The neural basis of flexibility in semantic memory retrieval

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Abstract

At the heart of adaptive cognition is flexibility – the capacity to focus on particular mental representations and to utilise distinct processes in a way that is appropriate for current goals. This thesis aimed to investigate the neural basis of flexibility in semantic retrieval, using cortical thickness, intrinsic connectivity and task-based fMRI. Chapter 2 investigated the structural basis of controlled semantic retrieval. We found that participants who performed relatively well on tests of semantic control showed increased structural covariance between left posterior middle temporal gyrus and left anterior middle frontal gyrus. This study provides converging evidence for a distributed network underpinning semantic control. Chapter 3 explored whether memory-related regions within the default mode network (DMN) represent goal information during semantic cognition. Participants were asked to perform a semantic feature matching task in which they decided whether a probe and target word shared a feature indicated by a cue. We found DMN regions, angular gyrus and posterior cingulate cortex, represented goal information, consistent with the view that DMN supports controlled cognition. Chapter 4 investigated how human cortex is organised to produce a spectrum of cognition, from efficient memory-based decisions to more flexible novel patterns of thought. We asked participants to match words on the basis of a specific semantic feature, such as colour, while parametrically varying other features. This created a ‘psychological gradient’ varying from strong to weak convergence between long-term memories and evolving task demands. We found the neural response to the task varied in a gradual way along a previously-described connectivity gradient which captures transition along the cortical surface from perception and action, through executive control areas, to regions of DMN. The findings of this thesis provide evidence for the structural and functional basis of flexibility in semantic retrieval and point to organizational principles of this conceptual flexibility in the brain.

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Declaration

I, Xiuyi Wang, declare that this thesis is a presentation of original work and I am the sole author. I undertook the research at University of York during 2016 – 2019, under the joint supervision of Professor Elizabeth Jefferies and Professor Jonathan Smallwood. This work has not previously been presented for an award at this, or any other, University. All sources are acknowledged as References.

Some parts of this thesis have been published in peer-reviewed journals or are currently under preparation for publication. Author contributions are noted at the start of each chapter.

Chapter 2: Wang, X., Bernhardt, B. C., Karapanagiotidis, T., De Caso, I., Alam, T. R. D. J. G., Cotter, Z., ... & Jefferies, E. (2018). The structural basis of semantic control: Evidence from individual differences in cortical thickness. NeuroImage, 181, 480-489.

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Chapter 1 : Introduction

The centrality of flexibility in human behaviour

At the heart of adaptive cognition is flexibility – the capacity to focus on particular mental representations and to utilise distinct processes at different points in time, in a way that is appropriate for the ongoing context and current goals. For example, people retrieve how to move their fingers on the keyboard when playing the piano, but also how to hold the body of piano when moving it (Saffran, 2000). To flexibly retrieve relevant conceptual knowledge that suits our current goals and context, we need to maintain the external goal, retrieve relevant knowledge from memory, monitor the whole process and update the current goal if necessary. However, the neural mechanisms underlying this capacity are poorly understood.

1. Controlled semantic cognition

Semantic cognition refers to our ability to use knowledge to produce appropriate patterns of thought and behaviour and, as such, it is critical to many aspects of everyday life. It involves at least two interacting components: semantic representations which encompass our stored knowledge about the meanings of objects, words, sounds and people, plus control processes that allow us to retrieve information that suits our goals and the context (Jefferies, 2013; Lambon Ralph, Jefferies, Patterson, & Rogers, 2017). These components have been widely studied using multiple convergent methods (Binder, Desai, Graves, & Conant, 2009; Binder & Desai, 2011; Martin, 2007): neuropsychology (Jefferies & Lambon Ralph, 2006), fMRI activation (Binder et al., 2009; Noonan, Jefferies, Visser, & Lambon Ralph, 2013), fMRI connectivity (Wang et al., 2016; Wei et al., 2012; Xu, Lin, Han, He, & Bi, 2016), transcranial magnetic stimulation (TMS) (Davey et al., 2015; Hallam, Whitney, Hymers, Gouws, & Jefferies, 2016) and MEG (Teige et al., 2019, 2018) and they are thought to draw on distinct large-scale networks in the brain. Lambon Ralph and Jefferies proposed a "controlled semantic cognition (CSC)" framework to describe the interaction of these two components (Lambon Ralph et al., 2017). The components of this account are described in detail below.

1.1 The neural basis of semantic representation

Over the last decade, researchers have intensively explored how semantic knowledge is represented. Relevant theories are placed on a continuum from strongly embodied to fully unembodied representations (Meteyard, Cuadrado, Bahrami, & Vigliocco, 2012) (Figure 1-1).

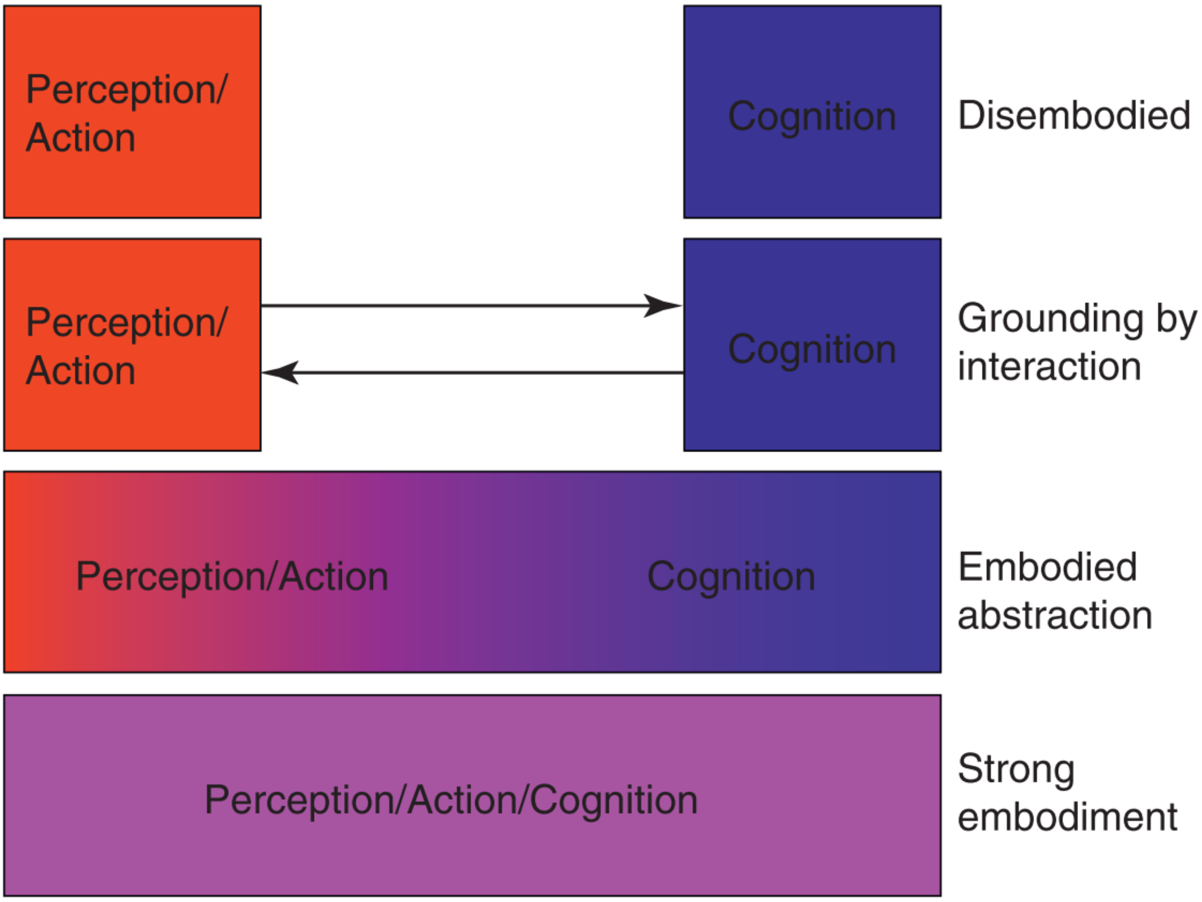


Figure 1-1: Possible relationships between perceptual and conceptual representation (Binder & Desai, 2011).

1.1.1 Embodied cognition hypothesis

Embodied theories (Gallese & Lakoff, 2005; Pulvermüller, 2001) assume that concepts directly reflect our accumulated knowledge from language, non-verbal experiences, or both. Such experiential knowledge is often referred to as ‘features’ and is coded by modality-specific neural circuits, which are distributed across the cortex. These neural circuits reactivate to represent familiar semantic object-concepts through direct connections among modality-specific regions without a common transmodal region.

This theory predicts if sensory or motor processing were damaged, patients would show some semantic deficit. However, this is not always the case (Patterson, Nestor, & Rogers, 2007). Moreover, large brain regions that participate in comprehension tasks are not modality-specific, such as anterior temporal lobe (ATL) (Lambon Ralph et al., 2017) and inferior frontal gyrus (IFG) (Lambon Ralph et al., 2017). In addition, semantic dementia patients lose all knowledge across modalities without concordant sensorimotor impairment (Patterson et al., 2007), thus supporting 'disembodied' semantic mechanisms can dissociate from sensorimotor functions and brain areas.

1.1.2 Domain-specific hypothesis

Caramazza & Mahon (2003) proposed a domain-specific hypothesis that assumes specialized (and functionally dissociable) neural circuits are dedicated to process, perceptually and conceptually, different categories of objects because of evolutionary pressures. This proposal is supported by evidence that different categories of knowledge can be differentially disrupted in neurological disorders (Caramazza & Mahon, 2003) or yield differential activation in specific healthy brain regions (Chao, Haxby, & Martin, 1999). Specifically, some patients show disproportionately and even selectively impaired conceptual knowledge of one category of objects compared with other categories (Caramazza & Mahon, 2003). Chao and colleagues (1999) observed that the medial aspect of the fusiform gyri differentially responded to 'tool' stimuli (pictures and words), whereas the lateral aspect of the fusiform gyri differentially responded to 'animal' stimuli.

However, this theory fails to explain some findings. This theory predicts processing information of each category activates its specific regions. However, naming pictures of animals and tools activated the same area: bilateral ventral temporal lobes (Martin, Wiggs, Ungerleider, & Haxby, 1996). This theory fails to explain why knowledge about multiple categories is impaired when bilateral ATLs are damaged in patients with semantic dementia (Jefferies & Lambon Ralph, 2006). This theory also predicts category information can be decoded only within its sensitive regions. However, the category being viewed can be decoded from response patterns of ventral temporal cortex, even excluding category-selective regions, (Haxby et al., 2001), or from whole-brain functional connectivity patterns, even excluding the contributions of regions showing classical category-selective activations (Wang et al. 2016).

1.1.3 Sensory/functional theory

Warrington & Shallice, (1984) proposed the sensory/functional theory to explain the category-specificity in semantic memory. This theory proposed that the semantic system is organized into modality-specific semantic subsystems (e.g. visual/perceptual, functional/associative); and the ability to identify different categories of objects depends differentially on the integrity of processes internal to distinct modality-specific subsystems. For example, the ability to identify living things differentially depends on visual/perceptual subsystem (e.g., tiger has stripes), while the ability to identify non-living things depends differentially upon functional/associative semantic subsystem (e.g., knife is used for cutting). Consequently, if brain damage leads to a loss of sensory knowledge then living tends to be more affected. Instead, if non-sensory knowledge is degraded, then the opposite dissociation results. Therefore, a patient with a specific disruption of knowledge involving sensory semantic features is more likely to show a specific impairment for living. Instead, a specific loss of non-sensory features is supposed to lead to specific impairment for non-living. In this view, category-specificity is an impairment caused by a co-existing Sensory knowledge impairment.

The sensory/functional theory predicts that the ability to recognize all living things differentially depends on information internal to the same (visual/perceptual) semantic subsystem, there should not be any dissociation within the category ‘living things’. However, dissociation within the category ‘living things’ have been observed (Hart, Berndt, & Caramazza, 1985). Some patients have been reported with disproportionate deficits for ‘fruit/vegetables’ compared with ‘animals’ (Hart et al., 1985; Samson & Pillon, 2003), while some patients showed disproportionate deficits for ‘animals’ compared with ‘fruit/vegetables’ (Blundo, Ricci, & Miller, 2006; Caramazza & Shelton, 1998). The sensory/function theory predicts that patients with category-specific semantic deficits will necessarily present with disproportionate deficits for the modality or type of information upon which successful recognition/naming of items from the impaired category is assumed to differentially depend. However, almost all case studies of category-specific semantic deficits reported equivalent impairments to visual/perceptual and functional/associative knowledge (Blundo et al., 2006; Capitani, Laiacona, Mahon, & Caramazza, 2003; Caramazza & Mahon, 2003b). This fact is true both of cases that presented with disproportionate deficits for living things, as well as non-living things.

1.1.4 Symbolic theory

Unlike previous theories that emphasize modality-specific cortices are important for semantic memory, symbolic theory proposes conceptual processing is based entirely on amodal, symbolic representations. It assumes that semantic memory is represented in some abstract, modality-independent regions which are remote from the mechanisms of perception and motor organization. Wang and colleageus (2019) found that a region in the left dorsal anterior temporal lobe supports object colour knowledge in both blind and sighted groups, indicating the existence of a sensory-independent knowledge coding system in both groups. However, they also found that some visual regions support colour knowledge only in the sighted, suggesting there are (at least) two forms of object knowledge representations in the human brain: sensory-derived and cognitively-derived knowledge supported by different brain systems.

Although this symbolic theory explains sophisticated concept processing and generalization, it fails to explain how concepts and their associated experiential features are linked or the genesis of the concepts themselves. It also failed to explain modality-specific sensory, action, and emotion systems are involved in language comprehension.

1.1.5 Hub-and-spoke theory

Patterson and colleagues (2007) proposed a hub-and-spoke model which assumes that conceptual and perceptual representations are distinct and separate but interact so closely that amodal symbols can derive content from perceptual knowledge (Figure 1-2). It assumes that multimodal verbal and non-verbal experiences provide the core ‘ingredients’ for constructing concepts and that these information sources are encoded in modality-specific cortices, which are distributed across the brain (the ‘spokes’). Unlike the aforementioned theories, this theory proposes that a single transmodal hub, which is located in bilateral ATLs, supports knowledge across virtually all modalities (such as words, objects, pictures or sound) and conceptual domains. The “hubs” or “convergence zones” for semantic information are proposed to have two key features: (1) they are amodal or multimodal in nature, because they represent information across multiple sensory modalities (e.g., auditory and visual knowledge); and (2) they are integrative, binding together separate features and mapping between different inputs and outputs (i.e., between seeing an object and knowing its name). These two features allow ATLs to extract conceptual similarities which may not be apparent in any one modality (Jefferies & Lambon Ralph, 2006; Lambon Ralph et al., 2017).

