how episodic and semantic regions connect to different subregions.

A core region of both the semantic and default mode networks, the mPFC, may have a general role in buffering information over time or planning action (Burgess et al., 2000; Lerner et al., 2011). An alternative explanation is that dorsomedial PFC is responsible for the retrieval of semantic knowledge when there are many different possible answers, such as in tests of semantic fluency (Binder et al., 2009). Patients with transcortical motor aphasia due to mPFC damage have been argued to have a specific impairment of self-guided semantic cognition (Binder et al., 1999). Understanding the role of the PFC may be complicated by separable roles of different regions, only some of which were shown to overlap between the semantic network and the DMN. A number of regions of the DMN did not overlap with the semantic network and are likely to be responsible for other processes previously considered to involve the DMN. These may be separable processes in different regions, for instance, the anterior cingulate has been linked to motivation and sustained attention (Grahn & Manly, 2012; Shen et al., in press). Alternatively, these core regions may reflect a process shared between DMN processes. Buckner and Carroll (2007) suggest remembering, prospection, assuming the viewpoint of others and some forms of spatial navigation, involve similar mental imagery and self projection processes dependent on the same set of DMN regions.

Chapter 7

Identifying Semantic Networks Within Rest and Task States: Putting the Anterior Temporal Lobe Back in to the Connectome

Rebecca L. JACKSON, Gorana POBRIC & Matthew A. LAMBON RALPH*
Neuroscience and Aphasia Research Unit (NARU)
School of Psychological Sciences (Zochonis Building)
University of Manchester

* Correspondence to:
Prof. Matthew A. Lambon Ralph
Neuroscience and Aphasia Research Unit (NARU)
School of Psychological Sciences (Zochonis Building)
University of Manchester
Brunswick Street
Manchester
M13 9PL
Email: matt.lambon-ralph@manchester.ac.uk
Tel: +44 (0) 161 275 2551
Fax: +44 (0) 161 275 2683

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1. Abstract

Preliminary analyses of resting state and task data using independent component analysis were employed to assess the dynamic connectivity of the anterior temporal lobe and elucidate the task relevance of overlapping networks identified with seed-based functional connectivity analyses. Dual echo gradient echo EPI imaging maintained signal in the anterior temporal lobes allowing assessment of the connectivity of semantic regions. ICA was performed on 71 resting state and 24 task-based data sets. This identified 43 resting state and 22 task components. The resting state components were used as VOIs in analyses of the task-based data to assess their task relevance. The task ICA components were also regressed against the design matrix to assess their task relevance. The ATL displayed dynamic connectivity, forming more than one cohesive network. Both the rest and task data included a semantic network involving regions critical for semantic cognition (ATL, mPFC, pMTG, IFG) although there appeared to be some differences based on the state. This network may be relevant for semantic control as well as semantic representation. Task-invariant control appears related to separate networks, including the left frontoparietal network. The anterior default mode network included ATL activity and appeared related to semantics when assessed based on the activity in the VOI but not in the task ICA when the temporal as well as spatial information could be considered. The ATL is highly functionally connected and involved in a number of key networks.

2. Introduction

Semantic cognition, the representation and manipulation of multimodal conceptual knowledge, is critical for everyday life, underpinning a large number of diverse activities, such as speech, reading and object recognition and use (Bozeat et al., 2000; Patterson et al., 2006; Patterson et al., 2007). Convergent evidence has recently highlighted the anterior temporal lobe (ATL) as a crucial neural substrate for the representation of multimodal concepts (see Lambon Ralph, 2014 for review). Information from sensory-specific inputs is combined in a graded fashion, with ventral ATL regions responding to semantic judgements regardless of the modality of input (Binney et al., 2010; Binney et al., 2012; Plaut, 2002; Visser et al., 2010a; Visser et al., 2012). In addition to the ATL 'hub' and sensory-specific 'spoke' regions, a number of areas support semantic control, the retrieval and manipulation of semantic information (Jefferies, 2013; Lambon Ralph, 2014; Noonan et al., 2013; Patterson et al., 2007). These include inferior frontal gyrus (IFG), posterior temporal cortex and inferior parietal cortex (Jefferies, 2013; Noonan et al., 2013).

Assessments of functional connectivity are integral to understanding how regions work together to support cognitive processes, such as semantic cognition (Catani et al., 2013; van den Heuvel & Pol, 2010; Van Essen et al., 2013). Signal loss and distortion within inferior temporal and frontal regions has impaired our ability to assess the functional connectivity during semantic tasks and in whole brain investigations of the connectome, as measured during the resting state (Embleton et al., 2010; Visser et al., 2010a; Wig et al., 2014; Zuo et al., 2012). Newly developed techniques to reduce these artefacts have been applied to the study of the ATL (see Chapter 5; Embleton et al., 2010; Halai et al., 2014; Visser et al., 2010a). Dual echo gradient echo EPI utilises parallel acquisition of an early and a late echo. The resulting images are combined thereby improving signal to noise in areas of high magnetic susceptibility (where signal loss is ameliorated to some degree in short echo imaging) without losing signal elsewhere (where a longer echo is optimal; Halai et al., 2014; Poser et al., 2006). Chapter 6 described the first dual echo fMRI study to assess the connectivity of semantic regions during the resting state, gaining good coverage of the ATL, unlike previous resting state investigations (Halai et al., 2014; Wig et al., 2014; Zuo et al., 2012). Seed-based functional connectivity analyses highlighted the connectivity of the ventral ATL with core semantic regions including IFG, medial frontal (MF) cortex, posterior middle temporal gyrus (pMTG) and angular gyrus (AG). A similar network was shown to be functionally connected during the performance of a semantic task. Hypothesised to be responsible for multimodal semantic cognition, this network included regions critical for semantic representation and control. A number of these regions are core parts of two previously identified resting state networks; the frontoparietal network (FPN) and the default mode network (DMN).

The correct interpretation of this widespread connectivity is not immediately apparent. The same area may be engaged in different networks at different times which may reflect the performance of different cognitive processes (Geranmayeh et al., 2012; Geranmayeh et al., 2014; Leech et al., 2011). The seed-based analysis shows which regions are connected to the seed region over the duration of the scan, but not whether these regions are connected to each other (thus forming a cohesive network), nor the precise temporal dynamics of these connections. As well as slower changes relating to task state, learning or ageing, functional connectivity has been shown to switch quickly between stable states lasting tens of milliseconds (Breakspear, 2004; Deco et al., 2008; Friston et al., 1997; Hutchison et al., 2013).

The seed-based connectivity analysis (see Chapter 6) showed connectivity between semantic representation and semantic control regions. Exploring the dynamics of this interaction is critical for understanding how control mechanisms are engaged. The ventral ATL was functionally connected to inferior parietal and frontal regions critical for semantic control (see Chapter 5). These are core regions of the frontoparietal network (FPN), considered critical for cognitive control and decision making, regardless of the type of operations being performed (Spreng et al., 2010; Vincent et al., 2008). A similar role has been attributed to the multi-demand network (MDN) which also includes overlapping frontal and parietal regions (Duncan, 2001; 2010). How semantic control and domain general control relate is an open question (Jefferies, 2013; Noonan et al., 2013). Overlapping areas, such as the IFG may display differential connectivity to process-specific areas, such as posterior MTG (Jefferies, 2013; Noonan et al., 2013). Thus, networks could relate to domain general control, semantic control or control related to non-semantic processes. Some of these areas may work together with the ATL, as an interface between representation and control. Although both left and right ATLs have been shown to be critical, the evidence for semantic control regions has so far, focused on the left hemisphere (Jefferies, 2013; Lambon Ralph et al., 2001; Noonan et al., 2013; Pobric et al., 2010a; Whitney et al., 2012). The relative importance of left and right control regions is not clear. Although most investigations have focused on the left, this has not been explicitly studied and a meta-analysis of semantic control found similar regions on the right (Badre et al., 2005; Noonan et al., 2013; Thompson-Schill et al., 1997; Whitney et al., 2012). ICAs may identify separable left and right FPNs (e.g., Leech et al., 2011) but the roles of each have not been elucidated.

DMN regions showed significant connectivity with the ventral ATL (see Chapter 6). The DMN is a commonly identified network which may involve medial frontal (MF) cortex, posterior cingulate, precuneus, lateral ATL, AG and medial temporal lobe (Andrews-Hanna et al., 2010b; Buckner et al., 2008; Greicius et al., 2003; Greicius et al., 2009; Utevsky et al., 2014). These regions have been shown to deactivate during the performance of most but, importantly, not all tasks (Buckner et al., 2008; Fox et al., 2005; Spreng, 2012). Sufficiently difficult tasks involving episodic or semantic memory fail to show the expected deactivation in all DMN regions leading to the suggestion that some kind of process occurs frequently during rest which relies at least in part upon semantic or episodic processing (Binder et al., 1999; Buckner et al., 2005; Shapira-Lichter et al., 2013; Wirth et al., 2011). The hypothesised process may be one or a combination of retrospection, prospection, maintaining a stream of consciousness or narrative, theory of mind and spatial navigation (Andrews-Hanna et al., 2014; Binder et al., 1999; Buckner et al., 2008; Buckner & Carroll, 2007; Shapira-Lichter et al., 2013; Spreng, 2012; Wirth et al., 2011). Overlap was found between the two networks in the lateral and ventral ATL, ventral and dorsal MF cortex, AG and a small region of the precuneus.

Independent component analysis (ICA) allows an examination of the cohesive networks present in resting state and semantic task data by taking advantage of the spatial and temporal information. ICA is a data-driven multivariate technique able to distinguish between spatially overlapping but separable networks (Calhoun et al., 2001; Cichocki & Amari, 2003; Geranmayeh et al., 2014; McKeown & Sejnowski, 1998). ICA of resting state data have been successful in identifying resting state networks (e.g., Beckmann et al., 2005; Calhoun et al., 2008; Smith et al., 2009). The variance of the BOLD signal over time is separated into a set of independent components, each consisting of a spatial map and time-course of activity (Calhoun et al., 2001; Geranmayeh et al., 2014; McKeown & Sejnowski, 1998). Different components may reflect separate cognitive processes. Although an important area of research, resting state analyses intrinsically lack information on the cognitive processes involved. For this reason, in this study, ICA was performed on semantic task data alongside the resting state data. Additionally, resting state components were used as VOIs in the task data to investigate the pattern of functionally-related activity in these regions. Although this does not use the temporal information to perfectly separate overlapping regions in different components, the activity in the network as a whole may be used to assess the task relation of the component.

In summary, this novel use of ICA to assess the connectivity between semantic regions may provide unique insights into the many questions that remain unanswered regarding the connectivity between semantic regions, how semantic control is performed and the relation between semantics and the DMN. By using both resting state and task data, the underlying cognitive processes may be examined, as well as the dynamic changes based on the task. The use of the dual echo technique allows us to examine critical semantic regions and highlight where the ATL may be missing from existing assessments of the connectome.

3. Method

3.1 Participants

Details of the resting state data were previously given in Chapter 5. Resting state scans were collected for 78 participants (57 female, age range 18-42, average age 24.71 years, standard deviation 5.49 years). 7 participants were excluded on the basis of high levels of movement (see Chapter 5). Participants had normal or corrected to normal vision and were strongly right handed (minimum laterality quotient 50, average 85.85, standard deviation 14.91 on the Edinburgh Handedness Inventory; Oldfield, 1971). 24 of the resting state participants completed the dual gradient echo fMRI study described in Chapters 4 and 5 (15 female, age range 20-42, average age 25.63 years, standard deviation 56.36 years). Participants gave informed consent and the study was approved by the local ethics board.

3.2 Procedure

During the resting state scan participants were instructed to fixate on a cross and lie still whilst wearing noise-cancelling Mk II+ headphones (MR Confon, Magdeburg, Germany; Van Dijk et al., 2012). A Phillips Achieve 3.0T system with 32 channel SENSE coil with a sense factor of 2.5 was used. Prior to the resting state scan a structural reference was obtained with an in-plane resolution of .938 and slice thickness of 1.173. The TR was 2.8 with a flip angle of 85°, resolution matrix of 80x80, reconstructed voxel size of 3mm and slice thickness of 4mm. 130 volumes were collected over 6.25 minutes. In order to successfully image the ventral ATL and inferior frontal areas critical for semantics, dual gradient echo EPI was adopted. Linear summation was used to combine the dual echo images. A short echo (12ms) maintains signal within the areas of high magnetic susceptibility and a standard long echo (35ms) conserves high contrast sensitivity throughout the rest of the brain (Halai et al., 2014; Poser & Norris, 2007; 2009; Poser et al., 2006). Whole brain coverage was obtained with a field of view of 240x240mm, which was tilted up to 45° off the AC-PC line to reduce the effect of ghosting on the temporal pole. TSNR exceeded 40 throughout all subregions of the ATL (see Chapter 5).

The imaging parameters were identical to the resting state except for run length which lasted 10 minutes, including 211 volumes. Three runs included a semantic judgement, orthographic judgement or rest. Each judgement involved pressing a button to indicate which of two targets was related to a probe. For the semantic judgement this meant which word was more related in terms of meaning. For the orthographic judgement this meant the set of letters that contained the most letters from the probe set. High and low control orthographic judgements were included, varying in the distance between the foil and target, i.e., how many more correct letters where in the target set than the foil set. A fourth run involved a high and low semantic control manipulation and rest. This manipulation varied the semantic distance from the foil to the probe compared to the distance from the probe to the target. See Chapter 4 for further details.

3.3 Analysis

3.3.1 Preprocessing

Preprocessing of the resting state data was conducted as described in Chapter 5, except for the removal of the global signal. Small movements may be less of a problem for ICA than standard functional connectivity analyses as, firstly, noise components have separate sources and can be identified as separate components by the ICA and secondly, the correlation between two regions is not the primary measure but whether the variance in activation in different regions may be explained by a shared source (Calhoun et al., 2001; Geranmayeh et al., 2014; Griffanti et al., 2014; McKeown & Sejnowski, 1998). Thus, the removal of the global signal is less necessary and imposing spurious negative correlations could affect the results of the ICA (Anderson et al., 2011; Weissenbacher et al., 2009). These preprocessing steps greatly reduce the effect of motion and are in keeping with prior research (Anderson et al., 2011; Calhoun et al., 2001; Geranmayeh et al., 2014; Power et al., 2014; Satterthwaite et al., 2013; Starck et al., 2013; Utevsky et al., 2014; Yan et al., 2013). The task data were preprocessed in SPM using a standard fMRI pipeline as described in Chapters 4 and 5. As both univariate analyses and task ICA rely on assessing the fit of the data to a model, small movements have less substantial effects on the results. The task ICA was performed on the 3 runs including the main tasks (i.e. the semantic and letter matching tasks but not the run including the semantic control task alone) whereas the univariate VOI analyses used all 4 runs.

3.3.2 Resting State ICA

An independent component analysis (ICA) was performed on the resting state data using the Group ICA of fMRI Toolbox (GIFT; Calhoun et al., 2001). GIFT removes the mean at each time point before performing two stages of data reduction using principal component analysis (PCA; Calhoun et al., 2001). ICA is performed on the concatenated results of the PCA. ICA assumes independent sources have been linearly combined to create the signal and attempts to separate these. The resulting mixing matrix allows reconstruction of the individual participant's components. This means statistics can be performed on the individual participant's data. A one sample t-test was used to test the voxels in which the spatial map of each component was significant. The results were corrected at the voxel ($p<.001$) and cluster ($p<.05$) level. The number of components found by the ICA must be set by the user. Using 60 components was considered a good balance between the specificity of a high dimensionality analysis and the ease of interpretation of a low number of components (Geranmayeh et al., 2012). Components were classified as noise if most of the activation was outside of the grey matter, around the edge of the brain or in the brainstem, as these are likely to be artefacts relating to movement or blood flow.

Resting state networks relating to sensory and motor processes were identified by comparison to networks described previously (Allen et al., 2014; Beckmann et al., 2005; Calhoun et al., 2008; Jafri et al., 2008; Smith et al., 2009). In addition, a number of higher cognitive networks could be identified in the same way. The components that were not identified as relating to noise or low level sensory/motor processing were used as VOIs in a univariate analysis of the task data in order to assess their relevance to cognitive functions. VOIs were created from the cluster corrected spatial maps using the MarsBar toolbox (Brett et al., 2002). VOI analyses were then conducted on the 4 runs of task data comparing the following 5 contrasts, semantic>letter matching, rest>letter matching, semantic>rest, high semantic control >low semantic control, high non-semantic control>low non-semantic control.

3.3.3 Task ICA

A separate ICA was performed on the task data. As less extensive cleaning had been performed on the data (i.e. standard fMRI processing only whereas the RS also had white matter, CSF and global signal tissue signal removal, filtering, scrubbing high motion time points and censoring high motion participants) more noise related to motion, cardiac changes and breathing was likely to remain. Thus, a higher number of noise components were expected to be identifiable. For this reason the number of components was set slightly higher, at 65. The optimal number of components is not known. Higher dimensionality may lead to increased separation of overlapping components and better removal of noise (Geranmayeh et al., 2012; Geranmayeh et al., 2014; Griffanti et al., 2014). 65 was considered to be a good initial number in order to be interpretable yet split the data into the relevant components. 43 noise components were identified on the same basis as the resting state ICA. The remaining components were regressed against the task model which included the semantic judgements, letter matching judgements and rest. Where an ANOVA identified a significant ($p<.05$) task relation, four planned t-tests were performed to assess the component's activation pattern (semantics>letter matching, rest>letter matching, task>rest and letter matching >semantics). The semantic task was compared to the high level baseline in order to assess whether the same components were being identified during rest.

4. Results

4.1 Resting State ICA

26 of the 60 components were classified as noise. This is a similar number to prior resting state studies (Smith et al., 2009). Components relating to cerebellar, sensorimotor (3 components;

motor, sensorimotor and supplementary motor), auditory, medial visual (4 components) and lateral visual (2 components) networks were identified (see Supplementary Figure 1). Many of the remaining 23 components included activity within the ATL. As the underlying cognitive functions of these components cannot be identified using resting state data alone, the pattern of activity within these regions was investigated using VOI analyses of the independent task data. The results are shown in Table 12. The reported p values were Bonferroni-corrected for five contrasts. This highlighted four components that were significantly more active for semantic judgements than letter matching judgements (C8; t(23)= 5.775, p<.001, C17; t(23)= 5.372, p<.001, C21; t(23)=2.903 , p=.040, C51; t(23)=6.339 , p<.001). These components are shown in Figure 15. The peak areas of these components are listed in Table 13.

Table 12. VOI analyses on the independent task data.

