The neural basis of automatic and controlled semantic cognition:

Spatiotemporal dynamics revealed by magnetoencephalography and brain stimulation

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Abstract

This thesis investigated the neural basis of different aspects of semantic cognition using magnetoencephalography (MEG) and chronometric transcranial magnetic stimulation (cTMS). The primary aim was to examine the evidence for a potential functional dissociation between ATL and pMTG; (i) in terms of how they support semantic retrieval, and (ii) whether they support different types of semantic knowledge. Chapter 2 investigated the predictions of the Controlled Semantic Cognition framework (CSC - Lambon Ralph et al., 2017). According to this view, ATL and pMTG within the temporal lobe have distinctive roles in semantic cognition: the ATL is argued to correspond to a semantic store and in this way shows processing advantages for patterns of retrieval that are highly coherent with the structure of long-term conceptual knowledge, whereas pMTG is implicated in more controlled aspects of retrieval that might promote the accessibility of weaker associations that are not dominant within the ATL representations. The brain’s oscillatory response to strongly- and weakly-related word pairs was characterised in left anterior temporal lobe (ATL) and left posterior temporal gyrus (pMTG). ATL showed a larger response to strongly-related words, while pMTG responded more strongly to weakly-related words, suggesting these regions contribute to automatic/coherent and controlled semantic retrieval respectively. The chapter also investigated the causal role of ATL and pMTG in automatic and controlled retrieval using cTMS. Results showed disruption for weak associations in pMTG at an early time point, and slightly later disruption for strong associations in ATL. Chapter 3 further contrasted the CSC framework with the dual hub view, which alternatively proposes that (i) ATL and pMTG (plus angular gyrus; AG) represent different types of semantic information – with taxonomic links in ATL (e.g., DOG and RAT) and thematic relationships in pMTG/AG (e.g., DOG and BONE). According to the CSC framework, the functional division between these brain regions is better characterised by automatic/coherent retrieval in ATL/AG and more controlled retrieval in pMTG. Results indicated that ATL, pMTG and AG all responded to both taxonomic and thematic relationships; thus, I did not observe empirical support for the dual hub view. There was greater engagement of ATL for strong associations and pMTG for weaker associations, consistent with the CSC view. These findings together suggest that pMTG may play a role in maintaining a semantic context and detecting situations in which controlled retrieval processes may need to be engaged. In contrast, ATL may support patterns of coherent semantic retrieval between highly-related concepts. Thus, the findings of this thesis help to elucidate the specific roles of these regions in the semantic network.

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Chapter 1 - Literature Review

Semantic memory refers to our conceptual knowledge about people, places, objects, faces, sounds and words (Patterson, Nestor & Rogers, 2007; Pulvermüller, 2013). It is both universal and personal, in that the information can be widely known in the population or more personal to the individual. For example, we know many things about bananas – they are yellow, curved, sweet, and have a waxy peel which is slippery if stepped on. We may also have more personal semantic knowledge about bananas, such as our friend being allergic to them (Renoult, Davidson, Palombo, Moscovitch & Levine, 2012; Binder & Desai, 2011). Some of these semantic features are strong and dominant for the concept, such as the colour yellow, while other features and associations may be a weaker part of the concept and consequently more difficult to retrieve, such as the slipperiness of banana skin (Lucas, 2000; Seidenberg, Waters, Sanders & Langer, 1984).

Semantic cognition refers to the application of conceptual knowledge to drive appropriate thought and behaviour (Jefferies, 2013), and it is thought to require distinct neurocognitive components working together: (i) the store of semantic representations, which underpins our ability to assign meaning and relevance to everything we hear, see, touch, taste and remember and (ii) semantic control processes, which are thought to be essential to our ability to retrieve and act upon our knowledge in a relevant way (Corbett, Jefferies, Ehsan & Lambon Ralph, 2009). Within our semantic store, we have a wide range of features and associations for any given concept, and only a subset of this information will be relevant for the current situation or task. If we see a banana peel on the ground, only the peel’s slippery nature is appropriate to the situation before us. However, if we are cooking for our previously mentioned friend, the appropriate thing to recall about bananas would be their allergy to them. The selection of non-dominant aspects of knowledge to suit the context is thought to require *semantic control*. In some cases, knowledge that is relevant to the task at hand can be retrieved in a relatively automatic, cue-driven (bottom-up) way, and is seemingly effortless: this type of semantic retrieval supports access to dominant aspects of concepts (e.g., bananas are yellow). Other times the appropriate information is not so readily available: under some circumstances, spreading activation must be ‘shaped’ to focus on unusual connections, or a more strategic "search" of memory is needed, increasing the semantic control demands (Badre & Wagner, 2007; Binder, 2016).

This thesis aims to elucidate the components of semantic cognition – in particular, their contribution to more automatic and controlled semantic retrieval – using convergent neuroscientific techniques, namely magnetoencephalography (MEG) and transcranial magnetic stimulation (TMS). MEG measures magnetic fields outside the skull induced by electrical currents in the brain, while TMS involves applying strong but brief magnetic pulses to the scalp to interfere with the functioning of the underlying cortical area. The majority of previous studies investigating semantic cognition have used functional magnetic resonance imaging (fMRI), which can reveal the network of brain regions active in a task; however, the BOLD (blood oxygenation level dependent) response, which is used as a marker for neural activity in fMRI investigations, has low temporal resolution (since blood flow changes happen over a period of several seconds). This means that transient effects may be missed and the technique is not ideal for identifying how sites within the semantic network are recruited over time, in the service of a task. MEG can address this limitation, as it allows us to trace the time course of the neural activation (in the order of milliseconds) and to make inferences about the temporal recruitment of areas implicated in the semantic control network. As such, MEG provides a unique opportunity to answer questions about *when* as well as *where* semantic cognition takes place, though this method has other drawbacks, such as lower spatial resolution, as well as difficulty resolving sources further away from the cortical surface (Hansen, Kringelbach & Salmelin, 2010).

Additionally, both MEG and fMRI are correlational methods and cannot test causal predictions from theoretical models: the modulation of signal strength by task conditions in imaging investigations does not conclusively show that these brain regions make a necessary contribution to the task. Causal predictions can be tested against neuropsychological data from patients with focal brain damage, though such patients are rare, and may not have damage in regions appropriate to experimental hypotheses. TMS allows us to test causal predictions in healthy participants in a more precise fashion, as TMS pulses create a temporary focal "lesion" (with a spatial resolution of a few millimetres). TMS can also be used to examine causal contributions to a task over time, if disruptive pulses are applied at different time points (Walsh & Coway, 2000; Sliwinska, Vitello & Devlin, 2014). This method is called chronometric TMS (cTMS) and has been used to reveal the points in time when brain regions are *critically* involved in aspects of cognition, complementing the inferences that can be drawn from MEG studies. In an online paradigm, each TMS pulse has an effect lasting 10-30ms, and cTMS is thought to have a temporal specificity of ~10-20ms (Walsh & Coway, 2000). This means that we can assess the recruitment and necessity of an area with great temporal specificity.

This literature review provides an overview of studies examining the neural basis of semantic cognition, with a focus on how semantic memory is represented in the brain and the regions supporting semantic control processes. The review outlines key findings from neuropsychology, fMRI, MEG and TMS. *Semantic representations* that capture the meanings of words and objects are thought to draw on both modality-specific regions and heteromodal regions of cortex, with the latter areas potentially acting as a representational hub or hubs. A hub draws together information from different sensory-motor systems to form an amodal conceptual representation, recruited across different tasks and modalities of input (Patterson, Nestor & Rogers, 2007; Binder, 2016). I discuss the critical role of the anterior temporal lobes (ATL) in this function. Next, to elucidate the brain networks crucial for more automatic and controlled forms of *semantic retrieval*, studies of control-demanding semantic tasks will be discussed. For example, within semantic priming paradigms, automatic spreading activation may be sufficient to uncover the link between strongly-linked prime and target words (such as *pear-apple*), but to establish a link between less strongly related words (such as *worm-apple*), controlled retrieval is necessary (Gold et al., 2006; Badre & Wagner, 2007; Binder, 2016). The approach taken in this thesis will be grounded in and motivated by this work.

Semantic representation

There is considerable debate about how conceptual knowledge about objects, people, sounds and words is represented in the brain. Different theoretical perspectives advocate different views about whether there are amodal semantic representations, and the degree to which knowledge emerges directly from distributed sensory-motor processes (Meteyard, Cuadrado, Bahrami & Vigliocco, 2012). The "embodied" view is based on the perspective that our knowledge is a sum of our experiences; we learn by building associations. By this view, the conceptual representation of banana may be supported by synaptic connections between cell assemblies representing the colour yellow and its sweet taste. The most influential early model of a distributed semantic system is arguably Allport (1985), who proposed that any object's semantic representation is located in a distributed, neural pattern of activation. Pulvermüller (1999; 2001) similarly proposed a system grounded in Hebbian learning, where different specialised cortical areas act together to achieve a representation of word meaning. For example, words tightly tied to distinct areas of the body (kick-leg) have been found to produce activity that overlaps with motor or premotor areas for the associated limb/body part (Hauk, Johnsrude & Pulvermüller, 2004), even in the case of idioms (Boulenger, Hauk & Pulvermüller, 2009). Intentional motor actions can affect the semantic processing of words involving a motor component, suggesting comprehension and motor execution depend on the same underlying neural population (Rueschemeyer et al., 2010). Furthemore, how an object is used can influence semantic representation; words describing objects that have a movement specifically tied to function elicit greater activation of sensimotor areas than objects that do not (pen and fan respectively; Rueschemeyer et al., 2009). Similarly, action areas (left inferior parietal lobule) show greater activity when action features of a word are relevant to the task (van Dam et al., 2012). More recently, however, there has been increasing consensus that distributed aspects of knowledge may be integrated within conceptual "hubs" (Damasio, 1989; Patterson, Nestor & Rogers, 2007). Despite the importance of sensorimotor areas in semantic cognition, it is not fully established how different aspects of knowledge encoded in these unimodal regions interact. For example, in Hauk et al. (2004), the words tied to specific areas of the body (kick-leg) produce activity in cortical area corresponding to the associated limb/body part, requiring a link between visual and motor cortex. This involves matching the visual symbolic input (i.e. the word 'kick') in visual cortex with corresponding body part areas (i.e. the leg) in motor cortex. There has been debate about how type of effect occurs – many researchers have argued that distant primary cortices do not link strongly and directly to one another, and therefore these long-range connections might recruit multimodal areas of cortex known as *convergence zones* or “hubs” in a relay-like system, bridging modality-specific areas (Damasio, Grabowski, Tranel, Hichwa & Damasio, 1996; Binder & Desai, 2011; Pulvermüller, 2013). Some accounts (e.g., Patterson et al., 2007) have focused on the role of one specific region in the integration of different types of information to form more abstract concepts (namely, the anterior temporal lobes), while other researchers have discussed the possibility that information convergence might occur in multiple brain regions, including the angular gyrus and the posterior cingulate (Binder & Desai, 2011; Pulvermüller, 2013).

The anterior temporal lobes (ATL) in particular are thought to provide an important convergence zone for the formation of abstract concepts, while some of the other potential convergence zones are implicated in cognitive integration beyond the semantic domain (Humphreys & Lambon Ralph, 2014; Humphreys et al., 2015). Historically the ATLs were under-sampled in imaging methods due to magnetic susceptibility artefacts in fMRI, and it is only in relatively recent years that modern neuroimaging techniques have been able to successfully image the region (Lambon Ralph, Jefferies, Patterson & Rogers, 2017). Due to this development, the ATLs are increasingly recognised as important for semantic cognition, even within theories that do not interpret its role as an amodal hub. Some accounts emphasise its role in combinatorial processes, as ATL activity has been found to be greater for combinations of adjectives and nouns. Adjective-noun combinations increase the specificity of an item (e.g. boat vs. red boat) (Clarke, Taylor & Tyler, 2011; Westerlund & Pylkkänen, 2014; Zhang & Pylkkänen, 2015). Another view of the ATL is that it is important for abstraction and for emotional and social concepts (Olson et al., 2013). Abstract words are not strong grounded in sensory or motor experiences but may draw more strongly on emotional features (Kousta et al., 2011), and emotion is as much a modality of experience as sensorimotor processing (Binder & Desai, 2011). ATL may be strongly influenced by social and emotional content represented in ventromedial prefrontal regions and connected to the ATL via the uncinate fasciculus (Lambon Ralph et al., 2017).

The first proposal of the ATL as an bilateral amodal semantic hub was in response to neuropsychological data from semantic dementia patients (with lesions centred on anterior ventral and polar temporal regions), who showed conceptual deficits across all modalities (this will be discussed in greater detail in the section the Hub and spoke model below). More recently it has been suggested that the ATL has a graded functional specialisation, with the different subregions reflecting their relationship with the rest of the network in terms of functional connectivity. Major white-matter fasiculi with partially overlapping termination points converge in in ATL, underpinning this graded specialisation (Lambon Ralph et al., 2017). This is based on the idea that subregions of the ATL contribute to all semantic processing, but slightly more to tasks involving the modality-specific cortex of highest anatomical proximity to them; i.e. medial ATL responds more to visual concepts due to its increased connectivity to this region, and temporal pole contributes more to social concepts (in line with its greater connections to areas supporting affect). At the same time, unlike other subregions of the ATL, ventrolateral ATL is highly engaged in semantic tasks irrespective of input modality, suggesting this as the *truly* amodal subregion of the area (Lambon Ralph et al., 2017).

The Hub-and-spokes model of semantic cognition

The hub and spoke model (Patterson, Nestor & Rogers, 2007) suggests that both sensory-motor areas (the “spokes”) and a convergence zone in the ATL (the “hub”) are crucial for the representation of semantic knowledge. The hub and spoke model is shown in Figure 1.1, and contrasted with a “distributed-only” view in which direct connections between regions capturing embodied aspects of knowledge are the basis for concepts. The ATL hub is argued to play a crucial role in semantic representation in several ways: (i) this region may allow translation between different inputs and outputs, for example, understanding the meaning of a written word may require connections between orthographic processes and the ATL hub, since the orthographic form of a word has an arbitrary relationship to its meaning. The same conceptual information can be accessed from objects and environmental sounds. (ii) The ATL hub may be critical to our capacity to understand the semantic links between items that do not share surface features in any given modality: for example, corgi and fox may share more visual characteristics than corgi and Dalmatian, yet we can readily understand the categorical similarity of the two types of dog

(Lambon Ralph, Sage, Jones & Mayberry, 2010). This might be possible because corgi and Dalmatian have greater similarity across the full range of features and associations beyond vision, and the ATL is able to extract these high-dimensional similarities.

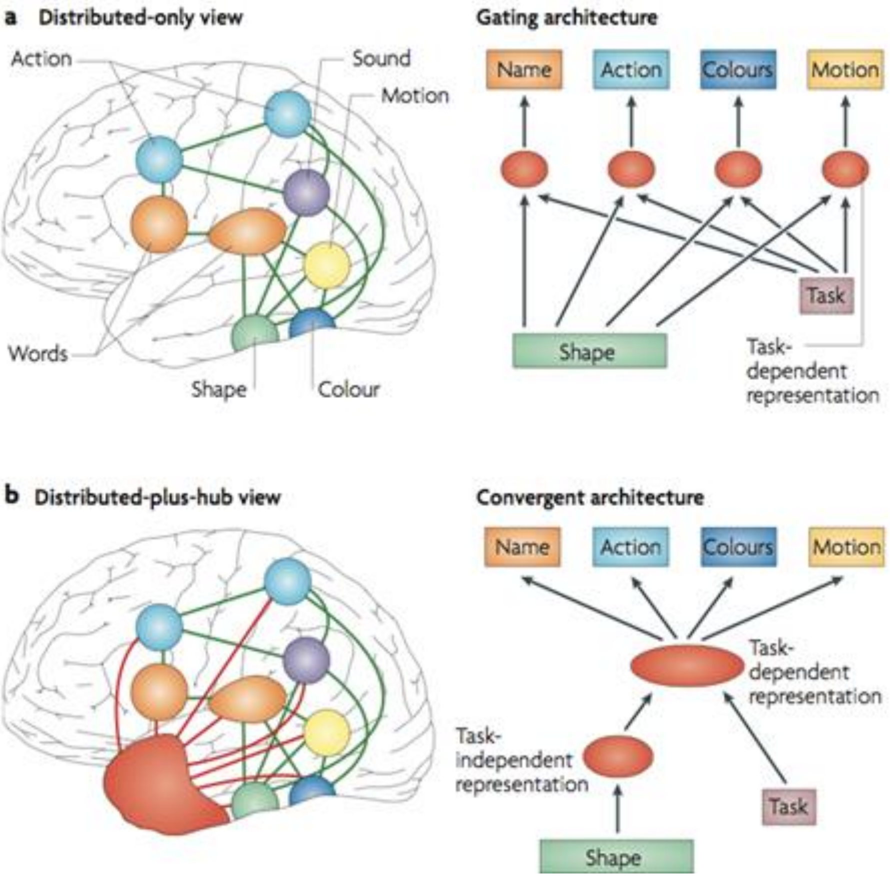


Figure 1.1: Conceptual illustration of how *distributed semantics* differs from the *hub-and-spokes* view; taken from Patterson, Nestor & Rogers, 2007 (page 977).

The primary evidence for the hub and spoke model was provided by studies of patients with Semantic Dementia (SD). These individuals show a remarkably pure semantic deficit. The symptoms of SD present themselves as a degradation of semantic knowledge while non-verbal reasoning and performance on visuo-spatial tasks remain intact (Hodges, Patterson, Oxbury & Funnell, 1992). The disease is associated with bilateral ATL atrophy, which correlates with performance on semantic tasks (Mummery et al., 2000; Mion et al., 2010). Semantic dementia patients have a high level of consistency on semantic tasks, both across tasks and for items tested with different input modalities, and they show little benefit of cueing (Bozeat, Lambon Ralph, Patterson, Garrard & Hodges, 2000; Jefferies, Baker, Doran & Lambon Ralph, 2007). This is consistent with the notion that central semantic representations within the ATL are degraded in patients with SD.

More recently, studies of healthy participants have provided converging evidence for the contribution of the ATL to semantic processing. This work is important because the atrophy in SD progressively extends beyond the ATL to more posterior temporal and inferior frontal areas (Martin, 2007), and it is difficult to rule out the contribution of abnormalities in these regions to the behavioural profile in these patients. However, fMRI does not always reveal a contribution of ATL to semantic cognition in healthy individuals, and this has contributed to controversy about the brain regions that store semantic information (with some researchers arguing that posterior temporal regions provide the key site for conceptual representation; Martin, 2007). It is increasingly recognised that magnetic susceptibility artefacts in fMRI studies produce signal loss and distortion in the ventral ATL, and therefore this method may not always reveal responses in this region during semantic tasks. Devlin et al. (2000) examined activation to the same semantic task using both fMRI and positron emission tomography (PET) (since this method is unaffected by magnetic susceptibility artefacts), to see if any differences emerged from the two different techniques. PET showed additional activation not found using fMRI in anteromedial temporal pole. Similarly, a meta-analysis of 164 functional neuroimaging studies (Visser, Jefferies & Lambon Ralph, 2010), found that one of the key factors influencing whether ATL activation was found, was the use of PET vs. fMRI. In contrast, task or stimuli type were not influencing factors in the likelihood of significant ATL activation in semantic tasks, in line with the proposal that this site is a ‘hub’ supporting central semantic representations. Convergent evidence for the engagement of ATL in synonym judgement was obtained from distortion-corrected fMRI, semantic dementia and TMS (Binney, Embleton, Jefferies, Parker & Lambon Ralph, 2010). The role of this region has since been supported by another fMRI meta-analysis which concluded that ATL activation in semantic processing is bilateral, but with stronger responses in left ATL for written word stimuli (Rice, Lambon Ralph & Hoffman, 2015).

Support for a causal contribution of the ATL to conceptual processing is provided by TMS studies of healthy participants, as inhibitory TMS creates a temporary focal “lesion” in the underlying brain area (with a spatial resolution of a few millimetres) (Walsh & Cowey, 2000). TMS to ATL slows naming, synonym judgements and semantic matching tasks involving words and pictures, with similar results for TMS to left or right ATL (Lambon Ralph, Pobric & Jefferies, 2009; Pobric et al., 2007; 2010a; 2010b; 2009). These studies are consistent with the proposal that the ATL provides a “semantic hub” – i.e., a point of convergence across different modality-specific inputs, to allow the formation of amodal semantic representations (Patterson et al., 2007). A recent chronometric TMS study found that the critical time point for ATL involvement in semantic processing was ~400ms post stimulus onset (Jackson, Lambon Ralph & Pobric; 2015), which fits well with M/EEG studies that have repeatedly found a negative potential around 250-550ms called the N400 (discussed later in this chapter). Indeed the authors postulate that ATL could be one of the neural generators of the N400.

While these methods converge to implicate ATL as a semantic hub, the hub and spoke model also recognises the importance of the spokes (Patterson et al., 2007). Spokes in this account are neural populations specialised for certain kinds of processing (colour, shape, motion, language, action etc.). Like the embodied approach, this account stipulates that these modality-specific representations are necessary for conceptual knowledge, but differs in that it suggests that the ATL also plays an essential role in their integration and connection. Evidence for this viewpoint is also provided by TMS: Pobric, Jefferies & Lambon Ralph (2010a) showed that inhibitory stimulation to the hand praxis area in inferior parietal cortex produced a specific deficit in naming manipulable tools, while stimulation to the ATL hub elicited disruption across all semantic categories.

How many semantic hubs?

The work reviewed above has focussed on the role of the ATL as a conceptual hub bringing together distributed sensory and motor knowledge to form amodal semantic representations. However, there is considerable debate about whether the ATL uniquely serves this function, or if there are multiple hubs that can act as convergence zones across modalities (Kiefer & Pulvermüller, 2012; Pulvermüller, 2013; Schwartz et al. 2011). If there are multiple hubs contributing to conceptual representation, these may serve different functions since they are likely to preferentially receive different aspects of knowledge. It has been suggested that taxonomic and thematic associations depend on different cortical areas, with thematic associations (representations of relations based items being found or used together – e.g., banana-slip) grounded in the temporo-parietal junction (TPJ), while taxonomic associations (similarity based on shared physical features - i.e., banana-tomato) are extracted in the ATL (Schwartz et al., 2011). This viewpoint is broadly consistent with the idea that the ATL lies at the end of the ventral visual stream, allowing it to integrate concrete features of objects (which are important for conceptual similarity – e.g., a banana is a fruit that is curved and yellow). In contrast, the TPJ may be better placed to integrate information about how objects are used and the contexts in which they are found.

Schwartz et al. (2011) analysed the type of errors produced by patients with patients with aphasia in relation to lesion location (voxel-based lesion-symptom mapping), and found that thematic errors were associated with TPJ lesions, while taxonomic errors were associated with ATL lesions. Neuroimaging studies have started to investigate the relationship between the type of conceptual link required by specific trials or semantic tasks and the activation of TPJ and ATL (Sass et al., 2009; de Zubricay et al., 2013; Kalénine et al., 2009), to assess the possibility that TPJ (particularly angular gyrus and posterior middle temporal gyrus) provides a second semantic hub supplying relations and situational similarities for event processing, in addition to the ATL supporting knowledge of featural overlap for object classification.

Semantic control

The section above focussed on the representation of semantic information; however a component process view of semantic cognition suggests that representations on their own are not sufficient to explain conceptually-driven behaviours and thoughts. We also need a mechanism to explain how the semantic system can produce flexible behaviour depending on the context. While, in some cases, automatic spreading activation to dominant features and associations would be sufficient for successful semantic processing (e.g., linking the words salt and pepper), other situations might require the recruitment of additional processes that control semantic retrieval (Badre & Wagner, 2007; Binder, 2016). An example would be identifying the link between salt and grain, when dominant links like ‘pepper’ are irrelevant (Whitney et al., 2011). Weaker associations may require more semantic control in order to focus retrieval on relevant non-dominant features of the concept (Badre et al., 2005; Jefferies, 2013). Semantic control may also be required to process ambiguous words with multiple meanings, such as bank, which refers to both a place of monetary exchange (dominant meaning) and the side of a river (subordinate meaning). If the context is unclear, this creates competition between possible interpretations and it is necessary to inhibit non-relevant yet dominant associations (Vitello, Warren, Devlin & Rodd, 2014; Vitello & Rodd, 2015).

Therefore, semantic control is thought to modulate semantic activation such that it is appropriate to the task or context (Wagner, Pare-Blagoev, Clark & Poldrack, 2001; Badre & Wagner, 2007; Badre et al., 2005; Ye & Zhou, 2009). This process involves selecting between competing alternatives held in working memory, inhibiting non-relevant semantic activation, and controlled retrieval of knowledge that cannot be generated through automatic, spreading activation. Furthermore, semantic control may be required when we drive semantic retrieval from goals in a top-down fashion, as well as for switching or updating the semantic focus when the task changes (Whitney, Kirk, O'Sullivan, Lambon Ralph & Jefferies, 2011; Moss, Abdallah, Fletcher, Bright, Pilgrim, Acres & Tyler, 2005).

Neuropsychological studies comparing patients with multimodal semantic deficits following semantic dementia (SD) and stroke (semantic aphasia; SA) indicate that semantic control is dissociable from semantic representations within the ATL (Jefferies & Lambon Ralph, 2006). SA patients have damage to left inferior frontal and temporoparietal areas, and show difficulty with tasks requiring semantic control (Noonan, Jefferies, Corbett & Lambon Ralph, 2010). While SA and SD patients fail the same range of word and picture tasks, SD patients have a high level of consistency in the items they can comprehend across tasks and input modalities, and show little to no benefit of cueing, while SA patients perform more poorly on difficult association-matching tasks, relative to simple word-picture matching tasks, and benefit greatly from cues (Corbett, Jefferies & Lambon Ralph, 2011; Jefferies & Lambon Ralph; Jefferies, Patterson & Lambon Ralph, 2007; Noonan, Jefferies, Corbett & Lambon Ralph, 2010). In picture naming, SD patients predominantly make superordinate and high-frequency co-ordinate errors (such as cat-animal, or cat-dog), while SA patients produce more associative errors outside the relevant category (such as squirrel-nuts), suggesting they retain associations that they fail to supress when they are irrelevant to the task (Jefferies & Lambon Ralph; 2006). SA patients also show difficulty in inhibiting strongly associated distractors and accessing less dominant associations between items (Jefferies, Baker, Doran & Lambon Ralph, 2007; Noonan, Jefferies, Corbett & Lambon Ralph, 2010). Thus, central semantic representations may be degrading in SD while SA cases retain a lot of conceptual information that they fail to retrieve appropriately. Similarly, patients with LIFG lesions have difficulty on semantic tasks where there is strong competition between response options (Thompson-Schill, Swick, Farah, D'Esposito, Kan & Knight, 1998).

Semantic control in the brain

Patients with SA demonstrate that semantic control may draw on different brain areas from those that support the conceptual store (i.e., ATL is largely preserved in these patients); however, the large frontotemporal lesions in these cases do not permit strong inferences about the crucial brain regions for semantic control. In functional neuroimaging studies, the most consistently implicated region in diverse manipulations of semantic control demands is the left inferior frontal gyrus (LIFG; see Noonan et al., 2013 for a meta-analysis), and this brain region is typically damaged in SA (Jefferies & Lambon Ralph; 2006; Jefferies, 2013). The response in LIFG increases when participants have to select targets in the face of strong distracters, retrieve weak associations or process words with ambiguous meanings (Vitello et al., 2014; Thompson-Schill, D'Esposito, Aguirre & Farah, 1997; Zempleni, Renken, Hoeks, Hoogduin & Stowe, 2007; Wagner, Maril, Bjork & Schacter, 2001; Bedny, McGill & Thompson-Schill, 2008). LIFG responds semantic information across word and picture tasks (Wagner, Desmond, Demb, Glover & Gabrieli, 1997; Krieger-Redwood, Teige, Davey, Hymers & Jefferies, 2015), consistent with the multimodal impairment of semantic control seen in patients with SA (Corbett et al., 2009).

There may be functional subdivisions within LIFG. First, studies show that anterior LIFG (pars orbitalis) is relatively specialised for semantic processing, while more posterior LIFG (pars opercularis) contributes to controlled phonological *and* semantic processing (Gold & Buckner, 2002; Gold, Balota, Kirchhoff & Buckner, 2005; Poldrack et al., 1999). This anterior-posterior distinction between semantics and phonology has also been demonstrated using TMS (Gouch, Nobre & Devlin, 2005; Devlin, Matthews & Rushworth, 2003). Secondly, it has been suggested that LIFG has sub-regions specialised for specific aspects of semantic control. Wagner et al. (2001) found increased activity in anterior parts of LIFG to the controlled retrieval of weak associations, while Thompson-Schill, D'Esposito, Aguirre & Farah (1997) found that dorsal and posterior LIFG activity was sensitive to selection demands – and this response fell within the area activated by lexical, phonological and semantic processing (Poldrack et al., 1999). While these responses were across studies, Badre et al. (2005) demonstrated a within-study dissociation between anterior/ventral and posterior/dorsal aspects of LIFG, using task contrasts that loaded on "controlled retrieval" (i.e., the recovery of weaker associations) and "selection" (i.e., overcoming competition from strong distractors). A related view emphasises the role of posterior LIFG in top-down goal-driven selection processes (Wagner, Pare-Blagolev, Clark & Poldrack, 2001; Miller, 2000). These top-down processes are involved in resolving interference from competing non-relevant representations, thus driving task-appropriate selection (Cardillo, Aydelott, Matthews & Devlin, 2004). This study also found that related semantic cues elicited little LIFG engagement compared to incongruent cues, suggesting that when automatic spreading activation is sufficient for retrieval, recruitment of top-down processes from LIFG may not be necessary(see also Gold et al., 2006).

Beyond LIFG: A distributed network for semantic control

SA patients have damage to left inferior frontal and/or temporoparietal cortex, with similar behavioural results following lesions in these different areas (Berthier, 2001; Jefferies & Lambon Ralph, 2006; Noonan, Jefferies, Corbett & Lambon Ralph, 2010). While the role of LIFG has been the focus of the neuroimaging literature, these patient studies suggest an involvement of areas beyond LIFG in semantic control, consistent with current perspectives in cognitive neuroscience that link aspects of cognition to distributed cortical networks. A recent meta-analysis contrasting semantic tasks with high > low executive requirements found that, alongside LIFG, right IFG, posterior middle and inferior temporal gyrus (pMTG; pITG) and dorsal angular gyrus were consistently activated by this comparison (Noonan, Jefferies, Visser & Lambon Ralph, 2013; see also Whitney, Jefferies & Kircher, 2011; Vitello, Warren, Devlin & Rodd, 2014). In fact, many of the studies reporting a response in LIFG to semantic control manipulations have also seen similar activity in posterior temporal and/or inferior parietal areas, although they have not always highlighted this fact (Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997; Wagner, Maril, Bjork & Schacter, 2001; Bedny, McGill, & Thompson-Schill, 2008). Further evidence is provided by TMS: studies have shown comparable effects of inhibitory stimulation to LIFG and pMTG, with no effect of TMS on easy semantic judgements based on strong associations, but disruption of harder semantic judgements based on weak associations and feature matching when global semantic similarity must be disregarded (Whitney, Kirk, O'Sullivan, Lambon Ralph & Jefferies, 2011; 2012; see also Davey et al., 2015 and Hoffman et al., 2010). Thus, the brain regions supporting semantic control appear to be distributed, and extend to areas beyond left prefrontal cortex.

Semantic vs. executive control in the brain

The regions that support semantic control overlap with brain areas that contribute to executive control more widely (e.g., Davey et al., 2016; Noonan et al., 2013). Duncan and Owen (2000) showed that a similar network was recruited for a wide variety of executively-demanding tasks (see Figure 1.2, taken from Duncan & Owen, 2000, page 477). Thus, inferior frontal sulcus (IFS), pre-supplementary motor area on the medial surface, and inferior parietal sulcus (IPS) may work together as a “multiple-demand network”, which is engaged by high executive load across domains (including the semantic domain, see Figure 1.3, taken from Duncan, 2010, page 173).

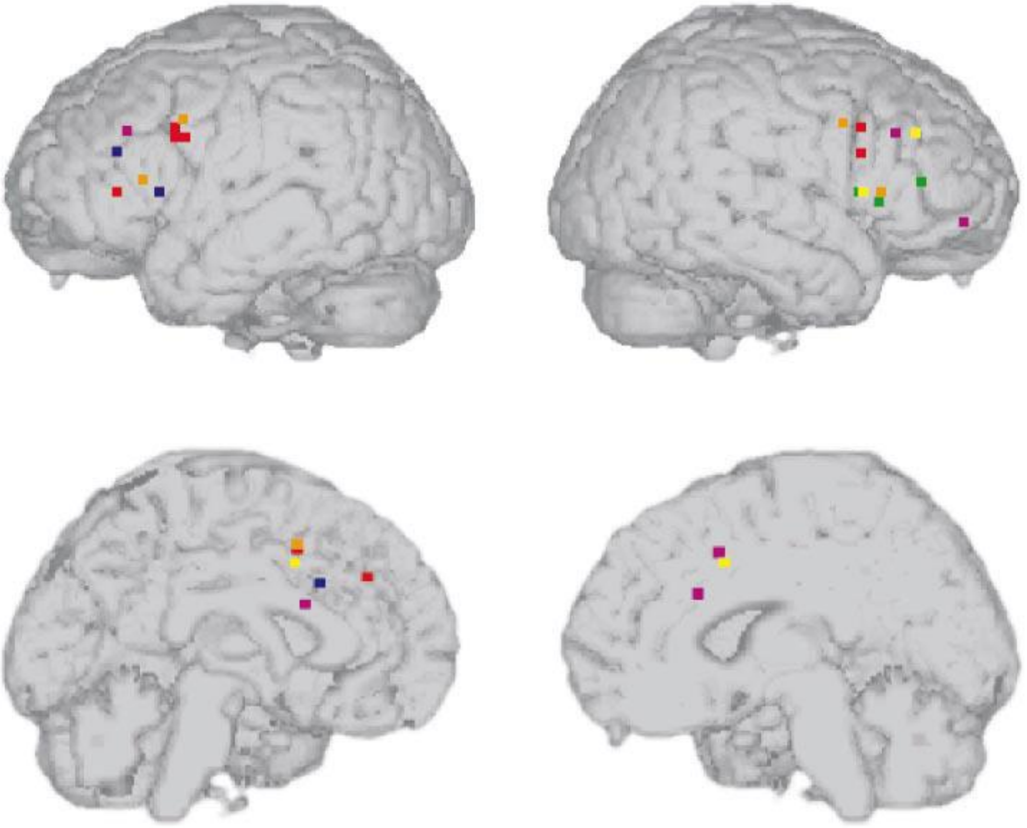


Figure 1.2: Showing prefrontal activations from six experiments; auditory discrimination (green), visual divided attention (blue), self-paced response production (yellow), task switching (orange), spatial problem solving (pink), and semantic processing of words (red). Figure taken from Duncan & Owen (2000), page 477.

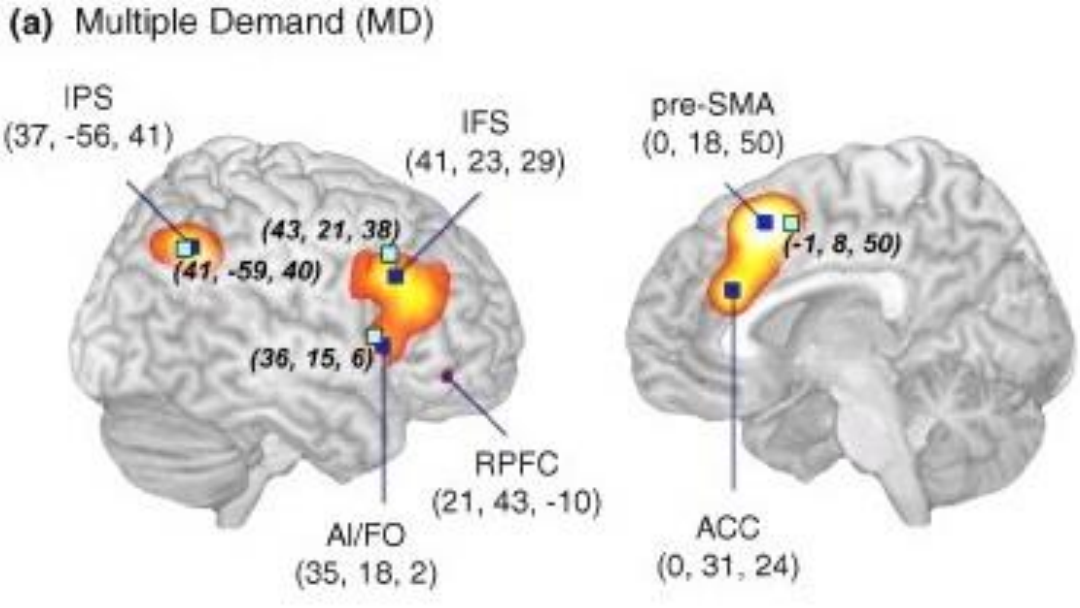


Figure 1.3: Brain regions in the multiple-demand network recruited by diverse executive tasks. Left hemisphere results are projected onto the right hemisphere surface. Taken from Duncan, 2010, page 173.