This ‘hub-and-spoke’ theory emphasizes both hub and spokes are important for semantic representation, which is supported by both inhibitory TMS and fMRI studies. TMS to lateral ATL slows down domain-general semantic processing, whereas TMS to ‘spoke’ regions affects processing of specific categories (Pobric, Jefferies, & Lambon Ralph, 2010). Coutanche & Thompson-Schill (2015) found that a target’s identity can be decoded in the left ATL, while specific features can be decoded in visual cortex (shape in lateral occipital cortex and colour in right V4).

The ATL-as-hub view was motivated by both empirical (Bozeat, Lambon Ralph, Patterson, Garrard, & Hodges, 2000; Jefferies & Lambon Ralph, 2006) and computational observations (Patterson et al., 2007). Individuals with semantic dementia, associated with predominantly bilateral ATLs atrophy, show semantic impairments across all modalities and virtually all types of concepts (Jefferies & Lambon Ralph, 2006). The behavioural pattern of semantic dementia can be mirrored by repetitive TMS over the ATL in healthy participants (Pobric, Jefferies, & Lambon Ralph, 2007) or gradually removing the ATL hub connections using computational model (Patterson et al., 2007). The aforementioned converging evidence suggests ATLs serve as the transmodal domain-general conceptual hub (Jefferies & Lambon Ralph, 2006).

Recent evidence suggests that there is no strong separation into hub and spokes. There is a representational gradient along the ventral temporal cortex, transitioning from the caudal ‘spoke’ zones preferring canonical feature processing to the rostral ‘hub’ zones preferring semantic relationship (Chiou, Humphreys, Jung, & Lambon Ralph, 2018). New evidence indicates not only that the ventrolateral ATL is the centre-point of the hub but also that the function varies in a graded manner across its subregions (Lambon Ralph et al., 2017) (Figure 1-3). The ventrolateral ATL activates strongly in semantic tasks irrespective of input modality or stimulus category (Binney, Embleton, Jefferies, Parker, & Lambon Ralph, 2010; Visser & Lambon Ralph, 2011; Visser, Jefferies, Embleton, & Lambon Ralph, 2012). Moving away from this centre-point, the cross-modal semantic function of the ATL becomes weaker and is more tied to a specific input modality. Thus, more medial ATL regions respond more strongly to picture-based materials and concrete concepts than to other types of material (Hoffman, Binney, & Lambon Ralph, 2015; Visser et al., 2012). By contrast, the anterior superior temporal sulcus (STS) and superior temporal gyrus (STG) respond more strongly to auditory stimuli, spoken words and abstract concepts (Hoffman et al., 2015; Visser & Lambon Ralph, 2011). Such graded functional specialization is determined by its distance-dependent cortical connectivity strength to the spokes (Binney, Parker, & Lambon Ralph, 2012; Plaut, 2002). Units that are anatomically closer to a given modality-specific spoke contribute somewhat more to tasks involving the proximal modality (Plaut, 2002). For instance, hub units situated near to visual representations, such as medial ATL, would contribute more to visual or concrete concepts than non-visual tasks by virtue of having greater connectivity to visual than to auditory or linguistic systems. The anterior STS–STG contributes more to abstract concepts and verbal semantic processing by virtue of its greater connectivity to language than to visual systems. The ventrolateral ATL contributed equally to all semantic tasks because its distance to all modalities are equal and it connects equally to these different systems.

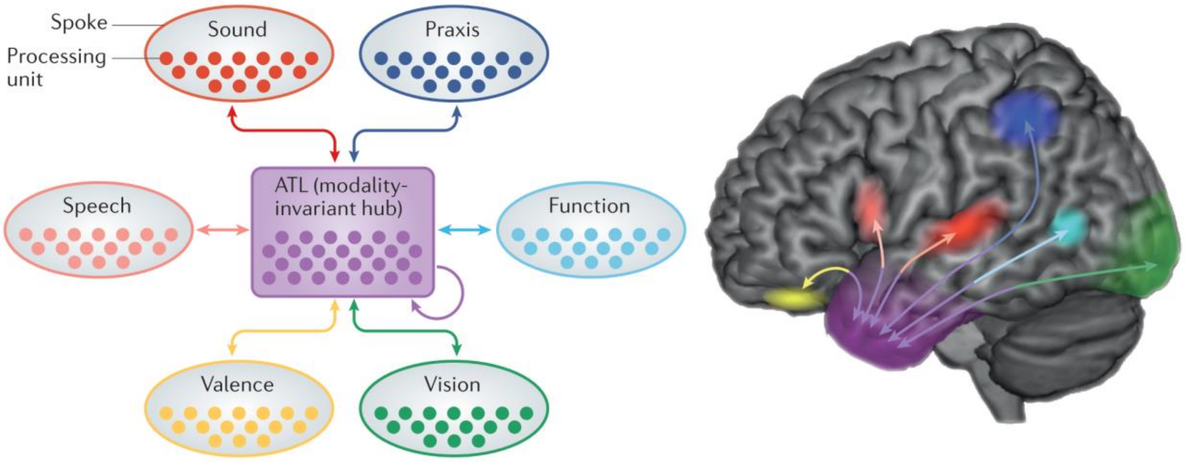


Figure 1-2: The original hub-and-spoke model (Lambon Ralph et al., 2017).

1.1.6 Multiple hubs account

Pulvermüller proposed that there are multiple hubs for semantic processing (Pulvermüller, 2013). They integrate semantic information from several modalities. They are located in higher association areas of the neocortex, that is multimodal convergence zones in prefrontal, posterior parietal, and temporal cortex where sensory, motor, and affective emotional information converges.

A purported heteromodal hub is angular gyrus (AG) (Binder & Desai, 2011). Given its anatomical location adjoining visual, spatial, auditory, and somatosensory association areas, AG may be the single best candidate for a high-level, supramodal integration area in the human brain (Geschwind, 1965). In line with this view, Xu and colleagues (2016) found that AG is a connector hub, showing stronger intrinsic functional connectivity with other semantic regions. AG, as a heteromodal cortical hub, integrates distributed semantic features into coherent representations. Geschwind (1965) proposed that "the AG is important in the process of associating a heard name to a seen or felt object, it is probably also important for associations in the reverse direction". In line with this view, AG activated strongly during retrieval of integrated multimodal (audio-visual) episodic memories compared with unimodal episodic memories (auditory or visual) (Bonnici, Richter, Yazar, & Simons, 2016).

Beyond the integration between semantic features and concepts, AG plays a causal role in conceptual combination (Friederici, Rüschemeyer, Hahne, & Fiebach, 2003; Newman, Just, Keller, Roth, & Carpenter, 2003; Ni et al., 2003). Price and colleagues (2016) found that anodal stimulation to the left AG modulated semantic integration but had no effect on a letter-string control task by applying high-definition transcranial direct current stimulation (tDCS). Specifically, after anodal stimulation to the left AG, participants were faster to comprehend semantically meaningful combinations like "tiny radish" relative to non-meaningful combinations, such as "fast blueberry", relative to the effects observed during sham stimulation and stimulation to a right-hemisphere control brain region. Moreover, the size of the effect from brain stimulation correlated with the degree of semantic coherence between the word pairs. Price and colleagues (2015) found that neural activity in the AG of healthy adults was modulated by combining concepts to form meaningful representations, independent of the modality of the semantic content integrated; individual differences in the structure of the AG in healthy adults were related to variability in behavioural performance on the conceptual combination task; in patients with neurodegenerative disease, the degree of atrophy in the AG was specifically related to impaired performance on combinatorial processing. These converging findings are consistent with a critical role for the AG in conceptual combination.

AG might play a role in integrating individual concepts into a larger whole (Friederici et al., 2003; Newman et al., 2003; Ni et al., 2000). During auditory sentence comprehension, the AG, alone among the regions activated, showed a late activation relative to baseline that began at the end of the sentence and occurred only when the constituent words could be integrated into a coherent meaning (Humphries, Binder, Medler, & Liebenthal, 2007). AG showed stronger activation when processing connected discourse than unrelated sentences or phrases (Fletcher et al., 1995). All the above evidence for AG's integration role suggests that it is at the top of a processing hierarchy underlying concept retrieval and conceptual integration.

AG and ATL are similar to each other in many aspects. They are both argued to act as heteromodal 'hub' regions (Reilly, Peelle, Garcia, & Crutch, 2016; Seghier, 2013). They are commonly implicated in processing coherent conceptual combinations (Bemis & Pylkkänen, 2013; Davey et al., 2015; Price et al., 2015; Price, Peelle, Bonner, Grossman, & Hamilton, 2016). AG also shows relatively strong intrinsic connectivity to lateral parts of ATL (Davey et al., 2015, 2016) and both sites show a pattern of intrinsic connectivity allied to the DMN (Power et al., 2011; Yeo et al., 2011). However, differences between these two regions have been proposed.

It has been suggested that AG and ATL may bind different kinds of semantic knowledge (Binder & Desai, 2011; Schwartz et al., 2011). According to this view, AG is particularly crucial for representing thematic/associative aspects of knowledge (Kalénine et al., 2009a; Lewis, Poeppel, & Murphy, 2019; Schwartz et al., 2011; Xu et al., 2018) while ATL lies at the end of the ventral visual stream and might play a role in object recognition and identity knowledge. Supporting evidence was obtained by Schwartz and colleagues (2011), who found that thematic errors localized to the left temporoparietal junction and in contrast taxonomic errors localized to the left ATL. Geng & Schnur (2016) presented thematic and taxonomic word pairs in an fMRI adaptation paradigm. The paradigm assumes that repeated viewing induces BOLD signal change in brain areas which are responsible for processing some aspects of the stimulus. They found that thematic pairs elicited AG adaptation and taxonomic pairs elicited ATL adaptation. These converging evidence suggests that AG supports thematic association and ATL supports taxonomic association.

However, studies observing this dissociation in conceptual representation have often failed to match the difficulty of taxonomic and thematic judgements, potentially contributing to differences in peak activations between studies (Sachs, Weis, Krings, Huber, & Kircher, 2008; Sachs, Weis, Zellagui, et al., 2008; Sass, Sachs, Krach, & Kircher, 2009). It has been found that ATL and AG are equally engaged in semantic judgments based on either associative relationships or conceptual similarity (Jackson, Hoffman, Pobric, & Ralph, 2015; Xu et al., 2018). Xu and colleagues (2018) also found that both the TPJ and ATL were involved in both kinds of association. However, when the two areas were contrasted, the TPJ was more involved in thematic association and the ATL in taxonomic association. The dissociation might be driven by the difference in difficulty. Using a strict separation and direct probing of associative versus conceptual knowledge, Jackson and colleagues (2015) found that the same core semantic network (ATL and AG) was equivalently engaged. Direct comparisons revealed small, weaker differences for conceptual similarity > associative decisions (e.g., inferior prefrontal cortex) and associative > conceptual similarity (e.g., ventral parietal cortex) which appear to reflect graded differences in task difficulty. Indeed, once reaction time was entered as a covariate into the analysis, no associative versus category differences remained. Teige and colleagues (2019) found that AG showed no difference between thematic and taxonomic trials when these were matched for difficulty (taxonomic vs. weak thematic contrast). These studies indicate that the same network supports both thematic and taxonomic association.

However, AG did show a stronger evoked response to strong vs. weak thematic associations, consistent with the view that this site responds to more "automatic" patterns of semantic retrieval (Humphreys & Lambon Ralph, 2015). A neuroimaging meta-analysis found that AG showed stronger activation for semantic tasks compared with non-semantic tasks (Binder et al., 2009) and is implicated in automatic semantic retrieval (Humphreys & Lambon Ralph, 2015). AG shows stronger deactivation for more difficult semantic tasks (Humphreys, Hoffman, Visser, Binney, & Lambon Ralph, 2015; Humphreys & Lambon Ralph, 2017). In this way, its activity shows an inverse relationship with inferior parietal sulcus, an area considered central to the multiple demand network (MDN) (Humphreys & Lambon Ralph, 2015). AG is implicated in both semantic and episodic memory retrieval, particularly when there is a strong cue and vivid recollection. Patients with parietal lesions, including AG, have deficient episodic memory when there is poor retrieval support and normal episodic performance when provided with strong external cues (Davidson et al., 2008).

In conclusion, theories agree that semantic representation involves convergence zones (Damasio, 1989) and the activation of modal content whether sensory and motor information is a necessary part of semantic representation and processing.

1.2 Semantic representation regions overlap with default mode network (DMN)

Researchers have noticed the resemblance between the semantic regions and DMN (Binder et al., 1999; 2009; Binder & Desai, 2011; Wei et al., 2012) (Fig 1-3). The semantic network and DMN engage some common anatomical areas (Humphreys et al., 2015). ATL and

AG have been proposed to be “semantic hubs” that help to represent multimodal semantic representations. They are also the core regions of DMN. Xu et al. (2016) found that areas consistently activated during semantic processing generated from a meta-analysis of 120 neuroimaging studies (Binder et al., 2009) were organized into three stable modules corresponding to the DMN, the left perisylvian network, and the left multiple demand network (MDN). I will introduce DMN and MDN in detail in the following section. The implicating overlapping neural regions and shared cognitive mechanisms between semantic network and DMN motivated researchers to investigate the relationship between these two systems (Humphreys et al., 2015).

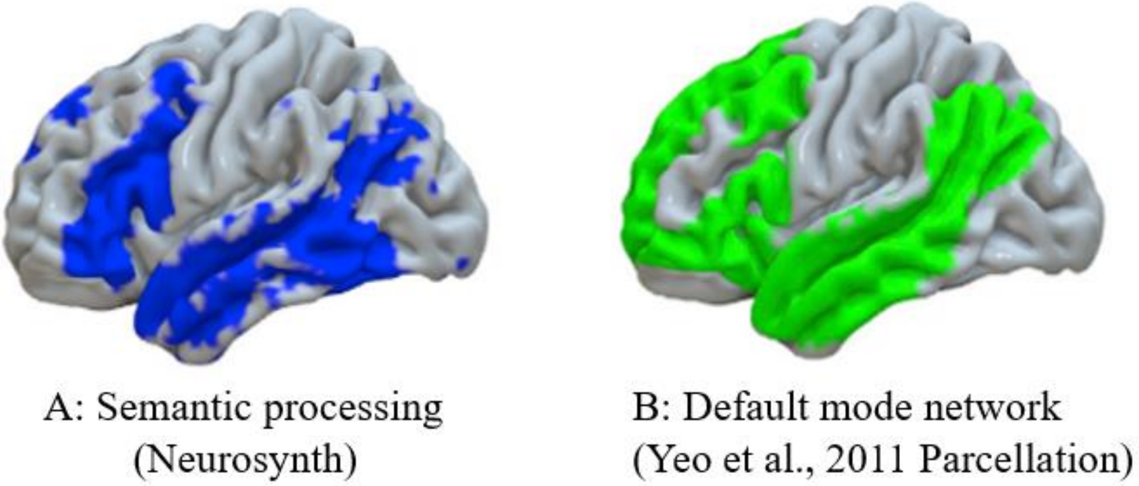


Figure 1-3: The semantic network and default mode network. A - The meta-analytic map derived for the term “semantic” from the Neurosynth database. B – The default mode network defined by Yeo et al. (2011) 7-network parcellation of whole-brain functional connectivity.