ROI	Contrast	Effect Size	T value	Bonferroni corrected p value
Component 2	Semantic>Letter Matching	0.114	1.737	.478
	Rest>Letter Matching	0.675	4.348	<.05
	Semantic>Rest	-0.793	-4.121	<.05
	High Semantic Control>Low Semantic Control	0.017	1.057	1.000
	High Non-semantic Control>Low Non-semantic Control	-0.058	-1.108	1.000
Component 3	Semantic>Letter Matching	-1.182	-11.706	<.001
	Rest>Letter Matching	-1.033	-5.826	<.001
	Semantic>Rest	-0.204	-1.185	1.000
	High Semantic Control>Low Semantic Control	0.017	1.140	1.000
	High Non-semantic Control>Low Non-semantic Control	0.195	3.663	<.05
Component 8	Semantic>Letter Matching	0.481	5.775	<.001
	Rest>Letter Matching	0.310	1.930	.330
	Semantic>Rest	0.206	1.409	.860
	High Semantic Control>Low Semantic Control	0.056	2.737	.059
	High Non-semantic Control>Low Non-semantic Control	-0.098	-1.685	.527
Component 10	Semantic>Letter Matching	-0.147	-2.330	.145
	Rest>Letter Matching	-0.505	-4.341	<.05
	Semantic>Rest	0.522	3.421	<.05
	High Semantic Control>Low Semantic Control	0.037	2.239	.175
	High Non-semantic Control>Low	0.079	1.472	.773

	Non-semantic Control			
Component 11	Semantic>Letter Matching	0.080	1.395	.882
	Rest>Letter Matching	0.753	6.007	<.001
	Semantic>Rest	-0.911	-6.600	<.001
	High Semantic Control>Low Semantic Control	0.021	1.352	.948
	High Non-semantic Control>Low Non-semantic Control	-0.036	-0.806	1.000
Component 15	Semantic>Letter Matching	-0.614	-8.082	<.001
	Rest>Letter Matching	-0.926	-5.218	<.001
	Semantic>Rest	0.475	2.039	.265
	High Semantic Control>Low Semantic Control	0.021	1.246	1.000
	High Non-semantic Control>Low Non-semantic Control	0.074	1.344	.960
Component 17	Semantic>Letter Matching	0.471	5.372	<.001
	Rest>Letter Matching	0.737	5.353	<.001
	Semantic>Rest	-0.362	-2.599	.080
	High Semantic Control>Low Semantic Control	0.022	1.186	1.000
	High Non-semantic Control>Low Non-semantic Control	-0.090	-2.213	.185
Component 78	Semantic>Letter Matching	-1.101	-9.879	<.001
	Rest>Letter Matching	-0.024	-0.169	1.000
	Semantic>Rest	-1.473	-7.543	<.001
	High Semantic Control>Low Semantic Control	-0.003	-0.140	1.000
	High Non-semantic Control>Low Non-semantic Control	0.104	2.226	.180
Component 20	Semantic>Letter Matching	-0.190	-2.273	.163
	Rest>Letter Matching	0.003	0.015	1.000
	Semantic>Rest	-0.219	-1.322	.996
	High Semantic Control>Low Semantic Control	0.047	2.422	.118
	High Non-semantic Control>Low Non-semantic Control	0.027	0.513	1.000
Component 21	Semantic>Letter Matching	0.282	2.903	<.05
	Rest>Letter Matching	1.430	6.899	<.001
	Semantic>Rest	-1.590	-6.290	<.001
	High Semantic Control>Low Semantic Control	-0.013	-0.522	1.000
	High Non-semantic Control>Low Non-semantic Control	-0.224	-2.988	<.05
Component 23	Semantic>Letter Matching	-0.353	-4.598	<.001
	Rest>Letter Matching	0.523	4.060	<.05
	Semantic>Rest	-1.238	-6.431	<.001
	High Semantic Control>Low Semantic Control	-0.035	-2.263	.167

	High Non-semantic Control>Low Non-semantic Control	-0.011	-0.198	1.000
Component 25	Semantic>Letter Matching	-2.797	-14.297	<.001
	Rest>Letter Matching	-2.640	-11.324	<.001
	Semantic>Rest	-0.133	-1.174	1.000
	High Semantic Control>Low Semantic Control	0.058	2.483	.104
	High Non-semantic Control>Low Non-semantic Control	0.456	7.041	<.001
Component 28	Semantic>Letter Matching	-0.671	-7.974	<.001
	Rest>Letter Matching	-0.722	-5.095	<.001
	Semantic>Rest	0.061	0.467	1.000
	High Semantic Control>Low Semantic Control	0.059	3.419	<.05
	High Non-semantic Control>Low Non-semantic Control	0.061	1.189	1.000
Component 35	Semantic>Letter Matching	-0.026	-0.285	1.000
	Rest>Letter Matching	0.829	5.371	<.001
	Semantic>Rest	-1.193	-5.862	<.001
	High Semantic Control>Low Semantic Control	-0.037	-2.145	.214
	High Non-semantic Control>Low Non-semantic Control	-0.023	-0.441	1.000
Component 38	Semantic>Letter Matching	-0.531	-6.021	<.001
	Rest>Letter Matching	-0.018	-0.146	1.000
	Semantic>Rest	-0.746	-4.224	<.05
	High Semantic Control>Low Semantic Control	0.021	1.217	1.000
	High Non-semantic Control>Low Non-semantic Control	0.109	2.065	.252
Component 42	Semantic>Letter Matching	-1.534	-8.908	<.001
	Rest>Letter Matching	-0.319	-1.380	.904
	Semantic>Rest	-1.740	-5.873	<.001
	High Semantic Control>Low Semantic Control	-0.018	-0.709	1.000
	High Non-semantic Control>Low Non-semantic Control	0.097	1.397	.879
Component 43	Semantic>Letter Matching	0.187	1.954	.315
	Rest>Letter Matching	0.720	5.280	<.001
	Semantic>Rest	-0.704	-4.288	<.05
	High Semantic Control>Low Semantic Control	0.016	0.927	1.000
	High Non-semantic Control>Low Non-semantic Control	-0.011	-0.224	1.000
Component 44	Semantic>Letter Matching	-0.469	-4.760	<.001
	Rest>Letter Matching	-0.971	-5.513	<.001
	Semantic>Rest	0.694	4.369	<.05
	High Semantic Control>Low	0.088	5.437	<.001

	Semantic Control			
	High Non-semantic Control>Low Non-semantic Control	0.158	3.109	<.05
Component 47	Semantic>Letter Matching	-1.484	-9.178	<.001
	Rest>Letter Matching	-0.907	-4.659	<.001
	Semantic>Rest	-0.778	-4.955	<.001
	High Semantic Control>Low Semantic Control	-0.778	2.680	.067
	High Non-semantic Control>Low Non-semantic Control	0.199	3.687	<.05
Component 51	Semantic>Letter Matching	0.625	6.339	<.001
	Rest>Letter Matching	0.638	5.385	<.001
	Semantic>Rest	-0.080	-0.134	1.000
	High Semantic Control>Low Semantic Control	0.038	1.745	.471
	High Non-semantic Control>Low Non-semantic Control	-0.106	-1.473	.772
Component 54	Semantic>Letter Matching	-0.380	-4.156	<.05
	Rest>Letter Matching	-0.547	-3.616	<.05
	Semantic>Rest	0.273	1.401	.873
	High Semantic Control>Low Semantic Control	0.059	3.064	<.05
	High Non-semantic Control>Low Non-semantic Control	0.153	3.069	<.05
Component 55	Semantic>Letter Matching	-0.293	-2.862	<.05
	Rest>Letter Matching	0.220	1.431	.830
	Semantic>Rest	-0.711	-4.306	<.05
	High Semantic Control>Low Semantic Control	0.050	2.599	.080
	High Non-semantic Control>Low Non-semantic Control	0.060	0.987	1.000
Component 59	Semantic>Letter Matching	-0.179	-1.695	.518
	Rest>Letter Matching	0.671	3.977	<.05
	Semantic>Rest	-1.190	-5.226	<.001
	High Semantic Control>Low Semantic Control	-0.010	-0.566	1.000
	High Non-semantic Control>Low Non-semantic Control	-0.103	-2.313	.150

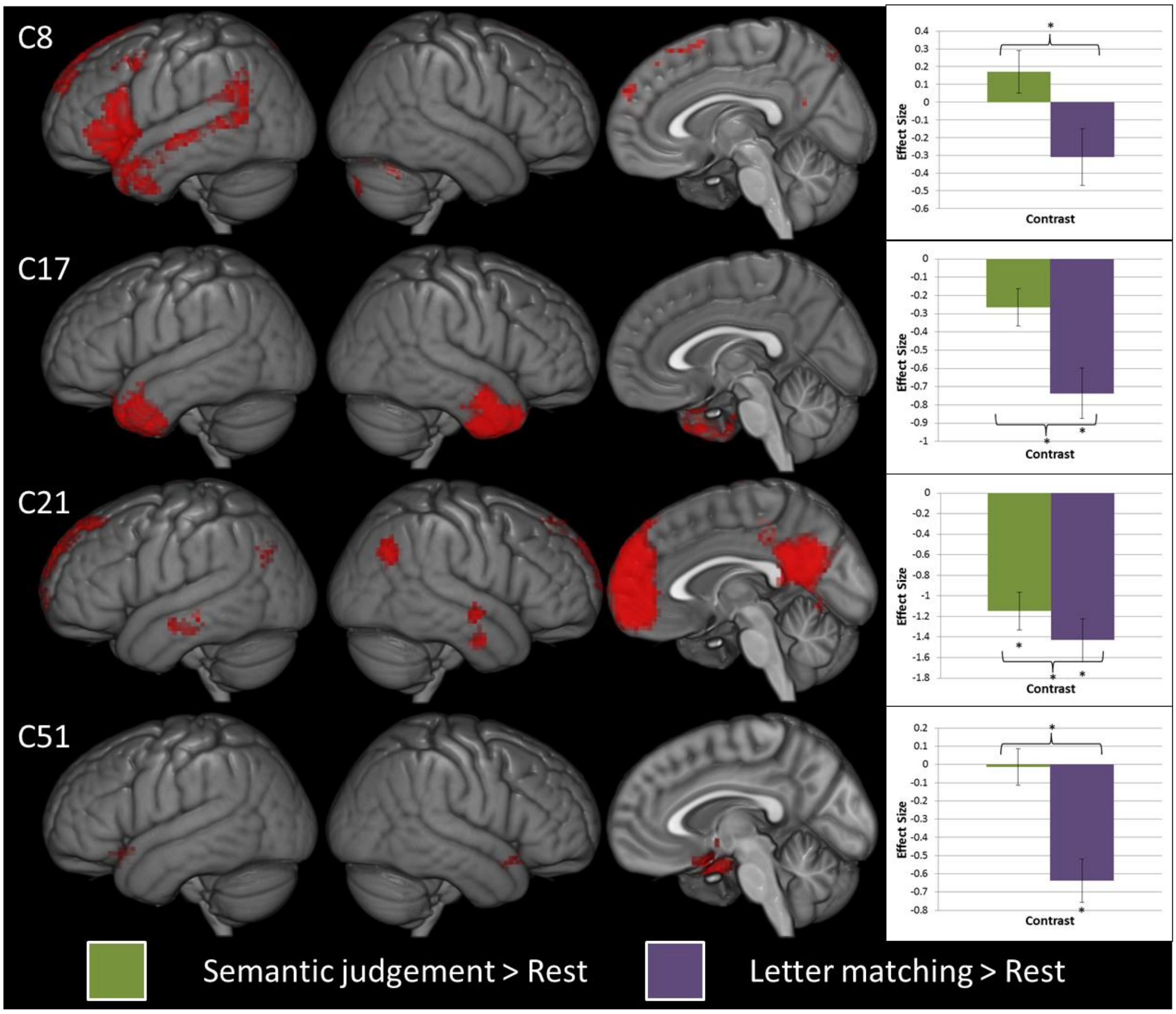

Figure 15. **Resting state components identified as semantic using VOI analyses of independent task data.** The results are thresholded at the voxel level at p<.001 and the cluster level at p<.05. The graphs show the activation in the task data for these regions for semantics (green) and letter matching (purple) over rest. Asterisks signify significant differences between the conditions and rest.

Table 13. Peak activation in the resting state components identified as semantic in the VOI analysis.

Component	Cluster extent (voxels)	Max z value	P value (FWE corrected)	Peak MNI Coordinate			Region(s)
				X	Y	Z	
8	1793	Inf	<.001	-48	27	-3	L IFG, TP, MTG, AG
	926	7.54	<.001	-6	12	63	L SMA ,mPFC, SFG
	105	5.84	<.001	-45	6	45	L precentral gyrus
	247	5.48	<.001	27	-78	-33	Cerebellum
	29	4.38	.012	9	-72	57	R precuneus
	29	4.13	.012	-3	-51	27	L PCC
17	972	6.97	<.001	39	12	-42	R TP, aFG, mid FG, PHG
	866	6.68	<.001	-24	-3	-39	L TP, aFG, hippocampus, PHG
	31	4.07	.005	27	-51	-51	Cerebellum
	31	3.99	.005	-27	-51	-57	Cerebellum
21	2106	Inf	<.001	3	57	-6	mPFC, SFG
	615	Inf	<.001	-3	-54	27	Precuneus, PCC
	86	5.83	<.001	-45	-66	27	L AG
	95	5.61	<.001	57	-66	30	R AG
	66	4.9	<.001	63	-6	-30	R aITG, aMTG
	43	4.66	.001	-51	0	21	L precentral gyrus
	39	4.19	.002	-66	-18	-18	L aITG, aMTG
	25	4	.029	24	-18	-12	R hippocampus
	32	3.98	.008	24	-18	60	R precentral gyrus
51	1092	Inf	<.001	-24	6	-21	aSTG, PHG, olfactory bulb

L = left R = right a = anterior m=medial IFG = inferior frontal gyrus TP = temporal pole MTG = middle temporal gyrus AG = angular gyrus SMA = supplementary motor area PFC = prefrontal cortex SFG = superior frontal gyrus PCC= posterior cingulate cortex FG = fusiform gyrus PHG = parahippocampal gyrus ITG = inferior temporal gyrus.

Component 8 includes key semantic regions such as ATL, IFG, mPFC and AG as well as some activation in DMN areas (precuneus, PCC). Component 17 also involves the ventral and polar ATL. In this component the ATL is connected to the medial temporal lobes. Component 21 is the anterior DMN, including mPFC, precuneus, PCC, AG, hippocampus and precentral gyrus. This also includes the lateral surface of anterior ITG and MTG. None of these VOIs showed significantly different activation during rest and semantics except the anterior DMN VOI which showed deactivation for both tasks but significantly less so for the semantic task (Semantic>Rest; C8; t(23)=1.41, p=.860, C17; t(23)=-2.60, p=.08, C21; t(23)=-6.29, p<.001, C51; t(23)=-.134, p=1, Rest>Letter Matching; C21; t(23)=6.899, p<.001).

The components relating to control are displayed in Figure 16. Three VOIs showed a significant effect of the semantic control manipulation (C28; t(23)=3.42, p=.012, C44; t(23)= 5.437, p<.001, C54; t(23)= 3.064, p=.028, see Figure 16). Component 28 is the left FPN and included frontal, posterior temporal and inferior parietal regions, heavily biased towards the left (see Table 14). The VOI based on the left FPN was significantly more activated for letter matching than semantic judgements (semantic>letter matching; t(23)= -7.974, p<.001). Despite this, an effect of the level of control was found for the semantic task only (high non-semantic control>low non-semantic control; t(23)=1.189, p=1). Component 8 also showed a trend towards a difference based on semantic control (t(23)=2.74, p=.059, see Figure 15). Components 44 and 54 also showed significant effects of non-semantic control (C44; t(23)= 3.109, p=.025, C54; t(23)= 3.07, p=.027). Component 44 mainly consisted of inferior frontal gyri and posterior middle temporal gyrus. Component 54 included supplementary motor area, anterior cingulate, frontal regions and anterior superior temporal gyrus. Two VOIs showed significant effects of non-semantic control only (high non-semantic control>low non-semantic control; C3; t(23)= 3.66, p=.006, C25; t(23)= 7.04, p<.001, high semantic control>low semantic control; C3; t(23)= 1.140, p=1, C25; t(23)= 2.483, p=.104). Component 3 is the dorsal attention network (DAN) and includes activation predominantly in supramarginal gyrus and posterior inferior temporal gyrus. Component 25 includes activity in supramarginal gyrus, inferior parietal lobe, posterior inferior temporal gyrus and frontal regions.

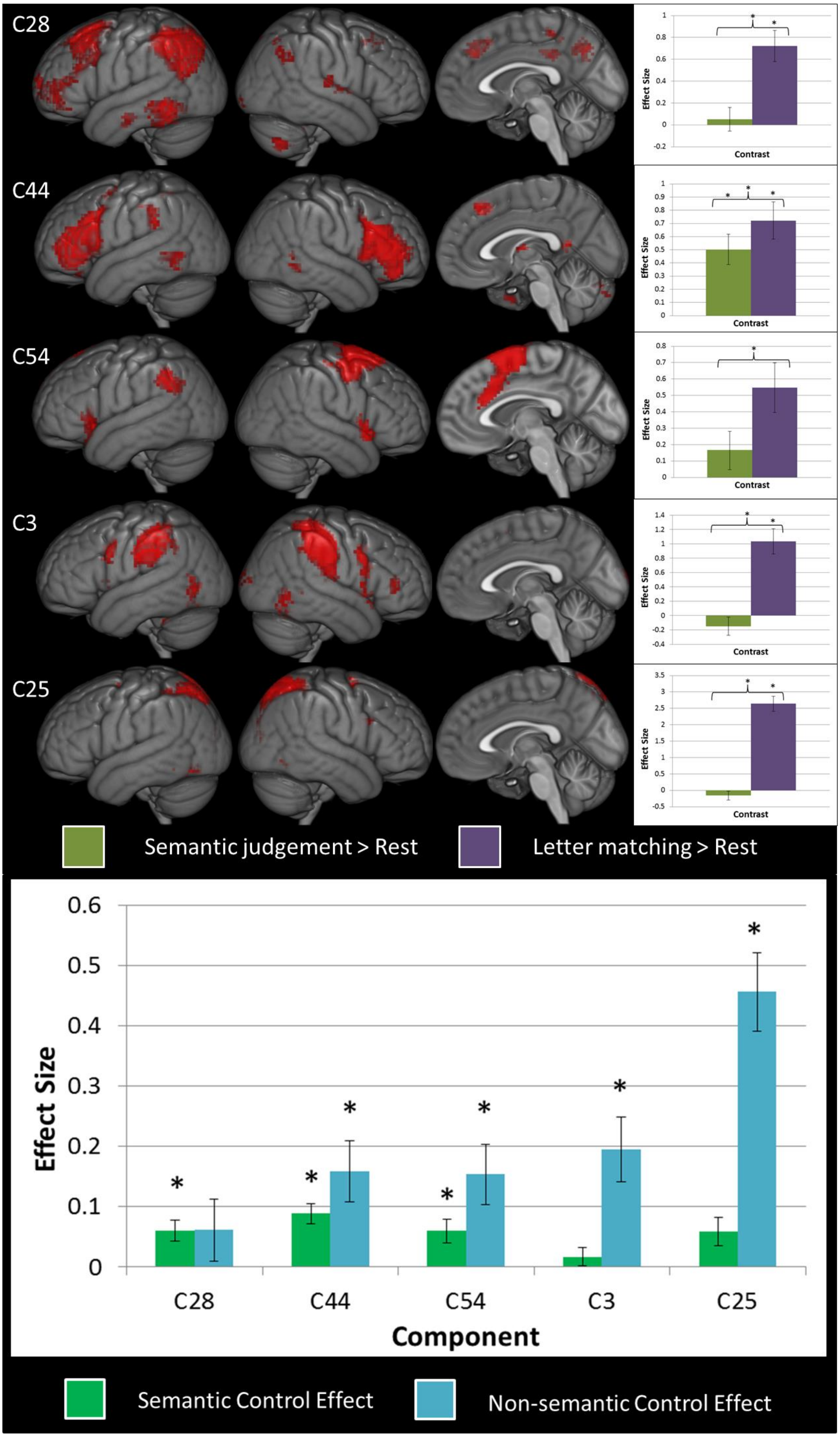
C28
C44
C54
C3
C25
Effect Size
Contrast
Semantic judgement > Rest
Letter matching > Rest
0.6
0.5
0.4
0.3
0.2
0.1
0
Effect Size
C28
C44
C54
C3
C25
Component
Semantic Control Effect
Non-semantic Control Effect

Figure 16. **Resting state components identified as control-related using VOI analyses of independent task data.** The components are thresholded at the voxel level at p<.001 and the cluster level at p<.05. The right-hand graphs show the activation in the task data for these regions for semantics (green) and letter matching (purple) over rest. Asterisks signify significant differences between the conditions and rest. The graph underneath shows the semantic (green) and non-semantic (blue) control effects. Asterisks signify significantly higher activity for the condition with higher control required.