Posterior and dorsal aspects of LIFG have been implicated in phonological as well as semantic processing (Wheat, Cornelissen, Frost & Hansen, 2010; Poldrack et al., 1999; Snyder, Feigenson & Thompson-Schill, 2007; Hagoort, 2005), consistent with the proposal that these regions contribute to language processing across domains. LIFG also supports syntax (Friederici, Ruschemeyer, Hahne & Fiedbach, 2003; Dapretto & Bookheimer, 1999; Moro, Tettamanti, Perani, Donati, Cappa & Fazio, 2001) and responds to pitch in languages where pitch carries meaning for the interpretation, in comparison to languages where it does not (Gandour, Wong & Hutchins, 1998; Gandor, Wong, Hsieh, Weinzapfel, Van Lancker & Hutchins, 2000; Klei, Zatorre, Milner & Zhao, 2001). Posterior and dorsal IFG bordering IFS shows a stronger response in people with higher general fluid intelligence in response to greater attentional demands (see Figure 1.4; Gray, Chabris & Braver, 2003), suggesting that this region overlaps with or lies adjacent to the multiple-demand executive network.

Figure 1.4: Regions in which general fluid intelligence predicted trials with high attentional demands, using *a priori* (red) and whole-brain (yellow) search criteria, in the following order; left lateral, left medial, right medial, right lateral cortical surface. Left and right cerebellums are shown under their respective cortical hemispheres. Taken from Gray, Chabris & Beaver, 2003 (p 318)

LIFG has extensive connectivity throughout the brain, with functionally specialised subdivisions of connectivity (Croxson et al., 2005). Perhaps most notably for semantic cognition, the more anterior parts of left PFC (BA47) show greatest connectivity to ATL through the uncinate fasciculus (Croxson et al., 2005; Petrides & Pandaya, 2002; Catani, Howard, Pajevic & Jones, 2002), which fits well with the hypothesised graded functional specialisation of LIFG with more posterior parts being specialised for phonology, and anterior parts being specialised for semantic processing (Gold, Balota, Kirchhoff & Buckner, 2005; Bodke, Tagamets, Friedman & Horwitz, 2001). Anterior IFG and ATL also both show strong connectivity to pMTG, consistent with the view that this brain region participates in a distributed network for semantic control (Davey et al., 2016).

Shalom & Poeppel (2008) postulate that LIFG is involved in the synthesis of aspects of language (creating combinations of stored representations), and that more dorsal areas are involved in phonological processing, middle areas in morpho-syntactic processing, and ventral/anterior areas in semantic processing. Haagort (2005) similarly proposes that LIFG supports *binding* processes, with a similar subdivision of functions: phonological processing in more posterior-dorsal areas (~BA44), syntactic processing in mid-LIFG (~BA45), and semantic processing in anterior regions (~BA47). According to Haagort, this binding (or unification) involves the integration of lexically-retrieved information into a representation of multi-word utterances, i.e. sentences or context. While an extension of these theories may be necessary to account for multimodal semantic control (beyond language to encompass non-verbal aspects of semantic cognition), these accounts all converge on the idea that anterior LIFG plays a specific role in *semantic* control, while posterior LIFG contributes to other aspects of language processing and executive control more widely. Moreover, anterior-to-posterior regions of IFG show differential connectivity and the areas that they are connected to form large-scale functional networks that support different aspects of controlled behaviour – with the semantic control network including pMTG and dorsal AG, while the executive control network includes IPS and potentially more ventral posterior temporal lobe (pITG).

Recent work has considered how these networks may interact in the service of memory tasks. The default mode network shows activity that is correlated through time with memory stores including the hippocampus and the ATL; however, the activity of these systems is anti-correlated with that of the dorsal attention system (Vincent et al., 2006; Vincent, Kahn, Snyder, Raichle & Buckner, 2008): i.e. when activity increases in one system, the other will decrease (Fox et al., 2005). The dorsal attention system supports externally directed cognition; shifting spatial attention, hand-eye-coordination, and searching/detection of external targets (Vincent et al., 2008), and it spatially overlaps with the multiple-demand network which responds to executively-demanding task states (Duncan, 2010). In contrast, the default mode/memory system has been linked to internally directed cognition; thinking about the past and the future, conceiving the perspectives of others, and episodic memory (Buckner, Andrews-Hanna & Schacter, 2008). In light of these two networks' anti-correlated activity, Vincent et al. (2008) postulated a third, executive network, which can direct activation between (and integrate information from) these two networks, as well as maintaining task objectives and supporting working memory. This network (the frontoparietal control system) is left lateralised, and includes anterior cingulate, lateral parietal and prefrontal cortex. It appears to overlap with areas implicated in semantic control by Noonan et al. (2013) and is spatially interposed between the two previously mentioned networks. By this view, semantic cognition is likely to involve the default mode network interacting with executive areas, potentially via the left-hemisphere network identified by Vincent et al. (2008; see also Davey et al., 2016).

Semantic vs. executive control summary:

As reviewed above, some areas implicated in the semantic control network overlap with the executive control network, perhaps most notably in posterior and dorsal aspects of LIFG. However, there are also regions in the semantic control network that do not overlap with the executive network. A recent meta-analysis by Noonan et al. (2013), contrasted executive and semantic control demands, and pMTG and anterior IFG were implicated to a greater extent in semantic-only control. These regions lie outside the multiple-demand network implicated in domain-general executive control. It is not surprising that semantic control mechanisms draw on similar neural resources as domain-general executive control, as demanding semantic tasks no doubt draw on executive processes (such as applying a goal to a task, or selection processes to deal with competition). However, some demands associated with challenging semantic judgements are to do with the structure of knowledge itself; if there is not a specific goal for retrieval, but rather, the high semantic control demands are due to difficulty integrating a concept into a context (as in the case of weakly related associations), pMTG shows an increased response. This highlights the importance of investigating this region and its contribution to semantic control (Gold et al., 2006; Davey et al., 2016). Recent work showed that the semantic control network (pMTG and anterior IFG) lies in between the domain-general executive system and the default mode network, a typically task-negative network implicated in coherent and automatic memory retrieval – both in terms of its location on the cortical surface and its pattern of connectivity at rest (Davey et al., 2016).

Temporally sensitive methods of exploring semantic cognition

Normal speech has a rate of ~three to five words per second (normal reading proceeds at an even faster rate): consequently, matching, integration and comprehension operations must be carried out very quickly during language processing. Semantic cognition must also guide visual processing at rapid speeds (within 250ms of stimulus presentation) to facilitate object recognition (Clarke et al., 2011; 2012). Since semantic cognition involves the interaction of several large-scale cortical networks, neuroimaging methods with high temporal resolution, such as MEG or EEG, may be very informative with respect to how dynamic processes support semantic cognition in the brain.

Semantic priming

Semantic priming methods are often used to examine the time-course of processes that support semantic retrieval. In semantic priming, a word such as *pepper* is processed more quickly when preceded by a related word, such as *salt*. The priming effect can be thought of as facilitated spreading activation through the semantic system (Binder, 2016), which speeds up semantic access from vision and increases the richness of semantic retrieval by pre-activating relevant features and associations. Semantic priming studies have examined different kinds of relationships between prime and target words. Taxonomic relationships are based on shared features of objects. In this way, dog and bear have a strong semantic relationship, as they share many features like “big teeth”, “furry” and “four legs”. Thematic relationships are based on strong associations between concepts that do not necessarily share any physical features; their relatedness is based on a purely associative link because the objects are often found or used together, i.e. dog and collar (Hutchison, 2003; Kalénine et al., 2012). Priming occurs for both thematically and taxonomically related words; for thematically related words, this reflects the frequency of co-occurrence, while for taxonomically related words, this is thought to reflect shared features of items within the same category (McRae & Boisvert, 1998; Hutchinson, 2003).

It has been proposed that automatic priming is based on spreading activation between highly-linked words, and that this mechanism is distinct from strategic, effortful search for an association (Lucas, 2000), underpinned by the application of situational constraints (i.e., top-down and bottom-up processing respectively). Automatic semantic priming is thought to reflect the structural organisation of the semantic network, while strategic search does not (Seidenberg, Waters, Sanders & Langer, 1984).

However, it has been shown that this facilitation is mediated by many factors, such as the inter-stimulus interval (ISI) between the target and prime, the type of task utilised, and proportion of related trials (as compared with unrelated) (Neely, 1977; 1991). Firstly, the ISI can be short when no response is required to the prime, without affecting priming results, and priming facilitation occurs at both long and short ISIs. Furthermore, when the ISI is 250ms or less, facilitatory priming effects remain similar to longer ISIs, but the negative priming yielded by unrelated/unexpected primes is greatly reduced. Shorter ISIs are also more automatic in nature; the participant is not given enough time to engage conscious attentional processes. Normally word naming or lexical decision tasks are utilised in priming experiments, and type of task has been shown to influence priming effects; using the same items, mediated priming (in which the target is related to the prime indirectly via a mediator) has been found in word naming but not lexical decision, while backward associative priming (which slows down processing of the target) has been found in lexical decision tasks, but not word naming. Interestingly, the priming is larger for low frequency targets in both task types. The proportion of related trials (as compared with unrelated) can affect amount of facilitation; typically an increased proportion of related trials increases the priming effect, though this is mainly true for long ISIs (Neely, 1977; 1991). In conclusion, the extent to which non-semantic tasks, including word naming and lexical decision are influenced by semantic information, in an automatic way, depends on a variety of experimental factors.

Electromagnetism and Semantic Priming

The neural correlates of priming have been reported as a decreased neural activity in response to a stimulus (Düzel, Richardson-Klavehn, Neufang, Schott, Scholz & Heinze, 2005; Kujala, Vartiainen, Laaksonen & Salmelin, 2012), and semantic priming occurs whether the stimulus is attended to or not (Relander, Rämä & Kujala,, 2013). On the other hand, semantically-related (as compared with unrelated) word pairs can elicit stronger activation in areas known to be involved in semantic processing (Graves, Binder, Desai, Conant & Seidenberg, 2010; Mechelli, Josephs, Lambon Ralph, McClelland & Price, 2007; Binder, 2016). Thus, there are potentially two distinct neural consequences of priming: more efficient access to conceptual knowledge from inputs (reduced activation, for example in the visual-to-semantic pathway in the ventral visual stream), and richer semantic retrieval within the same time period (increased activation, for example, in the anterior temporal lobes).

Furthermore, while decreased neural activation is often seen in response to primed stimulus, increased coherence (greater neural synchrony between critical regions) may be critical to the behavioural effects seen in response to priming (Ghuman, Bar, Dobbins, & Schnyer, 2008). Prefrontal-temporal interactions have been shown to be stronger at stimulus onset for words that showed subsequent behavioural facilitation (Düzel et al., 2005), and greater neural synchrony between prefrontal and temporal areas was seen in response to repetition, accompanying the decreased neural response (see Figure 1.5) (Ghuman et al., 2008; p 8406).

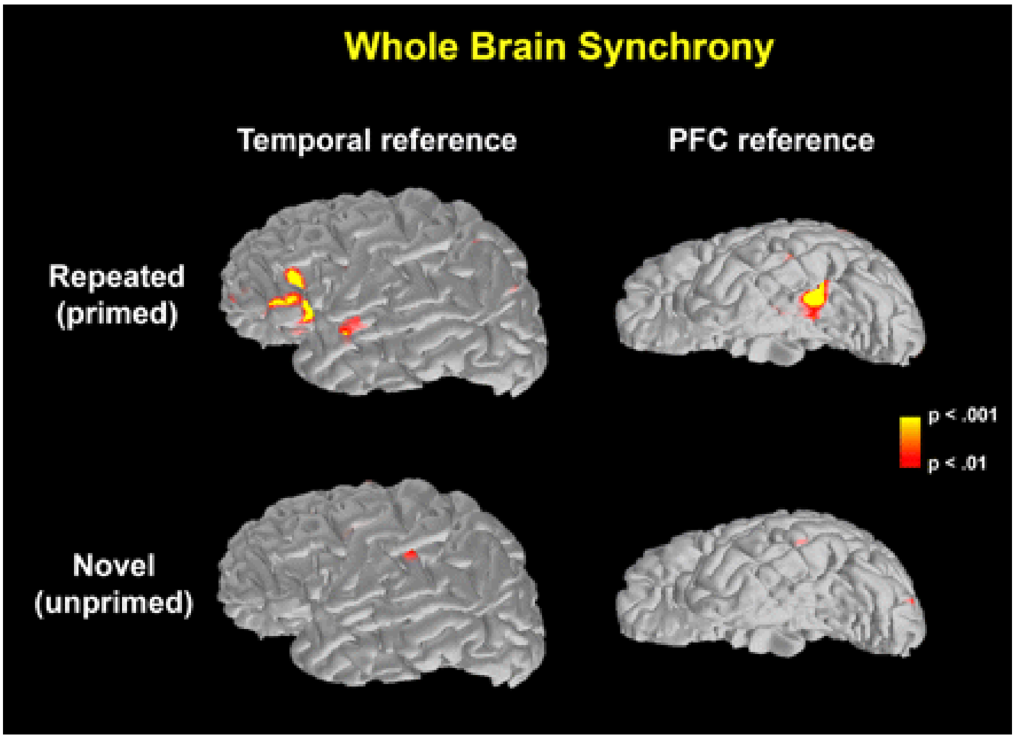


Figure 1.5: Peak synchrony between a single reference ROI and the entire brain relative to prestimulus baseline synchrony. Images on the left side of the figure are lateral views of the left hemisphere, and the images on the right side are ventral views. Taken from Ghuman et al., 2008; p 8406.

The causal role of prefrontal areas in priming effects was shown by Wig, Grafton, Demos & Kelley (2005), who found that left frontal TMS significantly reduced the behavioural facilitation that normally accompanies follows priming, and attenuated the reduced neural response following priming in semantic control regions – both LIFG and left pMTG (BA21/37). Thus, priming can be seen as reflecting an economical neural system, supported by spreading activation and/or top-down expectations increasing processing efficiency for a primed stimulus. The increase in synchrony between prefrontal and temporal areas could reflect a preparation effect; priming could lead to 'setting up the system', with prefrontal areas already communicating with temporal areas to retrieve and select situation- relevant information. This could also explain the speeded response in response to primed stimuli, as this would be an example of facilitated semantic retrieval, with low semantic control demands.

The N400 and N400m

In 1980 Kutas & Hillyard published EEG results indicating a difference in event related potentials (ERPs) to semantically unexpected and physically unexpected words. While physically unexpected stimuli elicited late positive potentials, semantically unexpected stimuli elicited late negative potentials between 250-550ms after stimulus presentation. This is referred to the N400 effect (or N400m, when observed in MEG rather than EEG), and it has been found in a great number of studies on language, reading and semantics (Kutas & Hillyard, 1980; Lazslo & Federmeier, 2008; Van Petten, Coulson, Rubin, Plante & Parks, 1999). The N400 effect is larger when a semantic violation is present, as opposed to when not. When the stimulus fits the context (given by a preceding word or sentence – e.g., a strong prime), the effect is small, and thus the N400 might reflect controlled retrieval or integration demands (Nobre & McCarthy, 1995), though it is also interpreted as semantic access; i.e. a smaller N400 reflects facilitated access, which can also be seen in response to plausible but less common endings to sentences (Lau, Almeida, Hines & Poeppel, 2009). The N400 is smaller for within-category than between-category violations, i.e. for the sentence "they wanted to make the hotel look more like a tropical resort, so along the driveway they planted rows of ..." the word 'pine' elicits a smaller N400 than 'tulip' (Federmeier & Kutas, 1999): although both words are unexpected, "pine" shares more features with "palm". This suggests features of the expected sentence ending are pre-activated and unexpected endings that share more features with the expected ending elicit a smaller N400.

Using intracranial electrodes, one of the sources an N400 effect has been localised to is the anterior medial temporal lobe (McCarthy, Nobre, Bentin & Spencer, 1995), and it has also been shown that semantic priming diminishes the amplitude of these field potentials (Nobre &

McCarthy, 1995), presumably because priming pre-activates relevant features. Furthermore, the N400 is not restricted to the language domain: a similar effect is sensitive to the congruence between linguistic context and visual stimuli (Hirschfeld, Zwitserlood & Dobel, 2011). This means that the N400 effect is robust across modalities, i.e. an expectation set up in the auditory/verbal modality elicits an effect to unexpected stimulus in visual form, which could indicate an *amodal* priming effect in this time window (Kutas & Federmeier, 2000).

MEG and semantics

Electroencephalography (EEG) records electrical potentials from the scalp, produced by the electrical currents produced by active populations of neurons. This gives EEG a much higher temporal resolution than hemodynamic methods such as the BOLD response in fMRI. However, due to the low conductivity of the skull (1/80–1/100 that of the brain), the electrical potentials measured by EEG are prone to distortion, leading to much lower spatial resolution (Hämäläinen & Hari, 2002). In contrast, the magnetic fields recorded by magnetoencephalography (MEG) pass through tissue largely undistorted, and thus this method has good spatial resolution - at least for regions near the brain’s surface, as well as excellent temporal (ms) resolution, though these measures depend on the cortical depth of the generating source, and the sampling rate used when collecting data respectively (Hari & Salmelin, 1997; Hansen, Kringelbach & Salmelin, 2010).

We know a lot about the brain areas associated with semantic processing from fMRI and neuropsychology, but the temporal dynamics of semantic cognition within these areas is less well-characterised. The N400 effect has been localised to bilateral ATL and LIFG irrespective of auditory or visual input domain using MEG (Marincovic et al., 2003). However, many MEG studies have reported effects earlier than this time window: a clear semantic response has been observed 250-300ms after stimulus presentation in ATL (Yvert, Perrone-Bertolotti, Baciu & David, 2012) and middle superior temporal cortex bilaterally, (Vartiainen, Parviainen & Salmelin, 2009), and there is evidence that semantic information modulates visual processing even earlier (Pulvermuller et al., 2001; Clarke et al., 2012). Mismatches between linguistic and visual stimuli have been found to influence the response in occipital cortex at around 100-120 ms (Hirschfeld, Zwitserlood & Dobel, 2011; Dikker & Pylkkänen, 2011). Explaining these effects from a purely bottom-up processing view is challenging, because the integration of linguistic and visual information is necessary for differences between these conditions. Thus, these effects may reflect the influence of top-down contextual signals on the processing on new visual inputs.

The task being performed also modulates the semantic response in visual and semantic areas. In object naming, activity in ATL is increased when objects must be identified at a specific rather than a general level, and this response in ATL modulates early (120-220ms) activity in visual cortex when finer grained visual processing is needed to identify objects at a more specific level (Clarke, Taylor & Tyler, 2011). Ventral temporal cortex shows a sensitivity to shared semantic features (i.e. has eyes) by ~120ms, and to distinctive features (i.e. has a hump) by 200ms, demonstrating how the semantic system may first perform broad object identification based on shared features, followed by later differentiation of similar concepts (Clarke, Taylor, Devereux, Randall & Tyler, 2012). This result of early shared and later specific feature identification, is in line with predictions by the hub and spoke model about how the amodal store may underpin identification, considering that in order to successfully identify specific concepts such as ‘robin’, it is necessary to activate the distinctive features such as ‘red chest’, as opposed to general features of birds, such as ‘wings’ and ‘beak’ (Patterson, Nestor & Rogers, 2007). Similarly, words tightly tied to distinct areas of the body (kick-leg) have been found to produce early activity that overlaps with motor or premotor areas for the associated limb/body part (Hauk, Johnsrude & Pulvermüller, 2004). Furthermore, in addition to the specificity of a word being an influencing factor, combinations of adjectives and nouns also enhanced ATL activity, suggesting that this region may also be important in combinatorial processes (Westerlund & Pylkkänen, 2014; Zhang & Pylkkänen, 2015). Combinations of words have richer and more specific meanings than individual words and the response in ATL may reflect these factors.

Measures of oscillatory power and their relationship to memory

Traditionally, power increases are thought to reflect neural populations firing in synchrony (for example, in response to an input) and thus it might be assumed that power decreases, relative to a resting baseline, reflect reduced neural activation. However, the oscillatory synchronisation and desynchronization framework suggests that *decreases* in total oscillatory power reflect active engagement of the neocortex in the encoding and retrieval of memories (Hanslmayr, Staresina & Bowman, 2016). These decreases in total power are thought to reflect an *increase in neural activity that is not synchronised in time and/or phase* (Hanslmayr et al., 2012). This proposal comes from principles from mathematical models of information theory, which show that increased synchrony reduces the richness of information that can be represented. When applied to the firing of neurons, information theory indicates that there is an inverse relationship between the richness of information encoded in the firing rate of a neural population and the synchrony of firing (illustrated in Figure 1.6, taken from Hanslmayr et al., 2012, page 8). Furthermore, reductions in power also correlate with an increased BOLD response in fMRI (Hanslmayr et al., 2011; Singh et al., 2002; Hall et al., 2014), in line with this hypothesis.

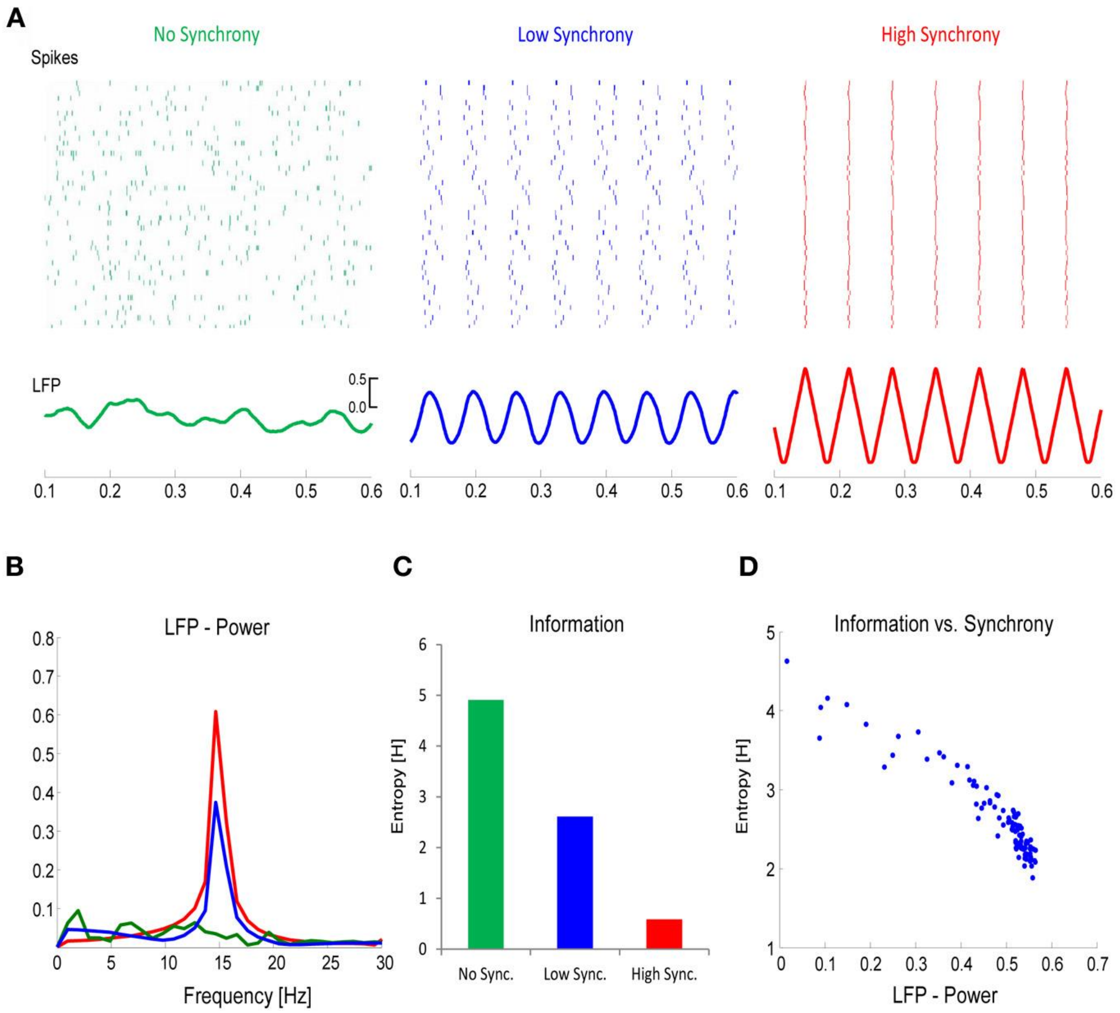


Figure 1.6: Illustration of the relationship between synchrony and informational content; **A** shows a simulation of firing rates of a neural population from no to high synchrony, **B** illustrates that power increases as a function of synchrony, **C** shows a graph of information in relation to firing rates of the different degrees of synchrony, and **D** plots the relationship between power and information for varying degrees of synchrony. Taken from Hanslmayr et al., 2012, p. 8.

This theoretical framework has two important implications: first, it motivates examination of total oscillatory power in semantic cognition (which often shows task-related reductions relative to baseline), as well as evoked power increases following a stimulus. Secondly, the framework raises the possibility that these two dependent measures may be sensitive to different neurocognitive processes. Evoked power only includes the component of oscillatory power that is aligned both in time and phase, whereas total power includes signals that are not aligned in phase (i.e., both evoked and induced power changes). A strong evoked response to salient visual inputs soon after stimulus presentation would be expected, since their onset is likely to re-set oscillatory activity such that it is aligned. In contrast, spreading semantic activation implies ongoing cognitive activity focussed on internal memory retrieval, and under these circumstances, phase-alignment may be less likely, potentially explaining why decreases in total power have been previously linked to memory processes (see Hanslmayr et al., 2016 for a review). Moreover, in semantic priming paradigms where one stimulus (prime) precedes and often predicts a second stimulus (target), it might be that the onset of the prime word is characterised by a strong evoked response, since this time point is characterised by a marked visual change. In contrast, the response to the target word might be seen more strongly in total power, since the onset of this second word reflects a less dramatic visual change but makes it possible to establish semantic retrieval processes that identify a connection between the two items. I would expect semantic priming to facilitate richer semantic retrieval (i.e., to make available more features and associations over a short duration, by pre-activating some of these aspects of knowledge), and according to Hanslmayr et al.'s theory, this rich information would be reflected in desynchronised neural activity and consequently reductions in total oscillatory power.

Summary

The aim of this thesis was to elucidate the components of semantic cognition using MEG and TMS. Key theories of semantic representation were considered, with focus on the degree of embodiment. The anterior temporal lobes have been highlighted as a potential amodal semantic store, working in unison with an embodied, distributed representational system across the cortex. Evidence for a distributed semantic control network was also reviewed, particularly the contributions of left inferior frontal gyrus and posterior middle temporal gyrus to this function. These brain regions may act together in a left-lateralised network that lies between the default mode network and the executive network, both in terms of its position on the cortical surface and in its pattern of resting-state connectivity. Finally, I considered temporally sensitive measures of semantic cognition, and the effects of semantic priming: memory allows the use of contextual cues in a predictive manner, reducing controlled retrieval demands.

Key findings

- Semantic representation is likely supported by ATL bilaterally as an amodal hub, interacting with a network of distributed interconnected nodes that is embodied in nature.
- Semantic control is likely supported by a distributed network with main contributors being LIFG and pMTG
- Priming has an effect on the response amplitude; it can both decrease and augment the neural response, as well as increase coherence (greater neural synchrony between critical regions) - and this increased synchrony is correlated with subsequent behavioural facilitation
- The N400 effect is not only variable with ease of integration in context, but could also reflect the fact that we use context to predict possible future events.
- MEG has found an effect of context on cortical response in visual cortex as early as 100ms, including a greater cortical response to words with stronger multimodal associations.
- Findings indicate a distributed semantic network with nodes working together, interacting and exchanging information in a continuous manner. Some of these nodes have also been implicated in other cognitive functions, possibly reflecting the similarity in processes, and that not only the spatial nature of the network, but the temporal interplay between regions could be crucial in elucidating the dynamics of the network

Questions addressed in the thesis

As reviewed above, the temporal recruitment of semantic processes is unclear, with conflicting evidence of both when and where semantic access is achieved, and there has been little empirical work investigating the temporal engagement of semantic *control* processes during retrieval and how different brain regions show dissociations through time that can linked to the difference between automatic and controlled semantic retrieval. Therefore, the primary aims of this thesis were:

- To investigate how automatic and controlled semantic retrieval are reflected in oscillatory activity within the semantic network, recorded using MEG. The thesis focuses on the left temporal lobe and left angular gyrus, since these brain regions are strongly implicated in semantic processing, and yet controversial since alternative theoretical perspectives have made alternative predictions about the contribution of anterior temporal, posterior temporal and angular gyrus regions to semantic representation and controlled retrieval processes.
- To determine the causal engagement of brain areas implicated in automatic and controlled semantic retrieval over time, using an online inhibitory TMS paradigm
- To contrast the retrieval of taxonomic and thematic relationships in oscillatory activity in MEG

In this way, the thesis work examines the evidence for a potential functional dissociation between ATL and pMTG. According to the Controlled Semantic Cognition framework (Lambon Ralph et al., 2017), these two temporal lobe sites have distinctive roles in semantic cognition. The ATL is argued to correspond to a semantic store; consequently when meaningful inputs are predicted by the structure of long-term conceptual knowledge in this store, facilitation of retrieval might be expected (giving rise to more automatic semantic processing). In contrast, pMTG is implicated in more controlled aspects of retrieval that might promote the accessibility of weaker associations that are not dominant within the ATL representations, yet that are required for the current trial in a semantic task. This framework therefore sets up predictions for the response of ATL and pMTG over time in MEG experiments and for the effect of chronometric TMS applied to these sites. I contrast these predictions with an alternative theoretical perspective which argues that ATL and temporoparietal areas (pMTG and/or AG) maintain different aspects of our semantic knowledge (Schwartz et al., 2011).

In Chapter 2, two experiments are presented, using MEG and online chronometric TMS (cTMS) to characterise the brain's oscillatory response and the critical engagement of ATL and pMTG to judgements about semantic associations between a pair of words. The relationship between these words is either highly coherent with the structure of long-term conceptual knowledge (i.e., the words are strongly associated) or less coherent with the structure of knowledge acquired over the lifespan (i.e., weakly associated). The focus was on how the semantic relationship between two successive items changes retrieval, in order to explore the time-course of changes in oscillatory power that support relatively automatic and controlled retrieval states (Binder, 2016; Lucas, 2000; Gold et al., 2006). ATL and pMTG were stimulated using an inhibitory TMS paradigm at four time points, during the retrieval of strong (largely automatic) and weaker (more controlled) associations, allowing assessment of when these sites showed critical engagement.

Chapter 3 contrasts predictions by the hub-and-spoke model (in which *one* semantic hub is proposed), with the view that ATL is one of *two* conceptual hubs, underpinning taxonomic or category-level knowledge, whereas the TPJ (including AG and pMTG) extracts event associations and thematic knowledge (Schwartz et al., 2011; de Zubicaray, Hansen & McMahon, 2013). This viewpoint is broadly consistent with the idea that the ATL lies at the end of the ventral visual stream, allowing it to integrate concrete features of objects (which are important for conceptual similarity – e.g., a bear is an animal that has fur and claws). In contrast, Schwartz et al. argue that the TPJ may be better placed to integrate information about how objects are used and the contexts in which they are found (e.g. bears are good at fishing and like to eat honey). However, an alternative organisational framework has linked AG in conjunction with ATL to relatively automatic patterns of retrieval, while pMTG in conjunction with LIFG may support controlled aspects of retrieval (Humphreys & Lambon Ralph, 2014; Davey et al., 2015; Whitney et al., 2011; Noonan, et al., 2013; Badre et al., 2005). Chapter 3 investigated this issue by contrasting both taxonomic and thematic relationships, and strong and weak thematic relationships to explore the merits of both proposed frameworks. In addition to the regions examined in Chapter 2 (ATL and pMTG), I included AG, due to its relevance to the dual-hub theory. The task format was the same as for the MEG part of Chapter 2: characterising the brain's oscillatory response to the presentation of written words that were preceded by taxonomically related words, strongly related thematic concepts, and weakly related thematic concepts. In both empirical chapter the terms "prime" and "target" are used to refer to the 1st and 2nd word respectively. Chapter 4 discusses results, conclusions and limitations of the thesis.

Chapter 2: Dynamic semantic cognition: Using magnetoencephalography and chronometric brain stimulation to examine the time-course of automatic and controlled semantic retrieval

Abstract

Semantic cognition depends on both (i) a store of concepts and ideas, which can identify dominant aspects of knowledge relatively automatically, and (ii) controlled retrieval processes that allow non-dominant but task-relevant aspects of this knowledge to be the focus of processing. While the spatial distribution of the semantic system is well documented, the time course of automatic and controlled semantic retrieval remains unclear. This study used magnetoencephalography (MEG) and dual-pulse chronometric transcranial magnetic stimulation (cTMS) in separate experiments to examine the temporal dynamics of automatic and controlled semantic retrieval. In both experiments, participants made judgements about semantic relatedness to word targets preceded by a strongly or weakly related prime. MEG beamforming analysis revealed a functional dissociation within left temporal cortex: anterior temporal lobe (ATL), a key site for semantic representation, showed greater oscillatory response for strong than weak associations, while posterior middle temporal gyrus (pMTG), an area implicated in controlled semantic retrieval, showed the reverse pattern. This difference between conditions emerged at an early time-point in pMTG and was sustained throughout the analysis window, while the effect in ATL emerged more slowly following target onset. In the cTMS experiment, the effect of pulses at four time points (0-40ms; 125-165ms; 250-290ms; 450-490ms) was assessed, and demonstrated that stimulation at~150ms following a strong prime disrupted behaviour; this suggests a necessary role for ATL in relatively automatic semantic retrieval as a coherent pattern of conceptual activation is becoming established. In contrast, stimulation to pMTG at the earliest time point following a weak prime disrupted performance. This strikingly early effect of stimulation may be disruption of context brought from the prime, and may have disrupted the efficient engagement of semantic control when expectations from stable conceptual representations are violated by the input – i.e. a weakly related target. Together these studies provide converging evidence for a functional dissociation within the semantic domain in the temporal lobe, across both tasks and time.

Introduction

Semantic cognition allows us to understand the meaning of our environment to drive appropriate thoughts and behaviour. It comprises several distinct yet interacting components (Jefferies, 2013; Jefferies & Lambon Ralph, 2006; Lambon Ralph, Jefferies, Patterson & Rogers, 2017). Semantic representations capture the meanings of words and objects across contexts, allowing access stable conceptual knowledge from fragmentary inputs and generalisation across situations. However, the retrieval of specific aspects of our knowledge in a context dependent fashion requires control mechanisms that shape evolving retrieval towards semantic features, and away from dominant yet irrelevant associations. The Controlled Semantic Cognition framework suggests that while patterns of activation within the semantic store may be sufficient to uncover links between items that share multiple features or are frequently associated, such as *pear-apple* or *tree-apple*, engagement of control is required to recover non-dominant aspects of knowledge, such as *worm-apple*, since strong but currently-irrelevant associations (e.g., *worm-soil*) must be disregarded – and thus semantic activation must be ‘shaped’ to suit the demands of the task (Lambon Ralph, Jefferies, Patterson & Rogers, 2017; Gold et al., 2006). Although the spatial distribution of automatic and controlled elements of semantic processing are reasonably well described, the temporal dynamics through which these processes operate are less well understood: in particular, little is known about the temporal engagement of control processes when non-dominant aspects of knowledge to be brought to the fore.

Neuroimaging studies have highlighted the importance of a distributed left-dominant network underpinning semantic cognition, including anterior temporal lobe (ATL), posterior middle temporal gyrus (pMTG) and inferior frontal gyrus (LIFG) (Jefferies, 2013; Vandenberghe et al., 1996). These brain regions are recognised to make dissociable contributions to semantic cognition, although their specific roles remain controversial. The ventral ATL is proposed to form a store of amodal conceptual knowledge extracted from multiple inputs (e.g., vision, audition, smell): these representations are capture the conceptual similarity of *apple* and *banana*, even though these items have different sizes, shapes, colours and associated actions (Patterson, Nestor & Rogers, 2007; Lambon Ralph, Sage, Jones & Mayberry, 2010). Evidence for the contribution of ATL to conceptual representation is provided by patients with semantic dementia (SD), who show progressive degradation of knowledge following atrophy and hypometabolism in ATL (Binney et al., 2010; Mion et al., 2010; Rogers et al., 2006). Convergent evidence for the role of this region in multimodal conceptual processing is also provided by PET (e.g. Bright et al., 2004; Crinion et al., 2003; Devlin et al., 2000; Noppeney & Price, 2002; Rogers et al., 2006; Scott et al., 2000), fMRI (Visser et al.,2010a; 2010b) – particularly when magnetic susceptibility artefacts within ATL are minimised, MEG (Lau et al, 2013; Clarke et al., 2011; Marinković et al., 2003; Fujimaki et al., 2009), intracranial electrode arrays (Chan et al., 2011) and TMS (Lambon Ralph et al., 2009; Pobric et al., 2009, 2010a; 2010b).

Furthermore, ATL (as well as angular gyrus) is allied to the default mode network (DMN) (Binder et al., 2003; Davey et al., 2015; Wirth et al., 2016; Jackson et al., 2016). The DMN's core regions are distant from regions serving primary sensory and motor functions, both in terms of patterns of connectivity and across the cortical surface (Margulies et al., 2016), consistent with the hub and spokes account of ATL. Although the maximal semantic response in ATL and angular gyrus is not identical to the site of peak DMN connectivity (Humphreys & Lambon Ralph, 2015; Jackson et al., 2016; Seghier & Price, 2012), these regions resemble other parts of DMN in terms of connectivity and function: they show a larger response to easy or automatic aspects of semantic retrieval, such as identifying dominant aspects of knowledge (e.g., linking DOG with CAT; Davey et al., 2016) and are implicated in spontaneous semantic retrieval during mind-wandering (Binder et al., 2005; Smallwood et al., 2016). This research suggests that the parts of the semantic system that fall within the DMN show a strong response when patterns of semantic retrieval are consistent with the structure of long-term knowledge, and consequently relatively little constraint needs to be applied from additional control systems.