1.3 Default mode network

1.3.1 Default function of the brain

Shulman et al. (1997) first noted that a constellation of areas in the human cerebral cortex consistently reduced their activity while performing various novel, non-self-referential, goal-directed tasks relative to a resting state (Binder et al., 1999; Raichle, et al., 2001). These regions are collectively termed the DMN, including posterior cingulate cortex (PCC), ventral anterior cingulate cortex (vACC), ATL, and AG. They were thought to constitute a network supporting a default mode of brain function. The magnitude of the deactivation is related to the degree of task demand (Humphreys, Hoffman, Visser, Binney, & Lambon Ralph, 2015; Leech, Kamourieh, Beckmann, & Sharp, 2011; Mckiernan, Kaufman, Kucera-thompson, & Binder, 2003; Singh & Fawcett, 2008). These regions form a network as they show stronger functional connectivity during rest (Greicius, Krasnow, Reiss, Menon, & Raichle, 2003; Power et al., 2011; Yeo et al., 2011) and during various tasks (Greicius, Srivastava, Reiss, & Menon, 2004; Simony et al., 2016). Their intrinsic functional connectivity is anti-correlated with the MDN, a domain general control network (Fox et al., 2005).

1.3.2 Other high-level cognition functions

The deactivation of DMN is functionally important. Recent evidence found that the deactivation does not mean that a region is not involved in a task. For example, although PCC, a core region of DMN (Leech et al., 2011), showed deactivation, it exhibited greater functional coupling with prefrontal cortex during demanding semantic cognition, suggesting it is “down but not out” (Krieger-Redwood et al., 2016). This lower DMN activity is associated with better behaviour performance (Shulman, Astafiev, Mcavoy, D’avossa, & Corbetta, 2007; Weissman, Roberts, Visscher, & Woldorff, 2006; White et al., 2013). Furthermore, the deactivation might be important for the preservation of cognition. Samu and colleagues (2017) found fluid intelligence declines with age and deactivation of DMN decreases with age when performing these tasks. However, there is no significant age-related behaviour difference and DMN suppression for sentence comprehension (Samu et al., 2017). In line with this view, Krieger-Redwood and colleagues (2019) found that older adults with stronger connectivity within DMN showed particularly inefficient retrieval of weak associations, suggesting older adults may struggle to harness DMN to support demanding patterns of semantic retrieval, resulting in a performance cost. These findings suggest that DMN suppression is functionally important.

In addition, DMN regions do not always show task-induced deactivation. Task-induced increases have been observed across tasks involving mind wandering, social cognition, introspection and prospection, autobiographical memory, semantic memory and task transition (Gusnard & Raichle, 2001; Harrison et al., 2008; Murphy et al., 2019; Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010). The evidence suggests that DMN is involved in higher-level cognition instead of a pure default mode of brain. However, the exact functional role of the DMN in human cognition remains elusive. One purpose of this thesis is to explore the networks that support semantic cognition. Specifically, I investigated the role of DMN in controlled semantic cognition using a demanding semantic feature matching task.

1.3.2.1 Memory functions of DMN

DMN is thought to be important when cognition is guided by representations from memory. Mnemonic word fluency elicits greater DMN activity and stronger within-network functional connectivity compared with phonemic fluency (Shapira-Lichter, Oren, Jacob, Gruberger, & Hendler, 2013). Compared to the resting state, the DMN is significantly less deactivated for semantic memory tasks compared to perceptual or phonological tasks (Binder et al., 1999; 2009; Humphreys et al., 2015; Seghier, Fagan, & Price, 2010; Wirth et al., 2011). One view is that the DMN does not process semantics and its activation during semantic tasks is actually differential deactivation, reflecting the lower attentional demands of semantic tasks relative to other tasks (Humphreys et al., 2015). In line with this view, the magnitude of DMN deactivation in visual tasks (Singh & Fawcett, 2008) and semantic tasks (Humphreys et al., 2015) is related to task demands. However, DMN activation in semantic memory tasks can be observed even when task demands (defined by reaction times) are equated across semantic and non-semantic control tasks (Wirth et al., 2011), when the semantic task is more demanding (Seghier et al., 2010) or when the task demands are explicitly regressed out (Binder, Westbury, Mckiernan, Possing, & Medler, 2005), suggesting the engagement of the DMN in semantic memory processing is not only due to the effects of general difficulty. DMN is also involved in autobiographical memory, which has a strong semantic component. Autobiographical planning engages DMN and, during this task state, its activity is coupled with the frontoparietal control network (Spreng et al., 2010). The evidence suggests that one potential function of DMN is memory processing.

In some studies, other functions of DMN were proposed to explain its stronger activation at some stages, such as automatic information processing (Vatansever, Menon, & Stamatakis, 2017) or cognition transition (Crittenden, Mitchell, & Duncan, 2015; Smith, Mitchell, & Duncan, 2018). However, the findings can be explained by the account that DMN supports external task processing when behaviour depends on pre-existing representations guiding cognition (Margulies & Smallwood, 2017). Vatansever and colleagues found that DMN is active and showed greater connectivity with hippocampal and parahippocampal areas after participants have acquired the rule and applied the rule in the Wisconsin Card Sorting Task (WCST), suggesting that DMN contributes to automated information processing (Vatansever, et al., 2017). In line with this view, DMN often shows stronger activation in easy, highly practiced tasks (Mcvay & Kane, 2010; Smallwood & Schooler, 2006). However, memory input is most relevant after the participants have acquired the rule and then apply the rule. Crittenden et al. (2015) found that DMN shows increased activity during a large and demanding switch in task set. Furthermore, they found that the activity pattern of DMN can be used to decode task-relevant information during task performance. This effect is replicated in another study in which Smith et al. (2018) found that DMN activates more when a task restarts after rest. However, in these two studies, the task rules are quite complex and participants have to acquire them before performing the tasks. At the task switch stage, participants have to retrieve the task rules from the memory. This can explain the stronger activation of DMN during the task switch. These findings suggest that DMN is important when memory retrieval is necessary for the task.

1.3.2.2 Information integration in DMN

A broad range of conditions activate DMN perhaps because DMN is important when information integration is required. These conditions include episodic (Schacter, Addis, & Buckner, 2007) and semantic memory (Binder et al., 2009; Humphreys et al., 2015; Jefferies, 2013), social cognition (Amft et al., 2015; Amodio & Frith, 2006), goal-directed working memory tasks (Crittenden et al., 2015; Spreng et al., 2010; Vatansever, Menon, Manktelow, Sahakian, & Stamatakis, 2015). All these conditions require integration between multiple sensory systems, suggesting that DMN might support information integration.

DMN may play an integrative role in cognition that emerges from its location at the top of a cortical hierarchy and its relative isolation from systems directly involved in perception and action (Margulies et al., 2016). Margulies et al., (2016) observed that four of the peak DMN nodes are equidistant from the central sulcus, which is the topographical landmark of primary somatosensory/motor cortex. They also observed a similar correspondence with the calcarine sulcus, marking the location of primary visual cortex. These provide direct evidence for that core regions of the DMN—are maximally distant from regions that directly govern perception and action. The anatomical locations make them the best candidates for high-level, supramodal integration area in the human brain.

DMN located at the top of a cortical hierarchy (Huntenburg, Bazin, & Margulies, 2018; Margulies et al., 2016), suggesting that they are heteromodal regions. Margulies et al., (2016) recently described a whole-brain connectivity gradient recovered through diffusion embedding techniques that decompose connectivity into its principle components. The principal connectivity gradient of the human brain was found to correlate with physical distance along the cortical surface from sensory-motor regions; functionally this connectivity gradient extends from primary sensorimotor areas at one end, through attention and executive areas of MDN, to heteromodal DMN regions at the opposite end.

Regions of DMN are the connector hubs, which are captured in studies focused on its connectional anatomy. By using diffusion spectrum imaging, regions of DMN are the connector hubs that link all major structural modules (Hagmann, Cammoun, Gigandet, Meuli, & Honey, 2008). Furthermore, there is a substantial correspondence between structural connectivity and resting-state functional connectivity measured in the same participants (Hagmann et al., 2008). The spatial and topological centrality of the core within cortex suggests an important role in functional integration.

In line with this view, core regions of DMN, such as ATL and AG, are transmodal regions and integrate information across modalities. I have discussed the integration function of ATL and AG in detail in section 1.1.5. Bilateral AGs, core DMN hubs, displayed the greatest change in global connectivity across three levels of n-back task load and robustly interact with other large-scale brain networks, suggesting a potential involvement in the global integration of information (Vatansever et al., 2015). DMN accumulates and integrates information over minutes as evidenced by the observation that stimulus-induced correlation patterns in the DMN were largest for the intact story, greatly decreased in the paragraph scramble condition, and were almost entirely abolished in the word scramble condition using the inter-subject functional correlation which filters out intrinsic correlations and noise and isolates stimulus-dependent inter-regional correlations between brains exposed to the same stimulus (Simony et al., 2016). The well controlled study provides direct evidence to support the integration function of DMN.

1.3.3 Heterogeneity of DMN

DMN is heterogeneous and can be divided into sub-networks. There has been persistent controversy regarding how to divide it, since there is relatively strong intrinsic connectivity between all of its components, and yet also some potential functional subdivisions. For example, not all DMN nodes appear to be relevant for semantic processing. Andrews-Hanna et al., (2010) have argued that the DMN separates into three sub-networks. Using graph theoretical analytic approaches with resting-state fRMI data, Andrews-Hanna et al., (2010) identified a core sub-network comprising bilateral PCC and anterior medial prefrontal cortex, a medial temporal lobe sub-network made up of ventromedial prefrontal cortex, bilateral hippocampal formation, parahippocampus, retrosplenial cortex, and posterior inferior parietal lobule (IPL), and a dorsomedial prefrontal cortex (DMPFC) sub-network which includes the DMPFC, bilateral temporal parietal junction (TPJ), lateral temporal cortex, and the temporal pole. Andrews-Hanna et al. (2010) argue for a degree of functional segregation between these sub-networks, with the middle temporal lobe (MTL) sub-network especially linking to construction of mental scenes based on memory, while the DMPFC network is more involved in mentalizing. Braga and Buckner found that the default network is comprised of two separate networks possessing adjacent regions in eight or more cortical zones. A distinction between the networks is that one is coupled to the hippocampal formation while the other is not (Braga & Buckner, 2017). These findings suggest that DMN is heterogeneous.

1.4 The neural basis of control

1.4.1 Semantic control

1.4.1.1 Putting concepts into context

Traditionally, semantic memory researchers have often focussed on the invariance of conceptual representation across different experiences – given the critical separation of semantic from episodic memory representations in anterior lateral (Jefferies, 2013) vs. medial temporal regions (Eichenbaum, 2017). However, current researchers claim that conceptual representations are more dynamic. For example, depending on the circumstances, certain features of a concept would be more active than others. The dynamic representation of concepts can be influenced according to long term experience, recent experience, or the concurrent context (Yee & Thompson-Schill, 2016). We flexibly retrieve currently relevant aspects of knowledge from the semantic store. Jefferies and colleagues have suggested that when the pattern of semantic retrieval required by a task is consistent with long term memory, we can perform goal-directed semantic cognition based on relatively automatic retrieval. When the retrieved pattern is not consistent with long term memory, we need controlled semantic retrieval to perform the behaviour (Davey et al., 2016). Cognitive control allows us to retrieve only features of concepts that are relevant to the current context and inhibit unrelated ones (Egner & Hirsch, 2005). For example, we only retrieve the subordinate meaning of river bank and supress the dominant meaning financial bank to focus processing on relevant features when our friend tells us he is building sand castle on the bank. Depending on whether the control process is specific for semantic domain, control can be divided into semantic control and general executive control.

1.4.1.2 The research paradigms of semantic control

Semantic control processes are thought to be recruited when there is a need to promote a particular semantic retrieval pattern which is not typical for that item. This requirement has been manipulated in a variety of ways, which nevertheless show a common neural response (see Noonan et al., 2013). More semantic control is required to process the meanings of ambiguous vs unambiguous words (e.g., bank vs water); to retrieve subordinate vs dominant meanings of ambiguous words (e.g., river vs money for the word bank) and to retrieve weak associations (e.g., saucer and ashtray) compared with strong associations (e.g., saucer and coffee cup). Semantic control is also required when selecting a response from among many potentially correct options; and to promote specific aspects of knowledge in the face of strong competition (Badre, Poldrack, Paré-Blagoev, Insler, & Wagner, 2005; Jefferies, 2013; Noonan et al., 2013; Thompson-Schill, D'esposito, Aguirre, & Farah, 1997). Another common way to manipulate semantic control is to employ feature matching tasks, in which participants decide whether words/objects have a specific feature in common (e.g., colour, shape, size), irrespective of their global semantic relationship. Feature matching tasks involve selection because a subset of knowledge must be retrieved, in line with current goals, and spreading activation to closely semantic associates must be inhibited (Thompson-Schill et al., 1997). This thesis used contrasts of weak versus strong association judgements, and feature matching to manipulate semantic control.

1.4.1.3 Regions of semantic control

All of these tasks activate a common large-scale distributed semantic control network. It includes left IFG, posterior middle temporal gyrus (pMTG), dorsal AG bordering intraparietal sulcus (IPS), as revealed by a meta-analysis of neuroimaging studies (Noonan et al., 2013). This is consistent with evidence from lesions studies (Martin & Cheng, 2006; Metzler, 2001; Thompson-Schill, Kurtz, & Gabrieli, 1998) and TMS studies (Devlin, Matthews, & Rushworth, 2003; Gough, Nobre, & Devlin, 2005; Whitney, Kirk, O'Sullivan, Lambon Ralph, & Jefferies, 2011). Patients with semantic aphasia, associated with left inferior frontal and temporoparietal infarcts, show semantic control deficits (Jefferies & Lambon Ralph, 2006). Specifically, they have difficulty in retrieving non-dominant aspects of knowledge across modalities, suggesting that this is a heteromodal semantic control system. They can retrieve more information when provided with strong external cues that reduce the need for internally-generated constraint over semantic retrieval, suggesting that they appear to retain conceptual information (Jefferies & Lambon Ralph, 2006; Noonan, Jefferies, Corbett, & Lambon Ralph, 2010).

Inhibitory stimulation of IFG and pMTG equally disrupts the retrieval of weak but not strong associations (Whitney et al., 2011). In addition, when delivering TMS to IFG, pMTG and pre-supplementary motor area (pre-SMA) activate more during the retrieval of weak but not strong associations, consistent with functional compensation and showing these areas act as a functional network (Hallam et al., 2018, 2016). These patient, fMRI and TMS studies provide converging evidence to support the proposal that left IFG and left pMTG are the core regions of semantic control.