Table 14. Peak activation in the resting state components identified as control-related in the VOI analysis.

Component	Cluster extent (voxels)	Max z value	P value (FWE corrected)	Peak MNI Coordinate			Region(s)
				X	Y	Z	
28	1719	Inf	<.001	-33	-66	45	L IPL, SPL, AG, mid occipital
	1812	Inf	<.001	-27	21	54	L IFG, MFG, SFG
	347	6.23	<.001	-54	-54	-18	L pITG
	201	5.69	<.001	-9	-39	36	L AG, pMTG, SPL, precuneus, mid occipital, MCC
	191	5.47	<.001	45	-60	-45	Cerebellum
	125	5.02	<.001	51	-54	36	R AG
	96	5.02	<.001	45	-18	9	R Heschl's gyrus, pSTG
	41	4.94	.01	36	9	-21	R aSTG
	26	4.68	.018	-63	-18	-18	L aMTG
	50	4.31	<.001	42	18	48	R MFG
	23	4.31	.033	24	-96	-9	R inferior occipital
	29	4.3	.01	-3	-39	51	L MCC
44	1593	Inf	<.001	-45	33	15	L IFG, MFG
	1388	7.8	<.001	51	24	27	R IFG, MFG
	113	6.06	<.001	0	30	42	Superior mPFC
	134	5.87	<.001	-57	-39	27	L SMG
	201	5.31	<.001	-48	-51	-15	L pITG
	76	5.19	<.001	-9	-81	-27	Cerebellum
	54	4.97	<.001	-3	-6	9	Thalamus
	145	4.92	<.001	-33	-63	45	L IPL
	26	4.69	.036	18	3	-39	R TP
	45	4.68	.002	36	-57	45	R AG
	34	4.53	.009	-3	-48	15	Precuneus
	34	4.26	.009	9	-75	-30	Cerebellum
	35	3.78	.008	63	-51	6	L pITG/MTG
54	2270	Inf	<.001	9	9	66	SMA, ACC, MCC, SFG, MFG, precentral gyrus
	345	6.97	<.001	-51	15	-6	L aSTG, IFG, insula

	163	5.56	<.001	48	18	-6	R aSTG, IFG, insula
	73	4.62	<.001	27	42	27	R MFG
	26	4.54	<.001	36	-57	-27	Cerebellum
	69	4.52	<.001	-24	42	24	L MFG
	30	4.33	<.001	-51	-24	-21	L MTG
3	936	Inf	<.001	-60	-27	39	L SMG, IPL
	1534	Inf	<.001	57	-27	42	R SMG, IPL, postcentral gyrus
	106	6.23	<.001	45	39	9	R IFG
	231	6	<.001	-54	6	36	L precentral gyrus
	228	5.72	<.001	57	-57	-6	R pITG
	239	5.68	<.001	57	9	36	R precentral gyrus
	100	4.99	<.001	-54	-69	-3	L pITG
	48	4.47	<.001	-18	-69	-57	Cerebellum
	46	4.46	.001	-24	3	51	L MFG
	30	4.42	.01	36	0	0	Putamen
	29	4.4	.012	-12	-66	45	L precuneus, SPL
	46	4.36	.001	18	-102	15	R cuneus
	32	4.26	.007	-42	-45	-36	Cerebellum
	63	4.19	<.001	24	3	57	R SFG
	24	4.14	.031	-42	33	18	L IFG
25	1584	Inf	<.001	24	-63	57	R mid occipital, superior occipital, SPL
	1129	Inf	<.001	-21	-72	51	L mid occipital, superior occipital, SPL
	183	7.73	<.001	27	-3	54	R MFG, SFG
	85	5.79	<.001	51	9	27	R IFG
	83	5.19	<.001	-42	-60	-9	L pITG
	64	4.93	<.001	-24	-3	51	L MFG, SFG
	50	4.75	<.001	51	-57	-12	R pITG
	23	4.31	<.001	-36	0	30	L IFG

L = left R = right a = anterior p=posterior IFG = inferior frontal gyrus TP = temporal pole MTG = middle temporal gyrus AG = angular gyrus SMA = supplementary motor area SFG = superior frontal gyrus MCC= middle cingulate cortex ACC= anterior cingulate cortex ITG = inferior temporal gyrus IPL = inferior parietal lobe SPL = superior parietal lobe MFG = middle frontal gyrus STG = superior temporal gyrus SMG = supramarginal gyrus.

4.2 Task ICA

The task ICA included 43 noise components. A greater number was expected than found in the resting state ICA due to differences in cleaning and the motion necessary for completion of the task (responding, shifting gaze). The task relevance of each of the remaining components was assessed by regressing the time-course against the task design matrix (see Table 15). Planned t-tests were used to elucidate the nature of this relevance. The cognitive 'signature' of all of the task-related components is displayed in Figure 17. Of the 11 components showing a task relation, four were more related to semantic processing than letter matching (Task C7; t(23)=3.294, p=.002, Task C31; t(23)=2.237, p=.029, Task C53; t(23)=2.625, p=.011, Task C54; t(32)=2.761, p=.007, see Figures 17 & 18). Task C7 mostly includes temporal lobe, inferior frontal gyrus and ventromedial prefrontal cortex (see Table 16). Task C31 included middle temporal, inferior frontal, angular, supramarginal and postcentral gyri. Task C53 is the left frontoparietal network. As in the resting state network, this included left inferior parietal, frontal and posterior temporal cortex. However, the task network included additional right activation in these areas and inferior temporal gyrus. Task C54 involved ATL, IFG, medial PFC and medial temporal lobes. All of these components were also significantly more active during rest than the letter matching task (Task C7; t(23)=2.714, p=.008, Task C31; t(23)=5.34, p<.001, Task C53; t(23)=2.707, p=.009, Task C54; t(32)=3.882, p=.003). A further two components were more active for rest than letter matching or semantic tasks (rest>letter matching; Task C32; t(23)=4.024, p<.001, Task C60; t(23)=3.154, p =.002, rest>semantic; Task C32; t(23)=2.688, p=.009, Task C60; t(23)=3.292, p=.002, see Figures 17 & 18). These are the anterior and posterior DMN networks and are very similar to the equivalent components from the resting state data (see Appendix 8). Task C32, the anterior DMN, includes mPFC, anterior and posterior cingulate cortex, precuneus, AG, superior parietal and anterior temporal cortices. Task C60, the posterior DMN, includes the precuneus and posterior cingulate cortex as well as some AG, superior parietal lobe and anterior middle temporal gyrus.

Table 15. Task relevance of the task ICA components

Component	F	p
2	3.643	.031*
6	2.840	.065
7	6.185	.003*
10	7.314	.001*
12	1.441	.244
22	2.378	.100
25	0.028	.973
28	5.476	.006*
30	0.123	.884
31	14.383	<.001*
32	8.401	.001*
33	2.147	.125
36	3.070	.053
37	1.034	.361
38	1.603	.209
44	0.643	.529
47	14.066	<.001*
48	115.419	<.001*
51	4.337	.017*
53	4.742	.012*
54	5.742	.005*
59	0.562	.572
60	6.934	.002*

Table 16. Peak regions in task ICA components.

Component	Cluster extent (voxels)	Max z value	P value (FWE corrected)	Peak MNI Coordinate			Region(s)
				X	Y	Z	
Task C7	3800	Inf	<.001	-27	-24	-12	FG, MTL, aSTG, L IFG
	308	7.3	<.001	6	45	-15	Ventromedial PFC
	228	6.72	<.001	-6	-36	-57	Cerebellum
	652	6.39	<.001	3	-3	6	Insula
	62	5.39	.012	-60	-12	6	L STG
	98	5.22	.001	-9	-51	3	Precuneus
	403	5.16	<.001	51	-66	27	R mid occipital, AG, IPL
	54	4.62	.023	-15	3	72	L SFG
	119	5.94	<.001	27	-84	-30	Cerebellum
	51	5.8	.029	63	-6	9	R STG
	127	5.63	<.001	54	39	0	R IFG
	47	5.14	.041	-15	-60	54	L Precuneus
	48	4.9	.037	6	6	69	R SMA
	86	4.89	.002	30	-96	12	R mid occipital
Task C10	5947	Inf	<.001	12	39	45	SMG, MCC, mPFC, R ACC, OFC
	2246	Inf	<.001	45	-57	39	R AG, SMG, IPL, pMTG
	2124	7.2	<.001	6	-69	36	R precuneus, PCC
	1529	6.52	<.001	-48	-3	-9	L STG, ATL, MTL
	430	6.2	<.001	-12	-33	69	Paracentral lobule
	146	6.14	<.001	9	-12	15	Thalamus
	446	5.99	<.001	-9	36	-6	L ventromedial PFC
	72	5.96	.006	-60	-6	-27	L aMTG
	198	5.81	<.001	-54	-60	33	L AG
	241	5.78	<.001	30	-54	-57	Cerebellum
	161	5.61	<.001	15	-9	-27	R MTL
	99	4.75	.001	33	-15	-6	R Putamen
	101	4.48	.001	63	-18	-15	R MTG
	55	4.18	.023	-30	-48	-57	Cerebellum
Task C28	4483	Inf	<.001	12	-78	3	Occipital, pFG
	189	5.97	<.001	-24	3	69	L SFG
	213	5.47	<.001	3	3	21	ACC
	435	5.43	<.001	-3	-42	33	L PCC
	204	5.35	<.001	27	6	66	R SFG
	93	4.69	.001	-27	42	42	L MFG
	49	4.45	.033	-60	-9	24	L postcentral gyrus
	60	4.4	.014	30	-21	42	R precentral gyrus
	141	4.39	<.001	-45	12	-30	L aSTG
Task C31	16585	Inf	<.001	36	-63	6	TP, MTG, pITG, pMTG, IFG, AG, SMG, postcentral

							gyrus
	426	7.64	<.001	-24	-81	-39	Cerebellum
	277	7.15	<.001	24	-75	-30	Cerebellum
	73	5.77	.005	9	-9	15	Thalamus
	357	5.69	<.001	3	48	-21	Ventromedial PFC
	224	5.24	<.001	9	-24	-39	Cerebellum
	69	4.91	.007	-51	-9	30	L postcentral gyrus
Task C32	5986	Inf	<.001	-6	42	-3	mPFC, ACC
	2641	Inf	<.001	-6	-57	21	Precuneus, PCC
	350	6.25	<.001	-24	-69	45	L SPL, mid occipital
	457	6.08	<.001	42	12	-45	R TP
	1080	5.91	<.001	27	-66	39	R SPL, AG, mid occipital, postcentral gyrus
	76	5.9	.004	-39	-12	-3	L insula, STG
	116	5.63	<.001	6	-57	-48	Cerebellum
	294	5.45	<.001	-54	-24	33	L IPL, postcentral gyrus
	222	5.44	<.001	36	36	-12	R inferior OFC
	95	4.67	.001	-48	-66	27	L AG
	183	4.65	<.001	57	-18	30	R SMG, postcentral gyrus
Task C47	2686	Inf	<.001	48	30	12	R IFG
	4570	Inf	<.001	-48	27	9	L IFG, MFG
	549	Inf	<.001	-6	-18	6	Thalamus
	3032	Inf	<.001	-51	-48	-18	Posterior temporal cortex, STG
	1291	7.65	<.001	9	-78	-24	Cerebellum, lingual gyrus
	578	6.13	<.001	33	-54	39	R AG, mid occipital
	216	6.06	<.001	-6	-54	6	Precuneus
	325	5.84	<.001	-21	-39	-48	Cerebellum
	105	5.19	.001	30	-6	-45	R aITG
	80	5.1	.003	21	-99	-3	R calcarine
	64	4.3	.01	-21	-39	69	L postcentral gyrus
	86	4.22	.002	30	-33	-24	R pFG
	51	4.17	.029	30	-33	66	R postcentral gyrus
Task C48	2057	Inf	<.001	24	-93	-12	R lingual, mid occipital, SPL, pITG
	3209	Inf	<.001	-27	-90	-12	L lingual, mid occipital, SPL, pITG
	463	6.46	<.001	57	-54	45	R IPL
	285	6.16	<.001	6	-27	42	MCC
	453	6.13	<.001	24	45	48	R SFG
	47	5.51	.044	-12	-12	18	Thalamus
	91	5.2	.002	-42	6	30	L IFG
	85	5.12	.003	-42	-18	66	L precentral gyrus
	56	5.03	.021	0	6	54	SMA
	126	5.02	<.001	-3	-51	-39	Cerebellum
	80	4.9	.004	0	-75	-24	Cerebellum

	62	4.72	.013	39	9	0	R insula
	100	4.54	.001	33	63	-12	R OFC
	54	4.33	.025	27	-60	-51	Cerebellum
	85	4.25	.003	-30	-6	-36	L aFG
	56	4.07	.021	-48	3	0	L insula
Task C51	6384	Inf	<.001	15	-60	-12	Occipital, precuneus, pITG, cerebellum
	67	6.32	.009	-21	-66	-57	Cerebellum
	188	5.99	<.001	36	-78	18	R mid occipital
	132	5.95	<.001	6	-42	-42	Cerebellum
	291	5.83	<.001	24	-3	12	R Putamen
	734	5.65	<.001	-18	54	18	SFG, MFG
	354	5.48	<.001	-24	-9	12	L Putamen
	204	5.47	<.001	-6	36	-15	Ventromedial PFC
	261	5.42	<.001	63	9	15	R IFG, SMG
	210	5.41	<.001	45	21	36	R IFG
	133	4.83	<.001	15	36	51	R SFG
	130	4.69	<.001	-60	-12	9	L aSTG
	65	4.66	.011	-39	12	-18	L aSTG, insula
	95	4.6	.001	24	6	-42	R aFG
	163	4.56	<.001	3	-9	51	MCC
	80	4.14	.004	-30	-60	57	L SPL, mid & superior occcipital
Task C53	12653	Inf	<.001	-36	18	51	mPFC, MFG
	5112	7.33	<.001	57	-60	33	R AG, IPL
	743	6.68	<.001	-42	45	-18	L IFG
	568	6.33	<.001	36	-42	63	R postcentral gyrus
	248	6.29	<.001	-15	-72	-51	Cerebellum
	351	6.23	<.001	-63	-36	-6	L MTG
	101	4.94	.001	9	36	-6	Ventromedial PFC
	92	4.63	.002	39	-54	-57	Cerebellum
Task C54	6234	Inf	<.001	48	9	-30	aFG, aITG, aMTG, aSTG, MTL, IFG
	275	6.74	<.001	-3	54	-12	Ventromedial PFC
	82	5.64	.003	-48	-27	42	L IPL
	204	5.62	<.001	0	-75	12	Calcarine
	406	5.53	<.001	24	-84	-42	Cerebellum, R pFG
	505	5.3	<.001	3	51	39	Dorsomedial PFC
	154	5.24	<.001	-15	0	69	L SFG
	69	5.19	.007	-24	-6	3	Putamen
	221	5.17	<.001	12	-69	39	R cuneus
	281	5.04	<.001	42	-51	51	R IPL
	109	4.94	<.001	6	-36	-57	Cerebellum
	66	4.73	.009	-3	-3	12	Thalamus
	132	4.61	<.001	30	9	51	R MFG
	94	4.28	.001	-12	-30	-3	L lingual

	104	3.94	.001	12	-9	48	R MCC
Task C60	4769	Inf	<.001	6	-63	36	Precuneus, PCC, MCC, AG
	185	5.37	<.001	27	-48	66	R SPL
	379	5.33	<.001	-51	-15	-15	L aMTG, postcentral gyrus
	84	5.27	.003	57	-27	21	R SMG
	241	5.25	<.001	6	-18	-6	Thalamus
	109	5.12	.001	12	48	-24	R OFC
	107	4.84	.001	21	-63	-6	R lingual
	116	4.8	<.001	-9	36	24	ACC
	71	4.79	.007	-12	39	-21	L ventromedial PFC
	52	4.75	.029	-3	-36	-21	Cerebellum
	122	4.71	<.001	-21	63	3	L SFG
	61	4.49	.015	51	-21	-9	R pMTG
	66	4.39	.01	33	27	3	R insula
	72	4.39	.006	-27	-45	63	L SPL
	61	4.37	.015	33	-66	-54	Cerebellum
	70	4.28	.007	-30	6	18	L insula

L = left R = right a = anterior p=posterior m=medial IFG = inferior frontal gyrus TP = temporal pole MTG = middle temporal gyrus AG = angular gyrus SMA = supplementary motor area SFG = superior frontal gyrus MCC= middle cingulate cortex ACC= anterior cingulate cortex PCC= posterior cingulate cortex ITG = inferior temporal gyrus IPL = inferior parietal lobe SPL = superior parietal lobe MFG = middle frontal gyrus STG = superior temporal gyrus SMG = supramarginal gyrus PFC = prefrontal cortex FG = fusiform gyrus MTL = medial temporal lobe ATL = anterior temporal lobe OFC = orbitofrontal cortex.