Brain regions distinct from ATL are implicated in the *control* of semantic cognition. fMRI studies have emphasised the recruitment of LIFG in control-demanding semantic judgements (Thompson-Schill, D'Esposito, Aguirre &Farah, 1997; Badre, Poldrack, Pare-Blagoev, Insler & Wagner, 2005; Noppeney, Phillips & Price, 2004; Bedny, McGill & Thompson-Schill, 2008), while evidence for a causal contribution of LIFG to semantic control has been provided by transcranial magnetic stimulation (TMS, Hoffman, Jefferies & Lambon Ralph, 2010; Whitney et al., 2011) and neuropsychology: patients with damage to LIFG have difficulty flexibly tailoring their semantic retrieval to suit the circumstances (Jefferies & Lambon Ralph, 2006; Corbett, Jefferies & Lambon Ralph, 2009). While the contributions of ATL and LIFG align well with the predictions of the Controlled Semantic Cognition framework, the contribution of pMTG remains controversial: some accounts have proposed that posterior temporal areas provide an important store of conceptual representations (Martin, 2007), with pMTG specifically implicated in knowledge of actions and events (Chao, Haxby & Martin, 1999; Martin et al., 1995). Alternatively, a growing literature supports the view that pMTG forms a distributed network with LIFG and other regions to support semantic control (Jefferies, 2013; Davey et al., 2016; Noonan et al., 2013; Gold et al., 2006). A recent meta-analysis showed that a widely distributed set of cortical regions is reliably activated across diverse manipulations of semantic control demands, with pMTG showing the second most consistent response after LIFG (Noonan et al., 2013). Semantic control deficits can follow from either left prefrontal or posterior temporal lesions (Jefferies & Lambon Ralph, 2006; Noonan et al., 2009). In addition, inhibitory TMS to pMTG and LIFG produces equivalent disruption of semantic judgements that require controlled but not automatic retrieval (Whitney et al., 2011; Davey et al., 2015).

Together these findings suggest a functional dissociation within the temporal lobe, with ATL supporting the efficient retrieval of dominant aspects of knowledge, and pMTG allowing non-dominant knowledge to be the focus of semantic retrieval. By this view, there are many forms of semantic representation; some are stable over time (like semantic long-term memory, hypothesised to be located in ATL), whereas others may be more adaptive, and may depend on semantic control regions that are flexibly able to focus on what is currently relevant. One might hypothesise that ATL will show a strong response in conditions in which the pattern of retrieval required by a task is consistent with the structure of long-term knowledge, whereas when a task requires more unusual aspects of knowledge to become the focus of semantic cognition, the response within ATL might need to be constrained by additional control processes and the overall response within ATL might be lower in these circumstances. In contrast, one might predict that pMTG will play a particularly greater role in situations in which the required pattern of retrieval is not consistent with long-term conceptual representations.

To explore this hypothesis two experiments were performed to examine the temporal dynamics of the contribution of these regions during automatic and controlled semantic judgements. In particular two questions were examined (i) Does semantic retrieval in ATL precede the application of control processes in pMTG? and (ii) Does the early engagement of pMTG allow the establishment of controlled retrieval? Existing studies have identified both early semantic responses (within 200ms of stimulus onset) and later effects (around 400ms) in the temporal lobe. The most robust temporal semantic effect is a negative potential between 250-550ms of stimulus presentation, referred to as the N400 (first reported by Kutas & Hillyard, 1980): this effect responds to semantic manipulations across modalities (Kutas & Federmeier, 2011; Marincovic et al., 2003) and has been localised to both ATL (McCarthy, Nobre, Bentin & Spencer, 1995; Lau et al., 2013) and pMTG (Helenius, Salmelin, Service & Connolly, 1998; Halgren et al., 2002). Moreover, a recent chronometric TMS study by Jackson et al. (2015) found that the critical time point of involvement for ATL was around 400ms. The N400 is greater for unexpected meanings (Brown & Hagoort, 1993; Maess et al., 2006), although it also responds to a wide variety of semantic and lexical manipulations (Halgren et al., 2002; Lau, Phillips & Poeppel, 2008) – and it remains unclear whether this effect differs between temporal lobe regions. In addition, emerging work suggests that preliminary semantic processing starts in ATL much earlier than 400ms post-stimulus (Hirschfeld, Zwitserlood & Dobel, 2011; Dikker & Pylkkänen, 2011; Clarke et al., 2012): there is strong early interaction between visual cortex and ATL during the identification of specific-level concepts (Clarke et al., 2011). Thus, there may be early and late semantic effects in the temporal lobe, with later effects related to coherent patterns of conceptual retrieval across modalities and successive items (Marincovic et al., 2003; Bemis &Pylkkänen, 2011) while early effects reflect the engagement of an appropriate neural network reflecting the demands of the task.

Two experiments were conducted to understand the temporal dynamics of controlled and automatic semantic processing in the temporal lobe. In Experiment 1 magnetoencephalography (MEG) was used to describe the rapid changes in neural processing that occur when participants process items following a prime whose association with a subsequent target is either strong or weak. The task required participants to make a decision about the relationship between the prime and target in an MEG-compatible adaptation of a task commonly used in semantic control paradigms (such as in Badre et al., 2005), in which the two items are presented sequentially. The Controlled Semantic Cognition framework (Lambon Ralph et al., 2017) predicts a dissociation between ATL and pMTG: ATL should show greater changes in oscillatory power for strong associations, while pMTG is expected to show a larger response for weak associations. In Experiment 2, chronometric TMS was used to determine the causal role that anterior and posterior regions of the temporal lobe play in semantic cognition when the relevant meaning was either highly or weakly constrained by the preceding stimulus. The Controlled Semantic Cognition framework expects a causal role for pMTG in the retrieval of weak associations which are not well-supported by experiences over the lifetime, while inhibitory stimulation to ATL might reduce the efficiency of semantic retrieval when inputs *are* aligned with experience. Together these two experiments, using different neuroimaging techniques, allow the characterization of how the neural basis of relatively automatic and more controlled retrieval within the temporal lobe emerges over time.

Experiment 1: MEG

Methods

Participants:

Participants were 20 right-handed native English speakers, with normal or corrected-to-normal vision, and no history of language disorders (14 female, mean age 23.3 years, range 20-35). Data from one participant was excluded because of low accuracy on the behavioural task (a minimum of 75% accuracy was required to ensure participants were performing the task successfully). Written consent was obtained from all participants and the study was approved by the York Neuroimaging Centre Research Ethics Committee.

Materials:

The task and stimuli were adapted from Badre et al. (2005). Word pairs were presented, one word at a time, with varying associative strength between the prime and target, and participants were asked to decide if the two words were related in meaning. Participants were presented with 440 target words, paired with either a strong association (n=110), a low association (n=110), or an unrelated prime (n=220). Target words were nouns with a concreteness rating of > 500 (selected using the MRC psycholinguistic database; Wilson, 1988), and were the same across conditions. Strong and weak association primes were created for these words using free association data from the Edinburgh Associative Thesaurus (EAT), by selecting words that were produced relatively frequently by participants (23%) or more rarely (1%); giving a highly significant difference in an associative strength between conditions, t(188)=16.053, *p*<.001 (see Table 2.1 & Table 2.2). Conditions were matched for frequency, length and imageability, with were no significant differences between them. Unrelated primes were created by randomly assigning these words to targets and manually excluding any semantic links when these arose by chance. Each target word appeared twice for each participant, in *either* the strong or weak association condition (not both) and the unrelated condition. All three conditions (strong association, weak association and unrelated) were examined for each target word. The order of items was counterbalanced across participants.

Table 2.1: Measures of frequency, length and imageability for individual conditions

Measure	Condition	Mean	SD
Frequency	Strong	26.6	64.3
	Weak	29.1	38
Length (letters)	Strong	5.5	1.8
	Weak	5	1.5
Imageability	Strong	567.2	60.6
	Weak	577.2	47.9
Association strength (with target)	Strong	0.23	0.189
	Weak	0.01	0.005

Table 2.2: T-tests of frequency, length and imageability between conditions

Measure	Contrast	T	Sig (2-tailed)
Frequency	Strong/Weak	-0.548	0.585
Length (letters)	Strong/Weak	1.417	0.158
Imageability	Strong/Weak	-1.887	0.061
Association strength (with target)	Strong/Weak	16.05	**0.001**

Procedure:

An illustration of the procedure can be seen in Figure 2.1. Nonius lines (acting as a fixation cross) were present at all times. Before each trial, there was a rest period of 800 ms, plus an unpredictable jittered interval from 0 to 1000 ms, designed to reduce anticipatory responses. Prime words were presented for 200 ms, there was an inter-stimulus interval (ISI) of 150 ms, and then the target appeared for 200 ms followed by a 1000 ms interval. After each trial, the nonius lines changed to a dimmer red (for 1200 ms) and participants were encouraged to confine blinking to this period. The task required participants to make a decision about the relationship between the two words; an MEG-compatible adaptation of the task in Badre et al. (2005). While this format closely resembles priming experiments, traditional priming experiments generally utilise lexical decision or pronunciation tasks (which crucially does not require participants to make any judgement on the relationship between the two words), and behavioural measures vary substantially across these tasks (and are furthermore mainly an issue at longer ISIs). From the priming literature you would expect most facilitation for strongly related primes, less (but significant) facilitation for weakly related primes, and no facilitation (but possibly inhibition) for unrelated primes (Neely, J. 1977; 1991). However, these results are for traditional priming tasks that do not require participants to make a judgement of the relationship between the two words. Given that this experiment was concerned with the difference between automatic and controlled semantic retrieval, an overt judgement on whether the words were associated was necessary.

On 10% of the trials, participants were cued to make an overt response by the presence of a question mark (on screen for 1000ms). They pressed one of two buttons with their left hand to indicate if the two words were related. These ‘catch trials’ were used to monitor performance in the task, and were disregarded from the analysis. Because of this small number of trials (designed only to keep participants attending to the task), a behavioural experiment was run out of the scanner, with the same participants, a minimum of 4 weeks before MEG data collection. This experiment was identical to that in the MEG scanner, except the pairings of stimuli – if target word was paired with a strong association prime in the behavioural experiment, the same target would be paired with a weak association prime in the MEG experiment (and vice versa). For data from the behavioural experiment and the catch-trials collected during scanning, see Figure 2.2.

Stimulus presentation:

The experiment was carried out in a dark, magnetically shielded room. Presentation version 16.1 (Neurobehavioral Systems) was used to present the stimuli and to record responses on catch trials. Stimuli were back-projected onto a screen with a viewing distance of ~75 cm, so that letter strings subtended ~1˚ vertically and ~5˚ horizontally at the retina. Light grey letters on a dark grey background were used, such that the screen luminance was in the mesopic range, and a neutral density filter was used to reduce glare.

Data collection:

Before MEG data acquisition, participants’ head shape and the location of five head coils were recorded with a 3D digitizer (Fastrak Polhemus). The signal from the head coils was used to localise participant’s head position within the helmet before and after the experiment. For each participant, a high-resolution structural T1-weighted anatomical volume was acquired in a GE 3.0 T Signa Excite HDx system (General Electric, USA) at the York Neuroimaging Centre, University of York, with an 8-channel head coil and a sagittal-isotropic 3-D fast spoiled gradient-recalled sequence. The 3D digitized head shape of each participant was used for the co-registration of individual MEG data onto the participant’s structural MRI image using a surface-based alignment procedure from Kozinska, Carducci, and Nowinski (2001).Participants were seated in an upright position, with the magnetometers arranged in a helmet shaped array, using a whole-head 248-

channel, Magnes 3600 system (4D Neuroimaging, San Diego, California). Data were recorded in continuous mode, with a sampling rate of 678.17 Hz and pass-band filtered between 1-200 Hz. MEG signals were subjected to a global field noise filter subtracting external, non-biological noise detected by the MEG reference channels, and converted into epochs of 1500 ms length, starting 800 ms before the target onset. All channels from all trials were inspected visually in an artefact rejection process. Data from three malfunctioning channels were automatically rejected for all participants; these channels were the same for all participants. Additional trials were rejected if eye blinks, movement artefacts or external magnetic noise sources were evident. Statistical analyses included only datasets with at least 75% of trials retained after artefact rejection. This cut-off was chosen to ensure quality of data; if the rejected trials reached a proportion higher than 25%, the data would be compromised, either due to participant movements or electrical artefacts, or alternatively, under-powered because of a lack of trials. 20 datasets reached this criterion. On average, 17% of the trials were rejected from these datasets (min 7.3% - max 25%).

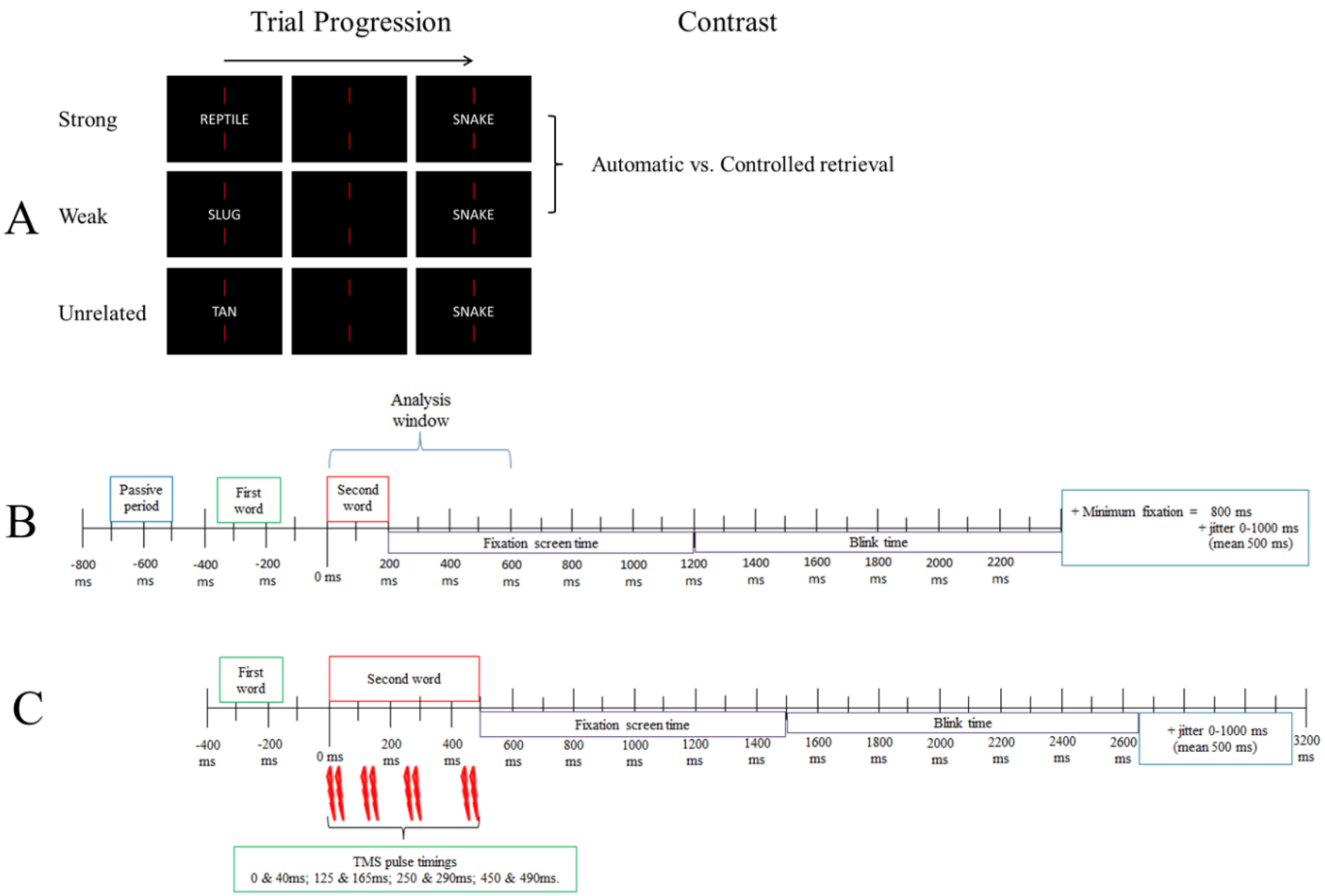


Figure 2.1: Example trials for each condition (text scaled up for visibility; **A**), and timeline of the stimuli presentation for MEG (**B**) and TMS (**C**).

MEG analysis:

The spatial and temporal resolution of the MEG recordings was exploited in a two-step analysis. First, whole-brain analyses examined the neural response to all the related trials (strong and weak) at a coarse frequency and time resolution. Secondly, the activity of specific cortical regions engaged by each condition was interrogated at a finer frequency and temporal scale. In these analyses, Points of Interest (POI) were defined within the temporal lobe (ATL and pMTG), selected on the basis of their importance to theories of semantic processing and defined with reference to local peaks in the whole-brain beamforming data. This analysis strategy allows the roles of specific regions with particular theoretical relevance to the Controlled Semantic Cognition hypothesis (ATL, pMTG) to be examined, using whole-brain beamforming only to select a site for analysis within each of these regions with relatively strong signal (i.e., a local peak).

For both whole-brain and POI analyses, the neural sources of the brain activity were reconstructed with a modified version of the vectorised, linearly-constrained minimum-variance (LCMV) beamformer described by Van Veen et al, 1997, and referred by Huang et al., 2004 as Type I beamformer, implemented in the Neuroimaging Analysis Framework pipeline (NAF, York Neuroimaging Centre), using a multiple spheres head model (Huang et al., 1999), with co-registrations checked manually. An MEG beamformer (spatial filter) allows an estimation of the signal coming from a location of interest while attenuating the signal coming from other points in the brain. This is achieved by constructing the neuronal signal at a given point in the brain as the weighted sum of the signals recorded by the MEG sensors. The sensor weights were determined using an optimisation algorithm, whereby the signal was maximised from the location of interest, and minimised for other locations. Independent beamformers were reconstructed for each point in the brain, in each of three orthogonal current directions. The covariance matrix used to generate the weights of each beamformer was regularized using an estimate of noise covariance as described in Prendergast et al. (2011) and Hymers et al. (2010). This procedure was performed separately for each condition and/or analysis window, in order to obtain an optimal sensitivity to the effect of interest (Brookes et al., 2008; 2011). The outputs of the three spatial filters at each point in the brain (referred to as a Virtual Electrode) were summed to generate estimates of oscillatory power. For the whole-brain analysis, a noise normalised volumetric map of total oscillatory power (i.e., including both the evoked and non-phase locked components) was produced over a given temporal window and within pre-specified frequency bands. For the point of interest analysis, the time course information at the location specified was reconstructed and the time-frequency decomposition was computed using Stockwell Transforms (Stockwell et al., 1999), to obtain higher resolution in time and frequency. This analysis strategy and the parameters used for the current study were similar to those used in recent MEG studies of visual word recognition and object naming (Wheat et al., 2010; Klein et al., 2014; Urooj, 2014). All information necessary to reproduce these analyses is stated below and the analysis pipeline is also in the public domain (http://vcs.ynic.york.ac.uk/docs/naf/index.html).

Whole brain beamforming:

The brain’s response to the task (collapsing the strong and weak trials) was characterised within broad frequency ranges and averaging across 200ms time periods. The purpose of this analysis was to identify brain regions important for the onset of the target in general terms, so these sites could be investigated in more detail in a points-of-interest analysis (see below). The main research question concerned how the brain’s response to the second word (i.e., the target) changed as a function of its relationship to the first word (the prime). Therefore, “active” and “passive” time windows of 200ms duration were contrasted. Active windows were from target onset (0-200ms, 200-400ms, and 400-600ms) until 600ms after target onset. In the passive time window (-700 to -500ms relative to target onset), participants observed the (always present) nonius (fixation) lines. A 3D lattice of points was constructed across the whole brain with 5-mm spacing, and beamformers were used to compute the total power at each point using the Neural Activity Index (NAI; Van Veen et al., 1997) – an estimate of oscillatory power that takes account of spatially-inhomogeneous noise – at each point independently, within the following frequency pass-bands: 5-15 Hz, 15-25 Hz, 25-35 Hz and 35-50 Hz. These frequency ranges were taken from previous MEG studies of reading (Klein et al., 2014; Wheat et al., 2010).

For each individual participant and each frequency band, this analysis produced an NAI volumetric map for the two time-windows or conditions being compared. A paired-samples t-statistic was used to characterise the difference between these maps at each point in space (see

Figure 2.3). Individual participant's t-maps were transformed into standardized space and superimposed on the MNI template brain with the cerebellum removed using MRIcroN software (Rorden, Karnath & Bonhila, 2007). In order to determine whether the difference between conditions or time-windows was statistically significant for each point on the lattice, a null distribution was built up by randomly relabelling the two time points for each participant and each voxel, using the permutation procedure developed by Holmes et al., 1996. The maximum t-value obtained with random relabelling across 10000 permutations was established. I then compared the real distribution of t-values in the data with the maximum t-value obtained from the permuted data. Maximum statistics can be used to overcome the issue of multiple comparisons (i.e. controlling experiment-wise type I error), since the approach uses the highest permuted t value across the brain to provide a statistical threshold for the whole lattice of points, over which the null hypothesis can be rejected (Holmes et al., 1996). Figure 2.3 shows those voxels in the brain with t-values equal or higher than the top 5% t-values present in the null distribution.

Time-Frequency Analysis: Point of Interest (POI):

Separate beamformers were used to reconstruct the neural activity for points of interest (POI) in ATL and pMTG, characterising the response of these regions over time and frequency with greater precision. The focus is on these two sites for comparison with Experiment 2 (cTMS). MNI coordinates for these POIs were local peaks of maximum activation in the group level, whole brain analysis in the 200-400ms time window – allowing the capture of stimulus-driven effects, while still retaining confidence that semantic processing would be ongoing (Pulvermüller, Assadollahi, & Elbert, 2001; Kutas & Hillyard, 1980; Clarke et al., 2011; Yvert et al., 2012). The data supported placement of VEs at the following locations: left ATL (MNI coordinates -48,8,-18) and pMTG (MNI coordinates -50,-52,8; the VE coordinate for pMTG was projected laterally towards the surface as the local peak was medial (actual peak location at MNI coordinates -42, -46, 4). It was also elected to examine left-hemisphere sites only since (i) stimuli used in experiments were written words only; (ii) fMRI and patient studies reveal a greater contribution of the left hemisphere to semantic processing in general (Binder et al., 2009); and (iii) right motor cortex was expected to show irrelevant responses related to the preparation of button presses with the left hand, even though button presses were only required on catch trials, given that the presence of a catch-trial was indicated by a question mark *after* the two words were presented).

After the time-series of each POI was reconstructed epoch by epoch, for each subject, by means of separate beamformers (Huang et al., 2004), time-frequency plots were computed using Stockwell transforms (Stockwell, Mansinha, & Lowe, 1996) over a time window from -800 to 700 ms (to avoid edge effects) and a frequency range from 5-50 Hz. The Stockwell transform, implemented in the NAF software, uses a variable window length for the analysis which is automatically adapted along the frequency range according to the sample rate and the trial length (4th order Butterworth filters with automatic padding).

To compare the time frequency representations between experimental conditions, generalized linear mixed models (GLMM) were computed using PROC MIXED in SAS (SAS Institute Inc., North Carolina, US). Time-frequency plots of percentage signal change were treated as two dimensional arrays of small time-frequency tiles, indexed in the model by three main effects, each of which is defined as a class variable: time, frequency and the interaction between time and frequency. Therefore, random effects were included in each GLMM to account for the fact that each participant's time-frequency plot is made up of multiple time-frequency tiles. Time-frequency (or spatial) co-variance in the spectrogram was controlled for by assuming the estimates of power followed a Gaussian distribution: consequently a Gaussian link function was used in the model. The time-frequency (spatial) variability was integrated into the model by specifying an exponential spatial correlation model for the model residuals (Littel et al., 2006). Finally, the data were resampled at a frequency resolution of 2.5Hz and time resolution of 25ms, the smallest time and frequency bin consistent with model convergence. This time-frequency resolution proved optimal in other similar published studies (Klein et al., 2014; Urooj et al., 2014; Wheat et al., 2010). PROC MIXED constructs an approximate *t* test to examine the null hypothesis that the LS-Mean for percentage signal change between conditions was equal zero in each time-frequency tile, and the procedure automatically controls for multiple comparisons (i.e. controlling experiment-wise type I error). This method has been used in multiple peer-reviewed papers (Klein et al., 2014; Urooj et al., 2014; Wheat et al., 2010).

The time-frequency representations of total power were normalized, separately for each condition and for each participant, with respect to the mean power per frequency bin in a baseline period prior to the start of trials in that condition (-700 to -500 ms). This window length was also used in earlier studies (Wheat et al., 2010; Klein et al., 2014), since it provides a compromise between the minimum length sufficient to estimate power at the lowest frequency reported here (i.e., 5Hz) and the requirement to characterise the state of the brain immediately before the onset of each trial. The statistical contours on the percentage signal change figures for total power encompass time-frequency tiles fulfilling both of the following criteria: a) the difference between conditions reached $p < 0.05$; b) any region in the time-frequency plot defined by (a) also showed a response that was significantly different from zero in at least one of the two contributing conditions.

Results

Behavioural experiment

Results from the behavioural experiment revealed faster reaction times in the strong compared with both the weak and unrelated conditions (t(19)=-6.80, p<.001 and t(19)=-5.46, p<.001 respectively), see Figure 2.2. Accuracy was lower in the weak condition compared with both the strong and unrelated conditions (t(19)=7.77, p<.001 and t(19)=-5.359, p<.001), but no significant difference between the strong and unrelated condition (see Table 2.3). While traditional priming experiments would normally show facilitation priming for weakly related concepts (as well as strongly) compared with unrelated primes, this is not found here. Traditional priming experiments measure the behavioural effect on the processing of a word preceded by a related word (like the task here), but does not require participants to make any judgement on the relationship between them (generally a lexical decision or word naming task is used). This is likely what is driving the longer reaction time in the weak condition; while weak associations may facilitate reaction time when the semantic relationship is not explicitly probed, it would seem that the weakly related concepts have a processing cost in semantic decisions – when required to respond in this condition, participants must reject the incorrect judgement that the two words are unrelated. Though reaction times are

generally longer in the experiment during MEG acquisition, the data follow the same pattern, with a significant difference between strong and weak conditions (t(19)=-4.11, p<.001), and very near significant difference between both strong and unrelated trials (t(19)=-1.961, p=0.057), and weak and unrelated trials
(t(19)=1.946,p=0.059).

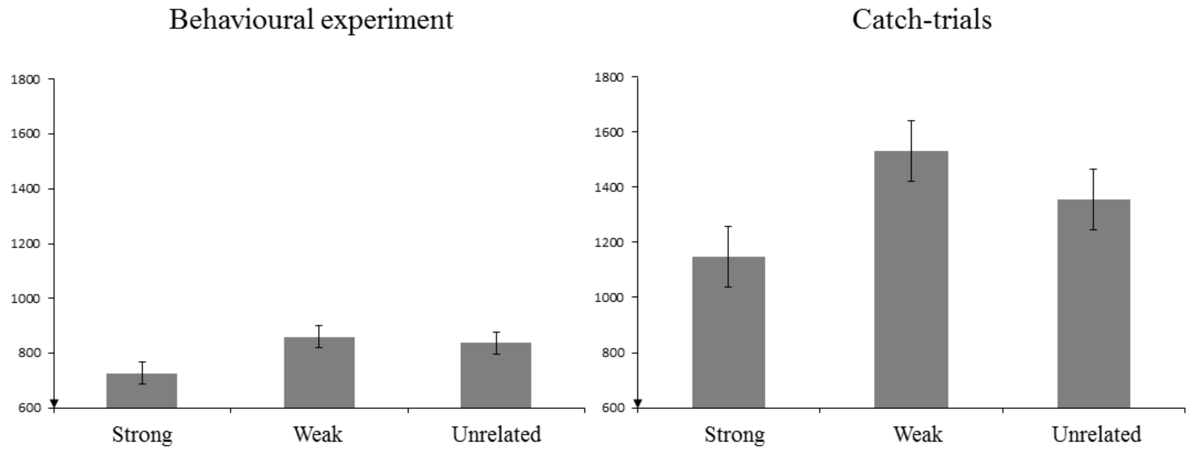


Figure 2.2 Reaction time data from the behavioural experiment (left) and the catch-trials collected during scanning (right).

Table 2.3: Accuracy data for the behavioural experiment and catch-trials.

	Mean	**SD**
Behavioural experiment		
Strong	0.946	0.048
Weak	0.826	0.095
Unrelated	0.948	0.028
Catch-trials		
Strong	0.948	0.029
Weak	0.777	0.071
Unrelated	0.946	0.047

Whole-brain results

The response to the task as a whole (i.e., the response to the second word of the pair, when the semantic judgement commenced, versus a period prior to the start of the trial), is shown in Figure 2.3. The most extensive changes in total power in response to the task were power decreases, relative to the resting passive period, in the 25-35Hz frequency band (shown below), although other frequency bands showed similar effects. These decreases in total oscillatory power were focussed on temporal, occipital and inferior frontal and parietal lobe regions implicated in visual and semantic processing (ATL, pMTG, LIFG), starting within the first 200ms and lasting for at least 600 ms after target presentation. Decreases in total power are commonly interpreted as reflecting an *increase* in neural activity that is not phase-locked to stimulus presentation (Hanslmayr et al., 2012): reductions in power have been shown to correlate with an increased BOLD response in fMRI (Hanslmayr et al., 2011; Singh et al., 2002; Hall et al., 2014), and a recent review proposed that decreases in total power reflect active engagement of neocortex in the encoding and retrieval of memories (Hanslmayr, Staresina & Bowman, 2016). Thus, the whole-brain beamforming results are consistent with an increase in visual and semantic processing.

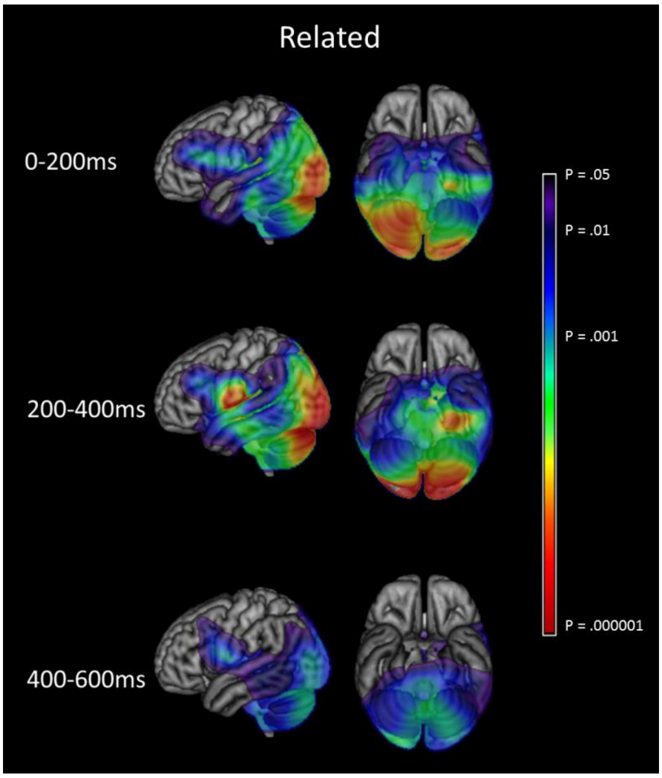


Figure 2.3: Whole-brain beamforming results for the 25-35 Hz frequency band, showing differences in total oscillatory power between an active period following target onset and a passive period prior to each trial. The first 600ms following presentation of target word are displayed, in 200ms windows. Task effects were decreases in total power in all cases. The images show a t-value map, thresholded at $p<.05$. Images were generated using MRICron (Rorden, Karnath & Bonhila, 2007).

Points of interest results

Whole epoch data for each site

Total power time-frequency plots of the whole epoch were examined for each POI. Figure 2.4 shows the response to the prime (1st word) and target (2nd word) in each semantically-related pair. Yellow-red colours indicate *power increases*, whereas cyan-blue colours indicate *power decreases* relative to the passive baseline period. Green indicates ‘no change from baseline’. In both sites, there was a subtle increase in oscillatory power in response to the first word, while the presentation of the second word was characterised by a large *reduction* in total oscillatory power relative to the passive period – this effect followed the offset of the first word (with slight timing variations across the three sites), and became stronger and encompassed more frequency bands in response to the onset of the second word.

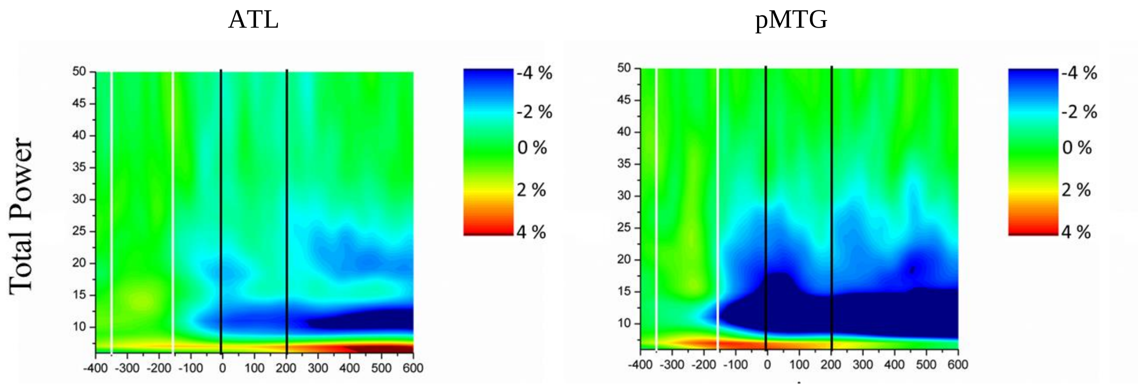


Figure 2.4: Total oscillatory power across the whole epoch for related trials, including both words presented in the relatedness judgement task. Presentation of the prime word (first word of the pair) is shown with white vertical lines, while presentation of target word (second word of the pair) is illustrated with black vertical lines. Yellow-red indicates regions of *power increase* relative to the baseline, while cyan-blue indicates *power decreases* relative to the baseline, and green indicates no change from baseline

Differences between conditions in POIs

ATL showed a greater change from baseline to strongly than weakly-related targets, from 400ms post-target onset until the end of the epoch at 7-12 Hz (see Figure 2.5). PMTG, in contrast, showed stronger changes in oscillatory power for weakly-related targets. This effect of the reverse contrast started within 50ms of target onset and lasted throughout the epoch (50-550ms, 12-33Hz). In addition, there was a significant response to both conditions of the task, relative to the passive period, throughout the epoch, in beta and low gamma, at both sites.

Summary of MEG results

The results suggested a temporal dissociation in the temporal lobe that depended on the ease with which the target stimuli could be associated with the prime. ATL showed a strong response to both conditions early but showed greater oscillatory power for strong than weak associations 400ms after target onset. This effect might reflect evolving patterns of activation within ATL that are strengthened by semantic priming (Feng et al., 2016; Binder, 2016). In contrast, pMTG showed greater oscillatory power for weak than strong associations immediately after target onset and throughout the epoch, suggesting this site might be critical for detecting when inputs are not consistent with the anticipated meaning, and then maintaining this information to bias ongoing retrieval in ATL, as anticipated by the Controlled Semantic Cognition model (Lambon Ralph et al., 2017). ATL showed a greater response to strongly related semantic concepts, consistent with this region’s hypothesised involvement in automatic semantic retrieval. PMTG on the other hand, showed a greater response to weakly related word pairs, consistent with this region’s hypothesised contribution to controlled semantic retrieval. In addition, the sites showed a dissociation in terms of the time-course of their differential response during the retrieval of strong vs. weak associations.