1.4.1.4 Selection versus retrieval

Although it is well known that left inferior prefrontal cortex (LIPFC) mediates control of semantic retrieval, the fundamental nature of LIPFC remains controversial. LIPFC might be implicated in a controlled retrieval process that activates goal-relevant knowledge in a top-down manner, or a post-retrieval selection process that resolves competition between simultaneously active representations (irrespective of whether these representations were activated in an automatic or controlled manner), or both (Badre & Wagner, 2007).

One theory posits that LIPFC specifically selects task-relevant knowledge from amidst competing knowledge (Thompson-Schill et al., 1997; 1998; Thompson-Schill, D'Esposito, & Kan, 1999). LIPFC is engaged when a subset of knowledge must be selected from other competing knowledge, but are not engaged when semantic retrieval does not require selection. Selection demands can be manipulated by varying the specificity of the semantic judgment, with participants making either a global relatedness judgment (i.e., which of the targets is most globally related to the cue) or a feature similarity judgment (i.e., which of the targets is most similar to the cue with respect to a particular feature, such as colour). When participants assess the global similarity, which depends on a comparison between the items along all semantic dimensions or features, they do not need to select subset of associated semantic knowledge against in favour of other knowledge. When they assess the similarity of two items along a single semantic dimension or feature (such as colour), they need to select each item's colour attributes from other competing semantic attributes (such as size, shape, etc) and therefore selection demands increased (Thompson-Schill et al., 1997). Consistent with the selection hypothesis, fMRI revealed that high selection (i.e., feature similarity decision) versus low selection relatedness (i.e., global similarity decision) elicited greater activation in left VLPFC inclusive of mid-VLPFC (~BA 45; pars triangularis), whereas this manipulation did not affect activation levels in left anterior VLPFC (~BA 47; pars orbitalis) (Badre et al., 2005; Chiou, Humphreys, Jung, & Lambon Ralph, 2018; Davey et al., 2016; Thompson-Schill et al., 1997; 1998; 1999). The same effect was replicated when using a congruency manipulation to increase selection demands by varying whether automatically retrieved knowledge is relevant or irrelevant (Badre et al., 2005).

Another theory proposes that LIPFC guides controlled semantic retrieval irrespective of whether retrieval requires selection against competing representations. Controlled retrieval demands were manipulated by varying the strength of association between the cue and the correct target during global relatedness judgments. Greater controlled retrieval is required under conditions of weak cue-target associative strength because of diminished bottom-up activation of relevant knowledge (Bunge, Wendelken, Badre, & Wagner, 2005; Wagner, Paré-Blagoev, Clark, & Poldrack, 2001). However, varying cue-target associative strength may also increase selection demands because (1) increases in retrieval can result in greater activation of both relevant and irrelevant information from memory, and (2) the weak activation of relevant target knowledge may render this information less competitively viable (Thompson-Schill & Botvinick, 2006). Consistent with this possibility, fMRI revealed that weak versus strong association elicited greater activation in regions that are sensitive to selection manipulations (i.e., left VLPFC, inclusive of mid-VLPFC) and regions that are insensitive to the selection manipulations, left anterior VLPFC (Wagner et al., 2001). When controlled retrieval was pitted against the amount of semantic knowledge retrieved – contrasting weak, two-target trials (high controlled retrieval/low overall retrieval) with strong, four-target trials (low controlled retrieval/high overall retrieval) – activation was evident only in left anterior VLPFC, with this activation overlapping with that seen in an earlier study using this same contrast (Wagner et al., 2001), suggesting that left anterior VLPFC is involved in controlled retrieval.

In conclusion, there might be a two-process model of mnemonic control, supported by a double dissociation among rostral regions of left VLPFC. Specifically, anterior VLPFC (~BA47; inferior frontal gyrus pars orbitalis) supports controlled access to stored conceptual representations, whereas mid-VLPFC (~BA 45; inferior frontal gyrus pars triangularis) supports a domain-general selection process that operates post-retrieval to resolve competition among active representations (Badre & Wagner, 2007).

1.4.2 General executive control

1.4.2.1 Multiple demand network (MDN)

In addition to semantic control regions, demanding semantic tasks also recruit regions of MDN that support executive control across domains, irrespective of whether cognition utilises conceptual information or not (Humphreys & Ralph, 2017; Noonan et al., 2013). MDN activates more for a variety of difficult tasks relative to easy tasks, such as spatial/verbal working memory, maths, music and language (Fedorenko, Duncan, & Kanwisher, 2013). The same network can be found using resting state analysis (Power et al., 2011; Yeo et al., 2011). This network includes sites with IPS, inferior frontal sulcus (IFS) and pre-SMA (Duncan, 2010; Fedorenko et al., 2013).

Across both human and nonhuman primate studies, regions of MDN are commonly linked to cognitive or executive control processes across domains, including focused attention, goal maintenance, strategy selection, performance monitoring, and other activities (Duncan, 2010). Activation patterns in MDN reflect category distinctions that are relevant to behaviour rather than task-irrelevant category distinctions (Erez & Duncan, 2015). These findings demonstrate the ability of the MDN to implement complex goal-directed behaviour by focused attention. Another key function of MDN is goal maintenance, as demonstrated by task-relevant information could be decoded from all regions of the MDN (Crittenden, Mitchell, & Duncan, 2016). In addition, MDN needs to keep updating the information.

1.4.2.2 Functions of MDNs: adaptive coding

To meet the requirements of our current goals, MDN needs to swiftly adjust its processing priorities in response to our constantly updated goals. However, the mechanism(s) remain largely unknown. A possibility is that the same neuron may flexibly code many different types of task, which is called adaptive coding hypothesis.

The adaptive coding hypothesis proposes that context-specific parameters shape the tuning profile of higher cortical neurons (Duncan, 2010). Rather than being tuned to specific features in the environment, these neurons are proposed to have highly adaptable response properties, coding information according to what is currently relevant. Single-cell recording studies have shown that many neurons in the frontal and parietal lobes exhibit substantial flexibility, adapting their response properties to code the specific information required in current behaviour, such as task-relevant objects, features and categories (see review in Duncan, 2010). For example, up to 50% of all cells recorded in lateral prefrontal cortex discriminated targets from non-targets. In line with the electrophysiological literature, Jackson and Woolgar (2018) found that the same MDN voxels code relevant stimulus features in two different tasks. Comparatively, in the visual system, distinct sets of voxels are required. Soreq and colleagues (2019) found that the patterns of network activity and connectivity of the same MDN regions can classify stimulus domains (spatial, number and fractal) and working memory processes (encode, maintain, probe). This evidence supports adaptive coding hypothesis.

To achieve flexibility, regions of MDN rapidly update their pattern of global functional connectivity according to task demands. Specifically, the MDN's brain-wide functional connectivity pattern shifted more than those of other networks across a variety of task states and that these connectivity patterns could be used to identify the current task (Cole et al., 2013). Connectivity patterns provide the most precise basis for classification and become fine-tuned as maintenance load increases (Soreq et al., 2019). These results accord with a network-coding mechanism, where the same brain regions support diverse demands by adopting different connectivity states. The above evidence emphasises the flexibility of the MDN regions to re-configure their responses and adaptively code relevant information across different tasks.

1.4.2.3 Different regions in prefrontal cortex support different demands

There may be some functional specialisation within the executive network. In line with this view, Badre & D’Esposito (2009) proposed a rostrocaudal gradient in prefrontal cortex (PFC), with rostral frontal areas supporting more abstract forms of control than caudal areas. Badre & D’Esposito (2007) manipulated the abstractness of stimulus–response rules over four levels. At the simplest level, participants responded based on stimulus–response associations (colour–finger). Then participants responded based on more complex rules (colour–feature–finger, colour–dimension–feature–finger, episode–colour–dimension–feature–finger). The manipulated level of representation revealed a systematic posterior to anterior gradient within the PFC. Activation in progressively rostral PFC regions tracked competition at higher levels of the task from dorsal premotor to anterior premotor to mid-dorsolateral PFC to rostral lateral PFC. However, this rostrocaudal abstraction gradient might be explained by difficulty. Crittenden and Duncan (2012) presented participants with 4 vertical lines on a screen and asked them to indicate the position of the shortest line. They manipulated the difficulty in 3 ways: by increasing the number of lines, by decreasing the difference between short and normal line length, and by changing the stimulus–response mapping. Only the latter manipulation increased rule complexity. They found that anterior PFC activated more when the complexity of the stimulus–response mapping was increased, but it also activated more when fine discrimination was required or there were high selection demands not related to the complexity of rules, suggesting that rostral regions of the lateral frontal lobes were recruited for difficult tasks apparently devoid of any strong abstraction requirements. However, similar abstraction gradients have been observed in other studies, with matched difficulty, suggesting that difficulty alone cannot explain the gradient in PFC. Christoff and colleagues (2009) manipulated levels of abstraction, with accuracy and reaction time being matched, to examine the effects of varying abstraction in the absence of variations in cognitive complexity. They found concrete, moderately abstract, and highly abstract information were associated with stronger relative recruitment of ventrolateral, dorsolateral, and rostrolateral PFC regions, respectively, suggesting a functional topography whereby increasingly anterior regions are preferentially associated with increasing abstraction. Collectively, these data support that the heterogeneity in function of PFC.

The hypothesis that different prefrontal regions support different demands can be tested by examining whether a region is domain general or specific. According to the gradient of abstraction, if processing in the left PFC becomes more abstract in progressively rostral areas, caudal areas should process concrete features such as stimulus-domain, whereas more rostral areas should instantiate control processes that act across domains (e.g. a plan that can be applied to spatial or verbal stimuli). Thus, abstract versus concrete processing would reveal itself through stimulus domain-generality versus specificity. A stimulus–domain manipulation identified rostral left PFC areas as domain-general, while dorsal and ventral caudal frontal regions were sensitive to spatial versus verbal information, respectively, consistent with a gradient of abstraction (Nee & D'Esposito, 2017). A similar pattern was revealed by examining the preference of voxels. Waskom and Wagner, (2017) found that different voxels prefer different contexts (motion, colour or orientation), although context representations are distributed across subnetworks within prefrontal cortex. Voxels with similar context preferences exhibited stronger functional correlations than those between voxels with opposite preferences during task and resting states. The above evidence suggests that different prefrontal regions support different demands.

The gradients in PFC are somewhat similar to gradients described for ATL, which also go from specific spoke features to more abstract heteromodal concepts. However, the new revised framework of Badre and Nee (2018) suggests that although the frontal lobes are organized hierarchically, there is no unidimensional gradient of abstraction or global difficulty (Badre & D'Esposito, 2009; Badre, Hoffman, Cooney, & D'Esposito, 2009; Badre & Nee, 2018; Koechlin, Le Ody, & Kouneiher, 2003). In line with this view, there are other anatomical dimensions (e.g. ventral-dorsal, lateral and medial) except rostral-caudal within PFC. Burgess and colleagues proposed that the stimulus orientation/stimulus independent distinction might provide one principle for understanding the functional organization of anterior PFC along a lateral-medial dimension (see review (Burgess, Dumontheil, & Gilbert, 2007)). They proposed that lateral anterior PFC is stimulus-independent while medial anterior PFC is stimulus-oriented (Burgess et al., 2007). This viewpoint is consistent with recent work showing that parallel networks can fall in closely juxtaposed regions in numerous cortical zones (Braga & Buckner, 2017).

1.4.2.4 Heterogeneity of MDN

Inspired by the rostral-caudal gradient in the PFC, it has been proposed that there might be one or more functionally distinct areas or networks (Cocchi, Zalesky, Fornito, & Mattingley, 2013). Crittenden et al., (2016) found that the MDN can be divided into two subnetworks centred on the frontoparietal control network (FPCN) and cingulo-opercular cortex. Although task-relevant information could be decoded from all regions of the MDN, classification accuracy scores were significantly higher in the FP subnetwork. These results suggest a nested picture with MDN regions as a whole showing coactivation and broad rule representation, but with significant functional distinctions between component subnetworks. Dixon et al. (2018) found that FPCN is heterogeneous. They identified two distinct subsystems within the FPCN, exhibiting distinct patterns of functional connectivity with the DMN and the dorsal attention network (DAN). This twofold FPCN differentiation was observed across four independent datasets, across nine different conditions (rest and eight tasks), at the level of individual-participant data, as well as in meta-analytic coactivation patterns. This evidence supports heterogeneity of MDN.

1.4.3 Semantic control versus general executive control

Although some regions of PFC demonstrate verbal-sensitivity (Krieger-Redwood, Teige, Davey, Hymers, & Jefferies, 2015; Nee & D’Esposito, 2016), it is controversial whether some sub-networks of MDN correspond to the semantic control network. One of the subnetworks of FPCN – FPCN_B identified by Dixon et al., (2018) – overlaps with semantic control regions and the Neurosynth topics that were preferentially associated with this subsystems are “attention”, “action”, “reading”, and “semantics”, which are consistent with the function of semantic control regions.

Converging evidence suggests that at least some regions are specific for semantic control. The peak of semantic control lies outside the MDN regions, although semantic control regions partially overlap with regions of MDN. These regions are specific for semantic control rather than domain general executive control. Using a series of tasks, Fedorenko and colleagues (Fedorenko, Behr, & Kanwisher, 2011) found that IFG and pMTG demonstrate language sensitivity. They are only sensitive to difficulty of semantic tasks rather than other non-semantic tasks (Humphreys & Lambon Ralph, 2017). This is evidenced by the fact that left IFG and pMTG are specifically activated by demanding semantic tasks but not demanding non-semantic tasks (Humphreys & Lambon Ralph, 2017; Noonan et al., 2013; Lambon Ralph et al., 2017) and inhibitory stimulation of these two regions disrupts demanding semantic but not non-semantic tasks (Whitney et al., 2011). By contrast, MDN regions, such as middle frontal gyrus, lack stimulus domain-sensitivity and therefore enable us adaptively implement a wide variety of tasks (Cole et al., 2013; Nee & D'Esposito, 2016).

Regions that are specific for semantic control can be revealed by lateralisation studies (Diachek, Blank, Siegelman, & Fedorenko, 2019; Alam, Karapanagiotidis, Smallwood, & Jefferies, 2019). MDN is bilateral, while control regions that are involved in language processing are left lateralised (Diachek, Blank, Siegelman, & Fedorenko, 2019; Alam et al., 2019). Diachek et al., (2019) conducted a large-scale fMRI investigation using data from 30 diverse word and sentence comprehension experiments (481 unique participants, 678 scanning sessions) and found that the MDN was active during many language tasks. Moreover, similar to the language-specific network, which is robustly lateralized to the left hemisphere, these responses were stronger in the left-hemisphere MDN regions (Diachek et al., 2019). The semantic control network is strongly left-lateralised, as evidenced by a recent resting state study (Alam et al., 2019). The intrinsic connectivity between IFG and pMTG is stronger in the left hemisphere than the right hemisphere. Furthermore, the degree of hemispheric lateralisation predicted behaviour in this study: participants with stronger intrinsic connectivity within the left hemisphere had better semantic performance, while those with stronger intrinsic connectivity between left pMTG and homotopes of semantic regions in the right hemisphere performed more poorly on judgements of weak associations, which require greater control (Alam et al., 2019). The left lateralisation of semantic control might be driven by the functional connectivity of MDN. The frontoparietal control network preferentially coupled to the default network and language-related regions in the left hemisphere but to attention networks in the right hemisphere. This arrangement may facilitate control of processing functions that are lateralized (Wang, Buckner, & Liu, 2014). This left lateralisation of IFG and pMTG implies they are more likely to be specific for semantic control rather than general executive control.