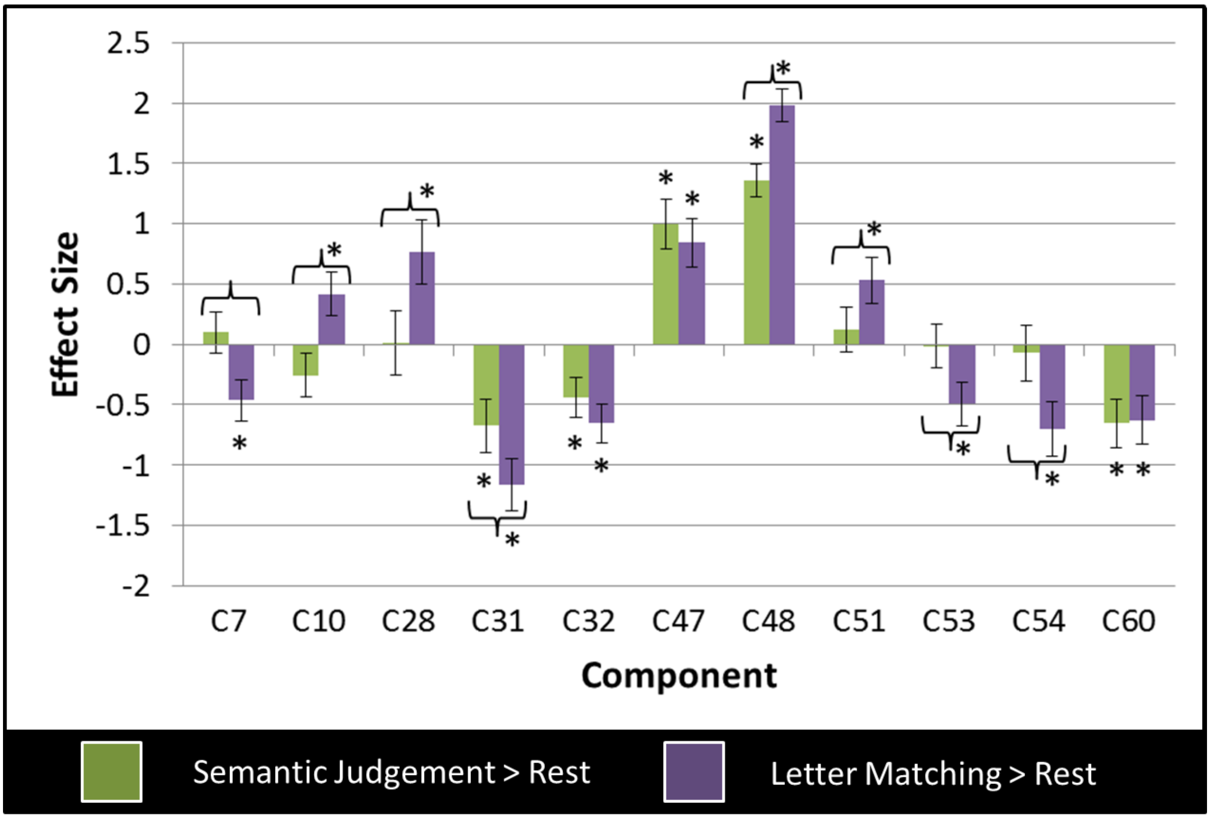

Figure 17. **Task-related ICA components relation to the task design.** Green bars show the activity in the semantic condition compared to rest whereas purple bars reflect the activity in the letter matching condition compared to rest. Asterisks show conditions significantly different from rest. Horizontal bars reflect significant differences between conditions.

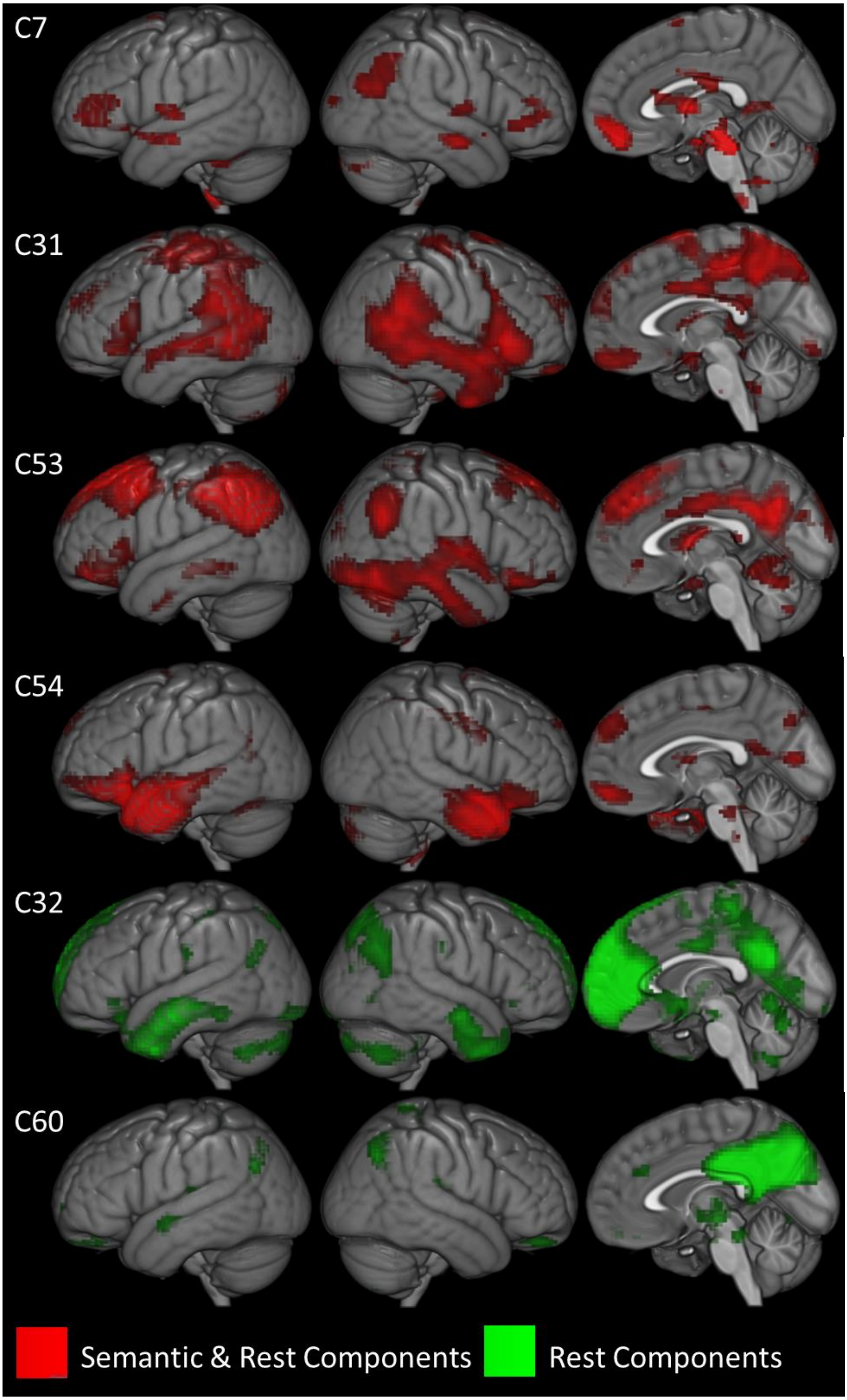
C7
C31
C53
C54
C32
C60
🟥 Semantic & Rest Components
🟩 Rest Components

Figure 18. **Task components identified as semantic and rest-related when the component time-course is regressed against the task time-course.** The components are thresholded at the voxel level at p<.001 and the cluster level at p<.05. The red components are related to both semantics and rest compared to the letter matching task whereas the green components are only related to rest significantly more than letter matching.

The opposite pattern (i.e. involvement in semantics and letter matching > rest) was found for two components (letter matching>rest; Task C47; t(23)=4.161, p<.001, Task C48; t(23)=14.858, p <.001, semantic>rest; Task C47; t(23)=4.929, p<.001, Task C48; t(23)=10.178, p<.001, see Figures 17 & 19). Component 48 was more strongly activated for the letter matching task whereas component 47 showed no significant difference between the 2 tasks (Task C47; t(23)=-.768, p=.445, Task C48; t(23)=4.681, p<.001). Task C47 included IFG as well as some occipital cortex and postcentral gyrus. Task C48 included posterior inferior temporal gyrus, superior frontal and parietal cortices and occipital cortex. A further 3 components were more active for the letter matching than semantic tasks but showed no evidence of involvement in the semantic task (Task C10; t(23)=3.788, p<.001, Task C28; t(23)=2.836, p=.006, Task C51; t(23)=2.156, p=.035, see Figures 17 & 19). Task C10 was the right FPN which primarily showed activity in right parietal and frontal regions but additionally included contralateral regions such as posterior cingulate cortex, precuneus and ATL. Task C28 included occipital regions, superior and middle frontal gyri and posterior fusiform gyrus. Task C51 predominantly included occipital and frontal cortex, precuneus, posterior inferior temporal gyrus and the cerebellum.

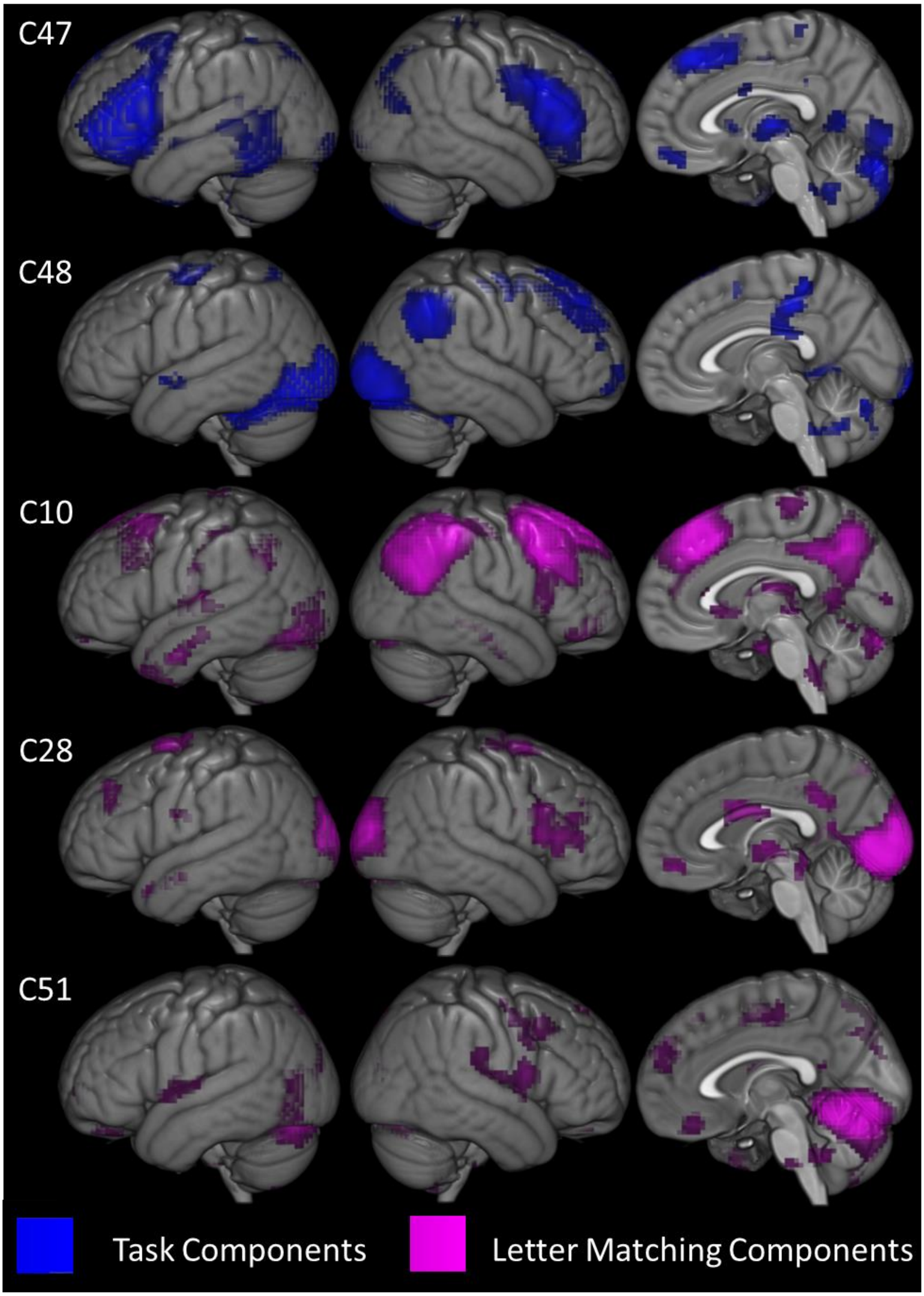

Figure 19. **Task components identified as task or letter matching-related when the component time-course is regressed against the task time-course.** The components are thresholded at the voxel level at p<.001 and the cluster level at p<.05. The blue components are related to both semantics and letter matching tasks compared to rest whereas the violet components are related to letter matching over rest only.

5. Discussion

Preliminary ICA analyses have been presented in this Chapter. Using dual echo imaging allowed us to explore ATL involvement in a large number of components (ATL was identified in 17 of the 23 non-noise, non-sensory/motor RS components). This suggests dynamic connectivity of the region, with the ATL working in conjunction with different areas in order to perform different cognitive processes. The components identified involved regions known to relate to semantic and language processing (Binder & Desai, 2011; Jefferies, 2013; Lambon Ralph, 2014; Price, 2010). A component in both the task and resting state ICAs showed connectivity of the ATL to core semantic regions including the IFG, pMTG, AG and mPFC (Task C54, C8). This formed a cohesive network shown to relate to semantic cognition in both the rest and task data although these two networks were not identical. The resting state component is left-sided whereas the task component is clearly bilateral. This could relate to the nature of processing during the resting state although left dominance is usually related to the use of verbal stimuli as used in this task (Price, 2012). Although including all of the same regions on the left, the task component was less extensive in posterior regions and included more anterior activation. This could reflect the involvement of posterior regions (pMTG, SMG) in a second semantic task component (Task C31) and much of the ATL in a second resting state component (C17). It is not clear why the analysis split the activity of these regions differently between the two states. This may reflect a true difference in how the regions are used together, for instance the relative importance of the posterior regions in control of the semantic processing. The posterior component involves key language areas including Broca's and Wernicke's areas and may relate to the language element of the task. Connectivity between Broca's and Wernicke's areas has been shown to increase when the language system is engaged (Hampson et al., 2002). Alternatively, the resting state TP component (C17) may not be truly semantic but may appear so in the VOI analysis due to the high overlap with semantic components in the ATL. In addition, there may be other reasons why ICA may split the activity of different regions in to separate components, such as differing levels of noise or lag in their connection to another area.

The semantic regions were also shown to work in conjunction with the medial temporal lobe during the task whilst the resting state analysis showed ATL-MTL connectivity as a separate component. This may be because the semantic task requires some episodic processing or encoding of the task experience for later recall. The interface of semantic and episodic cognition may be a separate process uncoupled from semantic processing when an explicit semantic task is not performed. This component was identified as semantic in the VOI analyses of the task data although this could be due to the ATL activity alone. The ICA components are more spatially selective than the seeded analyses and could be used to assess the critical roles of different subregions of the ATL. For instance, the lateral inferior and middle temporal gyrus is involved in the anterior DMN, whereas ventral and polar regions appear to connect to episodic and semantic regions. A number of prior functional connectivity analyses have highlighted similar networks in rest and language and semantic tasks although many fail to identify the ATL (Bzdok et al., 2013; Geranmayeh et al., 2014; La Joie et al., 2014; Pascual et al., 2013; Simmons & Martin, 2009; Xiang et al., 2010).

5.1 The Relationship between Semantic Cognition and Well-known Resting State Networks

As well as core semantic areas, the ATL was connected with the FPN and DMN in distinct components. The relationship of these components with semantic processing was assessed. Both resting state and task ICAs identified a left and right FPN. These were similar although the task ICA FPNs included more contralateral activity in the same regions and in temporal cortex. The inclusion of these contralateral regions may change at a higher dimension. These regions may form a separate component which could relate to noise. The use of 65 components appears to have left some noise in some of the cognitive components which may be removed at a higher dimensionality.

5.2 The Relationship between the FPN and Semantic Cognition

The VOI analysis of the resting state left FPN (C28) showed a significant effect of the semantic control manipulation and not the non-semantic control manipulation. However, the VOI showed significantly greater activation for the letter matching task with the semantic task deactivating non-significantly from rest. This suggests the left FPN may not be specifically involved in semantic control and may reflect a task general or general control effect. The left FPN identified in the task ICA (Task C53) related to semantic processing. However, this could be due to the contralateral temporal regions that are not usually part of the FPN. Further assessment of the task ICA at higher dimensions may be necessary to assess whether the components spatial map and cognitive signature change. It is possible that the left FPN is responsible for task general processes that may relate to control fitting with previous 'task positive' explanations of this component (Vincent et al., 2008). A number of other task general components showed activation in IFG, occipital cortex, postcentral gyrus, posterior inferior temporal gyrus, superior frontal gyrus and the parietal lobes. These regions relate to visual and motor processing as well as general control and attentional processes (Duncan, 2006; 2010; Price, 2010; Vincent et al., 2008).

The right FPN showed no task relation in the VOI analysis (C47) but related to letter matching over semantics in the task ICA (Task C10). It did not show a task general pattern instead only activating for the letter matching task. This suggests it may be involved in non-semantic cognition, perhaps related to assessing visual similarity. However, this component also includes contralateral regions that may affect these results including posterior ITG and DMN regions. A number of other networks show a greater relation to the letter matching task than the semantic task, involving occipital cortex, posterior inferior temporal and fusiform gyri, precuneus and frontal cortex. These regions may relate to controlled visual processing. Further assessment of the task data using ICA at different dimensions is needed to better assess the cognitive signature of the FPNs. Although the roles of the FPN components have not been fully elucidated, they appear to have different task relations and do not appear to relate specifically to semantic control. The component including the main semantic regions (C7) showed a trend towards an effect of the semantic control but not non-semantic control manipulation. This suggests there may be a cohesive network responsible for semantic representation and control with separate networks for general control and non-semantic control. The left hemisphere may be more important for general control. The component involving key semantic representation and control areas during the task (Task C54) was bilateral although this may not be true during the resting state. Although involved in FPN, IFG, posterior ITG and inferior parietal cortex were part of the cohesive semantic network alongside ATL, posterior temporal cortex and MF cortex. This suggests these regions are responsible for semantic and general control processes as part of different networks with differential connectivity. These regions have been previously identified as areas of convergence of multiple processing streams (Binder & Desai, 2011). Some regions may be more specific to semantic control (e.g. pMTG; Noonan et al., 2013).