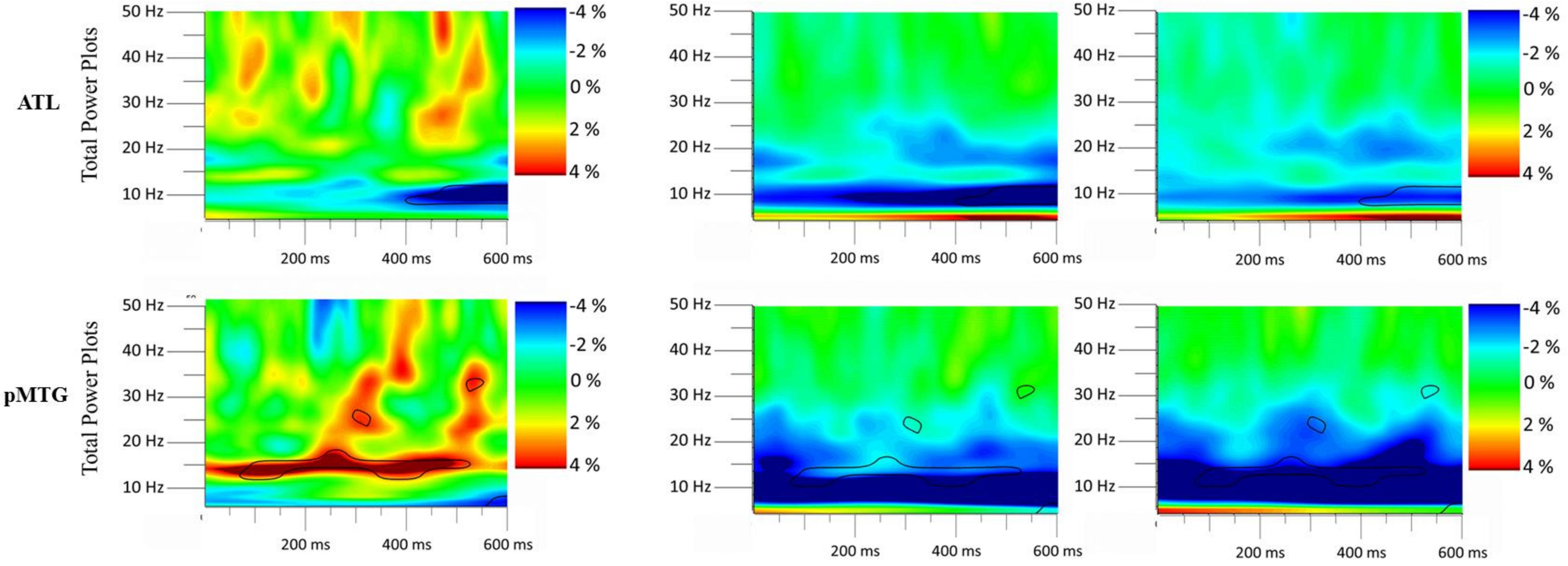


Figure 2.5: A) Difference TF plot**:** Percentage difference between strong and weak conditions for ATL and pMTG. Black lines on the plots indicate p<.05 statistical threshold fulfilling two criteria: i) conditions are significantly different from each other and ii) this also reflects a significant change from baseline in at least one of the two conditions. Yellow-red colours in this plot indicates regions of time-frequency where oscillatory power levels were higher for strong associations, while cyan-blue colours indicate the reverse, i.e. higher values for weak associations (note that since the effects are in power reductions, yellow-red colours actually means the weak condition is driving the effect). **B)** Strong associations TF plot: Percentage signal change in the strong condition (relative to baseline). **C)** Weak associations TF plot: Percentage signal change in the weak condition (relative to baseline). In both **B and C** plots, yellow-red colours indicate regions of *power increase* relative to the baseline, while cyan-blue indicates *power decreases* relative to the baseline, and green indicates no change from baseline.

Experiment 2: Chronometric TMS

Experiment One demonstrated that the temporal dynamics of neural processing across different regions of the temporal lobe depended on the ease with which a stimulus could be associated with a prime. Anterior regions of the ATL showed a pattern of activation that began early following stimulus and was subsequently reduced in trials when the association between stimulus and prime was relatively weak. By contrast, in pMTG a pattern of consistent neural activation was observed when the association between the target and the stimulus was harder to determine. To determine the causal role that these temporal dynamics play in semantic association, Experiment Two used chronometric TMS to disrupt processing in these two regions at different points during semantic cognition in order to identify whether (a) disrupting the pMTG at the moment of onset for a stimulus with only weak associations with the prime impaired semantic processing, consistent with a role of this region as inhibiting the spreading activation associated with dominant, and irrelevant, associations and (b) whether disrupting the ATL later during stimulus presentation impaired performance in strong trials consistent with a role of this regions as supporting the convergence on a dominant meaning through a pattern of spreading activation.

Methods

Participants:

Participants were 15 right-handed native English speakers, with normal or corrected-to-normal vision, and no history of language disorders (8 males, mean age 23, age range 20-32 years). Written consent was obtained from all participants and the study was approved by the York Neuroimaging Centre Research Ethics Committee.

Design

The experiment employed a 3x2x4 repeated measure design, with site (ATL, pMTG and sham mid-MTG, stimulated at 30%), task (semantic association task and digit parity judgement task), and TMS timings (0ms; 125ms; 250ms and 450ms) as the three within-subject factors. Sham stimulation at 30% was chosen because this intensity is thought to be too weak to produce a neural effect, but it still mimics the sound and scalp sensations of TMS stimulation (Duecker et al., 2013). At each time point, a pair of pulses 40ms apart were applied, since this dual-pulse method is thought to generate more significant behavioural disruption than single pulses (Gagnon, Schneider, Grondin & Blanchet, 2011; Strafella & Paus, 2001; Chen, 2000). Thus, pulse timings were 0-40ms; 125-165ms; 250-290ms; 450-490ms. The anticipation was that these stimulation times would allow me to explore very early effects (occurring before or around the onset of the target), effects linked to visual-ATL interactions at around 150ms (such as those characterised by Clarke et al., 2011), and early and later N400 effects. Unlike other chronometric TMS experiments, here the effect of online stimulation was examined from the onset of a second word in a pair (presented sequentially). Consequently, relatively early disruption might be expected – for example, effects within the first 200ms at ATL, corresponding to the time period when Clarke et al. observed interactions between visual and semantic processes, as opposed to late effects such as those observed by Jackson et al. (2015). Very early disruption following stimulation of pMTG might also be expected, given findings from Experiment 1 that pointed to rapid sensitivity to weak associations at this site, which could correspond to detection of the need to engage controlled retrieval processes.

Materials

The semantic task was the same as for Experiment 1. Word pairs were presented sequentially, and participants decided whether the two words were related or not. The pairs were either strongly or weakly associated, or were unrelated. Each session had 70% related trials (which were the focus of this analysis) and 30% unrelated trials (to maintain attention to the task). The same target words were presented across conditions, though each target was only presented once per session. The strong and weak conditions were matched for frequency, length and imageability with no significant differences between them (see Table 2.4 and 2.5).

Table 2.4: Measures of frequency, length and imageability for individual conditions

Measure	Condition	Mean	SD
Frequency	Strong	17.43	32.38
	Weak	19.28	32.91
Length (letters)	Strong	5.62	1.81
	Weak	5.48	1.51
Imageability	Strong	560.22	69.54
	Weak	554.79	70.37
Association strength (with target)	Strong	0.43	0.19
	Weak	0.03	0.06

Table 2.5: T-tests of frequency, length and imageability for individual conditions

Measure	Contrast	T	Sig (2-tailed)
Frequency	Strong/Weak	-0.44	0.66
Length (letters)	Strong/Weak	0.68	0.49
Imageability	Strong/Weak	0.52	0.61
Association strength (with target)	Strong/Weak	22.78	**0.001**

A non-semantic task involving numerical judgements was also used, which was designed to match the semantic task in overall difficulty. Two three-digit numbers were presented sequentially, and subjects were asked to decide whether *both numbers* were odd or even numbers. The proportion of yes/no trials was identical to the semantic task (i.e., 70% match trials; 30% non-match trials). One participant was tested on the same semantic tasks but a different number judgement task and is excluded from the statistical comparisons of semantic vs. digit task performance.

There were 25 trials per site and TMS time (25*3*4), for each condition (strongly related, weakly related and unrelated). For the digit task, 100 pairs of three-digit numbers were used; 25 for each TMS timing.

Stimulus presentation

The three experimental sessions were divided into 5 runs, each lasting approximately 12 minutes. TMS was delivered in 4 of the 5 runs, and a block without TMS was placed in the middle of the 5 runs for safety reasons. Each run was made up of 6 blocks for each task (numerical or semantic), each with 16 trials, lasting around 60 seconds. Blocks were arranged in pseudorandom order to minimise task switching costs. When switching between tasks, a short instruction screen informed the participant which task would be presented next. The first trial after the task switch was a dummy trial which was discarded from further analysis. Primes were presented for 200ms, followed by an inter-stimulus interval (ISI) of 150ms, and then the target appeared for 500ms. The nonius lines remained on screen for 1000ms, and were then dimmed for 1150ms after the participant’s response, to signal the end of the trial. Following this, the bright nonius lines returned, to cue the onset of the next trial, for a randomly variable interval of 0-1000ms (500ms on average) before the onset of the first word. Each trial lasted on average 3500ms. Participants responded with their right hand. Before starting the experiment, participants performed a practice session with 10 trials of both tasks (without TMS), and three practice trials with stimulation. Participants took self-paced breaks between the runs.

Stimulation sites

TMS was applied to left ATL, left pMTG, and a sham site in the mid-temporal lobe (halfway between these two sites). Stimulation sites were taken from published studies and were similar to the peak responses in the temporal lobe from whole-brain beamforming in Experiment 1. The left ATL site was in anterior ventrolateral temporal cortex (MNI -51,6,-39; coordinates from Binney et al., 2010). This site showed greater activation for synonym judgement vs. numerical magnitude judgement in fMRI, and was located close to the region of peak atrophy in semantic dementia. The left pMTG site was taken from a meta-analysis of imaging studies of semantic control by Noonan et al. (2013; MNI -58,-50,-6). This site activates across a wide range of manipulations of semantic control, including showing a stronger response to weak than strong associations (Davey et al., 2016; Gold et al., 2006). The sham control site was selected by finding the midpoint on the y-axis between the two experimental sites, varying the z coordinate to deliver stimulation to the middle temporal gyrus, and varying the x coordinate to maintain the stimulation target near the cortical surface area.

TMS stimulation protocol

Chronometric TMS was delivered using a Magstim Rapid2 stimulator and a 50 mm diameter figure-eight coil. Stimulation intensity for ATL and pMTG was 60% of the maximum output of the stimulator. Stimulation for the sham site was 30% of the maximum output of the stimulator. Dual-pulse TMS was delivered at 25Hz, with the two pulses 40 ms apart in each trial (see Figure 2.1 for illustration). Trials in the different timing conditions were arranged in an ascending or descending staircase of 4 trials (four trials with stimulation at 0ms followed by four trials of stimulation at 125ms etc.). This was done to limit the subjects' awareness of the different TMS timings, and reduce the tendency of participants to wait until stimulation has been delivered before responding (Sliwinska et al., 2012). Following safety guidelines (Rossi et al., 2009), an inter-train interval of 5000ms was added after 24 subsequent pulses. Where possible this interval corresponded to the task switching instruction screen, in other cases it was added after the response.

Analysis

The key research question considered the effect of TMS on judgements about strong and weak semantic relationships between a prime and a target word. A generalised linear mixed models (GLMM) was used to examine the effects of task condition (e.g., strong vs. weak association with the preceding prime word), site (ATL, pMTG), time of TMS (i.e., pulses at 0-40ms; 125-165ms; 250-290ms; 450-490ms after the onset of the second word), and their interactions, on the magnitude of the TMS effect (by computing the difference in response time between the post-TMS and the sham sessions, trial-by-trial), while controlling for effects of the structure of the experiment (session and block order). This model allowed the comparison of the effect of TMS for strong and weak words at each time point using pairwise contrasts, controlled for multiple comparisons. The key dependent measure was response time (RT), since previous TMS studies have reported consistent slowing for semantic decisions following inhibitory stimulation, and little effect on accuracy (Walsh & Cowey, 2000; Pasqual-Leone, Walsh & Rothwell, 2000; Devlin, Matthews & Rushworth, 2003). Supplementary analyses, characterising (1) the effect of TMS on accuracy for strong and weakly-related targets and (2) the effect of TMS on semantic judgements overall (vs. numerical judgements) highlighting non-specific effects of TMS on RT and accuracy, are reported in the Supplementary Materials. In the analysis of RT below, it was confirmed that the key results were unchanged when accuracy was controlled for in each block, and when performance on the numerical task was controlled for, by including these measures as covariates. This was an item-by-item analysis, which allows the inclusion of many more data points in the analysis. Though the study has 15 subjects, this analysis means that each condition is not the average per participant, but all trials within the condition for each participant; the total number of observations included in the analysis was 5041.

Results

Reaction time and accuracy data for each site and stimulation time can be seen in Supplementary Table 2.1 in Supplementary Materials. The TMS effect on high vs. low associations was examined using a generalised linear mixed model (GLMM) examining trial-by-trial RT data, implemented using PROC MIXED in SAS. Incorrect responses and outlying data points that fell more than 2 SD from each participant's mean RT were removed, for each session, prior to analysis. The fixed effects were site (ATL, pMTG), TMS time, condition (strong vs. weak) and their two- and three-way interactions using a fully-factorial design. In this analysis, it was possible to compute the trial-by-trial difference between RT in the ATL or pMTG session and the corresponding trial in the sham session, and these difference scores (which reflect the TMS effect) were used as the dependent measure. The model also included covariates controlling for effects of block and session order as above, as well as mean accuracy per block, and RT on the number control task to account for non-specific effects of TMS (see supplementary materials). The per-subject intercept was included as a random effect.

The results of this analysis are shown in Table 2.6. There were significant main effects of TMS time and site on the magnitude of the TMS effect, with a significant interaction between condition (strong vs. weak) and TMS time, and an interaction between site and TMS time that was approaching significance. The covariates of block and session order, and number RT (i.e., non-specific effects of TMS) were also significant. Pairwise t-tests, controlled for multiple comparisons, were used to examine the time-course of the involvement of ATL and pMTG in semantic decisions to strong and weak associates. Of the eight comparisons that compared the size of the TMS effect for strong and weak associations at each site and at each time, two were significant. There was a larger TMS effect for strongly-related than for weakly-related pairs following stimulation of ATL, when pulses were applied at 125-165ms after the onset of the second word ($t(5026) = 2.26$, $p = .024$; see Figure 2.6). At the other time points, the magnitude of the TMS effect was equivalent for the strong and weak associations ($t < 1$). Thus, these results suggest that around 150ms post-presentation of the second word, ATL makes a critical contribution to the efficient retrieval of strong semantic relationships: these trials are expected to be supported by unconstrained spreading activation within the conceptual store.

There was also a larger TMS effect for weakly-related than for strongly-related pairs following stimulation of pMTG when pulses were applied at 0-40ms post-onset of the second word ($t(5025) = -2.08$, $p = .037$; see Figure 2.6). At the other time points, the magnitude of the TMS effect was equivalent for the strong and weak associations: $t < 1$ at 125-165ms and 250-290ms; $t = -1.45$, $p = .15$ at 450-490ms. This very early differential response suggests that pMTG may make a critical contribution to the capacity to engage controlled retrieval when it is needed. Stimulation at this early point may disrupt the maintenance of current contextual information generated by the prime word. This could disproportionately affect weak associations if, for example, pMTG plays a critical role in detecting the need to employ controlled retrieval.

Table 2.6: Effect of TMS on RT for strong and weak associations

	d.f.	**F**	**p**
Fixed effects			
TMS time	3, 5018	7.69	<.001
Condition (strong vs. weak)	1, 5030	<1	> .1
Site (ATL vs. pMTG)	1, 4957	13.44	<.001
Condition by TMS time	3, 5025	2.92	0.03
Site by TMS time	3, 5025	2.29	0.08
Condition by site	1, 5025	2.68	0.10
3-way interaction	3, 5024	<1	> .1
Covariates			
Block order	3, 5024	15.83	<.0001
Session order	2, 4638	4.36	0.01
Mean task accuracy per mini-block	1, 5037	<1	> .1
Number RT per mini-block	1, 1972	190.63	<.0001

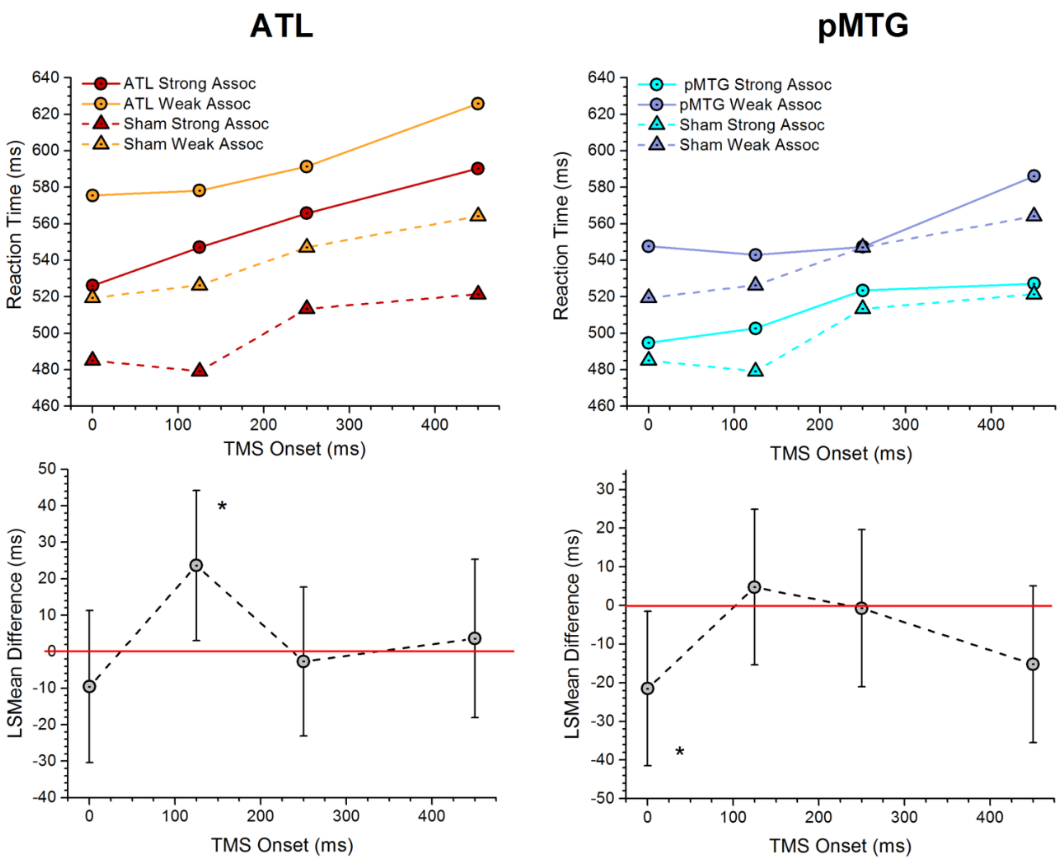


Figure 2.6: Effect of TMS on RT for strong and weak associations. TOP ROW: RT (in ms) for the strong and weak conditions for ATL (left) and pMTG (right). RT data for the strong and weak condition for the sham site is showed in dashed lines. These plots show the raw (un-modelled) means. BOTTOM ROW: A comparison of LSMeans differences for strong and weak conditions, comparing the experimental sites (ATL and pMTG) with sham stimulation trial-by-trial. Data points above the red line indicate greater disruption for the strong condition, while data points below the red line indicate greater disruption for the weak condition. Significant differences between strong and weak trials are marked with asterisks.

Discussion

A significant body of research has characterised the brain regions that support semantic processing but less is known about the temporal evolution of semantic retrieval across these regions. While studies have examined the time course of semantic access from written words and pictures (Dikker & Pylkkänen, 2013; Halgren et al., 2002), the focus here was on how the strength of the semantic relationship between two successive items is reflected in (i) changes in oscillatory power over time, as measured by MEG; and (ii) vulnerability to inhibitory online brain stimulation, using chronometric TMS. In both studies, the same behavioural paradigm was used to explore the functional and temporal organisation of semantic processing in the anterior and posterior temporal lobe (ATL and pMTG). Previous work has associated ATL with the retrieval of strong associations, in conjunction with other regions in the default mode network (Davey et al., 2016; Jackson et al., 2015; Humphreys et al., 2015), while controlled retrieval is thought to engage semantic control processes in pMTG, in conjunction with LIFG, to allow non-dominant aspects of meaning to come to the fore. In line with predictions, stronger task-induced changes in oscillatory power for strong > weak associations were found in ATL, plus weak > strong associations in pMTG using MEG, and confirmed a causal role for these sites in the retrieval of strong and weak associations respectively using cTMS. Strong semantic priming might facilitate access to semantic features and associations and increase the richness of semantic retrieval in ATL (Feng et al., 2016), while a strong response to weak associations might reflect the application of controlled retrieval processes (Gold et al., 2006). Timing differences between the sites were also found: ATL showed stronger oscillatory power for the strong associations around 400ms post-target onset, while pMTG responded more strongly to weak associations, throughout the analysis window, from the onset of the target. Moreover, TMS delivered to pMTG at the point of target onset impaired the efficient retrieval of weak associations, while TMS to ATL disrupted performance for strong associations at 150ms, at the point when a strong task-related response was observed in the MEG data (even though the difference between strong and weak conditions was not significant until later). Thus, the MEG and TMS results followed the same temporal sequence across sites, although the critical time for disruption preceded the emerge of condition differences in MEG. Below, the contributions of ATL and pMTG to semantic cognition in light of these findings are discussed:

Anterior temporal lobe: The ATL is proposed to form an amodal semantic hub, which represents conceptual information (alongside modality-specific ‘spokes’; Patterson, Nestor & Rogers, 2007; Rogers et al., 2006; Coutanche & Thompson-Schill, 2014). ATL is important for accessing conceptual knowledge from visual inputs – a process that activates the ventral visual stream which terminates in ATL (Visser, Jefferies, Embleton & Lambon Ralph, 2012; Visser, Jefferies & Lambon Ralph, 2009). MEG studies have already examined this aspect of ATL processing and have identified responses in this region within 120ms of stimulus onset (Clarke et al., 2013; Fujimaki et al., 2009; Yvert et al., 2012). In resting-state fMRI, this site also shows strong connectivity to regions of the default mode (Davey et al., 2015; Jackson et al., 2015), and it is implicated in automatic semantic access and retrieval (Lau et al., 2013; Davey et al., 2016). These findings are highly consistent with this emerging story about the contribution of the ATL to semantic processing but add several important elements:

Here beamforming was used to characterise the response in ATL to strong and weak associations in total oscillatory power. In contrast, other MEG studies localising semantic effects to ATL have largely used measures maximally-sensitive to evoked power (Halgren et al., 2002; Bemis & Pylkkänen, 2011; Westerlund & Pylkkänen, 2014; Zhang & Pylkkänen, 2015; Lau et al., 2014; Fujimaki et al., 2009). Total power includes both phase-locked components and signals that are *not* phase-locked to the onset of the stimulus. Since the emergence of coherent semantic activation over time draws on long-term knowledge of the meanings of words across contexts, one might expect this process to generate neural oscillations that are not directly linked to stimulus onset. In line with these considerations, strong task-induced decreases in total power to the target were found in both ATL and pMTG. Power reductions relative to a no-task baseline were not seen in response to the presentation of the prime word, and therefore this response to the target could be a marker of the retrieval of meaning at least partly decoupled from the stimulus itself. This interpretation of effects draws on the view that power decreases are not necessarily associated with a decrease in neural activity (Hanslmayr et al., 2012; Hanslmayr, Staresina & Bowman, 2016): according to Hanslmayr et al. (2012), decreases in total power can reflect an increase in desynchronised neural activity that allows the representation of richer informational content, and results may be interpreted within this framework – strong associations allow participants to recover richer semantic information within ATL, and this is associated with a stronger task-related decrease in total oscillatory power at 400ms post-target.

It was found that TMS to ATL disrupts the efficient retrieval of strong more than weak associations at 150ms post-stimulus onset – i.e., at the point when interactions between visual cortex and ATL are thought to become established (Clarke et al., 2011; 2012). In the MEG data, there was a strong task-related response in ATL by 150ms, although there was not yet a significant difference between the strong and weak conditions. Thus, the emergence of stronger coherent semantic activation for the strongly-linked items may have been vulnerable to perturbation from TMS at an early time point before the pattern of response within the ATL was well-established. Although a previous cTMS study found disruption when TMS pulses were applied to ATL at 400ms post-trial onset (Jackson et al., 2015), this study did not examine differential disruption of strong vs. weak associations, and used simultaneous rather than successive presentation of probe and target – thus the timings are unlikely to be comparable.

Posterior middle temporal gyrus: While the importance of ATL for conceptual representation is relatively widely accepted, there is considerable controversy about the role of pMTG in semantic cognition, since dominant theoretical frameworks have suggested that this site (i) represents particular aspects of lexical or semantic knowledge – such as event representations; or (ii) supports controlled semantic cognition as part of a large-scale network that includes LIFG. Studies have shown a common response in pMTG and LIFG using a wide range of manipulations of semantic control – including contrasts of ambiguous over non-ambiguous words, decisions with strong vs. weak distracters, and the retrieval of weaker vs. stronger semantic links, in paradigms similar to the one adopted here (Noonan et al., 2013). pMTG is functionally connected to both LIFG and ATL, suggesting this region may be well-placed to control retrieval from the semantic store (Davey et al., 2016). TMS studies have convergently shown disruption of weak but not strong semantic association judgements when inhibitory stimulation is applied to pMTG (Whitney et al., 2011; Davey et al., 2015). When the relationship between probe and target is weak, the probe will tend to activate features and associations that are irrelevant to the decision that has to be made, and consequently semantic retrieval may have to be shaped to suit the task demands – irrelevant information must be suppressed while non-dominant aspects of knowledge are brought to the fore. The current data support the role of pMTG in controlled aspects of semantic retrieval: moreover, while previous studies have commonly focussed on showing *similarities* between LIFG and pMTG (Noonan et al., 2013; Whitney et al., 2011a and 2011b), these findings show an important functional dissociation for the retrieval of weak and strong associations between different sites within the temporal lobe.

The temporal aspects of these results place important constraints on theories of controlled semantic retrieval: pMTG might show a relatively late response to the weak > strong contrast, if controlled retrieval takes time to become established, and reflects a re-interpretation or re-shaping of semantic activation following initial semantic retrieval driven by the written input. Alternatively, pMTG might show an early response to the weak > strong contrast, if this site is important for maintaining information that is currently relevant and triggering the recruitment of the semantic control network when incoming information is not strongly coherent with ongoing semantic retrieval. pMTG may be able to reduce the propagation of dominant features and associations recovered from ATL into the DMN when initial processing of new inputs suggests that these aspects of knowledge may be insufficient for comprehension.

The current data support the second of these two alternatives. In MEG, the weak > strong effect commenced within 50ms of target-onset and continued throughout the analysis window. Using cTMS, evidence for an early role of pMTG was found in the efficient retrieval of weak associations, since there was greater disruption of weak trials when TMS was applied at target onset. The experimental design presented words sequentially (not concurrently), and consequently the findings are consistent with the hypothesis that pMTG maintains currently relevant features or interpretations and detects situations in which incoming information is not well-aligned with these interpretations. This effect appears to occur prior to semantic processing for the second word, when the contribution of pMTG to “context maintenance” should be equivalent for the strong and weak conditions. However, disruption of this maintenance process might only disrupt the efficiency of semantic judgements when the associations being retrieved do not align with the structure of long-term conceptual representations (i.e., the weak associations). In contrast, for strong associations, information about the current context might not be required since the pattern of retrieval required by the task is well-supported by long-term semantic representations. The disruptive effect of stimulating pMTG might be greatest very early on, before semantic retrieval has been established for the second word, as at later points in the paradigm, the pattern of retrieval to the second item is expected to be already consistent with the requirements of the task. To confirm this interpretation, further research could assess the effect of inhibitory TMS delivered prior to the start of the second word.

The analysis of total power across the whole epoch also revealed task-related decreases in power in pMTG that were marked by the offset of the prime and sustained throughout the interval between the two words. This observation is consistent with the interpretation offered above; that pMTG may maintain currently-relevant semantic information determined by the context, allowing controlled retrieval processes to be engaged at an early stage when inputs are not readily coherent with features that are being maintained. This perspective is further consistent with studies showing that pMTG is not crucial for all forms of semantic control – for example, it does not show strong effects when a goal provided by the task instructions has to be applied to semantic retrieval in an effortful way: instead, it shows strong engagement when the inputs themselves determine a context that requires semantic retrieval to be shaped in a particular way (Davey et al., 2016; Badre et al., 2005).

Some limitations of the data are worth noting. First, this study focuses on the role of two key locations predicted to show a functional dissociation in the Controlled Semantic Cognition framework (ATL and pMTG). By combining targeted analysis of MEG data (examining local peaks within these regions) with chronometric TMS delivered to these sites, strong conclusions can be drawn about the nature of this dissociation, although the study is uninformative about other regions in the brain that might show a similar dissociation. Secondly, there is increasing evidence of functional subdivisions within ATL and pMTG (e.g., temporal pole, ventral ATL and aSTG appear to have different functional profiles – Lambon Ralph et al., 2017). The limited spatial resolution of MEG, and practical limits on the number of TMS sessions does not permit the separation of these regions.

Taken together, these results indicate dissociable roles of ATL and pMTG in semantic retrieval. ATL and pMTG showed opposite effects of the task contrast in both the MEG and cTMS experiments, supporting the proposal that these sites make a differential contribution to more automatic and controlled aspects of semantic retrieval. While both sites showed a response that included the N400 time-window, N400 effects are typically found to be strengthened by weak primes and unexpected completions (Kutas & Hillyard, 1984; Lau, Phillips & Poeppel, 2008). This pattern was observed in pMTG, yet the opposite pattern for ATL. There was also a temporal distinction between the sites: ATL showed stronger changes in oscillatory power for strong vs.

weak associations around 400ms post-target, and there was disruption of the efficient retrieval of these dominant associations when TMS was applied to ATL at around 150ms post-target onset, at a time-point when sustained semantic retrieval is thought to be initiated by visual input. In contrast, there was early and continued engagement of pMTG for weak associations, and disruption of the retrieval of these associations when TMS was applied at target onset, consistent with the view that pMTG plays a role in maintaining a semantic context elicited by the prime, and in detecting situations in which controlled retrieval processes may need to be engaged.

Supplementary analysis - Experiment 2:

Supplementary Table 2.1: Reaction time and accuracy means and standard deviations for all sites, conditions and times

Measurement	Site	Condition	0-40ms	125-165ms	250-290ms	450-490ms	NO TMS	0-40ms	125-165ms	250-290ms	450-490ms	NO TMS
					Mean					SD		
RT	ATL	strong	539.53	559.05	584.54	616.85	573.43	120.50	138.41	156.16	195.46	143.09
	ATL	weak	601.16	613.62	641.42	704.06	630.98	167.37	174.36	192.62	214.26	163.98
	ATL	number	535.45	565.54	576.62	616.55	571.87	144.29	163.49	187.26	210.41	165.70
	pMTG	strong	616.55	506.63	527.08	516.72	534.54	210.41	132.87	145.15	130.08	119.15
	pMTG	weak	498.46	512.79	529.29	543.91	595.16	105.49	100.93	116.69	141.97	123.20
	pMTG	number	578.90	590.26	585.17	610.58	531.61	156.50	142.16	139.25	164.37	129.47
	SHAM	strong	510.81	499.79	531.80	550.76	551.33	113.94	119.35	119.68	147.79	130.21
	SHAM	weak	559.64	573.55	588.73	617.25	606.62	133.06	144.95	145.19	158.97	125.16
	SHAM	number	492.95	512.32	513.29	524.02	517.83	126.25	132.99	127.71	145.03	127.27

Measurement	Site	Condition	0-40ms	125-165ms	250-290ms	450-490ms	NO TMS	0-40ms	125-165ms	250-290ms	450-490ms	NO TMS
			Mean					SD				
Accuracy	ATL	strong	0.96	0.95	0.96	0.96	0.94	0.04	0.06	0.04	0.05	0.05
	ATL	weak	0.82	0.76	0.83	0.78	0.83	0.13	0.17	0.11	0.18	0.08
	ATL	number	0.92	0.92	0.95	0.95	0.92	0.05	0.05	0.06	0.05	0.04
	pMTG	strong	0.97	0.97	0.97	0.97	0.95	0.05	0.03	0.04	0.03	0.06
	pMTG	weak	0.84	0.83	0.82	0.80	0.85	0.09	0.15	0.11	0.09	0.10
	pMTG	number	0.89	0.94	0.93	0.94	0.93	0.12	0.04	0.06	0.06	0.04
	SHAM	strong	0.97	0.97	0.97	0.97	0.95	0.04	0.04	0.04	0.04	0.06
	SHAM	weak	0.82	0.78	0.78	0.77	0.85	0.11	0.09	0.15	0.14	0.11
	SHAM	number	0.95	0.95	0.96	0.94	0.94	0.07	0.04	0.05	0.05	0.05

Additional TMS analyses

The supplementary analyses below encompass 1: the effect of TMS on accuracy for strong and weak associations, and 2: characterise the effects of TMS on the semantic and number tasks overall. In these analyses, there are 14 as opposed to 15 participants, since data for the even/odd digit task were not recorded for one participant. The results of analysis 1 motivated the inclusion of accuracy as a covariate in the analysis of response time above. Results from analysis 2 reveal non-specific effects of TMS and therefore motivated the inclusion of the number control task as a covariate in the main analyses reported above.

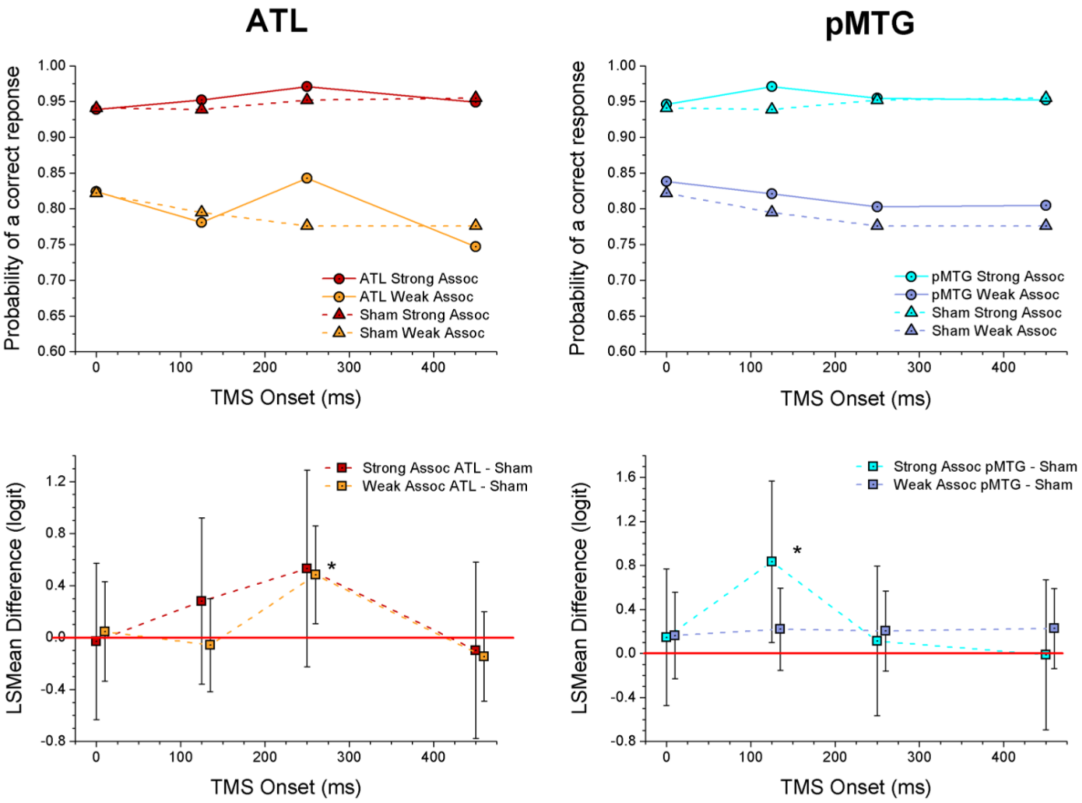
Effect of TMS on accuracy for strong and weak associations

The data were analysed using a generalised linear mixed model (GLMM), implemented in PROC GLIMMIX in SAS. The trial-by-trial accuracy data have a binomial distribution (where an accurate event equals 1 and an inaccurate event equals 0), and therefore a logistic link function was used in the model for the outcome. The fixed effects were site (ATL, pMTG, sham), TMS time, condition (strong vs. weak) and their two- and three-way interactions using a fully-factorial design. The model also included covariates controlling for effects of block number and session number (without interactions), and included the per-subject intercept as a random effect. The generalised chi-square per degree of freedom was 1.05, suggesting a well-fitting model with no over-dispersion.

This analysis revealed a main effect of condition, reflecting higher accuracy for strong vs. weak associations (F(1,1397) = 405,66, p < .0001), as well as an effect of block order (F(3.1397) = 3.91, p = 0.008) and session order (F(2,1397) = 3.23, p = 0.04), which were included as covariates. Additionally, the effect of site approached significance (F(2,1397) = 2.70, p = 0.07) (see Table 2.2). Paired t-tests between experimental sites and sham stimulation, controlled for multiple comparisons, revealed a significant difference between sham and ATL stimulation for weak associations at ~250ms (t(1397) = 2.49, p = 0.01 and between sham and pMTG stimulation for strong associations at ~125ms (t(1397) = 2.20, p = 0.03) (see Supplementary Figure 2.1). These results reflect facilitation of performance, potentially following increases in alertness or motivation (Devlin & Watkins, 2007).

Supplementary Table 2.2: Effect of TMS on accuracy for strong and weak associations

	d.f.	**F**	**P**
Fixed effects			
TMS time	3, 1397	1.00	0.39
Condition (strong vs. weak)	1, 1397	405.66	**<.0001**
Site	2, 1397	2.70	0.07
Condition by TMS time	3, 1397	2.81	0.39
Site by TMS time	6, 1397	1.52	0.17
Condition by site	2, 1397	0.12	0.89
3-way interaction	6, 1397	0.46	0.84
Covariates			
Block order	3, 1397	3.91	**0.0085**
Session order	2, 1397	3.23	**0.0400**



Supplementary Figure 2.1: Effect of TMS on accuracy for strong and weak associations; TOP ROW: Accuracy for strong and weak association for ATL (left) and pMTG (right) relative to sham data. BOTTOM ROW: LSMeans difference in accuracy for ATL (left) and pMTG (right) relative to sham site. Points above the red line indicates higher accuracy relative to sham, whereas point below the red line indicates lower accuracy relative to sham. Significant results are marked with asterisks.