1.5 Interaction between semantic representation and semantic control

Controlled semantic cognition relies upon dynamic and flexible interactions between the executive ‘semantic control’ and hub-and-spoke ‘semantic representation’ systems. In an fMRI study, participants paired unrelated concepts by canonical colours (a less accustomed task, e.g., pairing ketchup with post-box due to both being red) or paired well-related concepts by semantic relationship (a typical task, e.g., ketchup is related to mustard). Relative to typical pairing, atypical colour pairing activated more IFG, a key node of the control system, and occipitotemporal ‘spoke’ regions abutting areas of hue perception. Furthermore, IFG and occipitotemporal ‘spoke’ exhibited enhanced connectivity when performing colour pairing (Chiou et al., 2018), suggesting that control and representation together support controlled semantic cognition.

1.6 The interaction between DMN, semantic control network and MDN

Cognitive flexibility is hypothesized to require dynamic integration between brain areas or networks, including DMN and MDN. DMN activity is negatively correlated with MDN activity during tasks (Anticevic et al., 2012). Therefore, the DMN and MDN have previously been thought to operate in opposite functional directions, with greater anticorrelation being associated with better cognitive performance (see for instance this review (Anticevic et al., 2012)). Other studies, however, show the opposite, with increased internetwork correlation underlying cognitive performance (Hearne, Cocchi, Zalesky, & Mattingley, 2015; Hellyer et al., 2014; Piccoli et al., 2015; Spreng, Sepulcre, Turner, Stevens, & Schacter, 2013). The default network can be coupled with the frontoparietal control network to support goal-directed cognition, such as language comprehension (Elton & Gao, 2015), autobiographical planning (Smallwood, Brown, Baird, & Schooler, 2012; Spreng et al., 2010), and creative idea production (Beaty, Benedek, Kaufman, & Silvia, 2015). Furthermore, higher task-state DMN-MDN dynamics associate with greater cognitive flexibility (Douw, Wakeman, Tanaka, Liu, & Stufflebeam, 2016). The same effect is replicated. Braun et al., (2015) found that the effortful working-memory condition was characterized by a reconfiguration of frontoparietal (MDN) and frontotemporal networks (DMN) and the amount of reorganization in the modular structure and specifically the amount of interaction between modules is behaviourally relevant to working-memory performance and cognitive flexibility. These results indicate that the flexible interactions between the DMN and MDN under different task conditions may underpin the brains’ ability to cope with changing environmental demands.

Interaction between DMN, semantic control and MDN is thought to be necessary for demanding semantic processing (Davey et al., 2016). Controlled semantic cognition relies on dynamic and flexible interactions between the executive ‘semantic control’ and hub-and-spoke ‘semantic representation’ systems (Chiou et al., 2018). Specifically, relative to global relatedness judgment, feature judgments increased the effective connectivity between spoke region and semantic control region. When the semantic task is extremely difficult, the multiple demand network is required for successfully semantic processing (Humphreys & Lambon Ralph, 2017).

The interaction might be supported by the anatomical location of key nodes of the semantic control network, which falls midway between DMN and MDN. The spatial adjacency of the semantic control network to both DMN and MDN might allow semantic control regions to integrate long-term conceptual knowledge with more adaptive representations of currently-relevant goals, supporting flexible patterns of semantic retrieval (Davey et al., 2016). In line with this view, both left anterior IFG and pMTG show connections with both DMN and MDN regions, which are typically anti-correlated across tasks and resting states (Davey et al., 2016). It was replicated in other studies. For example, the fronto-parietal network showed connections with both DMN and DAN (Dixon et al., 2018). This distinctive pattern of connectivity might be critical for semantic control, which involves the coordination of brain regions allied to the DMN that support heteromodal conceptual representations (e.g., (Murphy et al., 2018)), with control regions that support demanding tasks.

1.7 Gradient accounts of cortical function

1.7.1 Local gradient in function

Contemporary accounts of cognitive neuroscience often focus on the functional specification of regions by mapping specific cognitive computation to unique brain areas. For example, it has been found that ventral visual pathway is not homogeneous, but contains some regions (including fusiform face area (FFA) and parahippocampal place area (PPA)) that are primarily involved in the analysis of a single class of stimulus (Spiridon & Kanwisher, 2002).

Fedorenko and colleagues (2011) use functional MRI to define classic language regions functionally in each subject individually and then examine the response of these regions to the nonlinguistic functions most commonly argued to engage these regions: arithmetic, working memory, cognitive control and music. They found little or no response in language regions to these nonlinguistic functions, supporting the functional specificity for high-level linguistic processing in the human brain. The above evidence supports the specificity of brain areas.

It has been proposed that there is abrupt changes in function along the cortex. For example, Fedorenko, and colleageus (2012) demonstrated that regions that are specific for language processing are surrounded by regions of MDN, suggesting the abrupt transition in function. However, local gradients have been observed in multiple regions. Along the visual hierarchy, low-level visual features are increasingly abstracted and integrated with information from other systems (Van Essen & Maunsell, 1983). For example, ventral visual pathway shows graded transitions from low-level visual feature representation in early visual cortex, to a more categorical representation in late object vision cortex (ventral temporal cortex) with intermediate organization at the middle stage (lateral occipital cortex) (Connolly et al., 2012). A similar gradient was revealed by Chiou et al (2018) along the ventral temporal cortex, transitioning from the caudal ‘spoke’ zones preferring canonical colour processing to the rostral ‘hub’ zones preferring semantic relationship.

The local gradient in ATL and rostral-caudal gradient in PFC have been introduced before. This graded function might be related to graded connectivity change in each region. For example, Badre and colleagues proposed a rostrocaudal abstraction gradient in the lateral frontal cortex, with rostral frontal areas supporting more abstract forms of control than caudal areas (Badre & D’Esposito, 2009). Nakae and colleagues found a connectivity gradient along the anterior-posterior axis of IFG, with the more anterior part of the IFG connecting to the more anterior part of the lateral temporal area, and the more posterior IFG connecting to the more posterior temporal area (Nakae et al., 2019).

Furthermore, this type of graded function is not unique to semantic processing or control. A spatial gradient for mentalizing in medial prefrontal cortex, with ventral and dorsal medial prefrontal cortex falling at the opposite ends of a functional gradient, has been reported (Chester & DeWall, 2019; Denny, Kober, Wager, & Ochsner, 2012; Sul, Tobler, Hein, et al., 2015). This graded function might be related to graded connectivity change, too. Jackson and colleagues accessed the structural and functional connectivity of each voxel in the ventral medial prefrontal cortex (vmPFC) to delineate changes in the pattern of connectivity across this region. They identified a highly graded change in both the structural and functional connectivity of the vmPFC, with regions with distinct connectivity being distinguished at either end of this gradient (Jackson, Bajada, Ralph, & Cloutman, 2019). The multiple local gradients in visual area, ATL, PFC and vmPFC suggests that whole-brain gradients might be a general principle of brain organization.

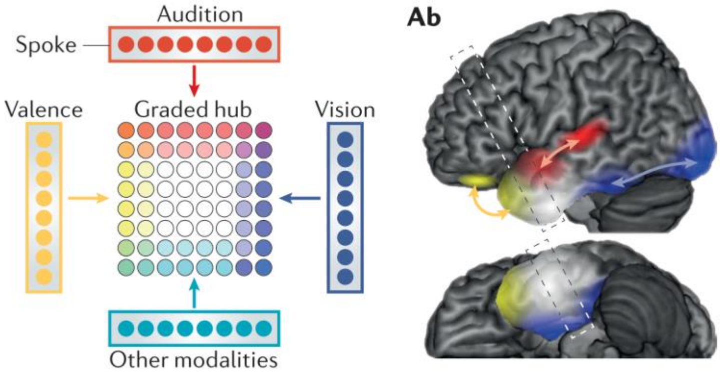


Figure 1-4: The graded ATL semantic hub (Lambon Ralph et al., 2017)

1.7.2 Global gradient in cortical organization

Recent evidence suggests that whole-brain gradients might be a general principle of brain organization. Prior parcellations of each region have only considered hard splits between distinct regions, although both hard and graded connectivity changes may exist (Power et al., 2011; Yeo et al., 2011). Although discrete network parcellations suggest the brain is composed of discrete networks (Power et al., 2011; Yeo et al., 2011), Margulies and colleagues (Huntenburg et al., 2018; Margulies et al., 2016) proposed that a key feature of human cortical organization is the spatial arrangement of areas along a global gradient between sensorimotor and transmodal regions. Margulies et al. (2016) recently described a whole-brain connectivity gradient recovered through diffusion embedding techniques that decompose connectivity into its principle components. The principal connectivity gradient of the human brain was found to correlate with physical distance along the cortical surface from sensory-motor regions; functionally this connectivity gradient extends from primary sensorimotor areas at one end, through attention and executive areas of MDN, to heteromodal DMN regions at the opposite end. The principal gradient of connectivity provides a framework for the spatial ordering of large-scale networks identified through parcellation approaches – it captures repeating transitions between these networks, which occur across cortical lobes. The same organization which gradually progresses from primary (motor) to transmodal (DMN) regions was revealed in the cerebellum (Guell, Schmahmann, De Gabrieli, & Ghosh, 2018). A corresponding gradient was found in the macaque monkey (Margulies et al., 2016) and in the mouse cortex (Fulcher, Murray, Zerbi, & Wang, 2019), suggesting that systematic structural variation across cortical areas is a core organizational principle that may underlie hierarchical specialization in mammalian brains. The cross-species correspondence of the principal gradient suggests that it is phylogenetically conserved and may represent a primary dimension of cortical expansion. In summary, the connectivity gradient is relatively consistent across species, individuals and imaging modalities, providing comprehensive evidence for the functional gradients as a general principal for the brain organization.

In conclusion, several questions that emerge from the literature are: 1. What is the structural basis of controlled semantic retrieval? Are individual differences in semantic task performance predicted by the structure of specific cortical regions or by their structural co-variation, suggesting a distributed network architecture? 2. Are these individual differences specific to semantic control, or do they reflect domain-general control? 3. Where are semantic goals represented? Is MDN the only network that represents goal information? 4. What is the role of the DMN in semantic cognition? 5. How are the different networks involved in semantic cognition organised on the cortical surface, and what principals might explain this organisation? These questions are addressed in this thesis.

2. Empirical questions for this thesis

Chapter 2

Tasks requiring semantic control activate a large-scale network including left IFG and pMTG – this network responds when retrieval is focussed on weak as opposed to dominant associations. However, little is known about the biological basis of individual differences in this cognitive capacity: regions that are commonly activated in task-based fMRI may not relate to variation in controlled retrieval.

We used cortical thickness measures in around 200 individuals to characterise the structural covariance networks of left IFG and pMTG, two key sites for semantic control in previous group-level neuroimaging analyses. We examined how these structural covariance networks are modulated by individual differences in the efficiency of semantic control. Specifically, we assessed the identification of weak associations, after controlling for performance on strong associations.

Chapter 3

Previous studies have demonstrated that information about current task demands or goal states can be decoded within regions of the MDN, which is thought to support cognitive flexibility. However, the contribution of the DMN, which is frequently associated with automatic aspects of cognition, remains unclear. In this study, we presented a semantic feature matching task, in which participants were asked to focus on specific features of concepts (colour, shape or size) according to the instructions on each trial. We examined which brain areas can classify goal, using multivariate fMRI analyses of the semantic feature matching task. To characterize the way in which MDN and DMN might support semantic retrieval and decision making, we employed MVPA within the goal instruction period, probe word and target period in which participants reached a decision. We conducted whole brain classification analysis for each period without predefining regions of interest (ROIs), allowing us to reveal all the potential regions that represent goal information.

Chapter 4

Human cognition is flexible, allowing us to efficiently deal with a spectrum of situations – ranging from highly familiar tasks (when cognition is supported by long-term memory) to novel scenarios (when cognition is driven by current goals). Traditionally, these aspects of cognition have been ascribed to dichotomous neural systems supported by the DMN and MDN. In reality, however, most situations are neither completely familiar, nor entirely novel, highlighting the need to understand how cognition is constrained in a graded fashion by these networks working together. We tested the predictions of a contemporary account which proposes a connectivity gradient along the cortical surface capturing the transition from unimodal regions concerned with perception and action, through MDN, to DMN. We parametrically manipulated the global semantic similarity of the words in a semantic feature matching paradigm to create a ‘psychological gradient’ and asked whether brain responses change linearly along the connectivity gradient in a way that reflects the match between task demands and long-term memory.

Chapter 2 : The structural basis of semantic control: Evidence from individual differences in cortical thickness

Declaration:

The study presented in Chapter 2 is a published paper (see reference listed below), which contains original work completed by the author under the supervision of Dr.Elizabeth Jefferies and Dr. Jonathan Smallwood.

Wang, X., Bernhardt, B. C., Karapanagiotidis, T., De Caso, I., Alam, T. R. D. J. G., Cotter, Z., ... & Jefferies, E. (2018). The structural basis of semantic control: Evidence from individual differences in cortical thickness. NeuroImage, 181, 480-489.

Author contributions: X.W., J.S. and E.J. designed research; X.W., T.K., I.C., T.A., Z.C. performed research; X.W. analyzed data; X.W., B.C., J.S. and E.J. wrote the paper.

Abstract

Semantic control allows us to shape our conceptual retrieval to suit the circumstances in a flexible way. Tasks requiring semantic control activate a large-scale network including left inferior frontal gyrus (IFG) and posterior middle temporal gyrus (pMTG) – this network responds when retrieval is focussed on weak as opposed to dominant associations. However, little is known about the biological basis of individual differences in this cognitive capacity: regions that are commonly activated in task-based fMRI may not relate to variation in controlled retrieval. The current study combined analyses of MRI-based cortical thickness with resting-state fMRI connectivity to identify structural markers of individual differences in semantic control. We found that participants who performed relatively well on tests of controlled semantic retrieval showed increased structural covariance between left pMTG and left anterior middle frontal gyrus (aMFG). This pattern of structural covariance was specific to semantic control and did not predict performance when harder non-semantic judgements were contrasted with easier semantic judgements. The intrinsic functional connectivity of these two regions forming a structural covariance network overlapped with previously-described semantic control regions, including bilateral IFG and intraparietal sulcus, and left posterior temporal cortex. These results add to our knowledge of the neural basis of semantic control in three ways: (i) Semantic control performance was predicted by the structural covariance network of left pMTG, a site that is less consistently activated than left IFG across studies. (ii) Our results provide further evidence that semantic control is at least partially separable from domain-general executive control. (iii) More flexible patterns of memory retrieval occurred when pMTG co-varied with distant regions in aMFG, as opposed to nearby visual, temporal or parietal lobe regions, providing further evidence that left prefrontal and posterior temporal areas form a distributed network for semantic control.