5.3 The Relationship between the DMN and Semantic Cognition

In both the resting state and task data, the DMN split in to the anterior and posterior DMN, a distinction previously identified and thought to relate to different cognitive processes (Calhoun et al., 2008; Uddin et al., 2009). These two components were very similar between the two sets of data. The anterior DMN included mPFC, anterior cingulate cortex, AG and lateral MTG as well as some precuneus and posterior cingulate cortex. The posterior DMN overlapped with the anterior DMN in the PCC and included a large extent of the medial precuneus. The VOI analysis based on the resting state components identified the anterior but not posterior DMN as related to semantic processing. The semantic task showed relatively less deactivation than the letter matching task. However, this component overlaps with the main semantic network and includes much of the mPFC region activated in semantics as well as some ATL and AG. As in the VOI analysis, the anterior DMN identified using the task data showed deactivation for both tasks. However, no significant differences were found between the deactivation for semantics and letter matching. This provides no strong evidence for the importance of the anterior DMN in semantic processing. The posterior DMN showed no relation to semantic processing in either analysis. It has been suggested that the reduced deactivation of the DMN for semantic tasks reflects the importance of the DMN for semantics and the high level of difficult semantic processing in the resting state (Binder et al., 1999; Buckner et al., 2005; Shapira-Lichter et al., 2013; Wirth et al., 2011). The presence of semantic processing during the resting state has been supported in this study as all the semantic task components were equally involved in the rest condition and similar components were identified in the resting state ICA. However, until now these comparisons always looked at total activity in each DMN area and thus did not separate the overlapping activity involved in the DMN and semantic networks in the ATL, mPFC and AG (Binder et al., 1999; Buckner et al., 2005; Shapira-Lichter et al., 2013; Wirth et al., 2011). Looking at the time-course of these differing components allowed separation of the times when these areas are connected to different areas and thus, assessment of the cognitive profiles of the networks as opposed to the constituent regions. Although this suggests that the anterior DMN relates to a process not involved in the visually presented verbal semantic judgement used here, it is of course, possible that its role is related to some other aspect of semantic processing, for instance, construction of a narrative or the use of semantic concepts in social cognition, prospection or retrospection (Andrews-Hanna et al., 2014; Binder et al., 1999; Buckner et al., 2008; Buckner & Carroll, 2007; Shapira-Lichter et al., 2013; Spreng, 2012; Wirth et al., 2011). Although ICA cannot be used to distinguish whether the overlapping networks engage the same or different neurons, efficient use of a finite brain would suggest overlapping networks may be responsible for similar processes or different processes requiring access to similar information. Further analyses may be used to assess whether the anterior DMN component shows differential deactivation for the two tasks throughout.

6. Conclusion

The components identified in the resting state and task ICAs are similar despite some differences. Core networks likely responsible for semantic representation and control were identified in both, although these may show differences in their laterality. The use of task data for VOI analyses based on the resting state components and to assess the task components has allowed some measure of understanding of the task relevance of the networks identified unlike standard resting state ICAs. Although useful, the VOI analysis does not give conclusive evidence of a component's cognitive profile as it does not include temporal information. In order to assess the task relevance further the optimal number of components to be identified by the task ICA needs to be determined. Further analyses will be conducted at every 5 components from 70 to 100. The use of dual echo imaging has highlighted an important gap in our knowledge of the connectome. The ATL shows dynamic connectivity in rest and task states with a large number of regions and is involved in networks related to semantic representation and control and general control as well as the DMN. The DMN is not responsible for core multimodal semantic cognition, but may appear so when judged based on activity alone. The connectivity of the ATL is an important part of the connectome, missing until now, and may reflect the behaviour of a hub or rich club node with an important role in the dynamics of the brain network.

Chapter 8

General Discussion

Convergent methods have elucidated the broad set of regions involved in semantic cognition (Jefferies, 2013; Lambon Ralph, 2014; Patterson et al., 2007; Pobric et al., 2007). In order to explore the roles of these areas, the precise areas involved, and when and how these areas interact, requires the continued use and advancement of a range of methods. The overarching aim of this thesis was to elucidate the spatial and temporal dynamics of the semantic network. This included studies using online and offline TMS and dual-echo gradient-echo EPI fMRI. The fMRI collected include task and resting-state fMRI and was analysed with univariate analysis, psychophysiological interaction (PPI), seed-based functional connectivity analyses and independent component analysis. The use of these convergent methods has provided insight into the network of regions involved in semantic cognition. The specific research objectives outlined in the Introduction were: to use TMS to assess when the ATL was necessary in semantic cognition, allowing a better understanding of its role within the network; to clarify results from the neuroimaging literature regarding the critical subregions of the ATL and the organisation of the ATL hub and posterior temporal lobe; to investigate the organisation of the semantic network; and, to explore the connectivity of the ATL during a semantic task and rest. A summary of the findings of these studies follows. The remainder of the Discussion is organised around the principal research topics outlined in the Introduction, emergent issues and a consideration of potential limitations.

1. Summary of Findings

Chapter 3 sought to establish when the ATL is involved in semantic cognition. Single pulse TMS allows assessment of the time at which an area is necessary for the completion of a task. On each trial two pulses were delivered separated by 40ms at one of four experimental time points (100, 250, 400, 800ms) or at a baseline time point before the stimuli was presented (-40ms). This allowed assessment of the time at which stimulation would reduce performance in a semantic judgement task but not a baseline number judgement task. Stimulation from 400ms after stimulus onset led to reduced performance on the semantic judgement task. It was therefore concluded that the left ATL is necessary for semantic cognition after 400ms. This provided convergent evidence for the necessity of the ATL in semantic cognition with the prior offline

TMS studies and neuropsychological evidence. Although all of these methods have limitations (the neuropsychological damage is rarely circumscribed and could relate to white matter connectivity changes, TMS effects may relate to distal changes and are often small), the convergent evidence makes a strong case for the necessity of the ATL. In addition, spTMS has a temporal specificity which the offline TMS lacks, allowing assessment of *when* the ATL is necessary. Although it is not possible to assess every point across the entire time-course in one experiment, this initial study demonstrated that the ATL was necessary at 400 and 800ms. Future studies will be needed to probe other time points and other semantic tasks.

The 400ms time point coincides with semantic processing effects in EEG (the N400 ERP) and MEG (Halgren et al., 2002; Kutas & Federmeier, 2011; Lau et al., 2008; Marinkovic et al., 2003). Studies using MEG show a convergence of the semantic processing of stimuli in different modalities in the ATL at this time, starting around 230ms (Halgren et al., 2002; Maess et al., 2006; Marinkovic et al., 2003). Although there is no clear evidence for ATL involvement before 400ms in this study there may be a small (non-significant) reduction in performance with TMS after 250ms which could be harder to assess with spTMS than imaging techniques. Alternatively, the ATL may be activated at this point (perhaps interacting with earlier critical regions) but not necessary until a later time. This convergence from differing modalities has been interpreted as multimodal semantic processing in the ATL (Marinkovic et al., 2003). The N400 may be interpreted in this way with the amplitude reflecting the necessary processing level (higher when violations are expected as further semantic processing is required) and could involve processing within the ATL (Halgren et al., 1994; Kutas & Federmeier, 2000; 2011; Maess et al., 2006; McCarthy et al., 1995; Nobre et al., 1994; Nobre & McCarthy, 1995). Alternatively, the N400 may specifically relate to contextual processing and expectation violation which requires semantic access and is therefore coincident in time to semantic processing (Kutas & Federmeier, 2011; Kutas & Hillyard, 1980b; Lau et al., 2008). This study demonstrated for the first time that TMS could be delivered online to the ATL and when the ATL was necessary for semantic cognition.

Chapter 4 used offline TMS to assess the spatial organisation of the temporal cortex in relation to semantic and phonological processing. Unlike neuropsychological studies, TMS has a fairly high spatial resolution (~20mm) and unlike fMRI, TMS shows the areas necessary for a task (Pascual-Leone et al., 2000; Silvanto & Pascual-Leone, 2012; Walsh & Cowey, 2000). As there may be automatic processing of different language-related processes (e.g. automatic phonological processing in a semantic task), it is critical to distinguish between epiphenomenal activation and the necessity of a region to identify the core areas for these different processes. Non-words (i.e., phonological strings with no semantic information) were also used in the phonological judgements in an attempt to distinguish between these processes. Semantic, phonological and number judgements based on visual stimuli were performed before and after 15 minutes of 1 Hz offline TMS was delivered to one of four regions. These areas included vATL, aSTG, pSTG and a control site not expected to relate to language processing (occipital pole). Thus, the variation in the necessity for semantic and phonological processing along anterior-posterior and dorsal-ventral dimensions of the temporal lobe was investigated. The ventral ATL was hypothesised to be critical for semantic but not phonological processing. In contrast, the pSTG was hypothesised to be necessary for phonological but not semantic cognition. Thus, a double dissociation was expected. The role of the aSTG is not clear, as activation may be found during semantic and phonological processing appearing to play a key role in speech intelligibility (i.e. semantic and phonological processing; Scott et al., 2000; Vigneau et al., 2006). The aSTG activity during semantic processing has been found to differ in relation to the stimuli of presentation, with auditory and verbal stimuli (including spoken words, written words and environmental sounds) showing more activation than visual non-verbal stimuli (i.e. pictures; Visser & Lambon Ralph, 2011). Thus, no clear hypothesis was formed as to whether the aSTG would be involved in semantic or phonological processing or both. In addition it was not clear whether this may depend on the modality of presentation of the stimuli.

No significant effects of TMS on semantic or phonological processing were observed at the target sites compared to the control site. A number of potential reasons for this null result were discussed within the chapter, including a general speeding effect of the TMS (previously documented in Dräger et al., 2004; Pobric et al., 2007), complex changes in performance over time (e.g. practice effects differing between tasks) and the difficulty of and variability in the phonological task. The pSTG (and possibly aSTG) may only be necessary for processing auditory stimuli. In addition, the precise simulation sites may not have been optimal; all were based on group fMRI peaks which may vary between individuals (Hunton et al., 1996; Perkins et al., 2013; Sandrini et al., 2011). Stimulation of a ventral ATL site (as opposed to aMTG) was novel and has methodological implications for future TMS studies relating to the ATL. Although no TMS effects were identified in order to support the necessity of the vATL subregion in semantic processing, a null result in TMS should not be interpreted as evidence against the necessity of a region (de Graaf & Sack, 2011) and convergent evidence suggests this region is critical (Binney et al., 2010; Galton et al., 2001; Patterson et al., 2007; Visser et al., 2010a). The stimulation target may have been too deep for TMS to reach (especially as the bone may be thick adjacent to this region) and the lateral ITG region stimulated may not have been critical. In summary, although this study provides no support for the necessity of vATL, aSTG or pSTG in semantic or phonological processing, little can be concluded from a non-significant result in a TMS study. Prior evidence suggests these regions perform important roles in the processing of language and meaning (see Chapter 4). The role of the aSTG was not elucidated. However, the novel use of TMS to assess subregions of the ATL and the unique ventral ATL target region may inform future research using similar methodologies.

Chapter 5 used dual echo fMRI to assess the areas involved in semantic cognition and how this differs based on relationship type and the necessary level of semantic control. The neural correlates of conceptual similarity (e.g., *DOG - WOLF*) and association (e.g., *DOG - BONE*) were compared. A manipulation of semantic control was included to assess whether any differences could be explained by a variation in the required level of semantic control. No differences were found between the regions involved in conceptual similarity and association after accounting for reaction time. Both association and conceptual similarity relied on a network of regions including ATL, posterior temporal cortex, IFG, mPFC and parietal cortex. Without including reaction time in the analysis, the harder conceptual similarity trials showed greater activation of frontal regions (particularly IFG), which appears to relate to reaction time and semantic control demands, and greater deactivation of parietal and temporal regions. None of these differences remained after reaction time was factored in. ROI analyses of ATL and TPC regions (previously hypothesised to be ‘hubs’ for conceptual similarity and association respectively) identified no significant differences between the associative and conceptual similarity conditions. The TPC ROI deactivated for both condition. Although the ATL ROI taken from the Schwartz (2011) peak showed non-significant deactivation for both semantic conditions, a ventral ATL ROI showed significant activation for both.

The manipulation of semantic control highlighted IFG, inferior parietal cortex and visual regions as well as some temporal cortex. This overlapped with the regions engaged more in the harder conceptual similarity conditions. It did not highlight significant areas of activiation in the TPC region. Thus, conceptual similarity and association were concluded to rely on the same set of regions involved in multimodal semantic processing (ATL, pMTG, AG, mPFC and IFG). This corresponds well with the role of the ATL as a multimodal hub for semantics including both associations and conceptual similarity, in keeping with the general impairment identified in semantic dementia (Jefferies, 2013; Lambon Ralph, 2014; Patterson et al., 2007). Although no role in semantic cognition could be attributed to the TPC region used as an ROI, nearby pMTG and inferior parietal regions were shown to be involved in semantic processing. Semantic control significantly related to IFG and inferior parietal cortex but not pMTG. However, this region was shown to relate to general semantic processing and this result may depend upon the particular semantic control manipulation used here (varying the distance between the probe and the foil) as the precise role of these regions is not well understood (Jefferies, 2013; Whitney et al., 2012). These regions are consistent with the damage found in aphasic patients with a semantic control problem, whose performance in explicit tests is not easily explained by a difference in semantic relationship type (i.e., association vs. conceptual similarity; Jefferies & Lambon Ralph, 2006).

The representational and control functions of regions within the semantic network can be separable on the basis of neuropsychological deficits, TMS results and imaging data (including the results reported in this thesis). Despite this, the type of relationship (associative vs. conceptual similarity) does not seem to affect which regions are involved in the semantic judgements. This is consistent with the neuropsychological data on explicit tests of conceptual similarity and association (Bozeat et al., 2000; Hoffman et al., 2013; Jefferies & Lambon Ralph, 2006). Schwartz et al. (2011) identified distinct regions related to errors based on association (TPC) and conceptual similarity (ATL). This result may relate to methodological issues or may be due to the use of errors as an outcome measure. Associative errors may not imply an impairment in associative semantic knowledge but instead a deficit at a different level of speech production (Dell & Reich, 1981). Previous investigations of relationship type have variable results and may be confounded by reaction time (de Zubicaray et al., 2013; Kalénine et al., 2009; Kotz et al., 2002; Sachs et al., 2008a; Sachs et al., 2008b; Sass et al., 2009). Differences based on reaction time identified within this study and prior experiments can easily be explained by the role of some regions in semantic control and the deactivation of others during many diverse tasks (i.e. DMN regions).

In Chapter 5 it was speculated that the same process occurs whether an association or a feature is identified: both are linked to a concept. Their co-occurrence in the environment with aspects of this concept may lead to co-activation in the semantic representation. This activation may function as an (often implicit) prediction of a further occurrence. As the ATL appears to be responsible for linking these pieces of information (coded in 'spoke' regions), it may be used to assess either relationship type. Although it cannot be concluded with certainty that the same process is occurring, identifying the involvement of the same network of regions has constrained the potential interpretations of how these two relationships may be processed within the brain. Previous theories have suggested that these relationships are stored in separable regions of the brain. This includes the dual hub model which specified an associative hub in the TPC and a conceptual similarity-based hub in the ATL (Kalénine et al., 2012b; Mirman & Graziano, 2012a; 2012b; Schwartz et al., 2011). Others have suggested the two relationship types must rely on distinct neural regions without clearly specifying regions. Assertions of this type seem to be at least partially based on an assumption that these seemingly distinct computations must rely on separate areas (Estes et al., 2011). The dual hub model of semantic processing (Kalénine et al., 2012b; Mirman & Graziano, 2012a; 2012b; Schwartz et al., 2011) is not supported by the finding that the same regions are responsible for explicit judgements of the two relationship types. The equivalent activation in the peak regions taken from Schwartz et al (2011) gives further evidence that these regions are not hubs for the different relationship types. Future theories of the development and processing of these relationship types should be compatible with the same network of regions involved in explicit computations of both.

The roles of the regions involved in semantic cognition may be elucidated further by assessing their connectivity. The functional connectivity of the ATL was assessed in Chapter 6 using seed-based analyses of task and resting state data. This allowed assessment of the semantic network, how this network varies by state and the differential connectivity of ATL subregions. The relationship between the semantic network and the DMN was also considered. Connectivity was demonstrated between the vATL and core semantic regions including IFG, mPFC, AG and pMTG. Connectivity was also demonstrated with MTL structures related to episodic processing. A PPI analysis was performed on the task data described in Chapter 5.The same core semantic regions were connected to the vATL regardless of task state. Additional occipital and frontal regions thought to relate to difficult semantic and visual processing were identified in the PPI analysis. The connectivity of different subregions of the ATL during rest was investigated. The aSTG connected to a network of regions implicated in language processing including superior and posterior temporal cortex, frontal cortex, pre- and postcentral gyri and SMA. The aMTG connectivity more closely matched that of the vATL, suggesting a role in multimodal semantic convergence. The aMTG could be a principal region for the initial convergence between the auditory and visual pathways. In summary, a network of regions implicated in multimodal semantic processing was identified during a semantic task and at rest and different regions of the

ATL displayed different connectivity patterns and may perform different functions. The vATL was connected to a number of regions previously shown to be involved in different networks including the DMN. The DMN was identified in this resting state dataset in a fashion consistent with prior studies. This clearly reflected a distinct network from the semantic network. The DMN included mPFC, precuneus, mid and posterior cingulate cortex, AG, cerebellum, MTL and ventral and lateral aspects of the anterior temporal lobe. Overlap between the two networks was present in the vATL, MTL and mPFC. Potential implications for semantic processing were discussed.

The presence of semantic regions in the DMN including the vATL region critical for multimodal semantic cognition, suggests a relationship between the DMN and semantic processing. The idea that semantic processing may occur during rest and be reflected within the DMN has been posited previously although the main evidence in support of this hypothesis is the lack of a change in activity in many semantic areas between rest and performance of a semantic task (Binder et al., 1999; Shapira-Lichter et al., 2013; Wirth et al., 2011). This could be due to different processing in overlapping regions. The implications of these two overlapping networks are unclear as seed based functional connectivity analyses merely show which areas are connected to the seed region and not the broader network interactions between these areas, nor whether the region forms different connections at different times which may relate to different cognitive processes.