Effect of TMS on response times in the semantic word vs. number control task

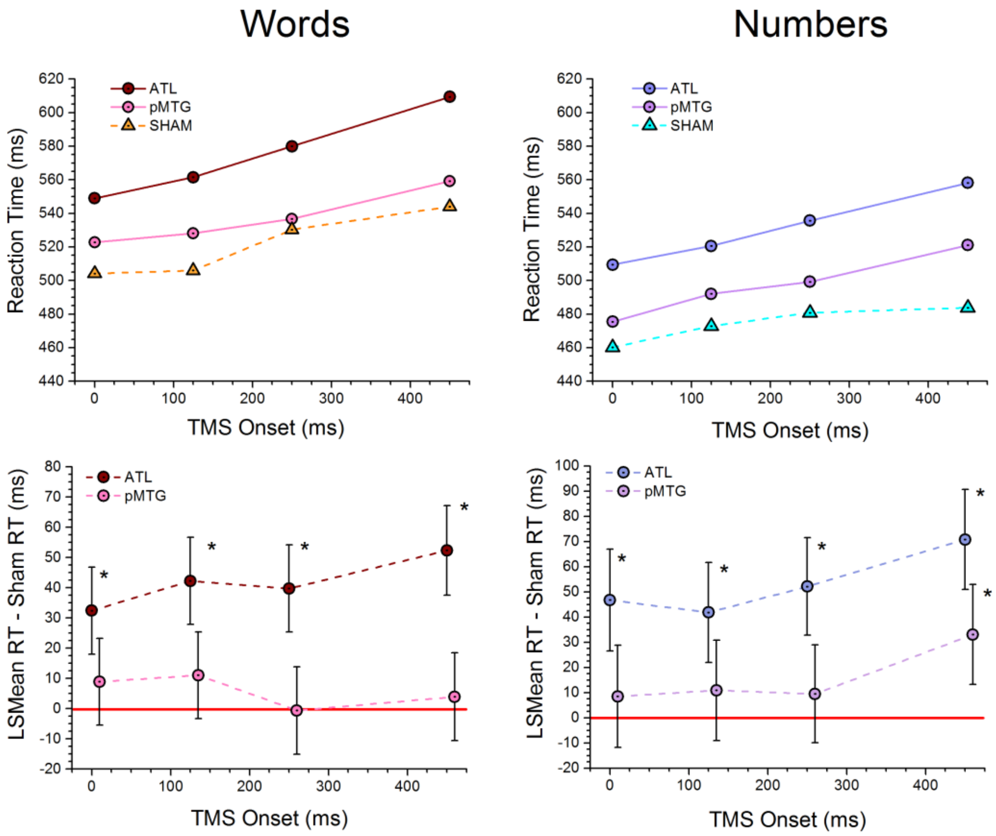
The data were analysed using a generalised linear mixed model (GLMM) examining trial-by-trial RT data, implemented using PROC MIXED in SAS. Incorrect responses and outlying data points that fell more than 2 SD from each participant’s mean RT were removed, for each session, prior to analysis. The fixed effects were site (ATL, pMTG, sham), TMS time, condition (semantic words vs. numbers) and their two- and three-way interactions using a fully-factorial design. The model also included covariates controlling for effects of block number and session number as above, and also mean accuracy per block. The per-subject intercept was also included as a random effect. The model showed a good fit, with a change in Log likelihood from the empty model of 1313.7, p<.00001.

The results of this analysis are shown in Supplementary Table 2.3. There were significant main effects of TMS time, condition (numbers vs. words) and site, with no significant interactions. The covariates of block and session order were also significant.

Supplementary Table 2.3: Effect of TMS on RT for semantic and digit parity task

	d.f.	**F**	**P**
Fixed effects			
TMS time	3, 1331	53.80	<.0001
Condition (semantic vs. digit)	1, 1331	331.32	<.0001
Site	2, 1331	122.78	<.0001
Condition by TMS time	3, 1331	0.88	0.4517
Site by TMS time	6, 1331	1.47	0.1851
Condition by site	2, 1331	1.86	0.1556
3-way interaction	6, 1331	0.77	0.5936
Covariates			
Block order	3, 1331	41.10	<.0001
Session order	2, 1331	178.80	<.0001
Mean accuracy	1, 1331	3.78	0.052

Paired contrasts for the semantic task, corrected for multiple comparisons, showed differences in LS means between RT for the ATL stimulation vs. sham session at all four time points (0ms: t(1331) = 4.38, p <.0001; 125ms: t(1331) = 5.72, p <.0001; 250ms: t(1331) = 5.38, p <.0001; 450ms: t(1331) = 6.90, p <.0001), with no significant differences with sham for pMTG. Paired t tests for the number task showed differences in LS means between RT for the ATL stimulation vs. sham session at all four time points (0ms: t(1331) = 4.50, p <.0001; 125ms: t(1331) = 4.10, p <.0001; 250ms: t(1331) = 5.25, p <.0001; 450ms: t(1331) = 6.97, p <.0001), as well as for pMTG relative to sham at 450ms (t(1331) = 3.25, p = 0.0012) (see Supplementary Figure 2.2). These results indicate that despite the use of a staircase procedure (Sliwinska et al., 2012), designed to reduce sensitivity to the variability in TMS onset time (see methods), RT increased with later pulse timings, which could reflect expectancy effects (waiting for the pulse before responding).



Supplementary Figure 2.2: Effect of TMS on RT for semantic and digit parity tasks; TOP ROW: Showing RT (in ms) for three sites for semantic (left) and digit task (right). BOTTOM ROW: LSMeans difference in RT for ATL and pMTG relative to sham site for semantic (left) and digit (right) task. Points above the red line indicate higher RT relative to sham, whereas points below the red line indicate lower RT relative to sham. Significant results marked with asterisks.

Discussion of supplementary TMS analysis:

Subtle facilitation in accuracy for weak associations was found at 250ms for ATL and for strong associations at 125ms for pMTG. TMS may reduce error rates due increases in alertness or motivation (although these effects were statistically controlled for in the main analysis of RT). In addition, the supplementary analyses demonstrate that, despite the use of a staircase procedure (Sliwinska et al., 2012; see Methods), there was a linear increase in RT with pulse time. This pattern could reflect expectancy effects (i.e., the tendency of participants to wait for the pulses to be delivered before responding). A similar trend was seen following sham stimulation at 30% of stimulator output, which is not thought to produce a neural effect (Duecker et al., 2013), although does produce scalp sensations, making this interpretation especially plausible. The increase in RT, relative to sham, was more marked for ATL than for pMTG, which could reflect the stronger scalp sensations associated with ATL stimulation. An increase in RT with time was also found for ATL stimulation by Jackson et al. (2015). However, unlike their study, this experiment also found an effect for the number control task in ATL, and thus these effects cannot be interpreted as specific disruption of semantic processes.

Chapter 3: Oscillatory dynamics of taxonomic and thematic relationships in the semantic network: Evidence from MEG

Abstract

Semantic relationships can be based on (i) conceptual similarity, i.e. taxonomic relationships, and (ii) contextual co-occurrence, i.e. thematic associations. A key question in semantic cognition is how the brain represents the relationship between items with high featural overlap (i.e. mole and cat) and relationships between items formed through contextual co-occurrence, but with low physical similarity (i.e. milk and cat). Two views of semantic cognition yield different predictions: 1) the dual-hub view postulates that taxonomic relationships are underpinned by perceptual feature similarity in ATL, and TPJ extracts thematic associations for event-related processing, and 2) the hub and spoke model, which predicts that both types of relationships are represented in ATL, with TPJ areas (namely AG and pMTG) recruited for automatic or controlled retrieval respectively. Here MEG was used to contrast the two views, exploring how taxonomic and thematic relationships, as well as strong and weak thematic associations, are reflected in oscillatory power changes over time. I examined the brain's response to a word preceded by a related prime word, either taxonomically, or thematically related (strongly or weakly) to the target. Virtual electrodes were placed in ATL, pMTG, LIFG and AG, to characterise the response of each site in the frequency domain, in both evoked power (phase-locked to the stimulus) and total power (which combines both phase-locked and non-phase locked components). While evoked power analyses showed taxonomic-only effects in ATL and LIFG, predominantly thematic effects in pMTG, and both taxonomic and thematic effects in AG, total power analyses revealed that all sites responded significantly to both types of relationships, with some variation in timing and frequency of the oscillatory response. The contrast of strong and weak associations implicates ATL and AG in automatic retrieval, with pMTG supporting controlled retrieval of weak associations. The MEG data provided here shows a recruitment of known sites within the hub-and-spoke model of semantic cognition for all conditions, with a qualitative difference in the form of the response.

Introduction

Semantic memory encompasses our knowledge of the meanings of words, objects, sounds and people (Visser et al., 2012; Patterson, Nestor & Rogers, 2007; Pulvermüller, 2013). This includes our ability to identify objects and the categories that they belong to (taxonomic relationships), as well our knowledge about how objects are related in time and space, in an event or context (thematic relationships). Items that are taxonomically related, such as ‘dog’ and ‘mouse’, fall within the same superordinate category, and share attributes such as fur, tail and four legs (i.e., they have *featural overlap*). Thematically-associated items do not necessarily share physical features but are used or found together: for example, ‘dog’ and ‘leash’ co-occur within the context of dog walking (Lin & Murphy, 2001; Kalénine et al., 2012; Barsalou, 2013).

There is considerable debate about the cognitive and neural basis of these different aspects of knowledge – with some accounts proposing a single semantic store encompassing all aspects of knowledge (e.g., the hub & spokes model of Patterson et al., 2007), and others suggesting that distinct neurocognitive mechanisms support categorical and thematic knowledge (Schwartz et al., 2011; de Zubricaray, Hansen & McMahon, 2013). The hub and spoke model of semantic cognition postulates that an anterior temporal lobe (ATL) ‘hub’ integrates different sources of modality-specific information (colour, shape, praxis, movement etc.) captured by sensory-motor ‘spokes’ (Patterson, Nestor & Rogers, 2007; Rogers et al., 2006) to form amodal concepts. This view was originally proposed to explain the pattern of multimodal semantic deficits shown across tasks by patients with semantic dementia (SD) following atrophy and hypometabolism in the ATL, and is consistent with neuroimaging and TMS evidence implicating ATL in semantic representation in healthy participants (Pobric et al., 2007; 2010a; 2010b). Computational instantiations of the hub and spoke model show more similar patterns of activity across the hub units for related concepts that share more features (McClelland & Rogers, 2003). However, it is not fully articulated how this approach might capture thematic knowledge, since the ‘spokes’ are simple sensory and motor features, and computational modelling has focussed on taxonomic relationships.

Information about where objects are typically found and how they are used could be integrated in ATL along with their physical properties – by this view, the ATL would support the processing of both taxonomic and thematic relationships. This view is supported by studies of semantic dementia patients showing degradation of both aspects of knowledge (Bozeat et al., 2000; Hoffman, Jones & Lambon Ralph, 2013). Alternatively, a dual hub framework proposes that ATL underpins taxonomic knowledge while temporoparietal areas, such as angular gyrus and posterior middle temporal gyrus, extract event associations and thematic knowledge (Schwartz et al., 2011; de Zubicaray, Hansen & McMahon, 2013). This perspective was originally motivated by neuropsychological research showing that patients with lesions in temporoparietal areas make more thematic errors in picture naming (e.g., dog → bone), while those with lesions in ATL produce more categorical errors (e.g., dog → cat; Schwartz et al., 2011). A similar observation was reported by Jefferies and Lambon Ralph (2006), yet explained in a different way. SD patients with ATL atrophy were compared with semantic aphasia (SA) patients, who had left hemisphere strokes affecting prefrontal and/or temporoparietal cortex. Patients with SD produced more superordinate taxonomic responses (e.g., dog → animal), following degradation of fine-grained conceptual information (Patterson, Nestor & Rogers, 2007). In contrast, SA patients produced more thematic responses and showed a pattern of impairment on semantic tasks which suggested deficient control of semantic retrieval: unlike SD cases, they were inconsistent when the same concepts were probed in tasks with different control demands and they showed strong effects of cues and miscues on semantic retrieval. Jefferies and Lambon Ralph (2006) noted that these thematic errors (such as responding ‘leash’ to a picture of a dog) imply the *preservation* of semantic information – since to produce these errors, it is necessary to retain information that leash is associated with dogs. They instead proposed that SA patients have difficulty controlling retrieval to focus on the picture name as opposed to strong but irrelevant associations. Thus neuropsychological dissociations have been interpreted in terms of either damage to distinct semantic stores for thematic and taxonomic knowledge, or in terms of loss of knowledge vs. damage to control systems.

Neuroimaging evidence has also implicated temporoparietal areas in thematic processing, though there is some diversity in the specific areas identified, with studies reporting activation in angular gyrus, pMTG and superior temporal sulcus (Kalenine et al., 2009; Schwartz et al., 2011; Sass et al., 2009). Nevertheless, this reported distinction remains controversial, with recent fMRI (Jackson et al., 2015), MEG (Lewis, Poeppel and Murphy, 2015) and TMS studies (Davey et al.,

2015) showing common recruitment of temporoparietal cortex (AG and pMTG) for taxonomic and thematic decisions. Lewis et al. (2015) also found greater engagement of left ATL in taxonomic processing, and thus their results were partially consistent with Schwartz et al.'s proposal, as was an eye-tracking and lesion mapping study of taxonomic and thematic processing, finding that TPJ lesions lead to reduced and delayed processing of thematic associations (Mirman & Graziano, 2012). Studies have also found stronger recruitment of visual and executive control areas for taxonomic knowledge: this may reflect the visual similarity of objects belonging to the same category (Kalénine et al., 2009; Kotz et al., 2002), and increased cognitive demands (Sachs et al., 2008a; Sachs et al., 2008b; Sass et al., 2009) – consistent with behavioural work showing that people preferentially select thematic links over taxonomic ones (Barsalou, 2013). These neuroimaging studies have not commonly observed activation in ATL. Standard fMRI acquisition has a low signal-to-noise ratio in this region, due to magnetic susceptibility artefacts which produce signal loss and distortion (Visser, Jefferies & Lambon Ralph, 2009). However, a recent study using fMRI parameters optimised for preserving signal in ATL identified a common response to both categorical and thematic relationships in this region, consistent with the predictions of the single hub theory, in which the ATL supports semantic representation and links irrespective of relationships, and parts of temporoparietal areas (namely pMTG) supports controlled retrieval (Jackson et al. (2015).

These studies implicate a common set of cortical regions – including ATL, AG, pMTG and LIFG – in multimodal conceptual processing but there remains little consensus about whether functional divisions are best understood in terms of differences in representational content or process. In additional to the proposed distinction between ATL and temporoparietal areas for taxonomic and thematic knowledge, an alternative organisational framework has linked AG in conjunction with ATL to relatively automatic patterns of retrieval, such as spreading activation between highly related concepts (Davey et al., 2016; Humphreys & Lambon Ralph, 2014). A recent TMS study demonstrated a dissociation between AG and pMTG in the processing of strong and weak thematic relationships, with TMS to AG impairing retrieval of strong thematic associations, and stimulation of pMTG leading to impaired performance on weakly related thematic associations (Davey et al., 2015). PMTG's involvement in controlled semantic retrieval is further supported by it being co-activated with LIFG in situations with greater semantic control demands (Badre et al., 2005; Noonan et al., 2013), that TMS to both pMTG and LIFG produce similar deficits on processing of weakly related semantic relationships (Whitney et al., 2010), and neuropsychology data from SA patients who show deficits in controlled, but not more automatic aspects of semantic retrieval (Jefferies & Lambon Ralph, 2006). AG's role in automatic aspects of retrieval was demonstrated by the same TMS study that implicated pMTG in controlled retrieval (Davey et al., 2015), and has also been shown to have overlapping activation for automatic semantics, episodic retrieval, numerical fact retrieval, and overlaps with the default mode network (DMN) (Humphreys & Lambon Ralph, 2014).

These observations potentially provide an alternative way of thinking about the neuropsychological findings of Schwartz et al., and fMRI studies dissociating taxonomic and thematic judgements. Many taxonomic relationships also share a thematic relationship; e.g., cat and dog are both pets, found in similar places and contexts, and this makes these items easy to process. When taxonomic relationships do not also share thematic links (e.g., 'mole' and 'cat'), the task becomes much harder. Thus, in studies eliminating thematic associations for taxonomic trials, stronger recruitment may be seen in temporoparietal regions linked to semantic control, such as pMTG (along with LIFG). In studies that fail to remove thematic links for taxonomically-linked items (e.g., dog-cat), there may be recruitment of AG in the taxonomic condition due to automatic retrieval. Indeed, Jackson et al. (2015) found that differences between taxonomic (mole-cat) and thematic judgments were eliminated when adding reaction time as a covariate (Jackson et al., 2015).

To overcome these issues, this study was designed with one taxonomic condition and two thematic conditions (high and low association strength). The thematic condition with low association strength was matched in difficulty to the taxonomic condition, while the comparison with a thematic condition with strong associations allowed me to consider influence of control demands. I used magnetoencephalography (MEG) which has high sensitivity to transient effects, and can characterise power differences in time and frequency to provide a clearer image of *how* areas are recruited. There have been very few MEG studies of this issue (cf. Lewis, Poeppel & Murphy (2015)), and none that have previously characterised effects of semantic content and controlled processing requirements in time-frequency space. Here beamforming was used to identify the neural source of changes in total oscillatory power. Thus I was able to examine both evoked responses (phase locked to the onset of the stimulus) and the induced power (which is not phase-locked and might be sensitive to memory retrieval effects).

I used this method to test contrasting predictions about the functional roles of ATL, pMTG and AG, and to compare the responses of two sites implicated in automatic semantic retrieval (ATL, AG) with a site postulated to be engaged in controlled semantic retrieval (pMTG). The dual-hub theory of semantic cognition predicts that ATL is important for taxonomic relationships while left pMTG and AG support thematic knowledge. Alternatively, the Controlled Semantic Cognition framework (Lambon Ralph et al., 2017), postulates one representational hub (ATL) underpinning knowledge of all types of relationship, with pMTG supporting controlled retrieval for more difficult judgements.

Methods

Participants:

Participants were 19 right-handed native English speakers, with normal or corrected-to-normal vision, and no history of language disorders (6 males, mean age 26.7, range 18-37). The study was conducted in accordance with the Research Ethics and Governance Committee of the York Neuroimaging Centre, University of York, UK, and written informed consent was obtained. 20 participants were scanned, but one participant was excluded because of low accuracy (a minimum of 75% accuracy was required).

Materials:

There were three experimental conditions, strong thematic associations, weak thematic associations, and taxonomically related. To generate item pairs of comparable difficulty, participants who did not take part in the MEG experiment (n=30) rated word pairs on three questions relating to 1: Contextual co-occurrence (thematic association): “How associated are these items? For example, are they found or used together regularly?”; 2: Physical similarity (taxonomic): “Do these items share similar physical features? For example, do they have similar physical (visual/textural) characteristics?”; and 3: Ease of making the judgement (for both thematic and taxonomic decisions): “How easy is it to identify a connection between the words (either in terms of them being associated as in Q1, or sharing features, as in Q2)?”. Ratings were made on a Likert scale from 1 to 7 (1 = Not at all, 7 = Very), results can be seen in Table 3.1. Word pairs were selected if they were rated highly on one type of relationship and not the other. The conditions also differed on difficulty (rating 3): taxonomic and weak thematic association decisions were difficult, while strong thematic associations were easier to identify. There was a significant difference on question 3 between the strong and weak thematic conditions, and between the strong thematic and taxonomic conditions, but not between the taxonomic and weak thematic conditions (see Table 3.1). 95 target words were presented (these were the same across conditions), with 95 taxonomically-related primes, 95 strongly thematically associated primes and 95 weakly thematically associated primes. There were also 100 unrelated trials, which presented the same 95 target words, plus 5 additional targets. Primes for this condition were randomised prime words from the other conditions (removing unintended associations/similarity and repetitions). Stimuli were matched for frequency, length and imageability, and no significant differences were found between experimental conditions or targets (see Table 3.2).

Table 3.1: TOP: showing means and standard deviations for question 1, 2 and 3 (explained in Materials above). BOTTOM: Showing t-tests between conditions of scores on each question.

Condition	**Measure**	**Q1**	**Q2**	**Q3**
Taxonomic	Mean	2.73	4.79	5.51
	SD	0.98	1.05	0.95
Strong thematic	Mean	6.48	1.46	6.01
	SD	0.58	0.85	0.77
Weak thematic	Mean	6.00	1.83	5.76
	SD	0.97	1.24	1.03
T-tests				
Taxonomic vs. strong thematic		**p<.001**	**p<.001**	**p<.001**
Taxonomic vs. weak thematic		**p<.001**	**p<.01**	**p<.05**
Strong thematic vs. weak thematic		**p<.001**	**p<.001**	P=0.09

Table 3.2: Frequency, length and imageability values for each condition

Measure	Condition	Mean	SD
Frequency	Taxonomic	21.854	43.496
	Strong thematic	37.999	71.115
	Weak thematic	29.927	40.103
Length (letters	Taxonomic	5.400	1.789
	Strong thematic	5.537	1.668
	Weak thematic	5.500	1.740
Imageability	Taxonomic	569.029	61.420
	Strong thematic	575.698	53.145
	Weak thematic	560.977	60.072

Table 3.3: T-tests of Frequency, length and imageability values for each condition

Measure	Contrast	T	Sig (2-tailed)
Frequency	Taxonomic/strong	-1.757	0.083
	Taxonomic/weak	-1.326	0.187
	Strong/weak	1.724	0.071
Length (letters)	Taxonomic/strong	-0.545	0.557
	Taxonomic/weak	-0.390	0.611
	Strong/weak	0.149	0.965
Imageability	Taxonomic/strong	-0.715	0.617
	Taxonomic/weak	0.769	0.466
	Strong/weak	1.569	0.132

In order to ensure the taxonomic and weak thematic conditions were successfully matched for difficulty, 5 participants were piloted outside the scanner (these did not take part in the main experiment). Though this does not allow statistical power to do contrasts at the group level, the conditions were contrasted within each participant, and found no difference between taxonomic and weak thematic associations in RT (t = -0.84183 to 0.36412; p > .4). Figure 3.1 shows RT data for these five participants. Two participants showed a difference in accuracy between the taxonomic and weak thematic condition, details can be seen in Tables 3.4 and 3.5.

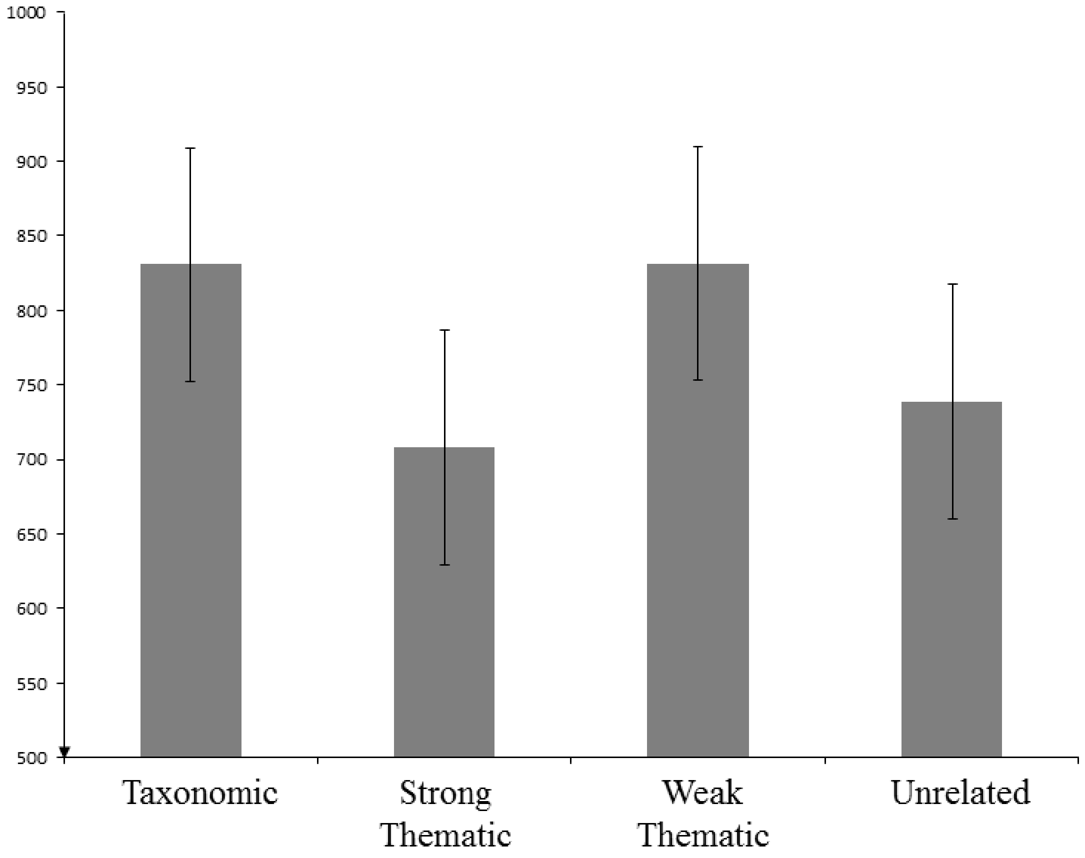


Figure 3.1: Reaction time data from 5 participants, with RT in ms on the y-axis and condition on the x-axis. Error bars display standard error of the mean.

Table 3.4: Accuracy data for 5 participants

Participant	**Taxonomic**		**Strong thematic**		**Weak thematic**	
	Mean	SD	Mean	SD	Mean	SD
1	0.94	0.22	0.96	0.17	0.91	0.33
2	0.86	0.34	0.86	0.25	0.82	0.37
3	0.89	0.30	0.93	0.21	0.87	0.32
4	0.94	0.27	0.94	0.19	0.76	0.27
5	0.92	0.16	0.90	0.22	0.90	0.30

Table 3.5: Chi-square tests of accuracy differences between conditions for 5 participants

Participant	**Taxonomic vs. Strong thematic**		**Strong thematic vs. Weak thematic**		**Taxonomic vs.Weak thematic**	
	χ^2	p	χ^2	p	χ^2	p
1	0.500	0.366	5.763	**<.05**	3.166	0.063
2	0.001	0.572	0.367	0.343	0.405	0.332
3	1.047	0.224	2.212	0.101	0.230	0.400
4	0.001	0.620	13.362	**<.01**	13.571	**<.01**
5	0.500	0.366	7.825	**<.01**	4.846	**<.05**

Procedure:

Each pair was presented one word at a time. The target word was the same in each of the conditions, with the prime varying according to condition, ensuring that the visual and lexical features of the stimuli being compared were the same. Nonius lines (acting as a fixation cross) were present at all times. Before each trial, there was a rest period of 800 ms, plus an unpredictable jittered interval from 0 to 1000ms (mean 500ms), designed to reduce anticipatory responses. Prime words were presented for 200ms, there was an inter-stimulus interval (ISI) of 150ms, and then the target appeared for 200ms followed by a 1000ms interval. A short ISI has been shown to produce priming effects for both thematic and taxonomic associations (Jones & Golonka, 2012). After each trial, the nonius lines changed to a dimmer red (for 1000 ms) and participants were encouraged to confine blinking/swallowing to this period. An illustration of the procedure can be seen in Figure 3.2. For analysis purposes, the time window of 700 to 500ms *before* target onset was chosen as the passive baseline. Three versions of the experiment, each with three blocks, were created. Trials were pseudorandomised within blocks, and block sequence was randomised between participants. On an added 10% of trials, participants were cued to make an overt response by the presence of a question mark (on screen for 1000ms) after the target presentation. They pressed one of two buttons with their left hand to indicate if the two words were related. These 'catch trials' were used to monitor performance in the task, and were disregarded from the MEG analysis.

Stimulus presentation:

The experiment was carried out in a dark, magnetically shielded room. Presentation v 16.1 (Neurobehavioral Systems) was used to present the stimuli and to record responses on catch trials. Stimuli were back-projected onto a screen with a viewing distance of ~75 cm, so that letter strings subtended ~1˚ vertically and ~5˚ horizontally at the retina. I presented light grey letters on a dark grey background such that the screen luminance was in the mesopic range, and a neutron density filter was used to reduce glare.

Data collection:

Data collection followed the same procedure as Chapter 2. Statistical analyses included only datasets with at least 75% of trials retained after artefact rejection. 19 datasets reached this criterion. On average, 10.9% of trials were rejected (min 4.6% max 25%).

MEG analysis:

The MEG analysis followed the same procedure as Chapter 2. Firstly, whole-brain analyses examined the neural response at a coarse frequency and time resolution for the related condition (taxonomic, strong and weak thematic conditions collapsed). Secondly, the activity of specific cortical regions engaged by the task was interrogated at a finer frequency and temporal scale. In these analyses, Points of Interest (POI) were defined and examined with virtual electrodes (VEs) at these points, which were selected on the basis of their importance to theories of taxonomic and thematic semantic processing, and defined with reference to local peaks in the whole-brain beamforming data. All information necessary to reproduce these analyses is in the public domain (http://vcs.ynic.york.ac.uk/docs/naf/index.html).

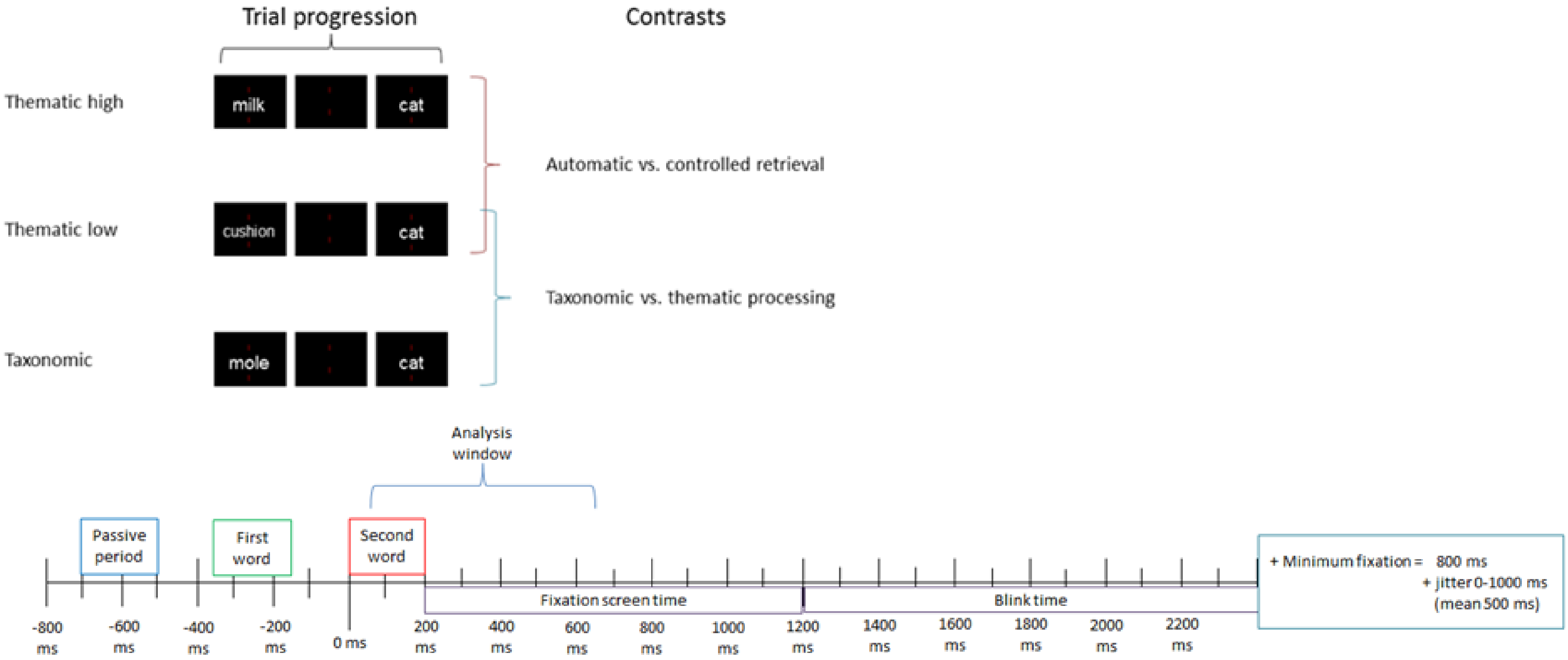


Figure 3.2: Illustration of strong thematic, weak thematic and taxonomic trials, with illustrations of contrasts (TOP), and the 3000 ms around trial presentation (BOTTOM). The words are not to scale; for visibility they have been made larger and white, while in actual experimental settings they were a dim grey colour.

Catch-trial results:

The behavioural data from catch- trials showed a significant difference in RT between the strong and weak thematic, as well as the weak thematic and unrelated condition. No other differences were found, which is particularly relevant for the taxonomic/weak thematic contrast, as it indicates that the difficulty matching of these conditions was successful. For accuracy there was a significant difference between the strong and weak thematic conditions, as well as between the strong and taxonomic, and the weak and unrelated conditions (see Figure 3.3 and Table 3.6).

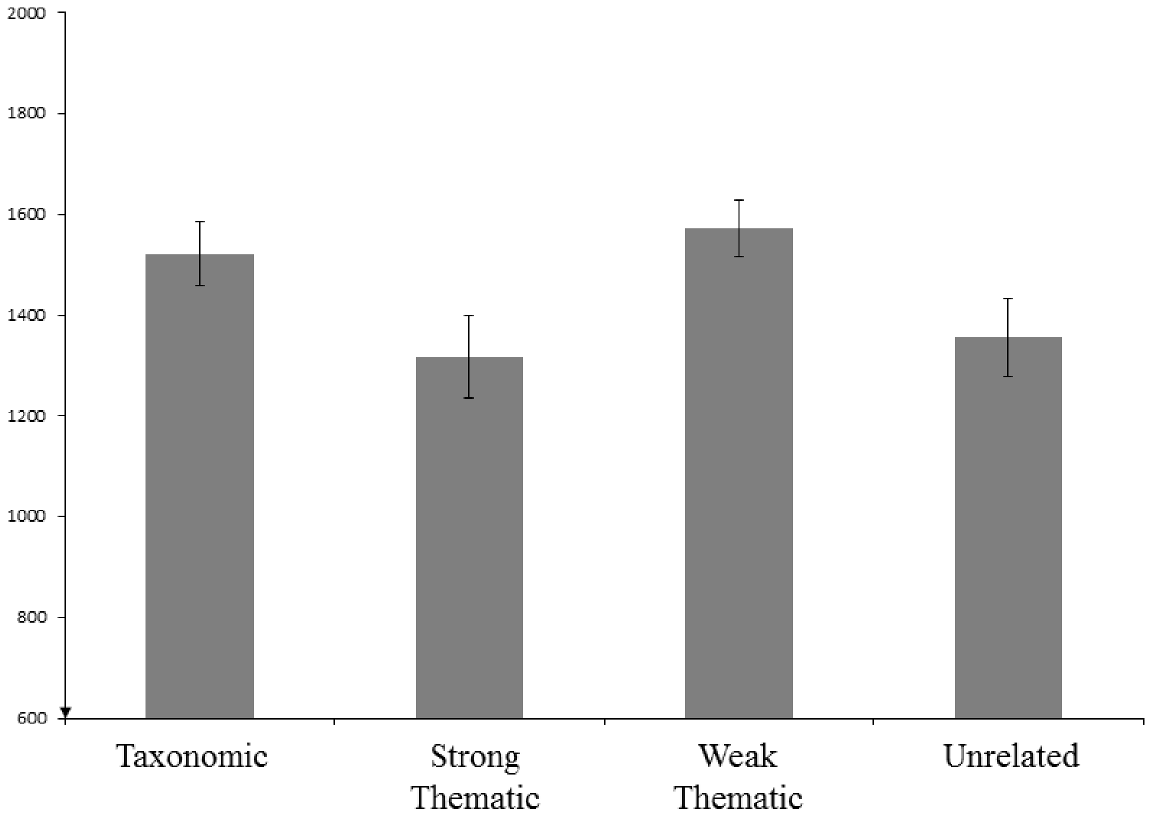


Figure 3.3: RT for catch-trial data for the taxonomic, strong thematic, weak thematic and unrelated conditions respectively.

Table 3.6: t-tests for RT and accuracy data from catch-trials collected during MEG recording.

Measure	**Contrast**	**T**	**Sig (2-tailed)**
Reaction time	Strong/Weak	-3.183	**<.01**
	Strong/ Taxonomic	-2.561	**<.05**
	Strong/Unrelated	-0.353	0.726
	Weak/ Taxonomic	0.593	0.557
	Weak/Unrelated	2.259	**<.05**
Accuracy	Strong/Weak	5.440	**<.001**
	Strong/ Taxonomic	4.569	**<.001**
	Strong/Unrelated	-0.390	0.0699
	Weak/ Taxonomic	-1.002	0.323
	Weak/Unrelated	-5.410	**<.001**

Whole brain beamforming:

The brain's response to the task was characterised within broad frequency ranges and averaging across 200ms time periods, in a procedure identical to Chapter 2. Here I examined the response of the whole brain to the related trials (i.e., the response to the onset of the second word of each pair, collapsing the taxonomic and strong and weak thematic association items). The purpose of this analysis was to identify brain regions important for the task in general terms, so that relevant sites could be investigated in more detail in a points-of-interest analysis (see below). The main research question concerned how the brain's response to the second word (i.e., the target) changed as a function of its relationship to the first word (the prime). I therefore analysed the whole-brain beamforming data by contrasting "active" and "passive" time windows of 200ms duration from target onset (0-200ms, 200-400ms, and 400-600ms) until 600ms after target onset. In the passive time window (-700 to -500ms relative to target onset), participants observed the (always present) nonius (fixation) lines. The 200-400ms window was used to define points of interest for more detailed time-frequency analysis, the details of which are the same as in Chapter 2.