Introduction

Our ability to use semantic knowledge to drive appropriate thoughts and behaviour is fundamental to our mental lives. Semantic cognition is thought to involve at least two interacting components: *conceptual representations* encompass stored knowledge about the meanings of objects, words, sounds and people; while *semantic control* processes shape retrieval to suit our goals and the context (Jefferies, 2013; Lambon Ralph et al., 2017). These components are thought to draw on distinct large-scale networks in the brain (Corbett, Jefferies, & Lambon Ralph, 2011; Davey et al., 2016; Díez, Gómez-Ariza, Díez-Álamo, Alonso, & Fernandez, 2017; Gold, Balota, Kirchhoff, & Buckner, 2005; Gold & Buckner, 2002; Hallam et al., 2018; Humphreys & Lambon Ralph, 2017; Jefferies, 2013; Jefferies & Lambon Ralph, 2006; Patterson et al., 2007; Snowden et al., 2018; Vatansever, Bzdok, et al., 2017; Wei et al., 2012). However, little is known about individual differences in these abilities – i.e., what are the structural and functional markers of efficient semantic cognition in healthy participants?

If the capacity to control semantic retrieval is separable from how knowledge is represented, individual differences in task performance should reflect this multi-component structure. Semantic tests will not always measure *what* people know: since concepts have diverse features and associations, the capacity to shape retrieval to suit the circumstances will also have a major impact on performance. Semantic control processes are thought to be required when we have to retrieve non-dominant aspects of knowledge or promote specific aspects of knowledge in the face of strong competition, in order to suit the requirements of the current task or context (Badre et al., 2005; Jefferies, 2013; Ralph et al., 2017; Sharon L Thompson-Schill et al., 1997). Semantic control demands are consequently higher when processing the meanings of ambiguous vs. unambiguous words (Humphreys & Ralph, 2017; Rodd, Davis, & Johnsrude, 2005; Whitney et al., 2011), matching items on the basis of a single feature such as colour rather than their global relatedness (Chiou et al., 2018; Davey et al., 2016), retrieving a specific semantic relationship in the face of strong competition, or retrieving weak associations (e.g., SAUCER and ASHTRAY) as opposed to strong associations (e.g., SAUCER and CUP) (Badre et al., 2005; Badre & Wagner, 2002, 2007; Davey et al., 2015; Wagner et al., 2001; Whitney, Kirk, O'sullivan, Lambon Ralph, & Jefferies, 2011). All of these manipulations have in common the need to promote a particular pattern of semantic retrieval which is not typical for that item, and all of these tasks activate a common semantic control network: a meta-analysis of neuroimaging studies including this range of tasks identified a distributed semantic control network that consisted of left inferior frontal gyrus (IFG), posterior middle temporal gyrus (pMTG), dorsal angular gyrus (dAG) bordering inferior parietal sulcus (IPS) ((Noonan et al., 2013); see Figure 2-1). Left IFG is the most reliably activated site across participants and tasks, while pMTG shows more variation (Vitello, Warren, Devlin, & Rodd, 2014), suggesting that pMTG might be especially critical to individual differences in the efficiency of semantic control processes.

Although difficult semantic decisions activate domain-general executive control regions along with other tasks, left pMTG and anterior portions of IFG fall outside the multiple-demand system; they are specifically activated by semantic (or memory) tasks (Humphreys & Ralph, 2017; Noonan et al., 2013). Left anterior IFG and pMTG show similar functional connectivity in line with the view that they form a network for semantic control (Davey et al., 2016; Humphreys & Ralph, 2017): interestingly, they show connections with both default mode and multiple-demand regions, which are typically anti-correlated across tasks and resting states (Davey et al., 2016). This distinctive pattern of connectivity might be critical for semantic control, which involves the coordination of brain regions allied to the default mode network that support heteromodal conceptual representations (e.g., (Murphy et al., 2018)), with control regions that support demanding tasks. By this view, individual differences in semantic control may occur somewhat independently of performance on difficult non-semantic tasks.

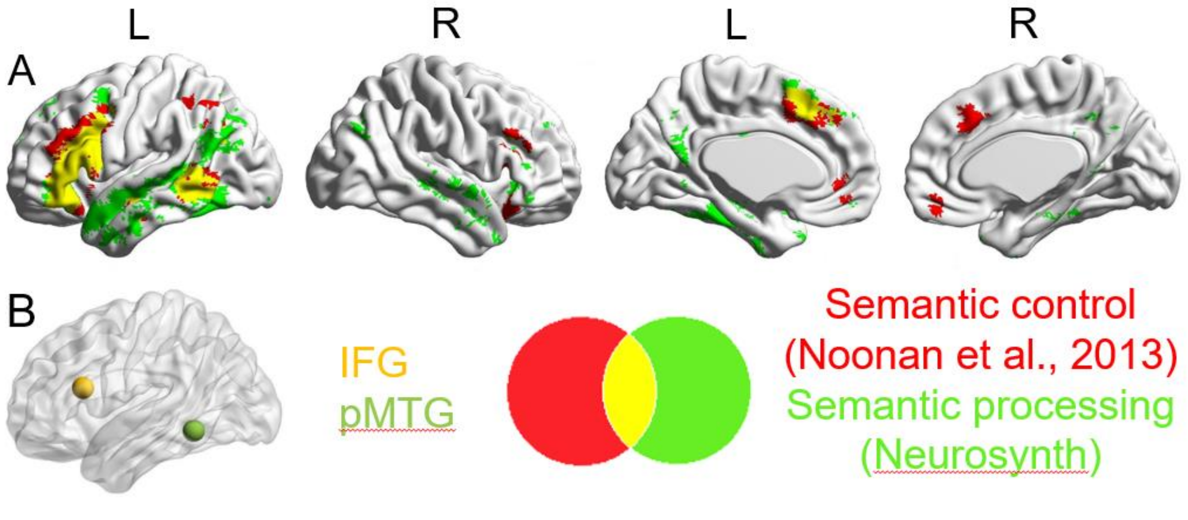


Figure 2-1. A: Meta-analyses of (i) task contrasts manipulating semantic control demands from (Noonan et al., 2013); (in red) and (ii) the term "semantic" from Neurosynth (in green). Semantic regions implicated in control are highlighted in yellow (showing the overlap of the two meta-analyses). B: Seeds for our analysis defined on the basis of these meta-analyses (Noonan et al., 2013). (L= Left hemisphere; R = hemisphere)

A causal role for left IFG and pMTG in semantic control has been established through neuropsychology and brain stimulation. Patients with multimodal semantic deficits in the context of stroke aphasia (i.e. semantic aphasia) have poor control over semantic retrieval, with largely intact conceptual knowledge, and this pattern is associated with damage to left IFG or temporoparietal regions including pMTG (Hallam et al., 2018; Jefferies & Lambon Ralph, 2006; Noonan et al., 2010; Sharon L. Thompson-Schill et al., 1998). While neuropsychology lacks spatial specificity when drawing inferences about brain-behaviour relationships, inhibitory TMS delivered to left IFG and pMTG elicits equivalent disruption of control-demanding semantic judgements: for example, there is an inhibitory effect on the retrieval of weak associations, yet no effect on either strong semantic associations or control-demanding non-semantic decisions (Davey et al., 2015; Hoffman, Jefferies, & Ralph, 2010; Whitney, Kirk, O'Sullivan, et al., 2011). Moreover, damage to left IFG in semantic aphasia and inhibitory TMS to this region in healthy participants elicits an increased response in pMTG to semantic judgements with high control demands (Hallam et al., 2018, 2016), consistent with a pattern of functional compensation within the large-scale distributed semantic control network. The current study supplements these methods by establishing how structural covariation between brain distant regions predicts the efficiency of controlled semantic retrieval across individuals, even after accounting for performance on dominant associations and a non-semantic task.

Although most research in cognitive neuroscience focusses on commonalities across individuals, inter-individual differences can be exploited to understand the neural basis of human cognition (Kanai & Rees, 2011). Cognitive differences between people can be predicted from variation in the structure of specific brain regions (Choi et al., 2008; Schilling et al., 2012). For example, the grey matter density of pre-supplementary motor area (pre-SMA)can account for inter-individual variability in the ability to select the correct response in the presence of response conflict (Van Gaal, Scholte, Lamme, Fahrenfort, & Ridderinkhof, 2011), while the cortical thickness of rostral medial temporal cortex correlates with verbal memory performance (Dickerson et al., 2008). However, cognitive variation is not only associated with the morphometry of individual brain regions but also with structural covariation between regions that form functional networks. For example, people with higher IQ have greater covariation in cortical thickness between IFG and other frontal and parietal brain areas (Lerch et al., 2006). For empathy and theory of mind tasks, structural covariance is more sensitive than regional differences between individuals (Bernhardt, Klimecki, Leiberg, & Singer, 2014; Valk et al., 2017). Consequently, the current study links individual differences in performance on tests of semantic control to structural covariation between posterior temporal and prefrontal regions, as opposed to structural markers for individual sites in pMTG and IFG.

We used cortical thickness measures in around 200 individuals to characterise the structural covariance networks of left IFG and pMTG, two key sites for semantic control in previous group-level neuroimaging analyses (see Figure 2-1). We examined how these structural covariance networks are modulated by individual differences in the efficiency of semantic control. Specifically, we assessed the identification of weak associations, after controlling for performance on strong associations. This paradigm has been used repeatedly to assess semantic control across different labs and multiple methods (neuroimaging, neuropsychology and TMS): all of these approaches have revealed greater involvement of IFG and pMTG for weak than strong associations (Badre et al., 2005; Badre & Wagner, 2002; Davey et al., 2015; Noppeney, Phillips, & Price, 2004; Wagner et al., 2001; Whitney et al., 2011a, 2011b). When a strong target is not present, control processes are potentially required, both to focus retrieval on the aspects of the probe that relate to the target, and also to select the most relevant potential target from the distractors (Whitney et al., 2011a). Consequently, weak association trials are thought to place greater demands on 'controlled retrieval processes' which shape patterns of retrieval away from dominant but currently-irrelevant knowledge and towards weaker yet relevant information (Lorch, 1982). We used a behavioural efficiency metric that combined response time with accuracy, since on this task individuals may trade-off speed and accuracy in different ways. To our knowledge, this is the first cortical thickness investigation of individual differences in semantic control. Previous studies have linked patterns of intrinsic connectivity in semantic regions to individual differences in performance (Mollo et al., 2016; Deniz Vatansever, Bzdok, et al., 2017; Wei et al., 2012); for example, Wei et al., (2012) found that functional connectivity between left pMTG and other semantic regions, such as IFG and anterior temporal lobe, was positively associated with semantic performance. However, this study did not distinguish between relatively automatic and more controlled aspects of semantic retrieval.

Since brain regions that serve the same functions show greater structural covariance (Lerch et al., 2006), and left IFG and pMTG (amongst other regions) are thought to form a network that supports semantic control (Jefferies, 2013; Jefferies & Lambon Ralph, 2006; Noonan et al., 2013; Lambon Ralph et al., 2017; Whitney et al., 2011b), we predicted that seed regions in left IFG and pMTG taken from the meta-analysis of Noonan et al., (2013) would show structural covariance with other regions involved in semantic control. Moreover, since pMTG has more variability than left IFG in the location of activation across individuals (Vitello et al., 2014), we expected that the structural covariance of pMTG with other semantic control regions might be particularly important for predicting individual differences in controlled semantic retrieval ability. We also hypothesised that the structural covariance of pMTG with other brain areas implicated in semantic control might be more important for performance than the cortical thickness of pMTG alone, since semantic control is supported by a large-scale network and structural covariation between regions forming large-scale functional networks has been shown to be more sensitive to behavioural differences than regional thickness metrics (Bernhardt et al., 2014; Valk et al., 2017). Better performance is often related to greater cortical thickness and great covariation in cortical thickness of task-relevant regions (Alexander-Bloch, Giedd, & Bullmore, 2013; Kanai & Rees, 2011; Lerch et al., 2006). Consequently, we anticipated participants with high performance on weak associations would show stronger structural covariance between left pMTG and other semantic control regions.

Method

Participants

The research was approved by the York Neuroimaging Centre and Department of Psychology ethics committees. We recruited 207 healthy adults from the University of York (137 females; age: mean ± SD = 20.21 ± 2.35, range: 18 – 31 years). This sample included the 154 participants studied by Vatansever et al. (2017) and Sormaz et al. (2017). All participants were right handed, native English speakers, with normal or corrected-to-normal vision and no history of psychiatric or neurological illness. All volunteers provided written informed consent, were paid or given course credit for their participation and were debriefed after the study was completed. We removed from the analysis fifteen participants with missing behavioural data; two without neuroimaging data; ten without appropriate cortical thickness pre-processing and two because accuracy was not higher than chance in at least one of the tasks.

Procedure

An initial MRI session included a structural scan and a 9-minute resting-state sequence. Within a week of the scan, participants completed a large battery of computer-based tasks in three behavioural testing sessions, each lasting two hours. These measures included weak and strong semantic associations and a non-semantic control task with similar perceptual and motor requirements. The contrast between strong and weak associations was selected from the task battery because it closely maps onto manipulations of semantic control used in previous task-based fMRI studies, and because the stimuli presented in these conditions were matched for psycholinguistic properties (see below). The order of these tasks and the order of sessions was counterbalanced across participants. For a more complete description of those aspects of cognitive testing that fall outside the scope of the current study, see (Vatansever et al., 2017).

Tasks

The tasks employed a three-alternative force choice design. A probe was presented with a target and two unrelated distracters, which were targets in other trials. Each trial started with a blank screen for 500ms. The response options were subsequently presented at the bottom of the screen for 900ms. Finally, the probe was presented at the top of the screen, triggering the onset of the decision-making period. The probe and choices remained visible until the participant responded, or for a maximum of 3 seconds. Both response time (RT) and accuracy were recorded. See Figure 2-2 for an example trial for each task.