Chapter 7 included preliminary analyses designed to address the questions identified in Chapter 6. Independent component analysis exploits both spatial and temporal information, allowing an assessment of the dynamic connections of the ATL. This permitted an investigation of how different regions connect to the ATL to form cohesive networks. The overlap between the semantic network and DMN could be investigated further as well as the interplay between areas responsible for semantic representation, semantic control and general control. Overlap with the frontoparietal network argued to relate to general control was also investigated (Vincent et al., 2008). Two different methods were used to assess the task relevance of these networks. Firstly, resting state components were identified using ICA and then VOIs based on these regions were applied to the task data. This meant that resting state networks (of importance within the literature) could be identified but the task relevance of these examined. However, as the VOIs did not include temporal information, the results depended on the regions identified as part of the component but not necessarily the full information contained within the component, i.e., activity in those regions throughout the run not just when they were interacting. An additional method employed was to conduct ICA on the task data itself allowing regression of the components time courses against the design matrix. This allowed an assessment of whether the component was involved in any of the conditions more than any others. In this way the relevance of the component (and not just the constituent regions) to the semantic task could be determined. However, this assessment was preliminary and requires further assessment of the optimal number of components to be identified in order to best fit the design matrix.

The dynamic connectivity of the ATL was also explored. The ATL was involved in a number of resting state components. A network including the ATL, IFG, mPFC, pMTG and AG appeared to relate to semantic cognition – i.e., areas responsible for semantic representation and control. VOI analysis showed a trend towards an effect of the semantic control manipulation. Differing components appeared to relate to general control, possibly including the left FPN. This suggested that semantic representation and control form a cohesive network, separable (temporally and based on further connectivity outside these regions) but overlapping with general control networks. In addition, it appeared that the right FPN was responsible for different aspects of control (e.g., controlled processing of visual information) related to the letter matching, but not semantic task. This suggests left and right FPN may be responsible for different aspects of control, perhaps differing on the basis of their importance to language. A number of other resting state components appeared to be related to semantic cognition including the temporal poles and a separate component involving the ATL and MTL. This aids understanding of the involvement of the MTL, suggesting that it may not be part of the core semantic network but that there may be an interface between semantic and episodic memory whereby the ATL and MTL work together when necessary.

A similar semantic network (including ATL, IFG, mPFC, pMTG and AG) was found for the task data, supporting the conclusion that this component is involved in semantic cognition. However, the task network was clearly bilateral whereas the resting state network was left sided. The two analyses appear to show some further differences in how these semantic regions are split into separate components. In the task ICA, the posterior regions appear to form a second network, whereas during rest less anterior activity is present, perhaps because of the separate TP component. It is not clear why these changes are present or whether they reflect true differences in the processing during rest and task states.

The ATL was also present within a component identified as the anterior DMN in both the task and resting state datasets. Both datasets included separable components previously referred to as anterior and posterior DMN (Calhoun et al., 2008; Uddin et al., 2009). These are likely to reflect different cognitive functions although the precise differences have not been established (Calhoun et al., 2008; Uddin et al., 2009). There was good correspondence between the posterior and anterior DMNs identified in the two sets of data. The VOI based on the resting state anterior DMN component showed greater activation for semantic processing. However, the task-based anterior DMN showed no relation to the semantic condition, instead showing preferential activation during rest alone and no difference between the semantic and letter matching conditions. This discrepancy is likely due to the overlap within semantic regions (ATL, mPFC, AG) and the lack of temporal information in the VOI analysis, i.e. whilst the aDMN regions are functionally connected they are not required for the semantic condition yet overall they may be involved. All previous suggestions of the involvement of the DMN in semantic cognition have relied upon differences in activation, i.e., deactivation from rest in DMN areas for non-semantic but not semantic tasks (Binder et al., 1999; Wirth et al., 2011). By including the temporal information we can see that the anterior DMN is not involved in core semantic processing and that these results may be due to the activity of overlapping regions alone.

Although not involved in semantic judgements of visually presented single words, the highly overlapping nature of the semantic and anterior DMN components (particularly within the multimodal semantic representation area in the ATL) suggests that the anterior DMN could relate to semantics in some way. This could involve semantic access for a separate process or may involve unconstrained or combinatorial semantic processing, such as that involved in maintaining a narrative (Binder et al., 1999; Hickok, 2009; Wilson et al., 2008). Alternatively, unrelated processes could use different neural populations in overlapping regions. Although these results are preliminary, an understanding of the dynamics of regions may be gained using ICA. Combining ICA with methods aimed at assessing the relevance of components to cognitive function can help address questions relating to the function and connectivity of areas responsible for semantic representation, general control and semantic control, as well as assessing the relevance of known networks, such as the DMN and FPN. Studying the relation of these networks to a diverse set of tasks may promote understanding of the associated processes. Further investigation may help assess whether some of these regions, particularly the ATL, are 'rich club' hubs with particular properties in terms of their interaction with other (e.g. membership of multiple networks, effective transmission between and within networks and vulnerability to damage; Crossley et al., 2014; Sporns et al., 2007; van den Heuvel & Sporns, 2011).

2. Semantic Memory and the Anterior Temporal Lobe

All of the research conducted as part of this thesis has contributed to our understanding of the role of the ATL in semantic cognition and the hub-and-spoke model of semantic memory. Previous work used neuropsychological assessments of semantically-impaired patients, offline TMS and fMRI to highlight the role of the ATL. Here convergent evidence of the central role of the ATL was found from online TMS, dual-echo fMRI and functional connectivity analyses. This has allowed greater precision with regards to when the ATL is important (shown to be a time critical for core semantic cognition), what semantic relationships are processed within the ATL (both conceptual similarity and associations) and which regions the ATL is connected to (a cohesive network for semantic representation and control, present during task and rest, including core semantic regions; the ATL, IFG, mPFC, inferior parietal cortex). All of these results are compatible with and add further support and detail to the hub-and-spoke model of semantic representation and its relationship with the semantic control network. The research presented in this thesis suggests the following additional information about the system for semantic cognition. The ATL hub is functionally connected to several regions responsible for semantic control. This network is preferentially active during explicit semantic tasks compared to non-semantic tasks. The ATL is critical for semantic cognition around 400ms after stimulus onset. Around this time information connected to a concept is activated which may include features shared across conceptually similar concepts as well as concepts associated in time and space. These two relationship types involve the same set of regions and may be explained within the hub-and-spoke framework. It had not previously been established that this network was responsible for the connections between co-occurring concepts. This may be acquired via the creation of connections between co-activated concepts or features within the multimodal semantic system. A similar method of acquisition had been suggested to occur within visual cortex, yet it was not clear how this explained knowledge of associations regardless of modality of input including those gained from verbal input (Albright, 2012). The involvement of multimodal semantic regions including the ATL hub in this process may explain the multimodal nature of associations. An alternate account, the dual-hub model asserts that different semantic hubs are responsible for these two types of information, yet no evidence was found to support this account. As the same set of regions were involved in both computations, this encouraged further development of the hub-and-spoke model in order to specify how associations are judged. These theories can be tested further and modelled in future investigations of semantic cognition.

A number of alternative theories for the role of the ATL have been posited. It has been hypothesised that the ATL is only involved in the comprehension of unique, concrete concepts (Tranel, 2009), in understanding social concepts (often argued to be right lateralised; Olson et al., 2007; Ross & Olson, 2010; Zahn et al., 2009; Zahn et al., 2007) or in combinatorial processing, where single words are combined in sentences, phrases or paragraphs in order to ascertain information not contained in any of the words in isolation (e.g., Hickok & Poeppel, 2007). These alternative theories are not supported by the findings of this thesis. The stimuli used in the offline TMS and fMRI studies (Chapters 3 & 5) involved single words, generally lacking affect or reference to social interaction. These words were not referring to unique objects. With these stimuli the necessity of the left ATL and the bilateral ATL activation were demonstrated. This is hard to explain based on theories of combinatorial, social or emotional processing or processing of unique identities in the ATL (Hickok & Poeppel, 2004; Tranel, 2009; Zahn et al., 2007). The right ATL could be preferentially involved in social or emotional processing despite the strong bilateral activation identified here (see Chapter 5). Alternatively, different regions within the ATL may be responsible for these different processes. The temporal pole regions forming a separate component in the ICA analysis of the resting state data could reflect differential processing involving social and emotional cognition (Olson et al., 2007). The DMN, including a lateral ATL region, may be involved in combinatorial processing at the level of narratives (Spreng et al., 2010). Although interpreted in relation to the theory of the ATL as a multimodal hub, theories that posit the role of the ATL in comprehension of verbal or visual stimuli may also be able to explain the results discussed within this thesis. The studies here all used written words (except the resting state analysis). However, prior experiments have shown the multimodal nature of the ventral ATL (Bozeat et al., 2000; Coccia et al., 2004; Patterson et al., 2006; Patterson et al., 2007; Visser et al., 2012; Visser & Lambon Ralph, 2011). In addition, the differential connectivity of the vATL and aSTG suggest that, whilst the aSTG may show connections related to language processing specifically, the vATL shows connections to regions implicated in semantic processing regardless of modality (see Chapter 6). Thus, an understanding of this thesis within the background literature is best placed within the hub-and-spoke model or similar accounts of a graded multimodal hub.

3. The Role of ATL Subregions

In Chapter 4, offline TMS was used in an attempt to ascertain the roles of different subregions of the temporal lobe and in particular separate their contribution toward semantic and phonological processing. This study proved inconclusive. However, in Chapter 6, the seed-based functional connectivity of the ventral ATL and anterior STG subregions was shown to differ. This supports the idea of a different role for the two subregions and suggests the aSTG is particularly involved in processing language and auditory information which may include auditory semantics and phonology. This corresponds well with the evidence that the aSTG is activated for auditory stimuli and visually presented words (Scott et al., 2000; Visser & Lambon Ralph, 2011). This may be due to the reliance of written language on the same network as higher level auditory processing including speech (Spitsyna et al., 2006). The vATL region was connected to multiple semantically-related regions supporting its role in multimodal semantic cognition (Binney et al., 2010; Noppeney & Price, 2002; Visser et al., 2012; Visser & Lambon Ralph, 2011). These networks were similar to those identified by Pascual *et al.* (2013) by seeding from the temporal pole. The connectivity appeared graded along the ventral-dorsal axis although aMTG connectivity more closely resembled the vATL pattern. This is highly consistent with the idea of two gradients of convergence within the temporal lobe (laterally towards the MTG and from posterior to anterior regions; Binney et al., 2012; Visser et al., 2012). Perhaps the aMTG is responsible for the integration of auditory and visual semantics whilst the vATL is increasingly multimodal. The similarity between the vATL and aMTG with a greater difference in connectivity in the aSTG is consistent with the gross anatomy of the temporal lobe identified in cytoarchitectural studies. Brodmann (2006) denoted a major boundary between BA22 (STG) and the rest of the temporal lobe but described the variation between BA21, 20, 38 and 27 as being much more graded in nature. Although the precise role of the aSTG network cannot be demonstrated using the resting state data alone and connectivity cannot be used to demonstrate the necessity of the area, the use of multiple methods to investigate the ATL has helped give an idea of the potential roles of subregions and the connectivity underlying these functions. Further investigation of the ICA components may help identify the ATL subregions important for interactions with different regions.

4. A Semantic Cognition Network

The fMRI study described in Chapter 5 identified a number of regions involved in semantic processing, particularly the ATL, posterior temporal cortex, inferior parietal cortex, IFG and mPFC. These regions are all commonly found in neuroimaging studies of semantic memory

(Binder et al., 2009; Jefferies, 2013; Noonan et al., 2013; Price, 2012). Most of these areas have been linked to semantic problems in neuropsychological studies including semantic dementia (ATL) and semantic aphasia (IFG, pMTG, inferior parietal cortex; Acosta-Cabronero et al., 2011; Galton et al., 2001; Jefferies & Lambon Ralph, 2006; Patterson et al., 2007). The functional connectivity analyses fit well with this result, showing connectivity between all these regions during task and rest states. The ICAs showed a cohesive network of these regions related to semantic processing. This network was separate from components involving areas connected to the ATL but not implicated in semantic cognition (see Chapter 7). The fMRI showed activity of the IFG, inferior parietal lobes and pITG (as well as visual regions) related to semantic control. This is consistent with prior assessments of semantic control (Jefferies & Lambon Ralph, 2006; Noonan et al., 2013; Thompson-Schill et al., 1997; Whitney et al., 2012). The pMTG was not identified in the semantic control manipulation. This may be due to the power or the specific type of manipulation as pMTG was found to relate to semantic cognition overall.

The semantic network identified in the resting state ICA showed a trend towards for the semantic control manipulation. These coherent analyses suggest that the core semantic regions are functionally connected, with the network performing both semantic representation and control. The IFG, parietal cortex and some posterior temporal cortex may be involved in general control and, as such, are also found in additional networks without semantic representation regions (in particular the FPN). The IFG was involved in both semantic (vATL) and language-related (aSTG) seeded networks. This fits the structural connectivity of the IFG, with anterior and posterior temporal lobe regions associated with semantics and phonology (Binney et al., 2012). ICA allows the assessment of separate overlapping networks and provides support for the involvement of these regions in semantic and general control. This suggests that the same control regions connect to diverse additional areas in order to perform different kinds of control, although the precise computations being performed remain to be elucidated. Differences in the roles of each region related to semantic control have proved difficult to identify, perhaps due to the strong connectivity between these regions (Jefferies, 2013; Whitney et al., 2012). The exact parietal region identified may vary between studies, often depending on the baseline used (Humphreys & Lambon Ralph, in press; Noonan et al., 2013). This may be due to distinct processes occurring in overlapping regions that may be better separated using multivariate analyses (Binder & Desai, 2011; Humphreys & Lambon Ralph, in press; Seghier et al., 2010). Performing an ICA with the semantic control manipulation data may further elucidate the role of different components.

The semantic network identified here fits well with prior assessments of the functional connectivity of the regions involved. Connectivity has been shown between a number of these areas, usually lacking ATL involvement due to poor signal (Abrams et al., 2013; Assmus et al., 2007; Bzdok et al., 2013; Husain et al., 2006; Snijders et al., 2010; Stamatakis et al., 2005; Tyler & Marslen-Wilson, 2008; Vitali et al., 2005; Yang et al., 2011). Xiang (2010) demonstrated differential connectivity of the pars orbitalis, pars opercularis and pars triangularis, with the overall network including posterior temporal cortex and parietal cortex as well as sensorimotor regions relevant to language. These regions are similar to those found in the seed-based RS analyses of the vATL and aSTG, yet no ATL involvement was identified, likely due to low signal in the ATL. Wu (2009) performed an ICA of a semantic task identifying a network similar to the semantic network identified here but left-sided and lacking ATL involvement. Simmons et al. (2010) assessed the regions connected to the ATL and found small regions of many of the areas identified here, yet appear to suffer from a lack of, or distortion in the signal despite some attempts to improve this. A number of studies have looked at the differential connectivity between social and tool concepts, yet have not elucidated the overall network involved in conceptual processing (Bianchi et al., 2013; Simmons & Martin, 2012; Simmons et al., 2010). Thus, the results within this thesis fit well with previous explorations of the functional connectivity of semantic and language regions yet expand this knowledge by clarifying the connections of the ATL and the regions as a whole, as well as forming a link between the resting state investigations and task relevance.

5. Connectivity within the Semantic Network

The functional connectivity results accord well with prior assessments of structural connectivity. The connectivity between temporal and frontal cortices may rely on the uncinate fasciculus (Binney et al., 2012; Catani et al., 2002; Grossman et al., 2004; Han et al., 2013; Harvey et al., 2013; Lu et al., 2002; Von Der Heide et al., 2013). The critical parietal regions do not appear to be directly connected to the ATL but are likely to connect via posterior temporal regions (Binney et al., 2012). The connection between posterior and ventral anterior temporal cortex appears direct (Matsumoto et al., 2004). This connection may rely upon the inferior and middle longitudinal fasciculi with connections from posterior temporal cortex to parietal cortex depending upon the arcuate fasciculus (Acosta-Cabronero et al., 2011; Binney et al., 2012; Borroni et al., 2007; Catani & Ffytche, 2005; Catani et al., 2003; Catani & Mesulam, 2008).

6. The Semantic Network and Conceptual Relationship Type

Semantic relationship type (i.e., conceptual vs associative similarity) was not found to be an organising factor within the semantic network. This is in disagreement with some of the prior literature. Previous fMRI experiments found mixed results, all of which may be explained by the difficulty-related effects found in this study which, if left uncontrolled in the experiment, would cloud the results found for each type of semantic relationship (Kalénine et al., 2009; Kotz et al., 2002; Sachs et al., 2008a; Sachs et al., 2008b; Sass et al., 2009). In addition, these studies have methodological issues relating to the strict separation of the two dimensions of association and conceptual similarity and the presentation of both of these items at once in order for participants to choose between them (Kalénine et al., 2009; Kotz et al., 2002; Sachs et al., 2008a; Sachs et al., 2008b; Sass et al., 2009). As noted above, no evidence was found supporting the dual hub model. Schwartz (2011) found a clear distinction in the lesion distributions associated with categorical vs. thematic relationships. In the explicit semantic judgement task used in this thesis, the activation in each region was found to be the same for the two types of semantic relationship. This may be due to a range of reasons, the simplest being that associative errors may not be due to the loss of the representation of associations (see Chapter 5). The thesis data are, however, consistent with the results of explicit neuropsychological tests (Bozeat et al., 2000; Butler et al., 2009; Hoffman et al., 2013; Jefferies & Lambon Ralph, 2006).

7. Semantic Cognition during the Resting State

Previous resting state analyses lacked signal in the ATL. This signal loss and distortion in prior resting state studies is likely to have led to the failure to find ATL involvement in critical networks. Assessments of global connectivity may have failed to identify the importance of the ATL, here shown to be involved in multiple networks. The ATL may be a hub belonging to and connecting with a number of networks. Some regions within the brain are highly connected and involved in multiple networks, more research is needed to assess whether the ATL may be one of these (Achard et al., 2006; Buckner et al., 2009; Crossley et al., 2014).

A large amount of difficult semantic processing has been argued to occur during rest (Binder et al., 2009). This hypothesis has arisen due to anecdotal evidence and the importance of a high level baseline in semantic contrasts (i.e. semantic regions are apparent when compared to a high level baseline such as letter matching or number judgement tasks but not when contrasted with rest; Binney et al., 2010; Visser et al., 2010a; Visser et al., 2010b). The ICAs presented here provide support towards this hypothesis as all the components identified as being more active in the semantic condition than the control condition were also more active in rest than the control condition. This shows these components are related to semantic processing but occur in both explicit semantic tasks and free thought.