Time-Frequency Analysis: Point of Interest (POI):

Separate beamformers were used to reconstruct the neural activity for three points of interest (POI), characterising the response of these regions over time and frequency with greater precision. The MNI coordinates for these POIs were defined within pre-specified regions identified from the literature, using local peaks of maximum activation in the group level, whole brain analysis. These peaks were taken from the “Related” condition (collapsing taxonomic and strong and weak thematic trials) and the 200-400ms time window – allowing me to capture stimulus-driven effects, while still retaining confidence that semantic processing would be ongoing (Pulvermüller, Assadollahi, & Elbert, 2001; Kutas & Hillyard, 1980; Clarke et al., 2011; Yvert et al., 2012).

Brain regions for POI analysis were constrained by the literature: I searched for local maximum power changes in four brain regions implicated in conceptual, taxonomic and thematic processing by the literature – namely left anterior temporal lobe (ATL), left posterior middle temporal gyrus (pMTG), and angular gyrus (AG). Analysis revealed maximum power change within ATL, and pMTG. Though AG did not show an individual max peak, it fell within the region of significant activation. Therefore, VEs were placed at max peak coordinates in ATL and pMTG that showed maximal oscillatory power across conditions, in line with previous studies using this analysis pipeline (Urooj et al., 2014), while for AG, the VE site was placed at coordinates taken from the recent meta-analysis of parietal lobe function (Humphreys & Lambon Ralph, 2014).

The data supported placement of VEs at the following locations: left temporopolar cortex (MNI coordinates -34,20,-32), pMTG (MNI coordinates -50,-46,-6), and AG (MNI coordinates -48,-68,28). The temporopolar peak in ATL was close to coordinates reported previously for verbal semantic tasks (Binney et al., 2010). For pMTG, the peak was found in a more medial region, so was projected laterally towards the surface (actual max power change at MNI coordinates -34,-46,-12). The more lateral coordinates correspond well to an area consistently activated by high > low semantic control demands, as determined by a recent meta-analysis (Noonan et al., 2013). For an illustration of VE placement, see Figure 3.4.

The analysis procedure for total power is the same as in Chapter 2, though in this chapter the virtual electrode analyses examined both evoked and total power. Evoked power responses are locked to the stimulus in both time and phase, whereas total power includes the non-phase-locked (induced), as well as the phase-locked (evoked) response. Both analyses are reported here since evoked power changes are expected to be particularly sensitive to the brain's response to the onset of visual stimuli, and this response may be attenuated by semantic priming, while total power may be more sensitive to higher-level cognitive effects reflecting sustained patterns of semantic retrieval (which may be increased by semantic priming), and could potentially show qualitative differences in taxonomic and thematic processing. In addition, including analyses of evoked power in this particular experiment allows me to relate the findings to a recent MEG study that contrasted thematic and taxonomic decisions again in the evoked domain (Lewis, Poeppel & Murphy, 2015).

For evoked power, covariance matrices for the whole epoch were used to generate time-frequency plots for each condition. The evoked signal was examined by computing the average signal in the time domain, for each participant, for each direction separately. The time-frequency representation of power in each condition was then averaged, for all participants, for each direction (x, y and z) separately. The three directions were then summed and averaged across participants to compute a grand average for each condition. Statistical comparisons between time-frequency representations were done using PROC MIXED in SAS (SAS institute Inc., North Carolina, USA), computing a generalised linear mixed model including repeated measures factors (to account for the fact that each participant's time-frequency plot is made up of multiple time-frequency 2D arrays). Time-frequency covariance was controlled for by assuming the estimates of power followed a Gaussian distribution and including a Gaussian link function in the model. For each ROI and each condition, mean power was computed in 2.5Hz and 25 ms tiles. The analysis included tiles from 0 to 600 ms after the onset of the second word and from 5-50Hz. Here LS means of signal change significantly different between conditions are reported. There are two statistical contours on the percentage signal change figures for evoked power; black and white. Black lines encompass time-frequency tiles fulfilling both of the following criteria: a) the difference between conditions reached $p < 0.05$; and b) any region in the time-frequency plot defined by (a) that also showed a response that was significantly different from baseline in at least one of the two contributing conditions, whereas white lines mark any region in the time-frequency plot that shows significant change in both conditions (either in power increase or decrease).

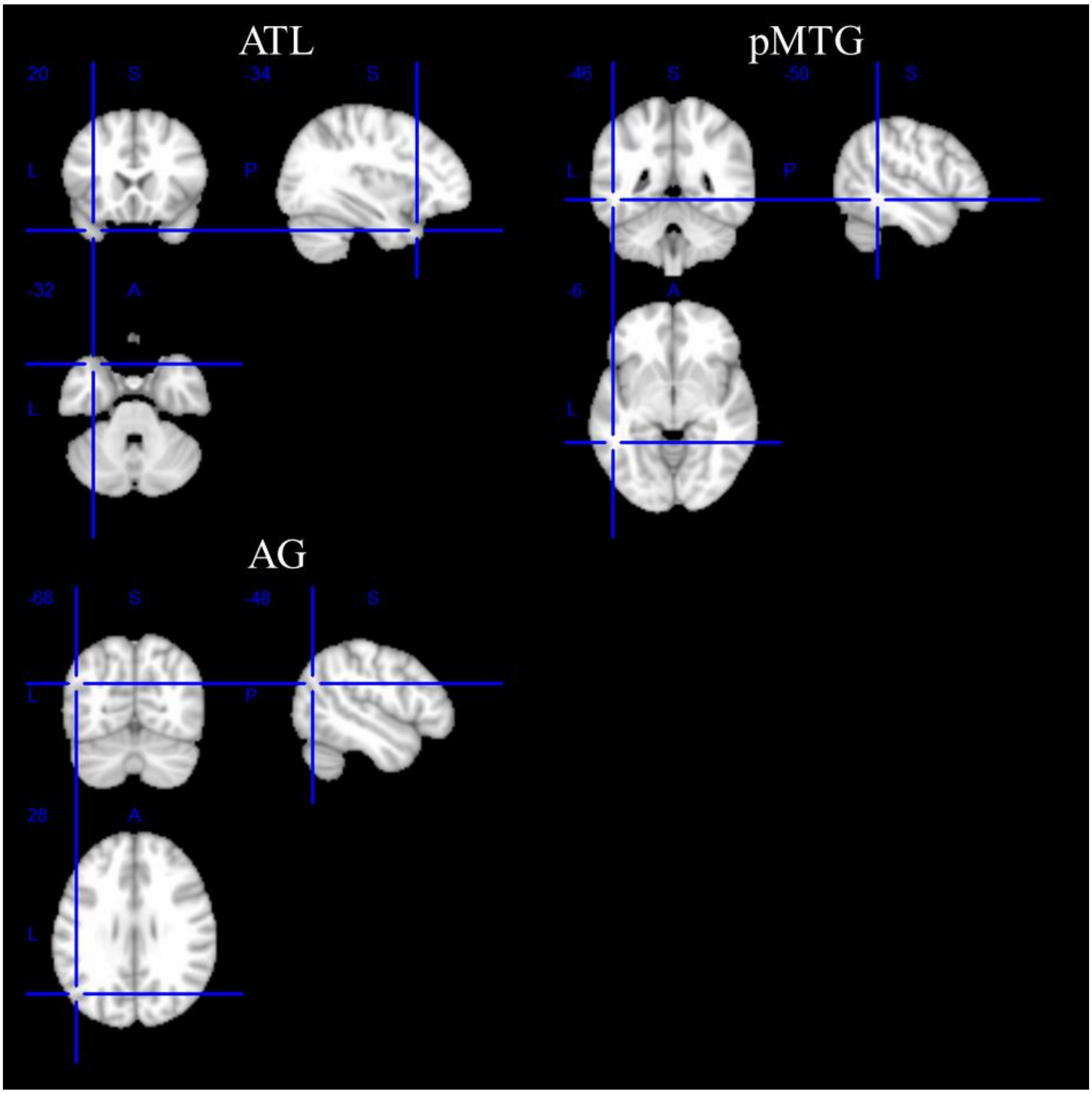


Figure 3.4: Showing POI placement for virtual electrode for three sites; left ATL (MNI coordinates -34,20,-32), pMTG (MNI coordinates 50,-46,-6), and AG (MNI coordinates -48,-68,28).

Results

These analyses contrast the views of the Controlled Semantic Cognition framework and the dual-hub theory. Briefly summarised, if the dual-hub theory is correct, ATL would be expected to deal predominantly (if not exclusively) with taxonomic associations, and pMTG and AG to deal predominantly (if not exclusively) with thematic associations. Furthermore, pMTG and AG should behave similarly due to lack of differentiation between them in the dual-hub theory (where the thematic hub is postulated to be located in the TPJ, which encompasses both pMTG and AG). Alternatively, if the Controlled Semantic Cognition framework is correct, it would be expected that ATL and AG process all types of associations, but show greater power change in the strong as compared with the weak thematic condition. In contrast, pMTG would be expected to deal with all associations, but show greater power change in the weak as compared with the strong thematic condition, and a comparable response in the taxonomic and weak thematic conditions due to increased semantic control demands.

Whole brain beamforming:

There were extensive changes in total oscillatory power from 200-400 ms post-target onset (see Figure 3.5). From 5-35Hz, all three conditions were associated with reductions in total oscillatory power relative to the baseline period, particularly visual areas and pMTG. From 35-50 Hz, there was also a strong response in a more dorsal region of left lateral cortex, in inferior frontal sulcus, for the thematic weak condition, and a similar area responded the taxonomic condition from 25-35 Hz. These are all cortical areas that are all known to contribute to semantic cognition. These decreases in power are likely to have followed disruption of strong resting rhythms following increases in neural activity not synchronised to the stimulus in time or phase (Hanslmayr et al., 2012); reductions in power have also been shown to correlate with an increased BOLD response in fMRI (Hanslmayr et al., 2011; Singh et al., 2002; Hall et al., 2014), and a recent review proposed that decreases in power reflect active engagement of neocortex in the encoding and retrieval of memories (Hanslmayr, Staresina & Bowman, 2016).

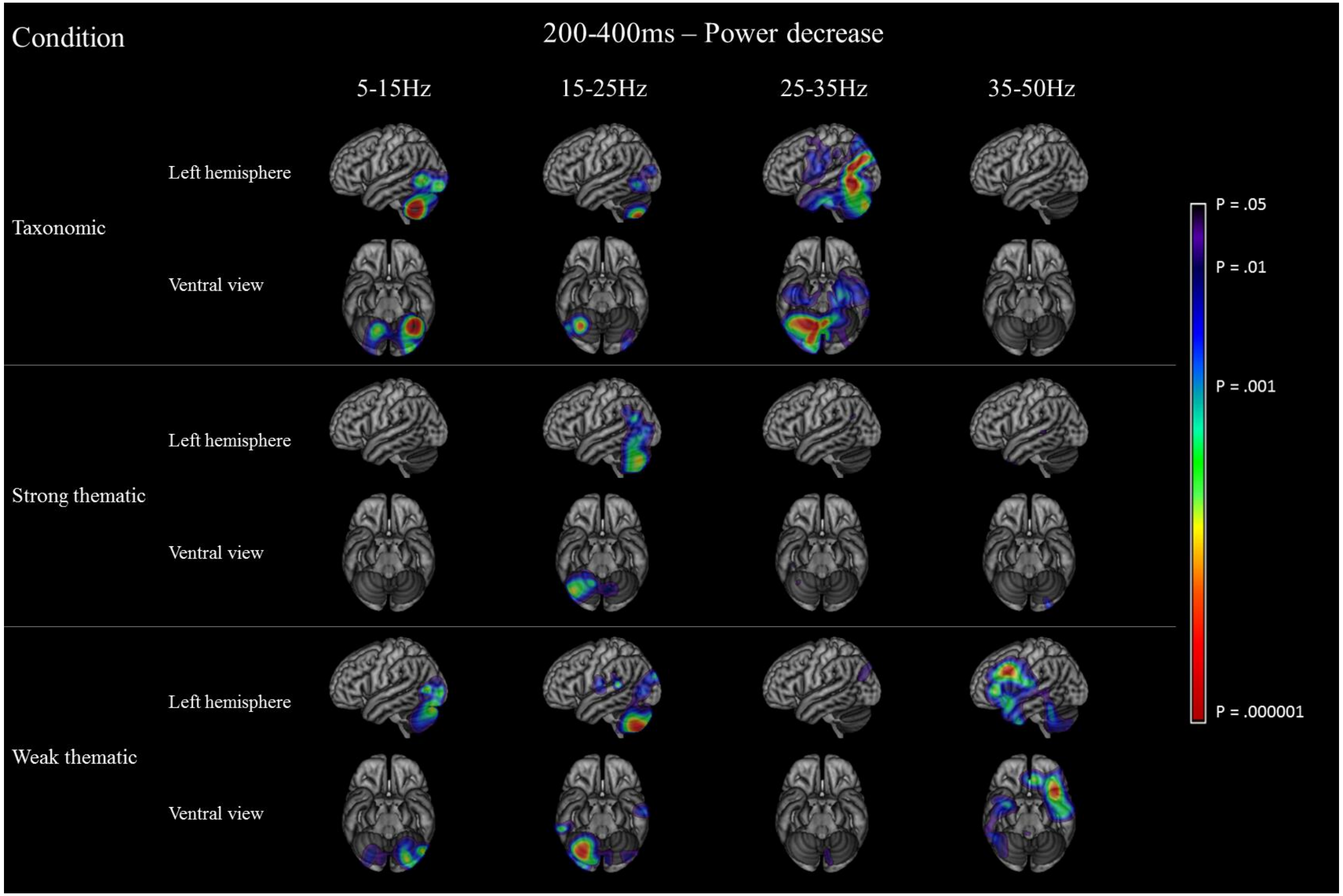


Figure 3.5: Showing whole brain beamforming for three experimental conditions in the four frequency bands analysed. T-values were converted to p-values to be shown on the same scale (p=.05 to p=.000001). Images created using MRICroN software (Rorden, Karnath & Bonhila, 2007).

POI results

Whole epoch data for each site:

Evoked and total power time-frequency plots of the whole epoch (related condition –three experimental condition collapsed) were examined for each POI. Figure 3.6 shows the response to the prime (1^{st} word) and related targets (2^{nd} word) in each semantically-related pair. For the evoked power plots, the scale goes from white to red; with red colours indicating higher oscillatory power (evoked power changes only occur in a positive direction). For the total power plots, yellow-red colours indicate *power increases*, whereas cyan-blue colours indicate *power decreases* relative to the passive baseline period. Green indicates ‘no change from baseline’.

In evoked power, a strong response following the second word was seen in all four sites. In total power, a low frequency (~6-12Hz) power increase, starting around target onset and lasting until 500-600ms (with some variation between sites) was seen in all four POIs. In pMTG and AG I also saw the beginning of a reduction in total power towards the end of the analysis window (~500ms). This is surprising in light of priming literature that predicts a reduction of power to the target (relative to the prime) (Düzel, Richardson-Klavehn, Neufang, Schott, Scholz & Heinze, 2005; Kujala, Vartiainen, Laaksonen & Salmelin, 2012). On the other hand, semantically-related (as compared with unrelated) word pairs can elicit stronger activation in areas known to be involved in semantic processing, and it is possible that it is these effects driving these results (Binder, 2016).

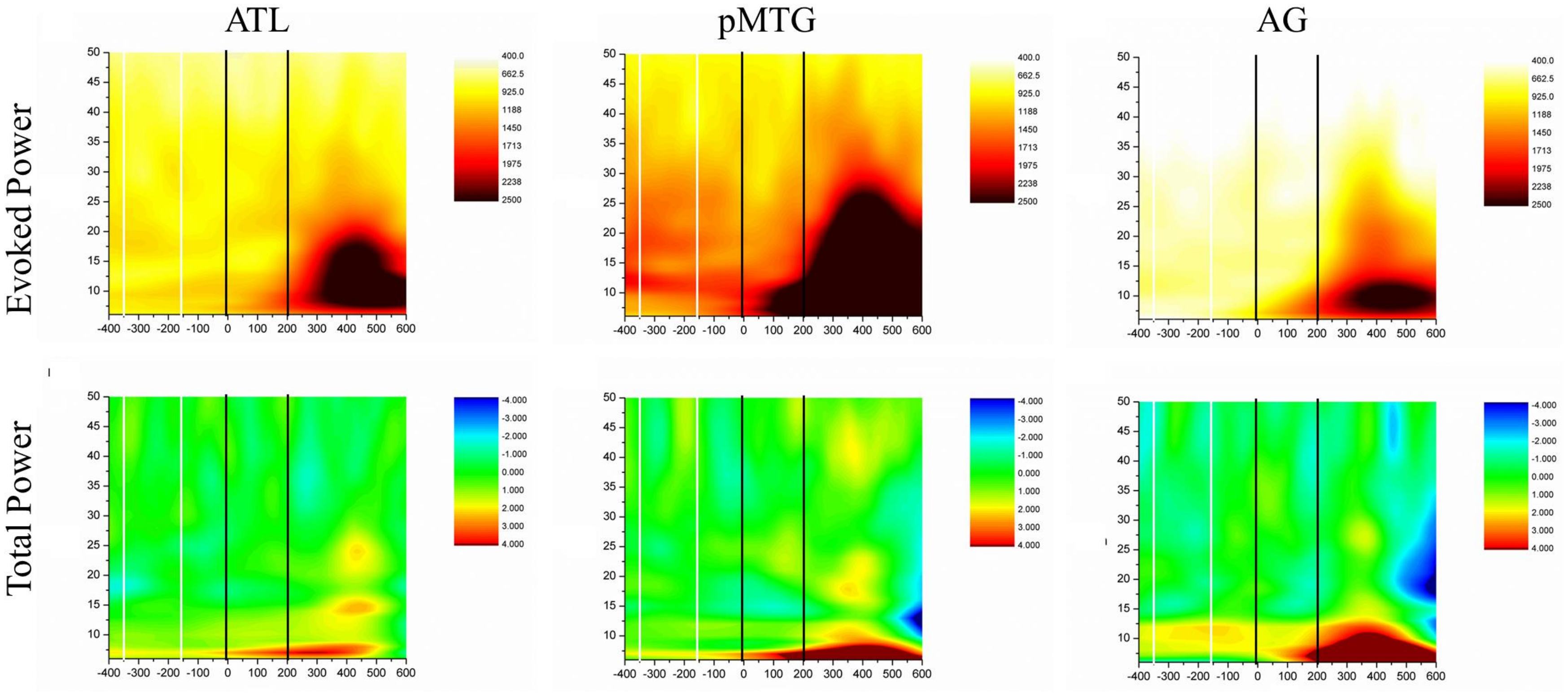


Figure 3.6: TOP ROW: Evoked (i.e., phase-locked) and BOTTOM ROW: Total oscillatory power (i.e., non-phase locked) across the whole epoch for related trials only. Presentation of the prime word (first word of the pair) is shown with white vertical lines, while presentation of target word (second word of the pair) is illustrated with black vertical lines. The three columns show time-frequency plots for three points of interest in the left hemisphere, ATL, pMTG, and AG. The TF plots of evoked power for each condition show raw power change multiplied by 10^11; TF plots of total power for each condition show percentage signal change relative to a passive baseline taken 500-700 ms prior to target onset. Total power plots can be in the form of increase or decrease in power, evoked plots for each condition show only increase. For this reason, I display TF plots of evoked power in each condition in a different colour scale to the total power plots.

ATL:

Taxonomic vs. thematic relationships

The evoked plots (Figure 3.7) show an early significant difference (50-150 ms) and a later component (~450-600ms), both effects driven by greater oscillatory power in the taxonomic condition. The earliest difference in total power between conditions can be seen from 0-50ms, centred around 35Hz, reflecting a small power increase to the taxonomic condition, immediately followed by a sustained power decrease. Additionally I saw a power increase to the thematic condition, reaching significance at ~300ms (see black significance lines), sustained until around 550 ms. There is also a power increase in both conditions between 6-8 Hz from 50-450 ms, denoted by white significance lines.

Strong vs. weak thematic relationships

The strongest evoked response to both strong and weak thematic conditions in ATL is sustained from 200-600ms at 15Hz (see Figure 3.8). This peak response is stronger in the strong thematic trials, relative to the weak thematic trials, but there are also some regions of the evoked response that are stronger for weaker associations. The total power contrasts support the view that ATL largely shows a stronger response to strong thematic than low trials. The peak response at 15Hz, again from 200-600ms was stronger for the strong thematic trials. However, there was a higher frequency response (around 25Hz) that was briefly stronger for thematic weak trials, around 300ms after the onset of the target word. Though the area of significant difference is brief in duration, this is due to there being a similar response of power increase in the high condition (see white significance lines at ~500ms), though it starts earlier and is stronger in the weak thematic condition. Given that the ATL arguably plays a role in automatic retrieval, this is expected since this is likely the process involved in the strong condition. There is also a low frequency (6-9Hz) power increase in both conditions at 225-425ms (see white significance lines).

Summary:

Early activation of ATL fits well with literature describing ATL activation within 120ms (Clarke et al., 2013; Fujimaki et al., 2009; Yvert, Perrone-Bertolotti, Baciu & David, 2012), and research finding ATL activation in the N400 time window (McCarthy, Nobre, Bentin & Spencer, 1995; Marincovic et al., 2003). Taking the two contrasts together, two conclusions can be made, namely i) Though there is a difference in the direction of power change (increase to thematic and decrease to taxonomic), ATL responds significantly to both conditions, inconsistent with the idea of this region as a taxonomic-only hub, and ii) the strong/weak contrast elicited more effects driven by the strong condition, consistent with the idea of this region being involved in automatic semantic retrieval.

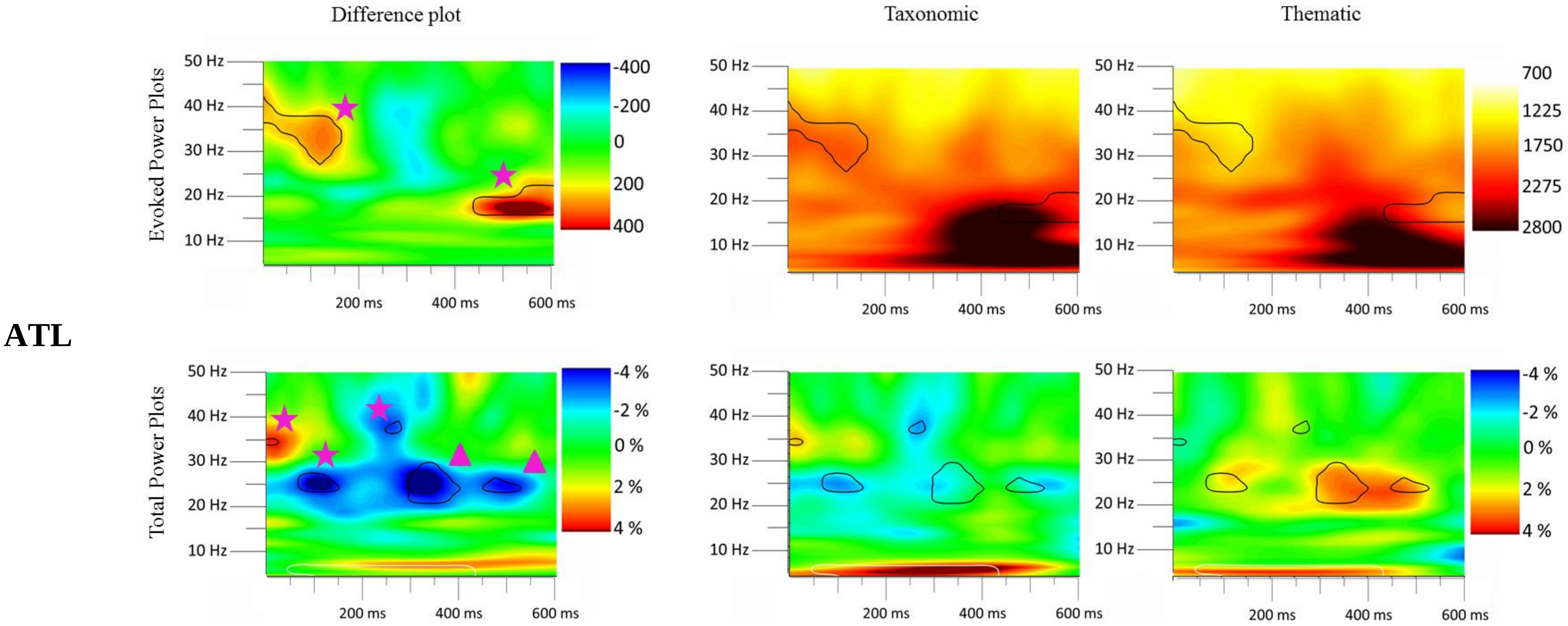


Figure 3.7: Evoked power: Difference TF plot**:** Signal change in taxonomic and thematic conditions relative to each other. Black lines on the plots indicate a statistical threshold (p<.05) which encloses regions where conditions are significantly different from each other. Taxonomic TF plot (middle panel): Oscillatory power plot of grand average of the taxonomic condition, multiplied by 10^11. Thematic TF plot: Oscillatory power plot of grand average of the thematic condition, multiplied by 10^11. Scale from white to red, with red colours indicating greater oscillatory power. **Total power:** Difference TF plot**:** Percentage difference between taxonomic and thematic conditions. Black lines indicate p<.05 statistical threshold fulfilling two criteria: i) conditions are significantly different from each other and ii) a significant change from baseline in at least one of the two conditions. Taxonomic TF plot: Percentage signal change in the taxonomic condition (relative to baseline). Thematic TF plot: Percentage signal change in the thematic condition (relative to baseline). Both difference plots are annotated with symbols in fuchsia: stars indicate stronger effects in the taxonomic condition, while triangles indicate stronger effects in the thematic condition.

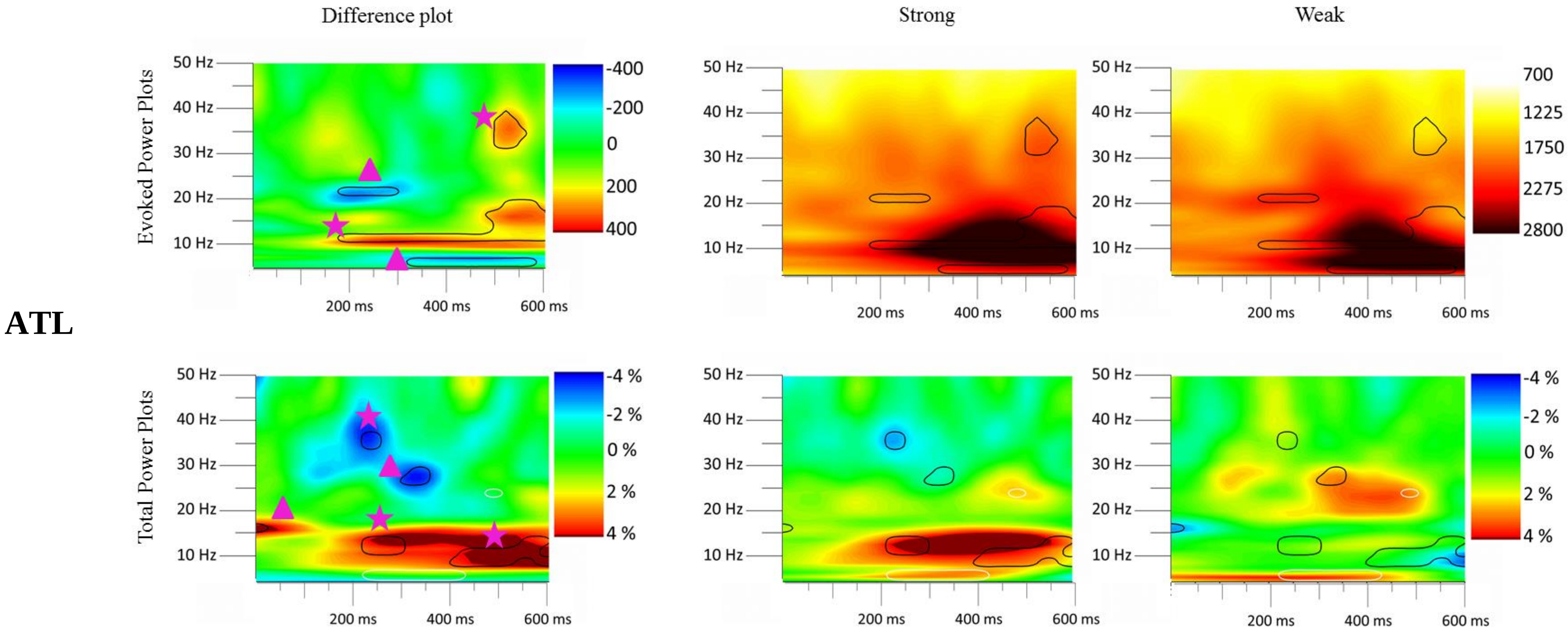


Figure 3.7: Evoked power: Difference TF plot**:** Signal change in strong and weak conditions relative to each other. Black lines on the plots indicate a statistical threshold (p<.05) which encloses regions where conditions are significantly different from each other. Strong TF plot (middle panel): Oscillatory power plot of grand average of the strong condition, multiplied by 10^11. Weak TF plot: Oscillatory power plot of grand average of the weak condition, multiplied by 10^11. Scale from white to red, with red colours indicating greater oscillatory power. **Total power:** Difference TF plot**:** Percentage difference between strong and weak conditions. Black lines indicate p<.05 statistical threshold fulfilling two criteria: i) conditions are significantly different from each other and ii) a significant change from baseline in at least one of the two conditions. Strong TF plot: Percentage signal change in the strong condition (relative to baseline). Weak TF plot: Percentage signal change in the weak condition (relative to baseline). Both difference plots are annotated with symbols in fuchsia: stars indicate stronger effects in the strong condition, while triangles indicate stronger effects in the weak condition.

PMTG:

Taxonomic vs. thematic relationships

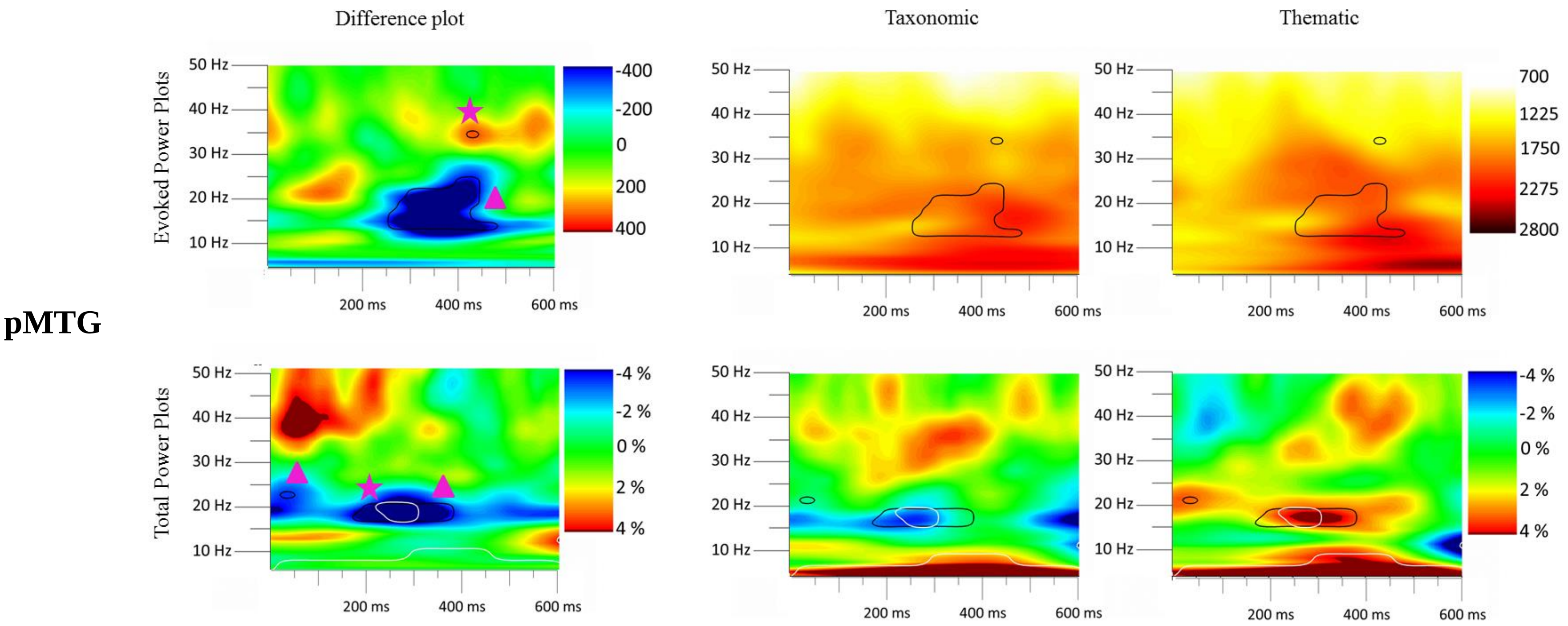
In the evoked analysis, pMTG showed a broadband and sustained response in both conditions, which was stronger for thematic decisions, consistent with the purported role for this site in event semantics. However, the total power plot showed a strong reduction in oscillatory power in response to taxonomic decisions relative to baseline from 200-400ms at 20Hz: this type of response is thought to reflect an increase neural activity that is not synchronised in time and phase (Hanslmayr et al., 2012; 2016), as well as power increase to the thematic pairs in the same time window. Furthermore, both conditions also showed an early and sustained difference from baseline in the same region of time-frequency space, both in power increase (white significance lines in Figure 3.9). These data do not strongly support the view that pMTG plays a selective role in thematic, but not taxonomic retrieval.

Strong vs. weak thematic relationships

Evoked shows similar response sustained for both conditions which is significantly stronger in thematic strong trials (see Figure 3.10). However, total power plots show that much of the response in pMTG is not aligned in time and phase, and these effects at a low frequency in the theta band, and around 20 and 40Hz, are stronger for the thematic weak trials, consistent with the purported role of pMTG in controlled semantic retrieval. PMTG also showed the earliest difference between conditions out of all the POIs, in the form of greater power increase to the weak condition. The general TF response is furthermore similar between the two conditions, and the differences are expressed as earlier and greater power change in the low condition, rather than a different response altogether (see white significance lines).

Summary

This site showed early and sustained power increase to both taxonomic and thematic conditions, as well as an overlapping area of significant activation in the form of power decrease to taxonomic pairs and power increase to thematic pairs. Though the strong/weak contrast showed stronger evoked power in the strong condition, total power analyses showed earlier and greater power increase to the weak condition. Taken together, these results do not support pMTG as a thematic-only site, but rather one that responds with greater power change when conditions require higher control demands, possibly with a qualitatively different response depending on relationship type.



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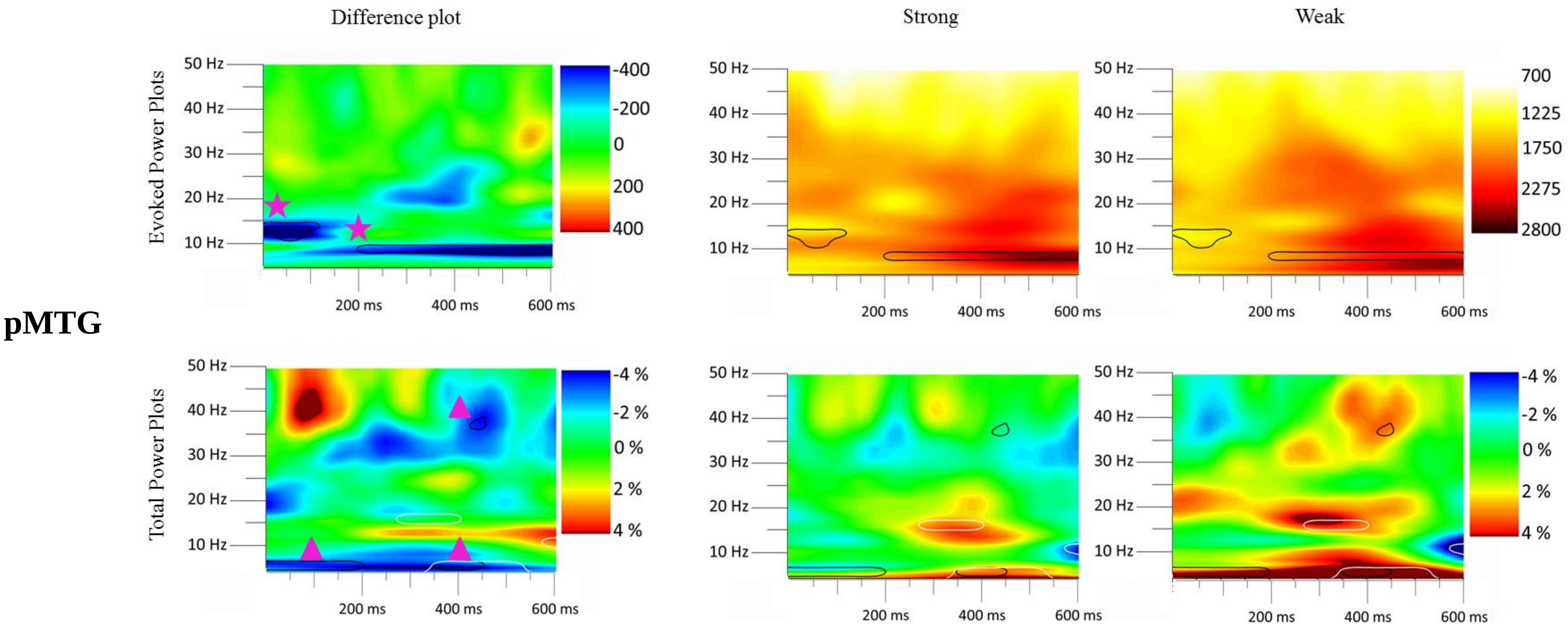


Figure 3.7: Evoked power: Difference TF plot**:** Signal change in strong and weak conditions relative to each other. Black lines on the plots indicate a statistical threshold (p<.05) which encloses regions where conditions are significantly different from each other. Strong TF plot (middle panel): Oscillatory power plot of grand average of the strong condition, multiplied by 10^11. Weak TF plot: Oscillatory power plot of grand average of the weak condition, multiplied by 10^11. Scale from white to red, with red colours indicating greater oscillatory power. **Total power:** Difference TF plot**:** Percentage difference between strong and weak conditions. Black lines indicate p<.05 statistical threshold fulfilling two criteria: i) conditions are significantly different from each other and ii) a significant change from baseline in at least one of the two conditions. Strong TF plot: Percentage signal change in the strong condition (relative to baseline). Weak TF plot: Percentage signal change in the weak condition (relative to baseline). Both difference plots are annotated with symbols in fuchsia: stars indicate stronger effects in the strong condition, while triangles indicate stronger effects in the weak condition.