Weak and strong association matching

Participants were asked to select the target word that was most strongly associated with a probe picture. The semantic association that linked probes and targets was either strong (BRASS INSTRUMENT – ORCHESTRA) or weak (BRASS INSTRUMENT – PARADE). For strongly-linked items, semantic control demands are thought to be minimised because task-relevant information is relatively easy to retrieve. In contrast, controlled retrieval processes are thought to be required to identify weakly-associated targets, since task-relevant aspects of knowledge are not the most strongly-encoded aspects of knowledge; therefore, semantic activation may need to be ‘shaped’ to focus on the specific aspects of knowledge that are relevant to the association being probed. This manipulation has been used in many previous task-based fMRI studies (Badre et al., 2005; Davey et al., 2016; Noppeney et al., 2004; Wagner et al., 2001)and TMS studies (Davey et al., 2015; Whitney et al., 2011) of semantic control, highlighting a role for pMTG alongside IFG in controlled semantic retrieval. The strong and weak trials were selected from a large database used in previous experiments (Krieger-Redwood, 2012; Davey et al., 2015). The strength of association between probe-target pairs was assessed using a 7-point Likert scale, along with the familiarity and imageability for each member of the pair. The mean association rating between probes and targets was 6.02 for ‘strong’ pairs and 3.32 for ‘weak’ pairs ($t(118) = 21.74$; $p < 0.001$). There were no differences between conditions in word length, familiarity, imageability or lexical frequency (Table 2-1). There were sixty strong and sixty weak association trials, presented in four blocks of thirty trials each. The order of trials within each block was randomized across subjects.

Figure matching task

This was a non-semantic control task, with similar perceptual and decision-making demands to the semantic judgments. The stimuli were sixty pixelated and scrambled black-and-white photographs of faces (taken from (Krieger-Redwood, 2012)). Participants were asked to select the target that was identical to the probe; the distracters were the same images rotated by 180° or 270°. The task was split in two blocks of thirty trials each.

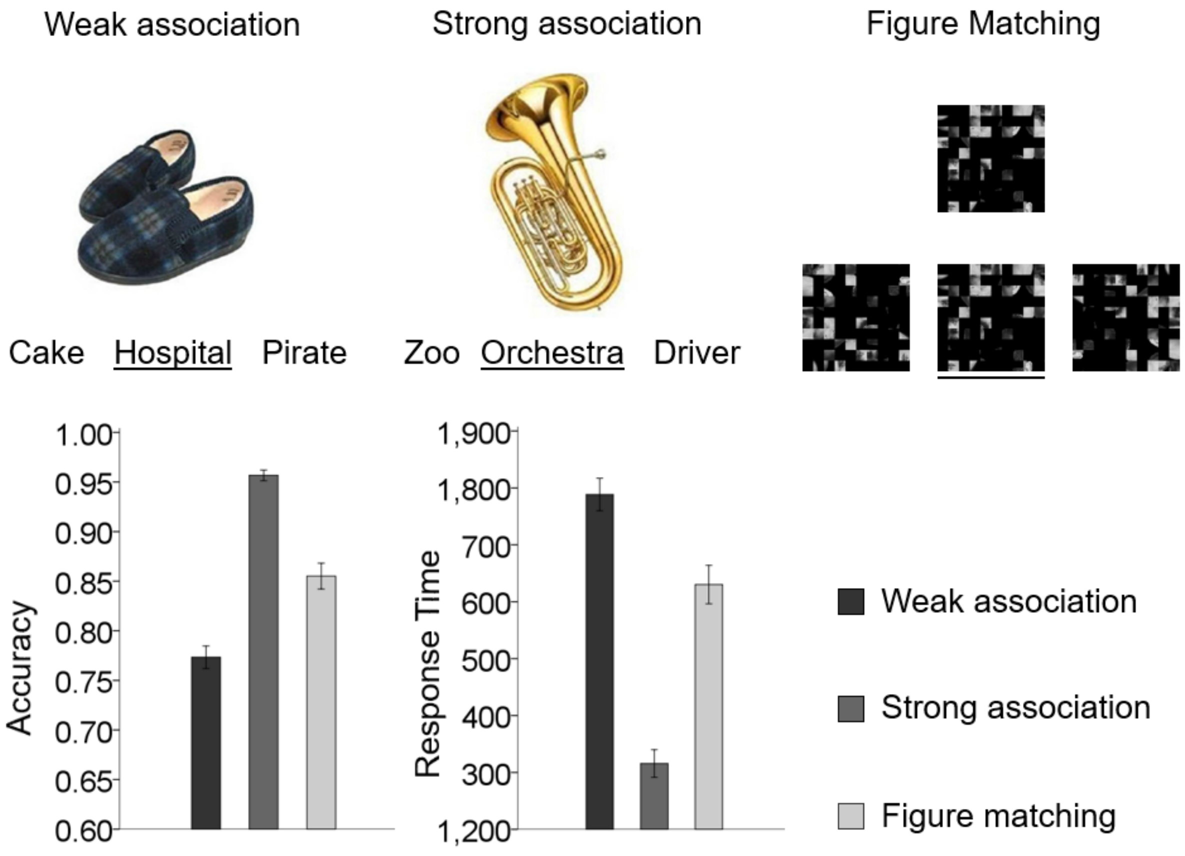


Figure 2-2. Top row: Illustration of the behavioural tasks. For all the tasks, correct answers are underlined. Bottom row: Mean accuracy and response time for each task. Error bars represent 95% confidence intervals.

Table 2-1 Psycholinguistic variables for weakly and strongly-associated target words.

Target		Mean	SD	t	Sig.
Word length	Strong association	6.43	0.39	-0.16	0.873
	Weak association	6.6	0.34		
Lexical Frequency	Strong association	13564.8	1887	0.89	0.374
	Weak association	11233.6	1805		
Familiarity	Strong association	6.02	0.09	-0.88	0.381
	Weak association	6.12	0.08		
Imageability	Strong association	5.16	0.13	1.07	0.287
	Weak association	4.96	0.13		
Semantic association	Strong association	6.02	0.07	21.74	0.000
	Weak association	3.32	0.10		

MRI data acquisition

MRI data was acquired using a 3T GE HDx Excite Magnetic Resonance Imaging (MRI) system utilising an eight-channel phased array head coil tuned to 127.4 MHz, at the York Neuroimaging Centre, University of York. Structural MRI acquisition in all participants was based on a T1-weighted 3D fast spoiled gradient echo sequence (TR = 7.8 s, TE = minimum full, flip angle = 20°, matrix size = 256 × 256, 176 slices, voxel size = 1.13 × 1.13 × 1 mm). A nine-minute resting state fMRI scan was carried out using single-shot 2D gradient-echo-planar imaging (TR = 3s, TE = minimum full, flip angle = 90°, matrix size = 64 × 64, 60 slices, voxel size = 3 × 3 × 3 mm^3, 180 volumes). Participants were asked to passively view a fixation cross and not to think of anything in particular during the resting-state scan. A FLAIR scan with the same orientation as the functional scans was collected to improve co-registration between subject-specific structural and functional scans.

Data pre-processing

Behavioural data

To account for potential speed-accuracy trade-offs, inverse efficiency scores were used as the dependent measure: i.e., the mean RT for correct responses in each task was divided by the proportion of correct responses. We reversed this measure so that higher efficiency scores would correspond to better performance. Inverse efficiency is commonly used to measure behaviour performance (Wei et al., 2012), because it accounts for differences between individuals in the way that accuracy and speed are traded-off against each other. To reduce the effect of influential outliers but do not change the original trend of raw data, outlying values which is greater than mean + 3SD were replaced with mean + 3SD, while outlying values which is less than mean - 3SD were replaced with mean – 3SD. Finally, we calculated z-scores for each task across subjects before performing any analyses.

Cortical thickness measurements

FreeSurfer was used to estimate vertex-wise cortical thickness (5.3.0; https://surfer.nmr.mgh.harvard.edu), using an automated surface reconstruction scheme described in detail elsewhere (Dale, Fischl, & Sereno, 1999; Fischl, Liu, & Dale, 2001; Bruce Fischl, Sereno, & Dale, 1999). Briefly, the following processing steps were applied: intensity normalization, removal of non-brain tissue, tissue classification and surface extraction. Cortical surfaces were visually inspected and corrected if necessary. Cortical thickness was calculated as the closest distance between the grey/white matter boundary and pial surface at each vertex across the entire cortex. A surface-based smoothing with a full-width at half maximum (FWHM) = 20mm was applied. Surface alignment based on curvature to an average spherical representation, fsaverage5, was used to improve correspondence of measurement locations among subjects.

Resting state pre-processing

All pre-processing of resting-state data was achieved using FMRIB Software Library (FSL version 4.0, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FEAT/). The Brain Extraction Tool (BET) was used to extract individual FLAIR and T1 weighted structural brain images. Structural images were linearly registered to the MNI-152 template using FMRIB's Linear Image Registration Tool (FLIRT). FMRI Expert Analysis Tool (FEAT) was used to perform the following standard analysis steps: (1) correcting for head movement using MCFLIRT; (2) slice timing correction using Fourier space time-series phase-shifting; (3) spatial smoothing with 6mm full-width half-maximum (FWHM) Gaussian kernel; (4) grand mean intensity normalisation of the entire 4D dataset by a single multiplicative factor; (5) high pass (sigma = 100s) and low pass (sigma = 2.8s) temporal filtering (Gaussian-weighted least-squares straight line fitting). In each analysis, eleven nuisance regressors were removed, including the confounding six head motion parameters and the top five principal components extracted from white matter (WM) and cerebrospinal fluid (CSF) masks using the CompCor method (Behzadi, Restom, Liau, & Liu, 2007). We did not perform global signal regression which was reported to introduce spurious anti-correlations (Murphy, Birn, Handwerker, Jones, & Bandettini, 2009). We generated WM and CSF masks from each individual’s structural image (Zhang, Brady, & Smith, 2001).

Data analysis

Cortical thickness analysis

The SurfStat toolbox for Matlab [http://www.math.mcgill.ca/keith/surfstat/] (Worsley et al., 2009) was used for structural covariance network analysis, as in previous studies (Bernhardt et al., 2014; Valk et al., 2017). Two seeds, left IFG (MNI -47 21 18) and left pMTG (MNI -58 -49 -9), were taken from an fMRI meta-analysis of semantic control (Noonan et al., 2013) (Figure 2-1). These sites were the regions with the highest t-values in the meta-analysis of semantic control studies (Noonan et al., 2013) and the most reliably implicated in semantic control across participants in previous fMRI and neuropsychological studies. We placed a sphere (radius = 3mm) around each peak to create the regions of interest (ROIs). To find regions that strongly co-varied with left IFG or left pMTG in cortical thickness, we constructed a structural covariance network for each seed by correlating the thickness of each seed with thickness measures across all cortical surface points. There is a well-established negative correlation between age and cortical thickness (Tamnes et al., 2010) and gender also influences cortical thickness (Luders et al., 2006); consequently, these variables were included as covariates of no interest. The model fitted at surface point *i* was:

$T_i = \beta0 + \beta1 * Sex + \beta2 * Age + \beta3 * T_{seed}$

where T_{seed} is the seed thickness. We determined significant clusters in this model using random field theory for nonisotropic images which controlled the Family-Wise Error rate at $p < 0.05$. We also applied Bonferroni correction to account for the fact that we included two models (IFG and pMTG); consequently, the final threshold set by FWE correction was $p < 0.025$.

To assess the relationship between structural covariance strength and individual differences in controlled semantic retrieval, we added performance on strong and weak associations, plus the interaction between performance on weak association trials and cortical thickness of the seed, to the model above. Therefore, the final model was:

$T_i = \beta0 + \beta1 * Sex + \beta2 * Age + \beta3 * T_{seed} + \beta4 * \text{Strong associations} + \beta5 * \text{Weak associations} + \beta6 * (T_{seed} * \text{Weak associations})$

where T_{seed} * Weak associations denotes an interaction. A positive interaction indicates stronger structural correlation with better performance on weak associations, while a negative interaction indicates weaker structural covariation for better performance. To assess the specificity of this effect to semantic processing, we performed a control analysis that included the non-semantic figure matching task as an additional covariate, using the following model: $T_i = \beta0 + \beta1 * Sex + \beta2 * Age + \beta3 * T_{seed} + \beta4 * \text{Strong associations} + \beta5 * \text{Weak associations} + \beta6 * \text{Figure matching} + \beta7 * (T_{seed} * \text{Weak associations})$.

Moreover, since weak associations are more difficult to retrieve than strong associations, we investigated whether similar results would emerge from the comparison of a more difficult non-semantic task with an easier semantic task, using the following model:

$T_i = \beta0 + \beta1 * Sex + \beta2 * Age + \beta3 * T_{seed} + \beta4 * \text{Strong associations} + \beta5 * \text{Figure matching} + \beta6 * (T_{seed} * \text{Figure matching})$

where T_{seed} * Figure matching denotes an interaction.

Finally, while most of our analysis focused on structural covariance between purported semantic control regions, reflecting the accepted view that cognitive abilities reflect the coordinated action of multiple brain regions, we also examined the relationship between task performance and cortical thickness within each of our ROIs (left IFG and pMTG). In these analyses, we examined partial correlations between cortical thickness in a specific region and performance on specific pair of tasks (e.g., weak associations controlling for strong associations).

Resting state functional connectivity analysis

Regions found in structural covariance analysis and corresponding seeds were subsequently used to define ROIs in an analysis of intrinsic connectivity, measured using fMRI at rest. We identified the peak vertex in each cluster in the cortical thickness analysis, obtained the coordinates of that vertex in MNI305 space and transformed to MNI152 space. We placed a sphere (radius = 3mm) around this peak. The time series from each ROI was extracted and used as an explanatory variable in the first-level connectivity analysis. In the high-level analysis, the averaged functional connectivity map derived from each ROI was generated. Finally, we conducted a conjunction analysis, exploring the regions that showed stronger functional connectivity with both regions via a formal conjunction analysis, using FSL's 'easythresh_conj' tool (Nichols, Brett, Andersson, Wager, & Poline, 2005). For all contrasts, age, gender and head movement parameters were included as covariates of no interest. To control for multiple comparisons, we considered the number of voxels in the brain and used a cluster forming threshold of $Z > 3.1$ ($P < 0.05$). Brain networks were visualized using BrainNet Viewer (Xia, Wang, & He, 2013).

Results

Behavioural results

Figure 2-2 shows mean accuracy and RT for each task. As expected, weak association matching was more difficult than strong association matching (inverse efficiency: $t = 41.787$, $p < 0.001$). Inverse efficiency for the non-semantic control task, involving meaningless figure matching, fell between strong and weak association trials (figure matching vs. weak associations: $t = -12.023$, $p <0.001$; figure matching vs. strong associations: $t = 20.237$, $p <0.001$).

Structural covariance network

To find regions that co-vary strongly with IFG and pMTG, we constructed the structural covariance networks of these two regions. The seed in left IFG was correlated with bilateral IFG and inferior frontal sulcus, right middle frontal gyrus and right middle cingulate cortex (FWE, $p < 0.025$; Figure 2-3A). Patterns of structural correlations from the seed in left pMTG encompassed regions in left anterior superior temporal gyrus, left inferior parietal sulcus and right lateral occipital cortex (FWE, $p < 0.025$; Figure 2-3B). Together, these patterns of structural covariance encompassed or lay adjacent to many of the key regions implicated in semantic control (i.e., by the meta-analysis of Noonan et al., 2013). Moreover, the sites within intraparietal sulcus and mid-cingulate cortex were distant from both seeds.