The importance of semantic processing in rest and the involvement of some semantic regions in the DMN, led researchers to consider whether the DMN may be responsible for semantic processing (Binder et al., 2009; Greicius & Menon, 2004). Less deactivation of DMN regions during semantic processing was taken as further evidence of this (Binder et al., 1999; Buckner et al., 2005; Shapira-Lichter et al., 2013; Wirth et al., 2011). The seed-based resting state analysis showed a large overlap between the semantic network and the DMN. The VOI analysis of the task-based resting state ICA component showed a relationship with semantic processing. This all supported the hypothesis that the DMN is responsible for semantic processing. However, the task ICA showed DMN involvement in rest alone. This is likely to be due to the inclusion of temporal information, whereby the activity in these regions is only relevant when they are functionally connected. Thus, some of the overlapping regions are semantic but the DMN itself does not appear to be involved in semantic processing of the sort present in a semantic judgement of single visually presented words. The DMN may relate to semantic and episodic processing that is not critical for this kind of task but is necessary for free thought or in longer information processing time frames. Alternatively, it may not relate to semantic memory but merely involve overlapping regions. By using task and rest data together in this thesis, a greater understanding of these networks was gained as well as the ability to assess the effect of state. The methodology to compare states and assess the task relevance of the resting state needs further development but has added to our understanding of the semantic network without the results being divorced from the resting state literature.

8. Laterality

A further organising factor is laterality. Although not directly assessed in this thesis, many of the studies may be informative in terms of the relative importance of the two hemispheres in semantic cognition. Activity during semantic judgements was found to be strikingly bilateral (see Chapter 5). This was true for regions responsible for semantic representation and control. The same was true for the seed-based functional connectivity analyses during the semantic task and the resting state. The aSTG-seeded network of language-related regions was bilateral despite the well-documented role of the left hemisphere for language in right handed adults (Berker et al., 1986; Hickok & Poeppel, 2007; Price, 2012; Vigneau et al., 2006). However, different aspects of language processing have been argued to be more or less left lateralised (Friederici, 2011; Hickok, 2009). These results all suggest that the semantic network is bilateral, including representation and control regions. Whilst the bilateral nature of the ATLs contribution to semantic cognition has been demonstrated in patients and TMS studies, the importance of right hemisphere control regions has not been clearly established (Jefferies & Lambon Ralph, 2006; Lambon Ralph et al., 2009; Patterson et al., 2007; Pobric et al., 2010a). The connectivity analyses presented support the idea that bilateral control regions are involved although do not provide direct proof of their necessity.

The ICA results are less clear in terms of the importance of the two hemispheres. Within the resting state ICA, the core network identified as semantic was left-sided including both representation and control regions. A further semantic component included bilateral temporal poles. The left and right FPNs were separate and only the left appeared to relate to control in the semantic task (although neither appeared to be specific for semantic control). This could be due to the ICA splitting the data based on a factor unrelated to the cognitive process, such as noise or time lag. Alternatively, left and right regions may separate due to small differences in the processes involved, with the VOI analysis only having highlighted the involvement of the left. Alternatively, semantic processing within the resting state may not rely on the right hemisphere. However, the seed-based analysis opposes this. As there may be differential processes in overlapping regions, each of which may be bilateral or unilateral, it may be difficult to grasp the importance of each hemisphere without a full understanding of the functional relevance of each component. This may require further investigation. The task ICA identified two bilateral components, one involving ATL and IFG, the other posterior regions as well as right ATL. The reason for this split is unclear. The task ICA is preliminary and needs further investigation. If this split is consistent at different dimensions this may suggest a difference between rest and semantic tasks although the significance of this would need to be investigated further.

The task ICA also identified left and right FPNs. However, both components showed activity in semantic areas on the contralateral side. This is likely to be due to the noise apparent in the data at this dimensionality and has not been identified previously. This makes it harder to assess the laterality of the control regions involved in semantic processing. However, the left FPN appears related to semantic cognition whilst the right does not. This fits with the resting state ICA results. An ICA was previously conducted on a semantic task involving judging whether two words both relate to an (unspecified) object (e.g. the correct response to ‘honey’ ‘stings’ would be ‘yes’ as they are both related to the concept of a bee). Separable left and right FPNs were identified but unlike here both appeared relevant for semantic cognition (Assaf et al., 2010). However, this task is likely to have different control demands as it involves searching for a third concept uniting the two probe concepts. As such this task may involve control-related processes that may not be utilised in a standard semantic judgement task. Overall, it appears that there is a bilateral semantic network involving core regions for representation and control. In addition there is a left-sided network which may be responsible for general or language-related control including semantic processing. There is however, some interesting variation in the results which requires further assessment.

9. Strengths and Weaknesses of the Methods Adopted

A variety of methods were used within this thesis. These studies have shown that online TMS, resting state and task based connectivity analyses can all contribute to the investigation of semantic cognition and the ATL. However, all of these methods have associated positive and negative attributes. For instance, online TMS has high temporal specificity and was able to confirm the necessity of the ATL for semantic cognition (Silvanto & Pascual-Leone, 2012; Walsh & Cowey, 2000). However, only one small region of the brain could be assessed at a few pre-selected time points. The resulting effects are subtle and depend on the development of a sensitive task (de Graaf & Sack, 2011; Sandrini et al., 2011; Walsh & Cowey, 2000). Offline TMS had the advantage of affecting a longer time period which might give rise to stronger behavioural effects and does not require *a priori* knowledge about the likely time-course of processing. The high spatial specificity of TMS means it was well suited to an investigation of the subregions of the temporal lobe (Pascual-Leone et al., 2000). There may also be non-specific effects of TMS, such as increased alertness or distraction (particularly during online TMS), that must be controlled carefully (here a number of baselines were employed including a control time and task; Dräger et al., 2004; Jahanshahi & Rothwell, 2000; Pascual-Leone et al., 2000; Walsh & Cowey, 2000). Methodological issues with the offline TMS study are likely to have led to the null result which cannot be interpreted further, highlighting the importance of the task and stimulation procedure.

Despite poor temporal specificity, fMRI analyses have quite high spatial specificity and allow spatial localisation throughout the brain (Pascual-Leone et al., 2000; Sandrini et al., 2011; Sliwinska et al., 2012; Walsh & Cowey, 2000). This allowed an investigation of whether any areas differed based on semantic relationship type. A number of issues with studying the ATL with fMRI were noted and lessened. The signal loss and distortion in inferior frontal and temporal regions was reduced by using dual echo imaging (see Chapters 5 & 6). The issues relating to baseline were addressed by using a high level baseline in addition to rest which allows a better picture of how regions varied between semantic and non-semantic tasks, and rest (Visser et al., 2010b). Although signal is still unequal throughout the brain when using dual echo imaging, the results suggest the signal is high enough to assess differences and identify networks. This increased signal allowed more complex analyses of the fMRI data, including seed-based functional connectivity analyses and ICAs. fMRI activity does not necessarily correspond to necessity and as such, different regions could still be argued to show differential necessity for relationship type. However, the neuropsychological results based on explicit tests do not support this hypothesis (see Chapter 5).

Use of the fMRI data to assess functional connectivity allowed a move from traditional assessments of isolated regions towards a network approach. The use of ICA allowed dynamic connectivity to be estimated and highlighted potential problems with the use of activity in one region as a measure of its function (i.e., different processes may involve overlapping regions and therefore average activity in an area may be misleading as to its cognitive function, as in the case of the anterior DMN; see Chapter 7). Changes based on state could be investigated by comparing the results of connectivity analyses on task and resting state data. Unfortunately, the seed-based approaches used a different method in order to factor out the confounding effect of co-activation based on condition in the task data (simple correlation vs. PPI) and thus are not perfectly comparable. However, both do show the functional connectivity of the ATL. Similarly, there may be differences in power between the task and resting state ICAs due to variation in the number of participants and runs as well as differences in cleaning and the expected level of motion prior to cleaning. However, the results are similar and the differences based on these factors are likely to be minimal due to the high power from the large amount of data in both analyses and good signal (the imaging parameters were identical). As well as assessing state changes, the task ICA was used to support the importance of the networks identified in semantic cognition. Resting state analyses have an intrinsic problem in understanding the cognitive relevance of each identifed network. This was addressed here through the use of VOI analyses of the RS components in the task data and by performing ICA on the task data. Although, the VOI analysis does not include temporal information and as such does not deal with overlapping networks perfectly it allows some assessment of the cognitive signature of a network. By using this in conjunction with the task ICA it is possible to glean some idea of the task relevance of networks and keep this connected with the resting state literature. An alternative way to assess the semantic task dynamics would be to use EEG or MEG. However, spatial resolution would be compromised. Further understanding of task dynamics could be gained in this way.

The findings within this thesis are argued to relate to multimodal semantic cognition yet the studies have only involved visually presented verbal semantic judgements. This is because these studies are understood in relation to the background literature. However, there may be differences based on modality or task requirements. In order to further support the network identified as responsible for multimodal semantic cognition, it is necessary to establish its importance in tasks involving different modalities and control requirements. The same is true for the timing of ATL necessity. However, only subtle differences would be expected in these results, based on the literature as a whole.

Although every method employed in this thesis has strengths as well as limitations, the precise issues vary between studies. The use of convergent methods to assess the semantic network has allowed flexible and targeted investigations of different elements of the spatial and temporal dynamics of the semantic network and the evidence from each contributes towards a coherent understanding of semantic cognition.

10. Future Directions

A number of opportunities for further development of this research exist. The task ICA is preliminary and needs investigating at a number of different dimensions in order to establish how many components need to be selected to give the highest number of task-related components and to exclude more noise. This will allow further assessment of related questions, including the importance of different subregions of the ATL in different components. The semantic control manipulation task may be included in the task ICA in order to assess further the importance of the components in semantic control. Although the anterior DMN does not appear to be semantic based on the task ICA, the cognitive processes it is associated with remain unclear. It is hypothesised to relate to episodic processing based on the same arguments as it was related to semantic memory (Andrews-Hanna et al., 2014; Buckner et al., 2005; Greicius & Menon, 2004). Alternatively, more complex semantic processes may be related such as narrative comprehension. An ICA involving relevant task data may help elucidate its role.

Further work may be done to assess the precise role of different regions within the semantic network, particularly those related to semantic control. The mPFC was shown to be activated during semantic processing and functionally connected to semantic regions. Activity in mPFC is consistently found in investigations of semantic cognition, yet its role has not been elaborated (Binder et al., 2009; Jefferies, 2013; Noonan et al., 2013). In addition the structural connectivity of many semantic regions, including the mPFC has not been well established. As the ATL has been missing from many assessments of the connectome due to poor signal, investigations of the overall network (i.e. local and global network based statistics such as degree centrality, modularity, participation coefficient, etc.) can be assessed using dual echo data to see if there are critical differences in overall structure and to examine the role of the ATL within the network (Buckner et al., 2009; Ferrarini et al., 2009; Rubinov & Sporns, 2010; Zuo et al., 2012). The finding of ATL involvement in multiple networks may suggest it is highly connected and may form a hub as part of the 'rich-club' network (Achard et al., 2006; Power et al., 2013; van den Heuvel & Sporns, 2011). Alternatively, this diverse connectivity may depend on distinct subregions of the ATL. These questions are of central importance to the study of connectomics and should be addressed further.

11. Conclusions

TMS and fMRI were used to assess the semantic network and ATL. Online TMS and dual echo imaging were applied in a novel fashion. This use of convergent methods allowed insight in to the spatial and temporal dynamics of the ATL. The ATL is necessary for semantic cognition 400ms after stimulus onset. The vATL acts as a multimodal semantic hub interacting with IFG, mPFC, pMTG and ventral parietal cortex. These regions are functionally connected and act as a coherent bilateral network responsible for semantic representation and control. This occurs during the performance of semantic tasks and during rest. This system is responsible for semantic cognition regardless of the type of semantic relationship. Overlapping areas in the left hemisphere relate to general control processes, whereas the right homologues of these regions may be responsible for control processes unrelated to semantic cognition. The ventral ATL appears particularly critical for multimodal semantic processing whereas more superior regions of the ATL may be involved in auditory and verbal processing. The ATL appears highly connected and is part of the semantic and default mode networks. The anterior DMN overlaps with the semantic network in a number of regions but appears to fulfil a different role, not critical for simple semantic judgements of single words. The dynamic connectivity of the ATL suggests it may be a hub region, belonging to multiple networks and affording effective transmission of information within and between these networks.

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APPENDICES

Appendix 1. Significant Activation Clusters for the Contrast Rest > Semantic.

Region of Activation	Cluster extent (voxels)	Max z value	P value (FWE corrected)	Peak regions	Peak MNI Coordinate		
					X	Y	Z
Bilateral occipital, parietal and frontal cortex, R temporal lobe	12806	6.63	>.001	L mid cingulate gyrus	-12	-39	39
				L precuneus	-12	-48	51
				R MTG	42	-72	21
L FG & lingual gyrus	114	5.94	.032	L FG	-27	-48	-9
L Cerebellum	547	5.70	>.001	L Cerebellum	-24	-78	-42
				L Cerebellum	-33	-78	-39
				L Cerebellum	-48	-63	-45
R FG & lingual gyrus	139	5.63	.015	R FG	30	-51	-9
L ventral parietal cortex	573	5.44	>.001	L SMG	-63	-33	36
				L AG	-63	-60	30
				L AG	-51	-69	45

Clusters significant at .05 after FWE correction. Up to 3 largest peaks listed per cluster. L = left. R = right. MTG = middle temporal gyrus. FG = fusiform gyrus. SMG = supramarginal gyrus. AG = angular gyrus.

Appendix 2. Significant Activation Clusters for the Reaction Time Modulator.

Region of Activation	Cluster extent (voxels)	Max z value	P value (FWE corrected)	Peak MNI Coordinate		
				X	Y	Z
L IFG	1201	5.46	>.001	-48	30	18
R IFG	1136	5.42	>.001	48	33	18
R mid occipital lobe	425	5.4	>.001	33	-63	30
L ITG	4032	5.4	>.001	-48	-57	-15
R mid cingulum	512	4.8	>.001	3	21	42

Clusters significant at .05 after FWE correction. Largest peak listed per cluster. L = left. R = right. MTG = middle temporal gyrus. IFG = inferior frontal gyrus. ITG = inferior temporal gyrus.

Appendix 3. Stimuli Presented in the Semantic Judgement Task.

Probe	Associated		Similar	
	Target	Foil	Target	Foil
bird	egg	tent	lamb	blacksmith
shop	basket	spoon	market	bottle
hoover	dirt	tomb	mower	synagogue
vase	tulip	elephant	bucket	platform
apple	orchard	map	lime	lecturer
exam	lecturer	eagle	programme	road
graffiti	wall	market	poster	saddle
finger	glove	dress	claw	referee
prisoner	dungeon	medal	pupil	pony
truck	road	college	gondola	duvet
yacht	bay	oven	automobile	basket
suit	tailor	beaver	robe	organ
trail	forest	rattle	street	athletics
dolphin	ocean	tale	pig	officer
badge	officer	student	medal	baggage
warehouse	pallet	gun	mansion	pond
pot	plant	chicken	pail	costume
shovel	hole	mosque	spoon	meal
surgeon	scalpel	pail	butcher	camel
rat	maze	monastery	otter	bride
flask	gin	slipper	goblet	maze
leopard	zoo	auditorium	fox	warrior
hen	cage	robe	robin	baby
panda	bamboo	nettle	mouse	author
tumbler	whiskey	trolley	chalice	scalpel
ferry	island	till	canoe	mug
pike	river	bill	shark	toe
armour	blade	submarine	dress	wall
python	jungle	stout	worm	detective
bell	tower	axe	rattle	gin
lorry	highway	furnace	limousine	trench
hair	brush	street	fur	vicar
portrait	gallery	juice	report	orchard
warrant	detective	ferret	bill	zoo
grass	rake	flute	lily	dentist
car	mechanic	pupil	wagon	barn
boot	toe	vine	slipper	burrow
jeweller	necklace	programme	student	plant
jail	robber	lobster	tomb	honey
fort	infantry	sack	bungalow	ink
abbey	monk	policeman	lodge	egg

squirrel	woodland	tank	ferret	deity
grill	sausage	chalice	furnace	jungle
whistle	referee	butcher	flute	tower
teeth	dentist	lime	beak	bamboo
bee	honey	automobile	eagle	choir
helmet	bike	limousine	crown	restaurant
muzzle	dog	brain	mask	ocean
seaweed	sand	park	nettle	tailor
lemonade	bottle	school	liquor	marsh
cocktail	bar	meadow	stout	harbour
tractor	hay	coat	tank	necklace
waitress	restaurant	coach	nurse	flower
desert	camel	robin	meadow	rifle
cart	pony	otter	jeep	cage
lager	glass	mower	juice	bay
reed	marsh	mansion	vine	mechanic
menu	meal	concrete	map	web
snake	venom	cape	lobster	monk
bayonet	trench	report	axe	bike
spider	web	canoe	lice	pastor
printer	ink	pasture	till	woodland
veil	bride	fox	cape	gallery
boat	harbour	essay	coach	dungeon
cloak	friar	mouse	coat	sand
millstone	corn	lice	concrete	infantry
forge	blacksmith	shark	oven	island
theatre	costume	jeep	saloon	dirt
cat	vet	lily	mole	friar
hymn	organ	photo	tale	forest
bedroom	duvet	gondola	dormitory	sausage
farm	sheep	bear	park	pallet
soldier	rifle	bucket	policeman	sheep
pulpit	pastor	pig	podium	venom
airport	baggage	bungalow	school	milk
stadium	athletics	poster	auditorium	hay
hotel	guest	fur	monastery	river
monarch	throne	liquor	president	corn
temple	deity	haddock	college	glass
tea	mug	mask	wine	blade
garden	flower	beak	pasture	throne
train	platform	lodge	submarine	brush
book	author	nurse	photo	highway
church	vicar	lamb	mosque	rake
pram	baby	bishop	trolley	hole
cow	milk	goblet	bear	robber

bible	god	president	essay	whiskey
cathedral	choir	claw	tent	beer
womb	midwife	mole	brain	vet
sword	warrior	worm	gun	bar
rabbit	burrow	podium	beaver	midwife
rabbi	synagogue	wine	bishop	dog
goldfish	pond	saloon	haddock	tulip
owl	barn	wagon	chicken	god
horse	saddle	crown	elephant	guest
keg	beer	dormitory	sack	glove

Appendix 4. Stimuli Presented in the Letter Matching Task.