AG:

Taxonomic vs. thematic relationships

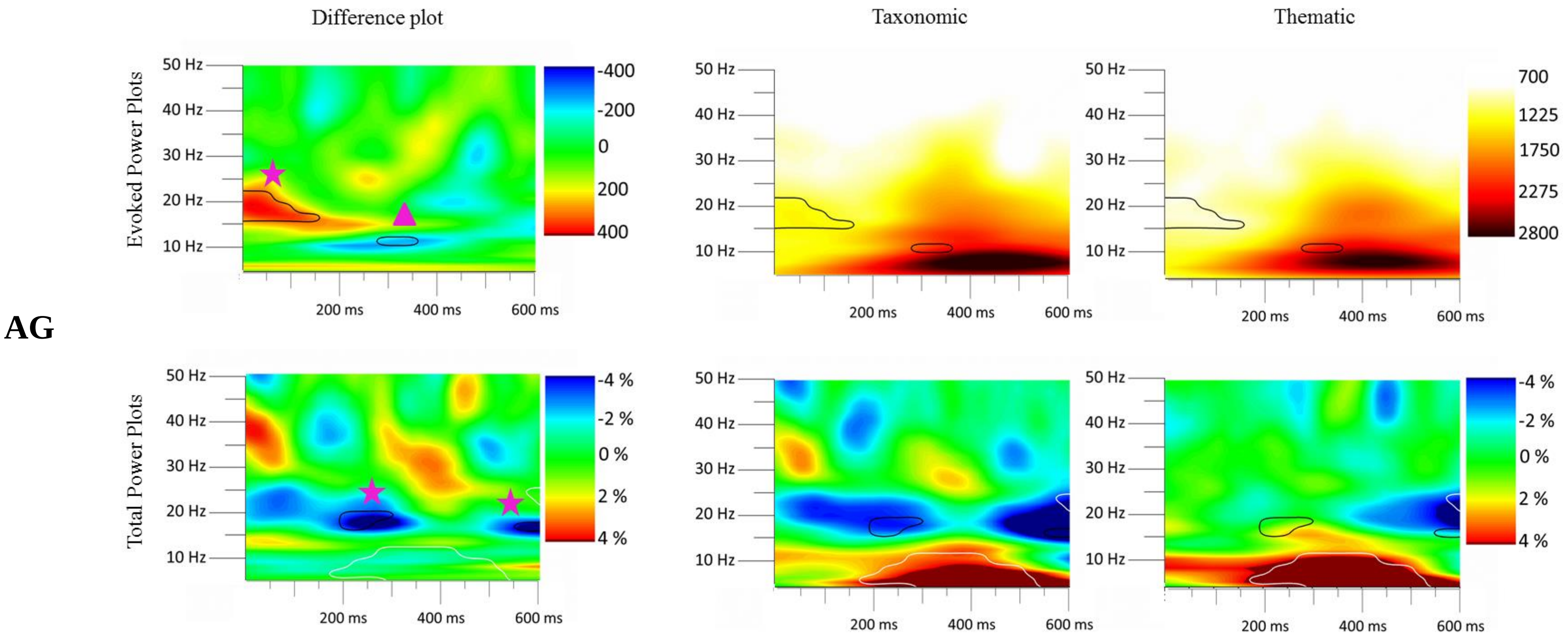
AG showed stronger changes in oscillatory power for the taxonomic decisions across both analyses, inconsistent with the view that this region is a “thematic hub”. This difference was apparent soon after stimulus presentation in both evoked and total power, although subsequent effects in both analyses did show the pattern of greater power changes for the thematic trials (by 300ms in the evoked response, and by 400ms in total power). The low-frequency response seen in the other ROIs is present here also, though is delayed compared to the other sites, starting at ~200ms and lasting throughout the analysis window (see white significance lines in Figure 3.11).

Strong vs. weak thematic relationships

In evoked power analyses AG shows effects predominantly driven by the strongly related trials, with one effect centred around ~200ms driven by the weakly related condition. Total power analyses also revealed early effects driven by the strong thematic pairs, with a later component driven by the weakly related condition, in the form of power increase and power decrease respectively. Additionally, a sustained low frequency power increase was seen throughout the analysis window in both conditions (see white significance lines in Figure 3.12).

Summary

Angular gyrus showed effect driven by both taxonomic and thematic stimuli, though unlike the other sites, this was in the form of power increase to the taxonomic condition and power decrease to thematic relationships. The strong/weak contrast revealed an early power increase to strong thematic links, and a later power decrease to weakly related pairs. Taken together, these results do not support AG as a thematic-only site, but rather one that responds rapidly to strong associations, consistent with its postulated role in automatic retrieval (Humphreys and Lambon Ralph, 2014).



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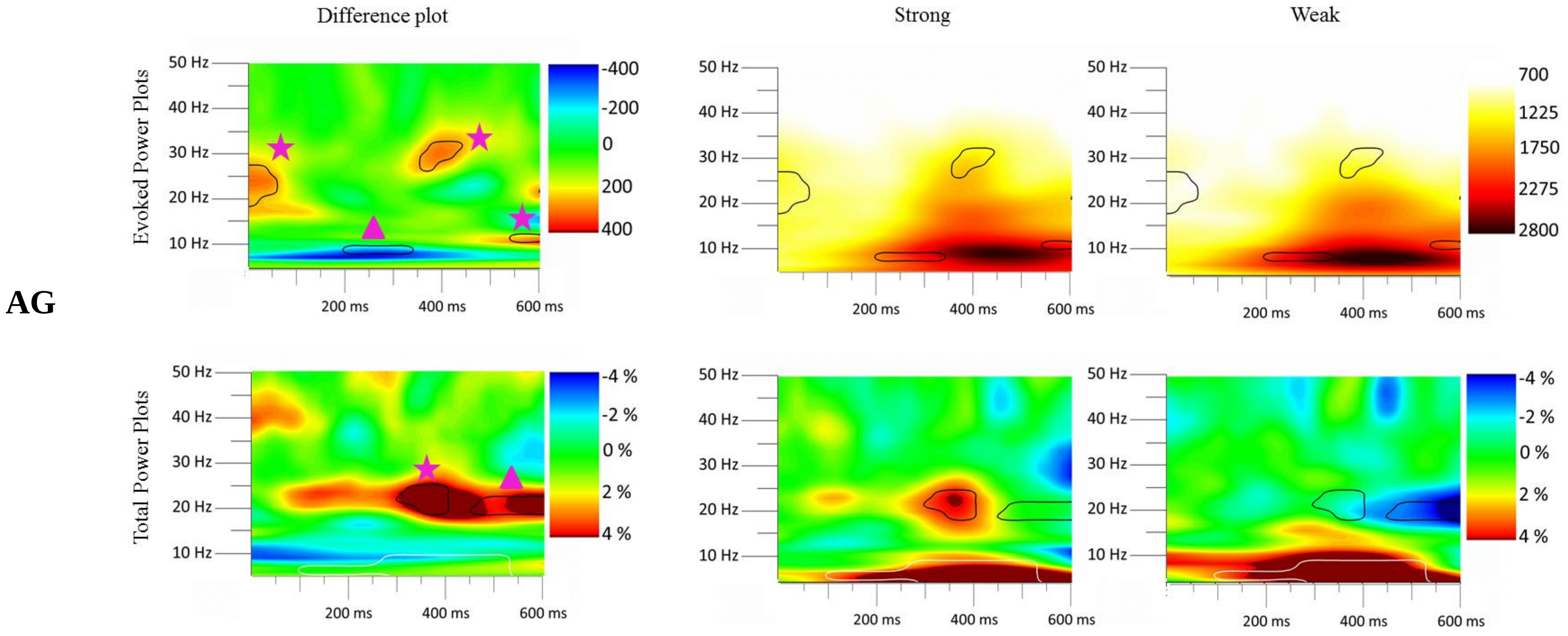

Figure 3.7: Evoked power: Difference TF plot**:** Signal change in strong and weak conditions relative to each other. Black lines on the plots indicate a statistical threshold (p<.05) which encloses regions where conditions are significantly different from each other. Strong TF plot (middle panel): Oscillatory power plot of grand average of the strong condition, multiplied by 10^11. Weak TF plot: Oscillatory power plot of grand average of the weak condition, multiplied by 10^11. Scale from white to red, with red colours indicating greater oscillatory power. **Total power:** Difference TF plot**:** Percentage difference between strong and weak conditions. Black lines indicate p<.05 statistical threshold fulfilling two criteria: i) conditions are significantly different from each other and ii) a significant change from baseline in at least one of the two conditions. Strong TF plot: Percentage signal change in the strong condition (relative to baseline). Weak TF plot: Percentage signal change in the weak condition (relative to baseline). Both difference plots are annotated with symbols in fuchsia: stars indicate stronger effects in the strong condition, while triangles indicate stronger effects in the weak condition.

Discussion

This study used MEG to explore two separate views of semantic cognition, namely the dual-hub theory of semantic cognition, and the Controlled Semantic Cognition framework. In a two word association judgement, comparing either taxonomically and thematically associated word pairs (mole-cat vs cushion-cat), or thematically associated word pairs of different levels of association strength (high semantic association (milk-cat) and low semantic association (cushion-cat)). This method was used to test contrasting predictions about the functional roles of ATL, AG, and pMTG, and to compare the responses of two sites implicated in automatic semantic retrieval (ATL, AG) with a site postulated to be engaged in controlled semantic retrieval (pMTG). The dual-hub theory of semantic cognition predicts that ATL is important for taxonomic relationships while left pMTG and AG support thematic knowledge. Alternatively, the Controlled Semantic Cognition framework postulates one representational hub (ATL) underpinning knowledge of all types of relationship, with pMTG supporting controlled retrieval for more difficult judgements. Thus, if the dual-hub theory is correct, ATL would be expected to deal predominantly (if not exclusively) with taxonomic associations, and pMTG and AG would process predominantly (if not exclusively) thematic associations. Furthermore, pMTG and AG should behave similarly due to lack of differentiation between them in the dual-hub theory (where the thematic hub is postulated to be located in the TPJ, which encompasses both pMTG and AG). Alternatively, if the Controlled Semantic Cognition framework is correct, it would be expected ATL and AG to process all types of associations, but show greater power change in the strong as compared with the weak thematic condition. Similarly, pMTG would be expected to deal with all associations, but show greater power change in the weak as compared with the strong thematic condition, and (if the difficulty manipulation was successful) comparable response in the taxonomic and weak thematic conditions.

ATL

Whole brain results show particular recruitment of this region to taxonomic and weakly related thematic trials in the same time window, in different frequency bins (25-35Hz and 35-50Hz respectively. The POI analysis showed significant response to both taxonomic and thematic stimuli, first to taxonomic (within 100ms of target onset), then to thematic (within 300ms of target onset). While the frequency range and timing of the response was very similar, it took the form of power decrease to taxonomic stimuli, and power increase to the thematic condition. When looking at the evoked power analysis, the significant differences are driven by more evoked power in the taxonomic condition. This could go some way to explain why other research has found predominantly taxonomic effects in ATL. While somewhat speculative, it is possible that the taxonomic condition's reliance on perceptual (visual) aspects of semantic information, means stimuli is inherently more phase-locked in this area, due to ATL's position at the end of the ventral visual stream. Clarke et al. (2011) showed increased phase-locking between left anterior temporal and fusiform both for basic > domain level naming around 120-220ms, as well as two periods of greater phase-locking for living compared to non-living items around 176 -202ms and 296-340ms. They take their data to indicate that greater semantic integration demands increase phase-locked recurrent interactions between cortical areas. This has implications for the results, as taxonomic decisions require an abstract representation of category to be applied, and may pose similar increased demands as the ones tested in Clarke et al. (2011). If taxonomic associations are inherently more phase locked in ATL because of this, only analyses that incorporate the induced component would be able to show greater oscillatory power to thematic stimuli here. Crucially, the analysis shows ATL responding to both conditions, which is inconsistent with the idea of this area as a taxonomic-only hub.

The strong/weak thematic contrast revealed qualitatively similar time-frequency responses to the strongly and weakly related trials in the form of power increase. Differences were driven by both conditions from around 225ms, though the strongest response is to the strong thematic condition, consistent with this site's postulated role in automatic retrieval (Davey et al., 2016). ATL responds significantly to both conditions, inconsistent with the idea of this region as a taxonomic-only hub, and furthermore, the strong/weak contrast elicited more effects driven by the strong condition, consistent with the idea of this region being involved in automatic semantic retrieval.

In this analysis, effects in ATL are present from the onset of the second word. More traditional views suggest semantic access around 400ms, and recent MEG experiments have presented results in support of this view (Vartainen, Parvainen & Salmelin, 2009), also locating the effect to ATL (Lau et al., 2014). However, recent studies utilising temporally sensitive imaging methods have indicated that visual and verbal semantic tasks can elicit effects more rapidly than this in ATL (Marincovic et al., 2003; Clarke et al., 2011; 2012; Bemis & Pylkkanen, 2011; 2012; Chan et al., 2011), with stronger effects from the relationship between two words (as opposed to single word/object processing), particularly if the first word increases the specificity of the second (Zhang & Pylkkanen, 2015; Westerlund & Pylkkanen, 2014). Given the sequential presentation, this provides further support for the early effects seen in this region.

pMTG

Whole brain analyses showed posterior temporal activation in pMTG/AG regions for all conditions. In the total power POI analysis, the first significant difference between taxonomic and thematic stimuli starts around 50ms driven by an increase in power to the thematic condition, and is followed by a response with overlapping time windows, in the form of power decrease to the taxonomic condition, and power increase to thematic associations. Additionally there is a significant power increase to *both* conditions from the onset of the target word, continuing throughout the analysis window. This is similar to results reported in Chapter 2, where associations requiring greater semantic control processes yielded stronger recruitment of this area from the onset of the target word - consistent with the hypothesis that pMTG maintains currently relevant features or interpretations and detects situations in which incoming information is not well-aligned with these interpretations. Because executive demands are high in both the taxonomic and thematic conditions, pMTG's involvement in both is not surprising, as the information that is being maintained needs to be broader to support more difficult associations. However, these results do not fit with the idea of posterior temporal (TPJ) areas being part of a *thematic-only* hub. The evoked analysis showed much larger effects to thematic stimuli, and only a later, brief effect of the taxonomic condition. Again, it is possible that this region's response to taxonomic stimuli is shown to a much greater extent by analyses that incorporate the induced component, and that this is why previous research has reported this region as thematic-specific.

Though the strong/weak contrast showed stronger evoked power in the strongly related condition, total power analyses showed earlier and greater power increase to the weak condition. In this contrast, this site showed the earliest difference between conditions, and all significant differences are driven by a greater increase in power to the weak thematic condition, consistent with this area's postulated involvement in controlled retrieval (Whitney et al., 2011).

AG

Whole brain analyses showed posterior temporal activation in pMTG/AG regions for all conditions. In the POI analysis, angular gyrus showed the earliest significant difference between taxonomic and thematic relationships. In this region, all significant differences until ~425ms are driven by power increase to the taxonomic condition, inconsistent with the idea of TPJ areas being part of thematic-only hub. Similarly, the evoked analysis shows significant effects driven by both conditions; an early component driven by greater oscillatory power in the taxonomic condition, and a later component driven by the thematic condition, further supporting the view that this region is not thematic-specific.

In the strong/weak contrast, AG shows differences from 275ms, driven by power increase in the strong thematic condition, consistent with automatic retrieval. Around 400ms there is a significant power decrease to the weakly related condition, so AG is unlikely to be a completely automatic retrieval site, and may play a role in allocating attention to activated concepts, as recently argued by Humphreys and Lambon Ralph (2014). Importantly, according to the dual-hub theory, pMTG and AG should behave similarly due to lack of differentiation between them (in this framework the thematic hub is postulated to be located in the TPJ, which encompasses both pMTG and AG), and they do not behave similarly – in fact AG's response profile is very different from the other sites in general, and more in line with the Controlled Semantic Cognition framework given its' response to both thematic and taxonomic stimuli.

Results across sites

In whole brain analyses I saw significant activation of the semantic network in the form of power decrease. As the whole-brain beamforming reflects total power results, this fits well with the power reduction effects seen in the POI analyses. Power decrease has been hypothesised to be linked to richer informational content (Hanslmayr et al., 2012), as well as having been linked to successful memory encoding and retrieval in EEG results (Burgess and Gruzelier, 2000; Khader and Rösler, 2011; Waldhauser et al., 2012). Results from 5-50Hz are reported, as the short-duration analysis windows are not optimal for effects below 5Hz. As such I cannot make claims for power increases below this frequency, though in the POI analyses there are power increases between ~5-8Hz across all sites and conditions, though particularly to conditions with higher control demands (taxonomic and weakly related thematic trials). For example, in pMTG the low frequency power increase to the weak thematic condition is greater than for the strong thematic condition, AG has a strong power increase to all conditions, and ATL shows greatest power increase for taxonomic pairs, followed by weak thematic and the least for strong thematic pairs. These results taken together indicate that these power increases are more associated with condition than site. The whole-brain analysis predominantly shows effects between 25-50Hz, which closely resembles the frequency band thought of as “gamma” band. The amplitude of gamma oscillations are thought to be influenced by theta (4-8Hz) phase, which is particularly prominent in hippocampal, prefrontal cortices, amygdala and visual cortex (Roux & Uhlhaas, 2014), and in the rat hippocampus it has been shown that the same cell populations are influenced by both oscillations (Lisman & Buzsáki, 2008).

Furthermore, it has been argued that low and high frequency oscillations may reflect different underlying processes, with high frequency oscillations (>30Hz) reflecting local interactions within a neural population, and low frequency oscillations (<30Hz) underpinning coordination of distributed neural populations (Donner and Siegel, 2011). Taxonomic associations are thought to be based on overlapping features, which arguably is reflected in overlapping representations (cell populations). In line with this, Clarke et al. (2012) found that increased shared features lead to decreased MEG response. It seems plausible that the thematic conditions - not sharing physical features - require greater integration between distributed neural populations, and cortical areas. The results seen in the whole-brain analysis with higher frequency (35-50Hz) results to the weakly related thematic trials compared with the taxonomic (25-35Hz) could reflect the hypothesis of Donner & Siegel (2011), in that the thematic condition (in addition to needing more distributed cortical areas working together, reflected in the low frequency power increase), the concepts themselves also need richer retrieval in order to make the connection between them.

When viewing the time-frequency plots of each area to each condition, there is more similarity in the form of the response between strong and weak thematic conditions than there is between the taxonomic and the thematic conditions, with taxonomic associations eliciting predominantly decreases in oscillatory power and thematic conditions eliciting predominantly increases in oscillatory power. The reason for the form of the response, with general power decrease across sites to the taxonomic condition (except AG), is unclear, though Clarke et al. (2012) found that increased overlapping features lead to a decrease in the MEG response. According to Hanslmayr, Staudigl and Fellner (2012), power decrease may have a greater informational content than power increase. As such, the different response profiles could reflect that taxonomic priming may represent activation at the conceptual level, whereas thematic priming reflects activation of concepts at the lexical form level. In addition to occurring together in the natural world, thematic relationships are also more likely to co-occur in text, which the purely taxonomic relationships are certainly less likely to do. While this inference goes beyond the scope of the presented data, it is possible that the decrease vs. increase in power in the two different types of processing reflects recruitment of these areas in different ways, namely the decrease in power in the taxonomic condition reflecting richer retrieval, and thematic associations might rely on comparatively shallow activation of distributed neural populations. Crucially, though there are some differences in how these areas are recruited in terms of oscillatory power, the whole-brain results support a single semantic network supporting both thematic and taxonomic relationships.

Conclusion

The results provide evidence in line with the representation vs. retrieval view of semantic cognition, as ATL responds to both taxonomic and thematic associations, as does pMTG and AG, making the dual-hub view an unlikely explanation of the results. The MEG data provided here shows a recruitment of known sites within the hub-and-spoke model of semantic cognition for all conditions, with a qualitative difference in the form of the response. The results are taken to show a unified semantic system for taxonomic and thematic associations, with differences in the oscillatory form and timing of the response within an area, rather than different types of association relying on different cortical areas.

Chapter 4 - General discussion

This thesis examined the neural basis of different aspects of semantic cognition using time-resolved methods – namely magnetoencephalography (MEG) and chronometric transcranial magnetic stimulation (cTMS). Semantic cognition allows us to understand the significance of items and situations that we encounter daily, and to drive appropriate thoughts and behaviour accordingly. It encompasses our knowledge of meanings of words, objects, sounds and people, and the application of this knowledge to drive appropriate behaviour and thought (Patterson, Nestor & Rogers, 2007; Pulvermüller, 2013; Jefferies, 2013). These processes are thought to require distinct neurocognitive components working together: First, *semantic representations* capture the meanings of words and objects. Secondly, since we have stored knowledge of many features and associations for any given concept, *semantic control processes* are thought to be essential to our ability to retrieve and act upon this wide variety of knowledge in a relevant way, through the selection and retrieval of situation-relevant knowledge, and the suppression of information irrelevant to the task/situation (Hodges, Patterson, Oxbury & Funnell, 1992; Corbett, Jefferies, Ehsan & Lambon Ralph, 2009). Thus, time-resolved methods in cognitive neuroscience are useful for examining how the brain systems that support these components of semantic cognition cooperate to support different tasks.

One controversial issue in the field, addressed by this thesis, concerns the nature of semantic representation, and whether different types of information are stored and processed in different brain regions (see Chapter 3). There are different theoretical perspectives which differ in the degree to which semantic representations are considered to be abstract, amodal and cortically localist, or to emerge from distributed and embodied sensory-motor processes. The influential hub and spoke model of semantic cognition occupies a middle position in this debate: it suggests that both sensory-motor areas (the “spokes”) and an amodal convergence zone in the ATL (the “hub”) are crucial for the representation of semantic knowledge (Patterson, Nestor & Rogers, 2007). Consequently, all of the empirical chapters examined the contribution of the ATL to semantic tasks. However, there is debate about whether the ATL is the only site that acts as a semantic hub. For example, it has been suggested that the ATL is one of two conceptual hubs, underpinning taxonomic or category-level knowledge, whereas the temporoparietal junction (TPJ; such as angular gyrus and posterior middle temporal gyrus) extracts event associations and thematic knowledge (Schwartz et al., 2011; de Zubicaray, Hansen & McMahon, 2013).

The brain regions that support the *retrieval* of conceptual information are a second focus of the empirical work presented in this thesis. Considering the wealth of information available to us at any given time, semantic control processes are engaged to retrieve relevant information and suppress irrelevant features and associations. In some cases, knowledge that is relevant to the task at hand can be retrieved in a relatively automatic, cue-driven (bottom-up) way, and is seemingly effortless: this type of semantic retrieval is thought to support access to dominant aspects of concepts (e.g., banana → yellow) without strong engagement of control processes. Other times the appropriate information is not so readily available, and a more strategic "search" of our memory is needed, increasing the semantic control demands (Gold et al., 2006; Badre & Wagner, 2007; Binder, 2016). Semantic control processes are thought to modulate semantic activation such that it is appropriate to the task or context. This involves selecting between competing alternatives held in working memory, inhibiting non-relevant semantic activation, and the retrieval of knowledge when automatic, spreading activation is not sufficient. Furthermore, semantic control involves extracting and applying the goals relevant to the task, as well as switching or updating the semantic focus when the tasks changes (Whitney, Kirk, O'Sullivan, Lambon Ralph & Jefferies, 2011; Moss, Abdallah, Fletcher, Bright, Pilgrim, Acres & Tyler, 2005).

An extensive fMRI literature has linked conceptual control processes to left inferior frontal gyrus (Thompson-Schill, D'Esposito, Aguirre &Farah, 1997; Badre, Poldrack, Pare-Blagoev, Insler & Wagner, 2005; Noppeney, Phillips & Price, 2004; Bedny, McGill & Thompson-Schill, 2008) but manipulations of executive-semantic demands activate a widely distributed set of cortical regions, including pMTG (Noonan et al., 2013; Davey et al., 2016). Furthermore, inhibitory TMS to pMTG and LIFG produces equivalent disruption of semantic judgements that require controlled but not automatic retrieval (Whitney et al., 2011; Davey et al., 2015).

Consequently, the MEG studies in Chapters 2 and 3 manipulated strength of association between the probe and target to modulate the engagement of controlled retrieval processes, and examined the response to this manipulation in pMTG. Moreover, in all of the empirical studies, the anterior temporal lobes and posterior middle temporal gyrus were expected to show an opposite response to this manipulation, since strongly-associated words should facilitate a stronger pattern of spreading activation within semantic representations in ATL, while weakly-associated words should engage controlled retrieval processes more strongly in pMTG. However, the temporal recruitment of semantic processes is unclear, with conflicting evidence of both when and where semantic access is achieved, and there has been little empirical work investigating the temporal engagement of semantic *control* processes during retrieval and how different brain regions show dissociations through time that can linked to the difference between automatic and controlled semantic retrieval. Therefore, the primary aims of this thesis were:

- To investigate how automatic and controlled patterns of semantic retrieval shape oscillatory activity within the semantic network
- To determine the causal temporal engagement of brain areas implicated in automatic and controlled semantic retrieval
- To explore the existence of one or two semantic hubs by contrasting taxonomic and thematic relationships

To this end, a series of neuroimaging experiments were employed, using MEG analysis of total and evoked oscillatory activity, and cTMS to assess the causal contribution of areas in the semantic network over time. MEG has the potential to be a very elucidating method to use in this regard; most studies investigating semantic retrieval use fMRI, which can reveal the network of brain regions active in a task, however, the BOLD response has low temporal resolution (since blood flow changes happen over a period of several seconds). This means that transient effects may be missed and the technique is not ideal for identifying how sites within the semantic network are recruited over time, in the service of a task. Furthermore, fMRI suffers from magnetic susceptibility artefacts that produce signal loss and distortion around air-filled sinuses, and therefore this method may not always reveal responses in regions like ATL, that have consistently been implicated in semantic tasks (Devlin et al., 2000). MEG on the other hand, has temporal resolution in the order of milliseconds, and offers different insights into neural activity since it is possible to characterise responses at specific frequency bands and to separate phase-locked and non-phase locked components of the signal, which may show different cognitive effects (Hansen, Kringelbach & Slamelin, 2010). The use of different methodologies gives the possibility of converging evidence across methods, bringing greater confidence in results. Total oscillatory power was therefore examined in key regions for semantic cognition – ATL and pMTG – using MEG in Chapters 2 and 3 (Chapter 3 also included analysis of AG). Compared with fMRI, MEG has relatively poor spatial resolution, and difficulty resolving and detecting deeper sources. Moreover, fMRI and MEG are both correlational methods; the modulation of signal strength by task conditions in imaging investigations does not conclusively show that these brain regions make a *necessary* contribution to the task. The thesis therefore included a TMS study to test causal predictions about the engagement of ATL and pMTG in automatic and controlled semantic retrieval over time (Chapter 2, Experiment 2).

Automatic and controlled semantic retrieval in the brain

Chapter 2 focused on the contributions of two sites in the semantic network: ATL, and pMTG. These sites are consistently activated in fMRI investigations, and are accessible for methods like TMS and MEG (**ATL**: Devlin et al., 2000; Visser, Jefferies & Lambon Ralph, 2010; Binney, Embleton, Jefferies, Parker & Lambon Ralph, 2010; Lau, Gramfort, Hämäläinen & Kuperberg, 2013; Martin, 1999. **PMTG**: Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997; Wagner, Maril, Bjork & Schacter, 2001; Bedny, McGill, & Thompson-Schill, 2008; Noonan et al., 2013; Davey et al., 2016). If ATL is a store of conceptual information extracted over a lifetime's experiences, then patterns of semantic retrieval that are highly consistent with these experiences should be facilitated within this region: consequently, stronger responses might be seen in ATL in tasks probing strong associations or coherent conceptual combinations (Lau, Gramfort, Hämäläinen & Kuperberg, 2013; Davey et al., 2016). In other words, the structure of representations in ATL might be able to support the retrieval of dominant aspects of knowledge relatively automatically. In contrast, when the pattern of semantic retrieval required in a particular situation is not strongly supported by representations in ATL, processing within the semantic store may need to be constrained by additional control processes, which are thought to engage pMTG as part of a larger distributed network (Noonan et al., 2013; Davey et al., 2016). This suggests there should be clear functional dissociation within the temporal lobe for tasks tapping relatively automatic and more controlled patterns of semantic retrieval; however, the oscillatory response in these regions and and the timing of their contribution to semantic cognition is unclear.

Chapter 2 presented two experiments using MEG and cTMS. In Experiment 1, MEG was used to characterise the brain's oscillatory response to the presentation of written words that were preceded by strongly related primes, weakly related primes and unrelated words. However, with correlational methods like fMRI or MEG, it cannot be ascertained whether these effects reflect *necessary* processes. The second experiment attempted to address this issue by using online chronometric TMS (cTMS). In Experiment 2, ATL and pMTG were stimulated at four time points, during the retrieval of strong (largely automatic) and weaker (more controlled) associations, allowing assessment of when these sites showed critical engagement.

Experiment 1: Neural processes underlying automatic and controlled semantic retrieval revealed by MEG

This experiment investigated the brain's oscillatory response to automatic or controlled retrieval situations. Studies have examined the time course of semantic access from a single written word, while the focus here was on how the semantic relationship between two successive items changes retrieval, in order to explore the time-course of changes in oscillatory power that support relatively automatic (i.e., strongly primed) semantic retrieval, and more controlled retrieval states in which it is necessary to discern a link between two weakly related words (Binder, 2016; Lucas, 2000; Gold et al., 2006). The sequential presentation of prime and target words also conforms to methodological constraints of MEG; this method is highly susceptible to movement artifacts (including eye-movement and saccades), so to minimise participant eye movement, stimuli were presented one word at a time. The analysis examined total power (which incorporates both evoked power - oscillations locked to the stimulus both in time and phase - as well as oscillations locked to the stimulus in time, but not phase; *induced* power). Total power is likely to be sensitive to evolving semantic retrieval driven by the relationship between two words, which is *not* likely to be phase-locked to the onset of either stimulus.

The response to the second word in the pair was characterised by event-related decreases in total power relative to baseline. These decreases are thought to be explained by an increase in oscillatory power that is not phase-locked (Hanslmayr et al., 2011). Visual-to-semantic access is more demanding for the first word in the pair, while for the second word the relationship between the two concepts is pertinent. It is also worth noting that one of the constraints of the analyses presented is that I discuss time points at which the two conditions are *significantly different from each other* (not significant change from a baseline for each condition), meaning that the underlying cognitive process could (and probably did) start earlier than the times discussed.

The pattern of oscillatory activity observed for each site elucidates their roles in automatic and controlled semantic retrieval: In ATL, when examining total power analyses, strong > weak effects were observed (around 400ms post-stimulus), consistent with a potential contribution of ATL to the capacity of relatively automatic spreading activation between associated concepts, which facilitates ongoing semantic retrieval. Conversely, in pMTG, a clear weak > strong effect was observed within 50ms of target-onset that continued throughout the trial, consistent with the view that this region plays a crucial role in supporting and potentially triggering controlled retrieval processes (since the stronger response to less anticipated concepts started soon after the onset of the second word). These findings are consistent with the hypothesis that pMTG maintains currently relevant features or interpretations and detects situations in which incoming information is not well-aligned with these interpretations – consistent with the early effects of strength of association that were observed. Furthermore, this measure shows a clear dissociation with the response in ATL, since ATL showed a strong > weak association difference, at a later point in time (when patterns of coherent semantic retrieval, as opposed to input recognition processes, might be established). These findings suggest that pMTG could be crucial for semantic control is situations in which the task requires a pattern of retrieval that is not strongly supported by the structure of long-term conceptual representations, in line with fMRI data using a similar paradigm (Davey et al., 2016; Badre et al., 2005), and adds temporal information to this literature.

This interpretation is consistent with the proposal that ATL is important to combinatorial semantics (Feng et al., 2016). Combinations of words have richer and more specific meanings than individual words, and priming paradigms have revealed an augmented response in ATL to words preceded by adjectives and nouns, and further, that the more specific the noun, the greater the response in ATL (Westerlund & Pylkkänen, 2014; Zhang & Pylkkänen, 2015). I further suggest that this might be most readily detected in total power analyses, since this measure includes the component of oscillatory power that is not aligned in time and phase (as well as phase-locked components), and it is not clear that neural signals linked to spreading activation within the semantic system would be phase-locked to the onset of a visual stimulus.

Experiment 2: The causal engagement of ATL and pMTG in automatic and controlled semantic retrieval, tested using transcranial magnetic stimulation

The results of Experiment 1 implicated early engagement of pMTG in controlled retrieval, and a later effect in ATL associated with automatic retrieval. In Experiment 2 ATL and pMTG were stimulated at four time points, during the retrieval of strong (largely automatic) and weaker (more controlled) associations, using an inhibitory chronometric TMS paradigm, allowing the assessment of *when* these sites showed critical engagement. A recent cTMS study of the ATL by Jackson et al. (2015) found disruption to semantic retrieval when pulses were delivered around 400ms after stimulus presentation. This study utilised a synonym judgment task, with three words presented concurrently on screen; a probe, a related synonym, and an unrelated foil, and participants were asked to select the related word. However, here the effect of online stimulation from the onset of the second word in a pair was examined (presented sequentially), since the focus was how the semantic relationship between two successive items changes retrieval. Dual pulses were applied at 0-40ms; 125-165ms; 250-290ms and 450-490ms after target onset: these times corresponded to effects in both sites in Experiment 1, as well as literature showing early engagement of ATL (Clarke et al., 2011), as well as later N400 effects. It was anticipated that this format of sequential presentation would elicit relatively early disruption in ATL, corresponding to the effects described by Clarke et al. (2011), rather than late effects observed by Jackson et al. (2015).

Given literature suggesting that ATL is a key store of semantic knowledge, it was also hypothesised that TMS to this region might disrupt the pattern of automatic spreading activation between related concepts that is thought to underpin strong associations. In contrast, fMRI and TMS studies have pointed to a role of pMTG in controlled retrieval, and I therefore predicted greater disruption for weakly related word pairs at this site. Furthermore, I cautiously predicted disruption within the first 50ms at pMTG, given the findings from Experiment 1 that pointed to an early sensitivity to weak associations at this time point for pMTG, which could correspond to detection of the need to engage controlled retrieval processes.

The current data are in line with these hypotheses, and critically show disruption for the weak condition at an early (0-40ms) time point for pMTG, and disruption for the strong condition somewhat later for ATL (125-165ms). A recent meta-analysis by Noonan et al. (2013) demonstrated that pMTG is consistently activated alongside LIFG by increasing semantic control demands. Offline TMS studies also show that stimulation to both LIFG and pMTG disrupts performance on semantic tasks that require controlled retrieval (Whitney et al., 2011; Davey et al., 2015). The strikingly early result for pMTG further suggests that this site may contribute to the maintenance of information elicited by the prime word, and that this maintenance may be critical for establishing a pattern of controlled semantic retrieval when spreading semantic activation is likely to be insufficient. Importantly, the latency of the response suggests that this site is not involved in resolving competition following retrieval (which would occur at a later time point), but rather in detecting the need to engage more controlled retrieval processes, when stimuli need to be integrated into a meaningful context by biasing retrieval to focus on only a subset of features. Following this, a novel hypothesis is proposed, whereby pMTG maintains currently-relevant conceptual information allowing this site to detect when inputs are unexpected, and potentially to interact with ATL to shape ongoing semantic retrieval within the long-term semantic store.

Furthermore, the disruption to the efficient retrieval of strong associations following TMS to ATL around 150ms after the target was presented (pulses at 125-165ms) corresponds well to the findings of Clarke et al. (2011). Although other studies have pointed to later engagement of ATL in semantic retrieval (around 400ms post-target onset), including time-resolved imaging methods (Kutas & Federmeier, 2011, McCarthy, Nobre, Bentin & Spencer, 1995; Marincovic et al., 2003) and previous cTMS results (Jackson et al., 2015), the rapid sequential presentation in this paradigm is likely to elicit spreading activation from the prime – and thus, in the case of strong associations, the target will already be "activated" by the onset of the second word. Although in Experiment 1, the MEG findings show preferential processing of strong semantic associations around 400ms in ATL, the MEG analyses detect time points at which two conditions are *significantly different from each other*, not necessarily when the cognitive processes started. Thus, it is plausible that retrieval processes common to both weak and strong associations start earlier.