Probe	Target	Foil	
		Low control	High control
##HΨz##	bqwcHΨz	ctkdLXQ	cHΨdLXQ
##XΘm##	bXΘmPkt	gYBgTTN	gYBgTΘm
##Bαj##	BαjgGdT	TCkDQXz	TCkDαjz
##Rζl##	CGWWζlw	gXjBPxD	gXjζPxD
##Hθm##	CHθmDZw	TYnbxyy	TYθmxyy
##bΘp##	cKNΘpRw	NyMlmTw	NyMΘmTw
##ZΣY##	CPΣYqFg	wdXpJSb	wdΣpJSb
##Cηl##	CηlQpjM	PHWxSQs	PηlxSQs
##QΛL##	dQΛspDX	zpmhzYf	zpΛhzYf
##SΠG##	DΠGzHXW	HzXJfbD	HzXΠfbD
##cξt##	FNqFcξt	QdjMjMB	QdjcξMB
##rΦM##	gBrΦMln	kzQGSCC	krΦGSCC
##zχb##	gDcTzχb	nPXcnmP	nPXlzχP
##XλP##	GfNjXλg	LtFcCdD	LtFcCλD
##cπk##	HMcπkBX	PgdrYZl	PπkrYZl
##jξs##	hQXjξsG	kFDfyCk	kFξsyCk
##Rιx##	hQιxZSt	hqqGfwz	hqιGfwz
##PΔY##	hrHΔYZL	KjhTDqR	KjhTΔqR
##hγf##	hγfWkYM	lgCnxSM	lhγnxSM
##Bξc##	JBξcHHF	nxqrkyg	nBξrkyg
##Rδw##	JdRδwFf	XZsmKCF	XZsmKδw
##hΔW##	jhΔRKtC	jNBzJjy	jNBΔJjy
##GΦm##	JNmGΦmD	nDNKdLZ	GΦNKdLZ
##KηN##	jpKηbbs	rytmfTR	rytηfTR
##tτz##	JqrGtτz	bxpLYDY	bxpLYτz
##xξm##	JRKtBξm	YZqpBBG	YZqpξBG
##TπH##	JTπPGky	DsQdcKx	DsQdcπx
##kΨF##	jxnBΨFX	gQyZlGZ	gQΨZlGZ
##RΩw##	jYRΩwdg	bQhdBSk	bQhRΩSk
##rΓD##	jZpHrΓD	smpQkwG	smpQkΓD
##WηZ##	jηZtMmT	xppgTfj	xpηgTfj
##Zθt##	jθtyPBc	DKQwBRn	DKQwBθn
##Jτs##	JτYHdbf	NCBWMYg	NτBWMYg
##bιF##	KbιFGPT	TZMxJqX	TZMxιFX
##QΣX##	KhΣXhFT	pDNPJHd	pDNΣJHd
##TβD##	KTβDzgJ	MwrbSgL	MwrβDgL
##Bδg##	KzBδdPs	dXhZsTX	dXhδsTX
##WΘJ##	kzmCWΘJ	xtKsXqp	xtΘJXqp
##kυM##	kυMXynR	HXzdLns	HXυMLns
##kψM##	kψMGrQW	fgDpRfF	fgDkψfF

##γτW##	lfγτWcX	dxjBrGl	dxjτWGl
##hΞw##	lhΞwMzt	GDlcksb	GΞwcksb
##dΣM##	LNRdΣMW	KsxwfHf	KsxwΣMf
##JΘX##	LySJΘXq	GzGMTKb	GJΘMTKb
##lτb##	lτbfLcD	pkwjSXN	pkwτbXN
##Hπl##	MDZπlxm	rbJwWRK	rbπwWRK
##lΠB##	mlΠkTHY	JqydfWp	JqydΠWp
##fμZ##	MNfμHtk	wbXTkMY	wbXTμMY
##GΨW##	mQGΨWbn	YcjNxpH	YcjNGΨH
##qμD##	mqμDjXZ	NKJXKGL	NKJqμGL
##Qψy##	MrQψyNf	jLNcggl	jLQψggl
##Sδp##	MxlKSδp	hNZcyhm	hNZcδpm
##MΩB##	MΩxGslr	YCcrfnq	YCΩrfnq
##MΔr##	nbcMΔrP	QFLFwdy	QFLΔrdy
##KΣp##	NyzKΣpm	LWsbbZB	LWΣpbZB
##zρy##	nzρpSfz	wXBHWFC	wXρHWFC
##NΓR##	NΓRGBLH	cTSYfLd	cTSYfΓR
##QδC##	nδCzjTY	WnNWrlF	WnNWδlF
##qβg##	PBjDqβg	JWNkNrP	JβgkNrP
##Dρw##	PkqQDρw	Lrgjbhc	LrDρbhc
##Lθk##	PwDLθkp	HHFpFQY	HθkpFQY
##xϕT##	QLϕTJrY	syzlhgH	sϕzlhgH
##gΛD##	QZcΛDCs	xjnzTWx	xΛnzTWx
##JΞl##	RFbJΞlf	fRwKrPq	fRwΞlPq
##kΓn##	rpSgkΓQ	sGpSbLG	sGΓSbLG
##rβp##	rβpkGKd	YNChDmm	rβChDmm
##zγK##	sCγKNJQ	qcPccRm	qcPcγRm
##cΦH##	SfcΦPWx	BjbqKKl	BjΦqKKl
##fλn##	sfλngkz	rspTlRd	fλpTlRd
##pΨn##	SmJyΨnw	SYyCtHH	SYyCΨHH
##FυQ##	SyFυQkh	MmyzZtK	MmyzυQK
##Pεx##	SzRHεxB	nQtBkYw	nεtBkYw
##sζP##	sζtTgNR	gjMxTwK	gζMxTwK
##sϕZ##	sϕybtbW	rrHgJCB	rrHϕJCB
##bπy##	TcQXNπy	pShJfDK	pSπJfDK
##jζK##	tjζKGgd	zLPXwDf	zLPjζDf
##TΩR##	TΩRlLPc	yxYHKjb	yTΩHKjb
##Tυh##	wgKTυQS	FrkWNLQ	FrkυNLQ
##ZΠD##	WpftZΠS	SgFyHWN	SgFΠHWN
##rΛL##	wScrΛxB	CnCnFQz	CnCnFΛz
##hϕG##	wsRhϕGT	WtBqRCM	WtBhϕCM
##dμt##	WxZdμtY	BSHyGrW	BSHyGμt
##yρf##	XDSBZρf	ndRLHjJ	ndRρHjJ
##KζY##	xfKζYNR	SzxftZc	SzζYtZc
##dωB##	xgdωFlr	RtJfWYk	RωJfWYk

##Sγm##	xjTYSγm	ZKWyZzB	ZKWγmzB
##tλf##	XlyFPλf	MWjDxZq	MWjDxλq
##YΩW##	xXqlsΩW	thTgslL	thTgsΩL
##GΠJ##	yGΠCZsk	tSFCpSs	tΠFCpSs
##dψw##	YjgψwCB	GZtFMlS	GZtψMlS
##Cµj##	yKtCµjh	bBXlzsL	bBXcCµL
##YΔN##	YΔbFwcq	hdMxJtR	hdMxΔtR
##gιj##	zqbQgιZ	DMStbnp	DιStbnp
##FΞK##	ZxΞKMnP	hnZQJYJ	hnZQJΞJ
##sιw##	ZYcLιwC	yPQznXP	yPQzιXP
##gηq##	zηqRLDp	PpJfCmM	PηJfCmM

Appendix 5. Stimuli Presented in the Semantic Control Task.

Probe	Target	Foil	
		Low control	High control
carrot	grape	telescope	bluebell
zebra	wolf	pedal	eel
mosquito	butterfly	hammock	hawk
lighter	lantern	hog	mirror
penguin	duck	chocolate	frog
daisy	dandelion	trumpet	rose
kettle	beaker	berry	tripod
revolver	missile	tiger	cigarette
hanky	shawl	crocodile	fleece
vest	girdle	stork	wallet
baton	wand	mink	fork
flyer	journal	clam	purse
barrel	box	plum	seat
lion	puppy	pan	pigeon
ivy	thistle	letter	trout
apricot	olive	jacket	spinach
tomato	peach	gem	cereal
algae	bush	hook	moth
willow	maple	frost	deer
panther	poodle	saxophone	walrus
lynx	beagle	wire	ant
swan	quail	accordion	ape
turtle	snail	palette	calf
wasp	dove	outhouse	herring
porch	cellar	bulldog	cavern
kilt	stocking	seed	ring
turban	hood	cedar	shield
arrow	bomb	pineapple	pipe
corkscrew	pliers	rice	pen
mop	hammer	skin	bin
clock	compass	walnut	bowl
diamond	gravel	eyeball	cork
canyon	quarry	elf	dome
lake	canal	fly	rain
tornado	snow	pup	bubble
hurricane	rainbow	leaf	metropolis
microwave	screen	kitten	carpet
bat	racket	doctor	plank
painting	newspaper	thorn	cushion
television	phone	root	microscope

pebble	brick	oyster	asbestos
fan	iron	tree	pillow
cleaver	razor	tongue	broom
dart	pin	clover	bandage
vinegar	bourbon	bone	morphine
bracelet	overcoat	flea	sheet
flag	blanket	lettuce	tobacco
knife	hatchet	birch	hose
wing	arm	engine	neck
newt	alligator	lightning	perch
vault	cave	ewe	chassis
pumpkin	raspberry	fountain	sycamore
horn	tooth	fence	bark
kiwi	cherry	locker	fungus
orange	pepper	wicker	shrub
kangaroo	bunny	aerial	geese
donkey	boar	landscape	banana
peacock	lark	typhoon	mackerel
prune	bean	poker	creeper
onion	chestnut	chisel	pine
turkey	crow	violin	mussel
ox	seal	linen	carp
shrew	mite	grate	pear
cod	catfish	lawn	mermaid
lavender	moss	wig	fawn
wheat	garlic	trophy	nectar
blazer	apron	foal	towel
syrup	gravy	ankle	beef
mould	hedge	piano	lemon
whale	toad	shelf	vegetable
albatross	wren	uniform	tortoise
rhinoceros	goat	rug	crab
antelope	mule	capsule	fowl
mice	hare	abyss	fruit
badger	cattle	guitar	cabbage
porpoise	shrimp	fog	weed
lord	king	cradle	infant
sailor	driver	mural	owner
mayor	emperor	syringe	dancer
painter	pianist	amethyst	professor
magician	clown	cliff	jockey
buckle	button	thumb	piston
taxi	ship	blossom	propeller
digger	crane	hound	jet
university	hospital	insect	shed

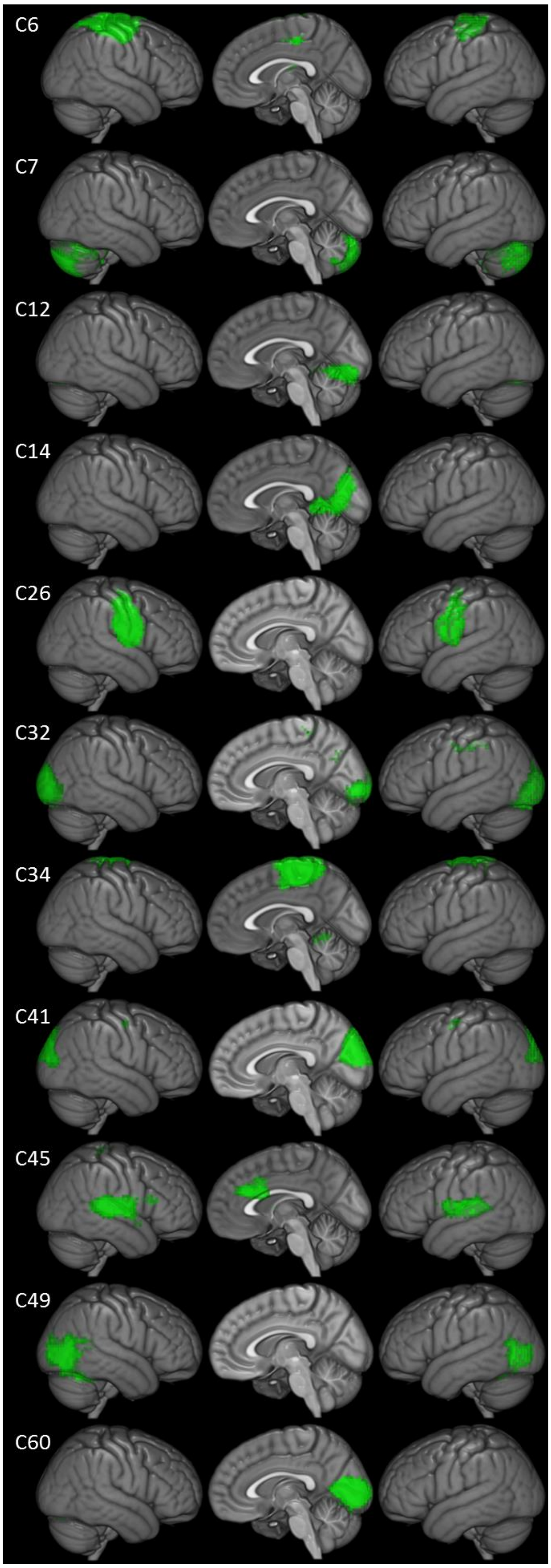
pew	couch	mouth	toilet
mountain	pyramid	doe	arch
cottage	cabin	thigh	belfry
office	bank	nutmeg	prison
fisherman	hunter	oil	teacher
spear	grenade	secretary	tablespoon
ambulance	caravan	bacteria	plane
sofa	stool	skull	desk
plumber	builder	page	actress
rocket	van	rogue	typewriter
farmyard	allotment	sergeant	coast

Appendix 6. Comparing the Functional Connectivity of the aMTG to the vATL and aSTG.

Contrast	Cluster Region	Cluster extent (voxels)	Max z value	P value (FWE corrected)	Peak MNI Coordinate		
					X	Y	Z
vATL> aSTG	Bilateral fronto-temporal cortex, precuneus, PCC & cerebellum, L AG	15220	Inf	>.001	-36	-9	-42
	R AG	656	Inf	>.001	48	-66	33
aSTG> vATL	Bilateral aSTG, IFG, pre & post CG, MFG, mCC, SMA, caudate, SMG, precuneus & occipital cortex	17931	Inf	>.001	-48	12	-12
					51	9	-12
					-39	-6	-12
	MFG	385	7.25	>.001	-33	42	24
	L PhG	105	4.78	.030	-3	-6	-30
					-15	-21	-27

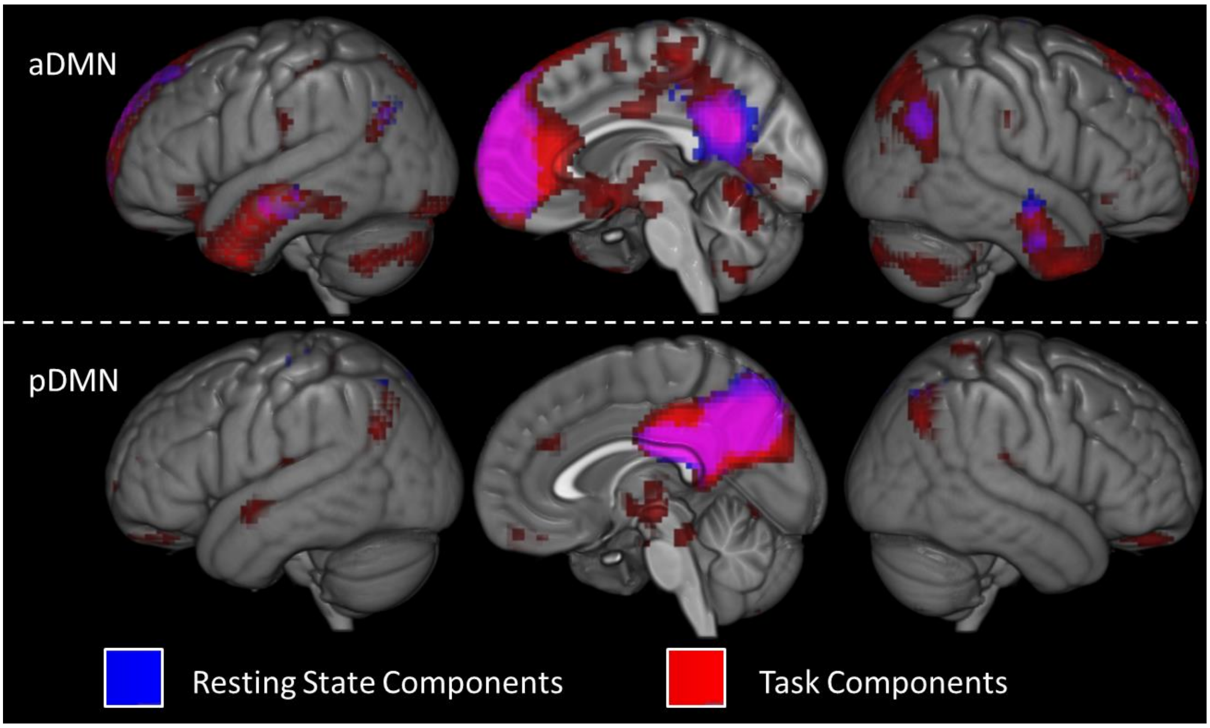
Clusters significant at .001 after FWE correction. Largest 3 peaks listed per cluster. L = left. R = right, a = anterior. STG = superior temporal gyrus, SMA = supplementary motor area, MTL = medial temporal lobe, PhG = parahippocampal gyrus, MFG = middle frontal gyrus, PCC = posterior cingulate cortex, MCC = mid cingulate cortex, CG = central gyrus, STG = superior temporal gyrus, SMG = supramarginal gyrus.

Appendix 7. Sensory and Motor Resting State Components.



The components are thresholded at the voxel level at p<.001 and the cluster level at p<.05. C6 is the supplementary motor network and includes pre- and postcentral gyrus, biased towards the right. C26 is the motor network including pre- and postcentral gyrus, supramarginal gyrus and the cerebellum. C34 is the sensorimotor network including paracentral lobule, postcentral gyrus, supplementary motor area as well as some inferior parietal lobe, precuneus and cerebellum. C7 is a cerebellar network. C45 is the auditory network including Heshl's gyrus, posterior STG extending into anterior STG on the right, operculum, insula and some inferior frontal gyrus and anterior cingulate cortex. The remaining 6 components are visual composing the medial (C14, C32, C41, C60) and lateral (C12, C49) visual networks. C14 includes lingual, calcarine and middle occipital cortex. C32 includes inferior and middle occipital and lingual cortex as well as some posterior fusiform gyrus, precuneus and paracentral lobule. C41 includes posterior temporal cortex (superior, middle and inferior temporal and fusiform gyri) and middle and inferior occipital cortex. C12 includes lingual and middle and inferior occipital cortex as well as posterior fusiform gyrus. C60 includes middle occipital, calcarine and lingual cortex.

Appendix 8. The Anterior and Posterior DMN Components from the Resting State (blue) and Task (red) ICAs.



The components are thresholded at the voxel level at p<.001 and the cluster level at p<.05. Overlap is shown in violet. The spatial maps are very similar from the two sets of data.