Taken as a whole, the current results indicate dissociable roles of ATL and pMTG in semantic retrieval. ATL has a critical, early involvement in the recovery of automatic associations, while pMTG may play a role in maintaining a semantic context and in detecting situations in which controlled retrieval processes may need to be engaged to understand the link between this context and new inputs.

How many semantic hubs?

In Chapter 2, the oscillatory response and the causal engagement of ATL and pMTG to the processing of written words preceded by semantically associated words, however, the type of relationship was not manipulated, and all words were globally associated: stimuli were taken from free association data to generate the strong and weak conditions. While strong and weak relationships are thought to engage automatic and controlled semantic retrieval respectively, this experiment did not address the view that different types of semantic relationships may depend on different cortical areas for their representation. Some research proposes that ATL is one of two conceptual hubs, underpinning taxonomic or category-level knowledge, whereas the TPJ (including AG and pMTG) extracts event associations and thematic knowledge (Schwartz et al., 2011; de Zubicaray, Hansen & McMahon, 2013). This viewpoint is broadly consistent with the idea that the ATL lies at the end of the ventral visual stream, allowing it to integrate concrete features of objects (which are important for conceptual similarity – e.g., a bear is an animal that has fur and claws). In contrast, the TPJ may be better placed to integrate information about how objects are used and the contexts in which they are found (e.g. bears are good at fishing and like to eat honey). However, an alternative organisational framework has linked AG in conjunction with ATL to relatively automatic patterns of retrieval, while pMTG in conjunction with LIFG may support controlled aspects of retrieval (Humphreys & Lambon Ralph, 2014; Davey et al., 2015; Whitney et al., 2011; Noonan, et al., 2013; Badre et al., 2005).

Chapter 3 investigated this issue by contrasting both taxonomic and thematic relationships, and strong and weak thematic relationships to explore the merits of both proposed frameworks. In addition to the regions examined in Chapter 2 (ATL and pMTG), AG was included due to its relevance to the dual-hub theory. The task format was the same as for Chapter 2's Experiment 1, with one added element: analyses of both total and evoked power were included, and characterised the brain's oscillatory response to the presentation of written words that were preceded by taxonomically related primes, strongly related thematic primes, and weakly related thematic primes. The two levels of thematic primes served two purposes: Firstly, this manipulation allowed me to equalise the executive demands across conditions, as eliminating thematic associations from taxonomic relationships made the task relatively difficult. For example, dog – cat is not an exclusively taxonomic relationship – they are both pets, are found in similar situations, there are expressions linking them ("they were fighting like cats and dogs"). Thus, to explore purely taxonomic relationships, stimuli that share a category-level relationship, but do not share such a thematic link must be presented (such as mole – cat). To equate task difficulty, it was necessary to compare these stimuli with weakly-related thematic links (such as cushion – cat) that are difficult to retrieve. Secondly, by comparing weakly related thematic trials with strong thematic links (such as milk – cat), an additional contrast of automatic and controlled semantic retrieval could be made, and this allowed opposing predictions from the two theoretical frameworks to be examined: the dual-hub theory suggests that functional differences between sites should be characterised in terms of the response to categorical vs. thematic trials, while the controlled semantic cognition framework suggests that these differences should reflect difficulty and strength of association.

One key task difference between the experiments described in Chapter 2 and 3 is that while Chapter 2 simply required participants to covertly answer the question "Are the two words related?", Chapter 3 added a qualification to the question; "Are the two words related; either by sharing features, or by being found or used together?". Consequently, participants were naïve to the type of relationship they were looking for until the second word appeared on the screen. Since not all of the pairs were linked by a global semantic relationship, it would not have been an effective strategy to drive spreading activation from the first word.

In ATL, a significant response to both taxonomic and thematic stimuli were observed within 100ms of target onset, and while the frequency range and timing of the response was very similar; other than an initial, transient power increase to the taxonomic condition, it took the form of power decreases to taxonomically-related stimuli, and power increases in the thematically-related condition. In the evoked power analysis, the significant differences were driven by more evoked power in the taxonomic condition. This could go some way to explain why other research has found predominantly taxonomic effects in ATL. Further research is needed to understand this difference in the response between conditions: one possibility is that the taxonomic condition's reliance on concrete features of objects resulted in inherently more phase-locked activity in this area, due to ATL's position at the end of the ventral visual stream. Clarke et al. (2011) showed increased phase-locking between left anterior temporal and fusiform both for basic > domain level naming around 120-220ms, as well as two periods of greater phase-locking for living compared to non-living items around 176 -202ms and 296-340ms. They propose that greater semantic integration demands increase phase-locked recurrent interactions between cortical areas. In contrast, analyses that incorporate induced power might be more sensitive to *thematic* relationships, which could be recovered through spreading activation within the semantic representations in ATL. Crucially with respect to the two-hub framework, ATL responded above baseline in both conditions, which is inconsistent with the idea of this area as a taxonomic-only hub.

Additional analyses examined strongly- and weakly-related thematic trials, providing a near-replication of the contrast used in Chapter 2. The peak response in the evoked domain for ATL, from 200-600ms, was more pronounced for strongly than weakly-related words, although some regions in the time-frequency plot showed the reverse pattern. Contrasts of total power also supported the view that ATL showed a greater response to strongly- than weakly-related thematic trials, with all condition differences in ATL (except one) driven by the strongly-related condition, consistent with a role for this site in automatic retrieval.

The contrast of taxonomic and thematic conditions in pMTG showed a broadband and sustained response to both conditions in the evoked analysis, which was stronger in the thematic condition. However, total power showed a response to the taxonomic as well as the thematic condition. As for ATL, there were event-related decreases in total power in the taxonomic condition, and total power increases in the thematic condition. In line with the 'information via desychronisation' hypothesis (Hanslmayr et al., 2011), power decreases might reflect an increase in desynchronised activity, meaning that in addition to the phase-locked component of the retrieval of taxonomic relationships, there is also a strong response not synchronised in phase, reflected in total power. When contrasting the strongly and weakly related thematic conditions, a difference could be seen from 50ms, consistently driven by a greater increase in power to the weak condition, consistent with this area's postulated involvement in controlled retrieval (Whitney et al., 2011). These data do not strongly support the view that pMTG plays a selective role in thematic not taxonomic retrieval.

There was no maximum peak in oscillatory change in angular gyrus, but this region did fall within the region of significant activation, and due to its relevance to the dual-hub theory, a virtual electrode was seeded in this area. AG showed the earliest difference between taxonomic and thematic conditions, with a greater response to the taxonomic condition 50-275ms, followed by a greater response to the thematic condition 425-525ms. Interestingly, all other sites responded with power decreases in the taxonomic condition (and power increases in the thematic condition), while in AG this pattern was reversed. Similarly, the evoked analysis showed significant effects driven by both conditions; an early component driven by greater oscillatory power in the taxonomic condition, and a later component driven by the thematic condition. Both these results are inconsistent with the idea of TPJ areas being part of a ‘thematic hub’. When contrasting strongly and weakly thematic concepts, AG showed differences from 275ms, driven by power increases in the thematic high condition, consistent with automatic retrieval. However, around 400ms there was a significant power decrease for weak thematic trials, suggesting that AG is unlikely to only support automatic retrieval, and might support the allocation of attention to activated concepts, as recently argued by Davey et al. (2015).

These results, on the whole, provide evidence in line with the Controlled Semantic Cognition framework (Lambon Ralph et al., 2017). ATL, pMTG and AG all responded to both taxonomic and thematic association trials, and thus, empirical support for the dual-hub view was not found. There were differences in the way these sites were engaged by these conditions, in terms of timing and whether effects were seen in evoked or total power, but little evidence that different types of association rely on separate cortical areas.

Comparisons of MEG results across Chapters 2 and 3 – timings and frequencies

Chapters 2 and 3 presented MEG data from experiments with very similar paradigms and analyses. Chapter 2 presented an experiment involving presentation of written words that were preceded by strongly associated, weakly associated and unrelated words, which required participants to covertly answer the question “Are the two words related?”. In Chapter 3, a qualifier was added to the question; “Are the two words related; either by sharing features, or by being found or used together?”

When strong/weak associations in Chapter 2 are compared with thematic strong/weak associations in Chapter 3, some clear similarities emerge. Firstly, most effects of this manipulation were found between 20-35Hz, with some additional low frequency effects that were predominantly power increases. This is broadly consistent with the whole-brain analyses, as the most extensive recruitment of the semantic network was in the 25-35Hz frequency band. With some variations in timing and frequency, ATL responded preferentially to strong associations in total power, and in both experiments there was a greater response to the strong condition starting around 400ms (from 8-15Hz), which fits well with literature implicating this area in the N400 (Kutas & Federmeier, 2011, McCarthy, Nobre, Bentin & Spencer, 1995; Marincovic et al., 2003; Jackson et al., 2015). PMTG on the other hand, responded more strongly to weak associations in both experiments, just after the onset of the second word of the pair.

Nevertheless, there were some important differences between the MEG studies: in Chapter 2, effects were found in differential decreases in total power (sustained decreases around 10-30Hz), which are thought to reflect event-related neural activity not aligned in phase. In Chapter 3, on the other hand, many of the effects were differential power *increases*, particularly in the thematic conditions, while power decreases were largely confined to the taxonomic condition. As can be seen in Chapter 3, decreases in total power were found in the same regions of time-frequency space as increases in evoked power, lending further credence to the idea that decreases in total power reflect increased neural activity. A summary of all of the effects is provided in Table 4.1.

Interestingly, ATL shows greater evoked power to taxonomic stimuli, whereas pMTG shows greater evoked power to the thematic condition (AG shows both; initially taxonomic, then thematic). At the same time, in *total* power the response from all regions (except AG) to taxonomic stimuli is in the form of power decrease.

It is not clear why the experiment described in Chapter 2 would be characterised by strong event-related decreases in total power, as opposed to power increases, as seen in Chapter 3. However, an important possibility is suggested by plots of oscillatory power examining the whole epoch (see Figure 4.1) – e.g., the prime, target and following retrieval period. The structure of this plot looks quite different across experiments. In Chapter 2, when participants made judgements about whether the prime and target words were globally semantically associated, there was an increase in total power, followed by a decrease in total power: this pattern is largely in line with the literature (Düzel, Richardson-Klavehn, Neufang, Schott, Scholz & Heinze, 2005; Kujala, Vartiainen, Laaksonen & Salmelin, 2012). Thus, when participants knew that they had to retrieve a global association (Chapter 2), there was a strong increase in power to the first word, which was greatly attenuated by the second word. There was also a strong power decrease following the first word which is maintained over the ISI and then increased by the onset of the second word. In Chapter 2, it was argued that the total power decreases might reflect ongoing semantic retrieval not strongly linked to the onset of the visual stimulus and thus the effects were in the non-phase locked component of the data.

The whole-epoch plot for the MEG experiment presented in Chapter 3 had a qualitatively different structure, despite the surface features of the paradigm being near to identical. As mentioned, in Chapter 3, participants were naïve to the relationship being probed until the second word appeared. In this experiment, there was a negligible evoked response to the first word (associated with a small increase in total power), followed by a substantial increase in evoked power following the target word (associated with an increase in total power). Thus, if participants did not know whether semantic associations or shared physical features would form the basis for their decision, they showed little response to the first word and a greater response to the second word. Consequently, more of the experimental effects related to condition differences are seen in evoked power, and increases in total power. This pattern suggests that task instructions can have a large effect on the neuromagnetic response, even when stimuli are presented in a very similar manner. The difference between the two experiments further contributes to the interpretation of evoked power increases and event-related total power decreases. While evoked power increases might reflect visual-to-semantic access, this response is attenuated by reduced knowledge of what pattern of semantic retrieval is required (as in Chapter 3), at least within the semantic regions examined in this thesis. Moreover, while event-related total power decreases might be sensitive to a pattern of spreading activation within conceptual representations that supports ongoing semantic retrieval (as in Chapter 2), this type of response is only observed when a set of features or predictions have been activated in response to the prime and then the overlap with the features of the target is being assessed. When the relevant features are only defined by the presentation of the target word (Chapter 3), more of this pattern of semantic retrieval is reflected in power increases (see Figure 4.1 below).

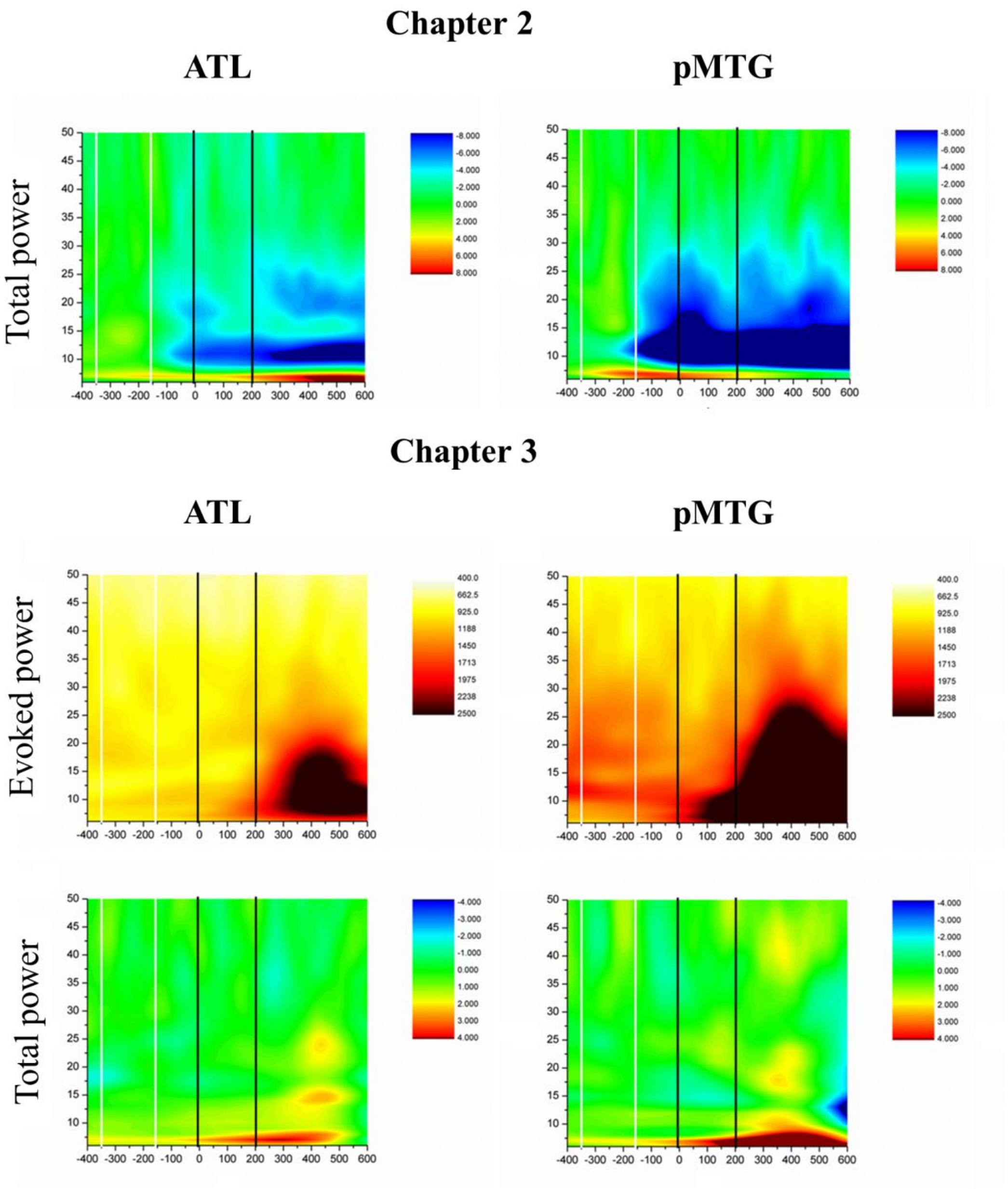

Figure 4.1: Showing the whole epoch (-400 to 600ms) for the related conditions in total power for experiments in Chapter 2 (top) and evoked and total power in Chapter 3 (bottom). White lines mark the time window of the prime, whereas black lines mark the time window of target words.

In Figure 4.1, for pMTG in Chapter 3, the beginning of a power decrease around 550ms can also be seen, though the epoch window is not large enough to see whether a similar response would be observed for the other two sites as well. It is possible that, due to the subtle difference in task, the response in this experiment was shifted in time. Since, in Chapter 2, participants knew that all word pairs with a relationship would be globally related, it would be useful to generate possible associations from the onset of the prime, whereas in Chapter 3, participants were required to decide which relationship type was supporting the link, and this could only be determined at target onset. Thus, in Chapter 3, participants may not have started to generate a pattern of spreading activation concerned with the link between the two words until *after* presentation of the target (i.e., considerably later in the epoch). This has implications for what is meant by “automatic spreading activation”: in Chapter 2, strong associations were argued to be generated “automatically”, without requiring conscious effort or constraint to be applied to the pattern of retrieval that would be generated by the long-term links within the ATL semantic store. Nevertheless, the difference in response to the first and second word in Chapter 3 suggests that when the task makes spreading activation to the first word unhelpful, this response can be supressed or delayed in a highly flexible way. Unfortunately the current paradigm did not allow me to extend the analysis window in time to see whether Chapter 3 would have had a similar structure over a longer period, due to the onset of the next trial. Future studies should further consider effects of task instructions and prior knowledge of the features that will be relevant to the task on the structure of MEG data, and continue to explore the relationship between response form (evoked increases or total power decreases) and spreading activation that can relate the features of successive words.

The difference in the structure of the data across the experiments presented in Chapters 2 and 3 has given rise to some hypotheses about the effect of task knowledge on the brain’s response, which warrant further investigation. Crucially though, the overarching conclusion that ATL, pMTG and AG respond to both thematic and taxonomic stimuli still holds, as does the rapid engagement of pMTG and ATL. These findings are largely consistent with the predictions of the Controlled Semantic Cognition framework (which expects ATL to support both thematic and taxonomic decisions), and inconsistent with the predictions of the dual hub theory of Schwartz and colleagues (2011), which anticipates a clear dissociation between ATL and the other two sites.

Comparison of TMS results to MEG results

Chapters 2 presented MEG and chronometric TMS data from experiments with near-identical paradigms. Both experiments involved the presentation of written words that were preceded by strongly related primes, weakly related primes and unrelated words, and required participants to covertly answer the question “Are the two words related?” The total oscillatory power to the target was shown to be modulated by the relatedness of the prime in Chapter 2’s Experiment 1, in ATL (strong > weak) and pMTG (weak > strong). In Experiment 2, I applied TMS to ATL and pMTG at four time points, to investigate the causal engagement of these regions. When comparing the two chapters, some similarities emerge:

Firstly, the order of engagement of these sites was the same; initially pMTG, followed by ATL. In ATL, the time point at which TMS elicited disruption for strong more than weakly-primed targets coincided with a significant change from baseline (relative to the passive period) in the MEG data, but not the region of significant difference between the strong and weak conditions. One possible interpretation is that the strong association trials are identified through spreading activation (which is disrupted by TMS), and if pulses are applied at the point when the pattern of spreading activation is first established, this has the biggest impact on the efficient retrieval of strong associations. In addition, the disruption observed was earlier than that reported by Jackson et al. (2015) in a previous chronometric TMS study, but this difference is likely to reflect the different paradigms, especially given what is know of task-driven differences from Chapter 3. In the study by Jackson et al., there was no prime prior to the onset of the trial, and consequently, it was not possible in their investigation that relevant semantic retrieval had already occurred by 0ms.

The timing of the contribution of pMTG is also similar across experiments, with Chapter 2 showing greater recruitment of pMTG in response to increased semantic control demands by ~50ms, and TMS results showing impaired performance on controlled retrieval when stimulated at 0-40ms. In line with interpretations of pMTG’s role from Chapter 2, one might imagine that pMTG is maintaining information from the first word and this early TMS stimulation disrupts the capacity to engage controlled retrieval processes when the input is inconsistent with expectations established from the prime.

A summary table of effects across sites and conditions and how they correspond to predictions from the CSC framework and the dual-hub theory can be seen in Table 4.1.

Table 4.1: Summary of predictions and findings across experiments

Predictions			Findings			
Site	CSC prediction	Dual-hub prediction	MEG1 (total power)	TMS	MEG2 (total power)	MEG2 (evoked power)
ATL	Strong > Weak	Tax > Them	Strong > Weak: 400ms; 15Hz	Strong > Weak: 125-165ms	**Both:** Strong > Weak: 200-300ms & 400ms+, 10-40Hz Weak > Strong: 175-300ms; 20-22Hz & 325-575ms; 5-7Hz **Both:** Them > Tax: 0-300ms; 23-47Hz Tax > Them: 300-550ms; 23-30Hz	**Both:** Strong > Weak: 175-600ms; 10-40Hz Weak > Strong: 175-575ms; 5-22Hz Tax > Them: 0-150ms; 27-42Hz & 450-600ms; 15-22Hz
pMTG	Weak > Strong	Them > Tax	Weak > Strong: 50-550ms; 10-30Hz	Weak > Strong: 0-40ms	Weak > Strong: 0-200ms, 350-450ms; 5-7Hz **Both**: Tax > Them: 150-250ms; 15-20Hz Them > Tax: 250-400ms; 15-20Hz	Strong > Weak: 0-600ms; 8-15Hz Them > Tax: 250-500ms; 13-25Hz
AG	-	Them > Tax	-	-	**Both:** Strong > Weak: 300-400ms; 18-25Hz Weak > Strong: 450ms+; 18-22Hz Tax>Them: 200-300 & 550ms+; 15-20Hz	**Both:** Strong > Weak: 0-75ms & 350-450ms & 550ms+; 10-35Hz Weak > Strong: 200-350ms; 8-10Hz **Both:** Them > Tax:0-175ms; 15-22Hz Tax > Them: 275-375; 10-12Hz

Theoretical implications

As summarised above, this thesis used MEG analysis of total and evoked oscillatory activity in areas involved in automatic and controlled semantic retrieval; processing of taxonomic and thematic relationships; and cTMS to assess the causal contribution of these sites to automatic and controlled retrieval over time. A few key findings can be taken from the results:

1. Dissociations between ATL and pMTG

Across both chapters and three experiments, evidence for increased involvement of pMTG in response to weak associations was observed, which are thought to have higher controlled retrieval demands, and the opposite pattern for ATL; i.e., an increased response to strong associations associated with automatic retrieval. These findings are informative about the organisation of semantic cognition in the temporal lobe and speak to the theoretical debate about where knowledge is stored: the hub and spoke model, which argues for a key semantic store in the anterior temporal cortex, contrasts with accounts such as the review by Martin (2007), which argued that knowledge is stored in posterior temporal regions. Although researchers increasingly recognise that ATL plays a crucial role in semantic representation, there is considerable debate about the role of pMTG; the notion that this region supports controlled retrieval processes is not universally accepted. The dissociation between these sites revealed in all three empirical chapters shows that while both sites might be involved in some way in semantic representation, they are not representing the same information, at the same time. Specifically, the data support the idea that ATL is crucial for relatively automatic spreading activation that recovers dominant features and associations encoded in long-term semantic memory, while pMTG is important for more controlled aspects of retrieval. Potentially, this site might maintain or re-represent information that is currently relevant – i.e., the context that must shape ongoing semantic retrieval. Consequently, there is a very early response in pMTG to violations of semantic expectations but also sustained engagement of pMTG in situations where the dominant features and associations encoded in ATL are insufficient to recover the relevant semantic relationships.

2. Representation of categorical and thematic relationships.

The data suggest that the same semantic network is engaged by categorical and thematic relationships, if in qualitatively different ways. In 2011, Schwartz and colleagues presented results from voxel-based lesion symptom mapping showing that patients with TPJ lesions make more thematic errors (e.g. dog → bone), whereas ATL lesions produce more taxonomic errors (e.g. dog → cat; Schwartz et al., 2011). They proposed that ATL is one of two conceptual hubs, underpinning taxonomic or category-level knowledge, whereas the TPJ (including AG and pMTG) extracts event associations and thematic knowledge. However, Jefferies & Lambon Ralph (2006) reported similar results, but interpreted the thematic errors as preserved semantic representations, combined with deficient control processes that result in the production of irrelevant associations that are not consistent with the task requirements in picture naming. Neuroimaging literature also links AG in conjunction with ATL to relatively automatic patterns of retrieval, while pMTG in conjunction with LIFG is thought to support controlled aspects of retrieval (Humphreys & Lambon Ralph, 2014; Davey et al., 2015; Whitney et al., 2011; Noonan, et al., 2013; Badre et al., 2005). Here I present results indicating that ATL, pMTG and AG all respond to both types of relationships, and that differences in processing the two types of relationships may be expressed in the form, magnitude and latency of the oscillatory response across sites.

3. Evidence for very early engagement of pMTG and ATL

The results speak against a simple view of semantic cognition in which first features are activated and then they are controlled or selected. Here I present MEG and TMS results indicating that pMTG has an earlier role than ATL; in MEG effects of weak associations are seen in pMTG before effects of strong associations are seen in ATL. Furthermore, TMS to pMTG disrupts the retrieval of weak associations before TMS to ATL disrupts the retrieval of strong associations.

One potential interpretation of these effects is that ATL is a long-term store of semantic knowledge, which represents associative links between semantically-linked information, while pMTG might maintain information in the short-term (i.e., a semantic context that shapes ongoing spreading activation in ATL). The ATL representations change slowly, so cannot represent information about what is *currently* relevant. In contrast, pMTG might maintain information about what is currently relevant, so that when new inputs are presented, this site can play a critical role in detecting whether these inputs can be rapidly assimilated into the existing contest, or whether there is a need for controlled retrieval to constrain the pattern of spreading activation in ATL.

Methodological implications

1. Evoked and total power can respond differently to task manipulations

In Chapter 3 I reported results in evoked and total power. Evoked power reflects oscillations locked to the stimulus in time and in phase, whereas total power incorporates both evoked power and oscillations locked to the stimulus in time, but not necessarily phase. These two analyses yielded different responses in time and frequency, highlighting the fact that they may reflect different cognitive processes. I take the results to suggest that in order to characterise ongoing semantic retrieval which is not tightly coupled to visual input, it may be necessary to examine total oscillatory power and not just the evoked component, as is done in many studies (Zhang & Pylkkanen, 2015; Bemis & Pylkkanen, 2012; Lau et al., 2014).

2. Chronometric TMS is vulnerable to non-specific effects of stimulation when applied to sites that have peripheral nervous system effects

In Chapter 2 I presented online cTMS results varying the time points at which pulses were delivered, allowing the assessment of time points of critical engagement. ATL and pMTG were stimulated with dual pulses at four time points (0-40ms; 125-165ms; 250-290ms; 450-490ms), during the retrieval of strong and weaker associations. In the supplementary analysis in Chapter 2, I characterised the effect of TMS on the tasks in general, and found non-specific effects of TMS; RT increased with stimulation time, and this effect was particularly strong for ATL. This increased delay when TMS pulses were applied at a later time-point, is consistent with the suggestion that since participants expect to receive stimulation, this influences the timing of their response (Sliwinska et al., 2012). A staircase method, in which TMS pulse timings are changed gradually as opposed to randomly, was previously proposed as a way of minimising the saliency of differences in pulse timings across trials and thus ameliorating this problem (Sliwinska et al., 2012), and this method was adopted in the study in Chapter 4 – however, the issue remained. This effect is likely to be particularly strong for the ATL site, since stimulation to this site is relatively uncomfortable and associated with involuntary eye-blinks, jaw contractions and strong scalp sensations. A similar increase in response latency was observed following sham stimulation, lending further support to this suggestion, since sham stimulation at 30% is thought to be too weak to produce a neural effect, but mimics the sound and scalp sensations of TMS stimulation (Duecker et al., 2013). A possible solution is to characterise these non-specific effects using a control task so that they can be controlled statistically when modelling the effect of TMS on the task of interest. This is the method utilised in the current analysis; non-specific effects of TMS were expected to be equivalent for the semantic task of interest and a number judgement task. Moreover, differential effects of TMS on strong and weak associations were examined, and since these trial types were presented in a mixed fashion, effects of 'waiting' for an anticipated TMS pulse should have been equivalent across these trial types.

3. Knowledge of trial requirements may have a large impact on the overall pattern of brain activity in MEG

The comparison of Chapter 2 and 3 yielded an interesting observation: When participants knew that they had to retrieve a global association (Chapter 2), there was a strong evoked response to the first word which is greatly attenuated by the second word. There was also a strong power decrease following the first word which was maintained over the ISI and was then increased by the onset of the second word. Conversely, in Chapter 3 (where participants were required to consider relationship type to make their response, which could only be determined at target onset), there was a negligible evoked response to the prime (associated with a small increase in total power), followed by a great increase in evoked power to (or immediately following) the target (associated with increase in total power). On the surface, these two experiments have nearly identical experimental paradigms, though one important difference is that in Chapter 2, it would be useful to generate possible associations from the onset of the prime. In Chapter 3 on the other hand, this would be likely to generate unhelpful semantic information on many trials. This highlights the flexibility with which elements of the semantic system can be recruited to support task performance, and the importance of considering task requirements and not only stimulus presentation when designing and interpreting MEG experiments. The low temporal resolution of fMRI may reduce the sensitivity of this method to effects of task requirements, but for temporally sensitive imaging methods like MEG, the way in which components are recruited may depend on relatively subtle changes in instructions/task demands as well as stimuli.

Theoretical and methodological limitations

This thesis aimed to elucidate the components of semantic cognition – in particular, their contribution to more automatic and controlled semantic retrieval – using convergent neuroscientific techniques, namely magnetoencephalography (MEG) and transcranial magnetic stimulation (TMS). Both methods are highly applicable for studying changes in response over time: MEG allows us to trace the time course of the neural activation (in the order of milliseconds), and TMS allows us to test causal predictions in healthy participants. If disruptive pulses are applied at different time points, it can also be used to examine causal contributions to a task over time (Walsh & Coway, 2000; Sliwinska, Vitello & Devlin, 2014). However, these methods also have associated limitations. MEG has lower spatial resolution than fMRI, as well as difficulty resolving sources further away from the cortical surface (Hansen, Kringelbach & Salmelin, 2010), which leads to a lack of anatomical precision. In both MEG experiments a 3D lattice of points was constructed across the whole brain with 5-mm spacing, and beamformers were used to compute the total power at each point. This means that the spatial resolution can never be better than 5mm, and sometimes poorer. In both MEG experiments virtual electrodes were placed in ATL and pMTG, yet their MNI coordinates are not identical, bringing about the question of whether this is data from *one* region, or indeed, sampling from two functionally distinct parts of a region and equating the results. This lack of spatial resolution is a general limitation of MEG experiments, and should be considered when interpreting the results from a theoretical perspective.

This lower spatial acuity also led to the selection of TMS stimulation point based on previous literature rather than maximum power peak. The peak in ATL was very close to the peak reported by Binney et al. (2010) (ATL MNI coordinates: Binney et al., 2010: MNI -51,6,-39, MEG experiment 1: MNI -48,8,-18), and the peak for pMTG in Experiment 1 was quite medial for TMS stimulation. For these reasons the stimulation points are different to the peaks in oscillatory power in the MEG experiment. Importantly, though it should be acknowledged that the spatial specificity of MEG is less than desired, the form of the signal in frequency over time is still informative to the underlying process.

Methodologically speaking, TMS has an unfortunate drawback; that it can be uncomfortable for the participant. This is the most common side-effect of TMS stimulation, and the intensity of the pain varies depending on (among other things) scalp location (Rossi et al., 2009). In general, the closer stimulation is to underlying muscles, the greater the discomfort, due to involuntary twitches and jerks brought on by the magnetic pulses. This is important to the current results, as one of the most uncomfortable regions to stimulate is ATL, due to its proximity to strong face and jaw muscles, which is exacerbated by the sensitivity of the facial region in general. In the results of Chapter 2's Experiment 2, an effect of site is seen, in that reaction time is higher for ATL than both sham and pMTG stimulation. This is unfortunately an unavoidable problem with ATL stimulation. However, importantly for the analysis of interest (the contrast of strongly and weakly related word pairs), the disruption caused by discomfort should be equivalent for the two conditions.

A further limitation of the empirical work presented here is that only word stimuli were used across all three experiments. Consequently, the data do not permit conclusions about the nature of semantic representations in terms of modality and do not test the prediction of the Hub and Spokes model (Patterson et al., 2007), which proposes that the ATL forms amodal concepts from the integration of modality-specific representations.

Finally, the experiments involve explicit semantic decisions between pairs of words presented sequentially. They resemble priming studies in terms of stimulus presentation although not in the nature of the judgement being made. The thesis work focussed on examining the effect of changing the nature of the semantic relationship between the words presented for a semantic decision, and held constant various factors of the experimental design, such as presentation speed, repetition frequency and the proportion of trials that were related vs. unrelated. Extensive research on semantic priming (e.g., Neely, 1977; 1991) suggests that these factors can have an important effect on the extent to which visual and phonological processing is influenced by word meaning. Some of the effects within the thesis might also be related to mappings between vision, phonology and semantics and further investigations could establish what effect changing the experimental design would have on these aspects of the results.

Future directions

The comparison of the two MEG experiments suggests an important next step will be to assess the impact of knowing what information needs to be retrieved. If the experimental paradigm in Chapter 3 allowed me to extend the analysis window in time, I would be able to assess whether the response was similar to Chapter 2 (but delayed), or whether knowledge of which features are relevant provokes a qualitatively different pattern of neural response. This issue would be best investigated in two experiments with identical stimuli and trial presentation, with the only difference being whether participants can anticipate the basis on which the words are related.

A further avenue of investigation would be to employ connectivity measures, especially those that are time-resolved and directional. This would allow the theoretical account above to be tested in a new way, since the assumption is that ATL would show different patterns of connectivity with semantic control regions depending on the extent to which the judgement is supported by the structure of semantic long-term memory. These tools are often based on coherence and neural synchrony of areas separated in cortical space (Friston, Frith, Liddle, Frackowiak, 1993; Klimesch et al., 2008). Though neural synchrony across cortical regions is not necessarily reflected in local changes of power (Tallon-Baudry, Bertrand & Fischer, 2001), these methods may be most informative when time-frequency analyses of local cortical areas are employed in conjunction with connectivity analyses. This is perhaps particularly important given the results presented in this thesis, highlighting the role of desynchronised oscillatory activity (at least within local neural populations).

A further useful follow-up study would be to apply TMS pulses during the interval between the two words in a pair, to test the emerging account of pMTG function which suggests that this site might maintain a currently-relevant semantic context, in order to facilitate ongoing retrieval and detect situations in which control is required (see Chapter 2).

Conclusion

The primary aims of this thesis were to use time-resolve neuroscientific methods to investigate i) how automatic and controlled semantic retrieval shape oscillatory activity within the semantic network; ii) to use cTMS to assess the causal contribution of brain areas implicated in automatic and controlled semantic retrieval; and iii) to explore the existence of one or two semantic hubs by contrasting taxonomic and thematic relationships. In both MEG experiments, there was recruitment of pMTG before ATL, which speaks against a simple view of semantic cognition in which first features are activated and then they are controlled. Furthermore, the rapid recruitment of pMTG for weak associations preceded the response to strong associations in ATL, highlighting these two brain areas' involvement in controlled or automatic retrieval respectively. This was later supported by a chronometric TMS experiment that showed early recruitment of pMTG was crucial for the successful retrieval of weak relationships, while slightly later but also rapid recruitment of ATL was critical to the successful retrieval of strong semantic relationships around 150ms post-target.

The second MEG experiment (Chapter 3) evaluated two conflicting accounts of semantic representation. Some research highlights the ATL as one of two conceptual hubs, underpinning taxonomic or category-level knowledge, while the TPJ extracts event associations and thematic knowledge (Schwartz et al., 2011). Alternatively, Jefferies & Lambon Ralph (2006) proposed a representation/retrieval account, in which TPJ lesions lead to deficient control processes. Chapter 3 provides evidence in line with the representation vs. retrieval view of semantic cognition, as ATL, pMTG and AG all responded to both taxonomic and thematic associations, making the dual-hub view an unlikely explanation of the results.

The results from these three experiments point to a unified semantic system for taxonomic and thematic associations, with both of these aspects of knowledge potentially represented in ATL. Spreading activation within this semantic store would then be critical for automatic retrieval. In contrast, pMTG may maintain a semantic context, and detect situations in which controlled retrieval processes may be needed to understand the link between this context and new inputs, explaining this site's rapid contribution to the retrieval of weak associations. In this view, ATL is a long-term store of semantic knowledge, which represents the features of concepts including their spatiotemporal associations, while pMTG might maintain currently-relevant semantic information in the short-term (i.e., a semantic context that shapes ongoing spreading activation in ATL). Given that long-term representations change slowly, ATL cannot represent information about what is currently relevant. In contrast, pMTG could maintain information about what is currently relevant, so that when new inputs are presented, this site can play a critical role in detecting the need for controlled retrieval to constrain the pattern of spreading activation in ATL. This dissociation between ATL and pMTG validates ATL's causal role in the automatic retrieval of semantic relationships (irrespective of type of association), and highlights pMTG's early causal role in controlled semantic retrieval.

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