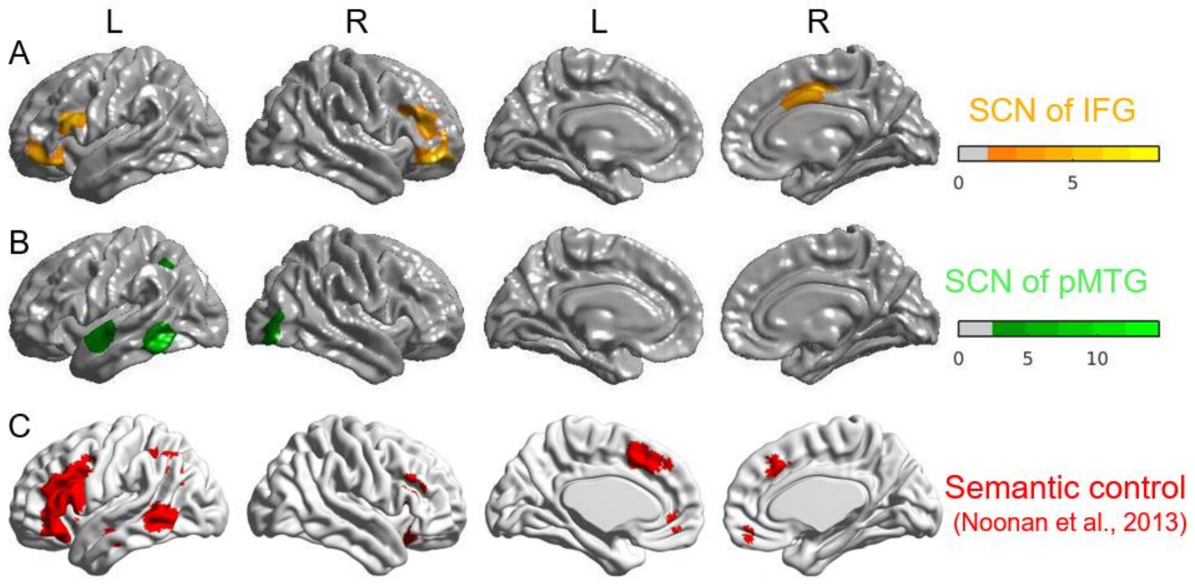


Figure 2-3. Structural covariance analysis seeding from (A) left IFG and (B) left pMTG (FWE-corrected, $p<0.025$). C: The meta-analysis of semantic control network (red colour) (Noonan et al., 2013). (L= Left hemisphere; R = Right hemisphere)

Relationship between structural covariance and controlled semantic retrieval

To assess the relationship between structural covariance networks and the efficiency of controlled semantic retrieval, we investigated the parametric interaction between seed covariance strength and inter-individual differences in performance on weak association trials, controlling for performance on strong associations. The structural covariance network of left IFG was not modulated by weak associations (FWE, $p<0.025$). However, structural correlations from left pMTG to left anterior middle frontal gyrus (aMFG) were positively modulated by weak associations (FWE, p<0.025) (Figure 2-4). In other words, individuals with higher weak association performance showed stronger structural covariance between left pMTG and left aMFG relative to those with lower performance. To further characterise this interaction, we subdivided the group according to performance on weak association trials (above and below median). Individuals who showed good retrieval of weak associations showed a positive correlation between the cortical thickness of left aMFG and pMTG. For participants who were poorer at retrieving weak associations, there was no correlation (Figure 2-4).

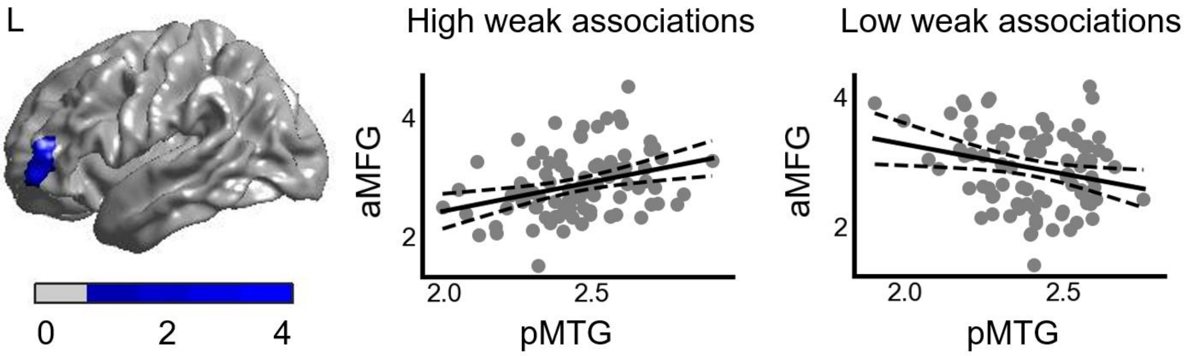


Figure 2-4. Interaction between the degree of structural covariance of left pMTG and weak associations after controlling for age, gender and strong associations (FWE-corrected, p<0.025). To illustrate the parametric interaction effect, regression fits are shown after the group has been split into two groups according to median performance on weak associations. (L= Left hemisphere.)

A series of supplementary analyses assessed the robustness and specificity of this effect. Identical results were obtained when figure matching was added as an additional covariate: the structural covariance between pMTG and aMFG still predicted weak associations after controlling for both strong associations and figure matching (FWE, p < 0.025). To establish if the same pattern of structural covariance between pMTG and aMFG would be observed for more difficult decisions in general, or whether the effect is specific to semantic control, we also contrasted the non-semantic figure matching task with the easier strong association judgements. This analysis did not highlight structural covariation between pMTG and aMFG. Instead, pMTG co-varied with a region of dorsal anterior cingulate/pre-SMA to a greater extent in people who were more efficient at making perceptual decisions in the figure matching task

(FWE, p < 0.05, Figure 2-5). This effect did not survive Bonferroni correlation for the number of seeds used in the analysis, although it was robust to FWE correction for multiple comparisons and therefore it is included here for completeness.

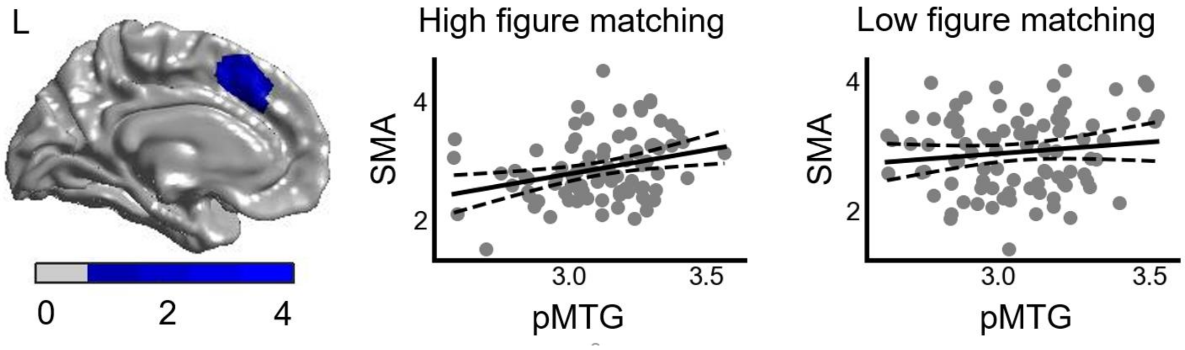


Figure 2-5. Interaction between the degree of structural covariance of left pMTG seed region and figure matching after controlling for age, gender and strong associations (FWE-corrected, p<0.05) To illustrate the parametric interaction effect, regression fits are shown after the group was split into two groups according to the median of performance on figure matching. (L = left hemisphere.)

ROI-based cortical thickness analysis

We conducted ROI-based cortical thickness to examine the relationship between cortical thickness in pMTG and IFG individually and semantic control performance. These regions were defined by a meta-analysis of task-based fMRI studies of semantic control (Noonan et al., 2013). The cortical thickness of left pMTG correlated with weak associations (r = 0.186, p = 0.013), but this effect only approached significance after controlling for performance on strong associations (r = 0.135, p = 0.075). There was no correlation between cortical thickness of left IFG and weak associations (r = 0.107, p = 0.157). This suggests that the structural covariation of pMTG with aMFG predicts the efficiency of controlled semantic retrieval more successfully than the cortical thickness of individual regions previously implicated in this function.

Resting-state functional connectivity

Given the evidence above that structural covariance between left pMTG and aMFG predicts the efficient retrieval of weak associations, we examined the intrinsic functional connectivity of these two sites using resting-state fMRI. The peak from the cortical thickness analysis in left aMFG (MNI coordinates: -40, 47, 9) and the pMTG peak from Noonan et al.'s (2013) meta-analysis (MNI coordinates: -58 -49 -9) were used as seeds. We found substantial overlap between the patterns of intrinsic connectivity for these sites. They both showed correlations through time with extensive regions of left prefrontal cortex, including inferior frontal sulcus, plus anterior and dorsolateral aspects of prefrontal cortex, similar but less extensive prefrontal regions in the right hemisphere, posterior middle and inferior temporal cortex, dorsal angular gyrus bordering intraparietal sulcus and pre-SMA. We computed a formal conjunction of these patterns of functional connectivity. This showed striking similarity with the semantic control network established from a meta-analysis of task-based fMRI studies (Figure 2-6).

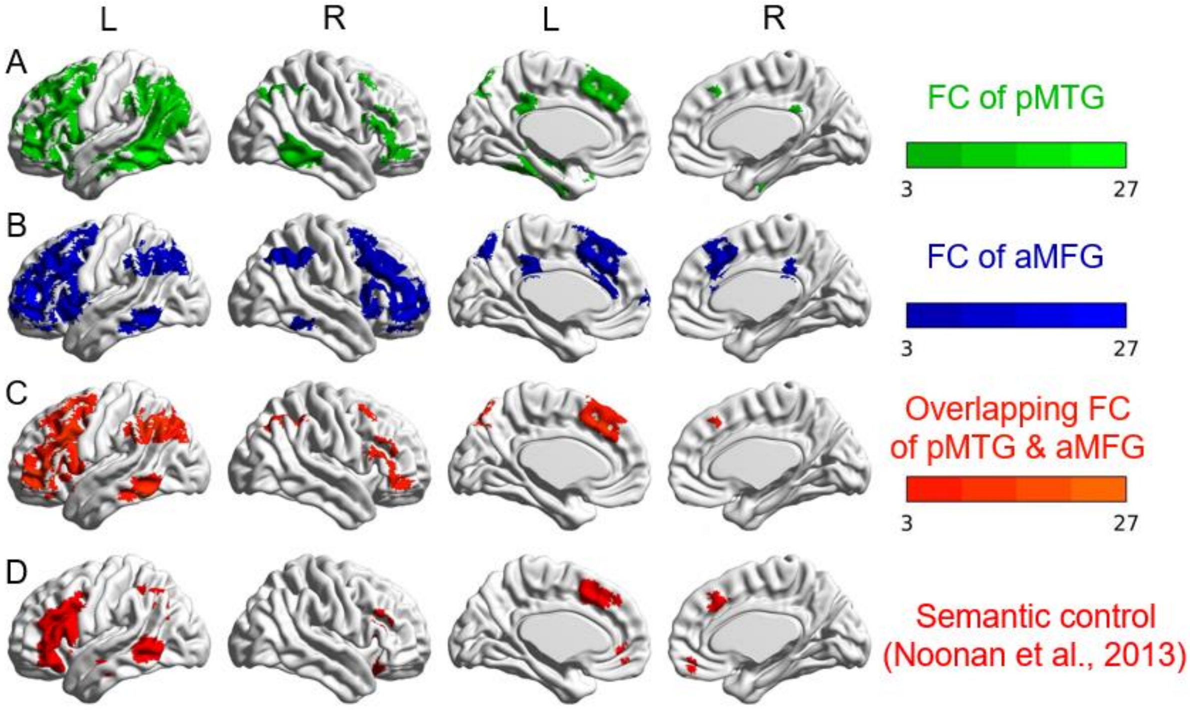


Figure 2-6. The positive functional connectivity (FC) networks from (A) pMTG and (B) aMFG (FWE-corrected, $p<0.025$). A direct comparison between (C) the conjunction of functional connectivity for pMTG and anterior MFG and (D) a meta-analysis of semantic control (Noonan et al., 2013). (L = Left hemisphere; R = Right hemisphere.)

Discussion

This study investigated the biological basis of individual differences in semantic control using cortical thickness metrics in a large sample of around 200 participants. We found that a key semantic control region from the task activation literature, left pMTG, showed stronger structural covariation with aMFG in people who showed relatively efficient controlled semantic retrieval. A similar network including posterior temporal and anterior and inferior prefrontal regions shows activation during fMRI studies of control-demanding semantic tasks. This pattern of structural covariation was observed even when we controlled for performance on similar non-semantic decisions. Moreover, the structural covariance between pMTG and aMFG did not predict performance when a relatively demanding non-semantic figure matching task was contrasted with easier judgements of strong semantic associations, suggesting the effect was specific to control-demanding patterns of semantic retrieval. The two sites showing structural covariation also had highly overlapping patterns of intrinsic connectivity at rest, consistent with the view that these regions form a functional network. This intrinsic connectivity network resembled the set of distributed brain regions that show stronger activation when semantic control demands are high (Noonan et al., 2013). The overlapping intrinsic connectivity for pMTG and aMFG included domain-general executive control regions, such as inferior frontal sulcus and pre-SMA, as well as sites within the default mode network, in left angular gyrus and dorsolateral prefrontal cortex, in line with the findings of Davey et al. (Davey et al., 2016) who proposed that semantic control regions show strong connectivity at rest to these two networks that are normally anti-correlated.

The suggestion that pMTG contributes to semantic control remains controversial since temporal lobe regions are not traditionally thought to contribute to the executive control of behaviour. However, a meta-analysis of task-based fMRI studies identified pMTG as the second most reliably activated region across diverse manipulations of semantic control, after left IFG (Noonan et al., 2013) and numerous individual studies have reported responses in both left IFG and pMTG for the contrast of weak over strong associations (Davey et al., 2016; Gold et al., 2006). The interpretation of these effects has remained unclear since greater activation in pMTG could arguably reflect increased activation of conceptual knowledge in more demanding tasks. Studies have shown that inhibitory stimulation of pMTG disrupts the retrieval of weak associations more than strong associations (Davey et al., 2015; Whitney, et al., 2011), suggesting that this region does play a critical role. However, the potential for individual differences analyses to inform our understanding of brain-behaviour relationships is under-exploited. The current results therefore make an important contribution to knowledge by showing that if pMTG co-varies in cortical thickness with a region in aMFG, participants tend to be more efficient at retrieving weak associations. These observations are also consistent with a previous study which found that pMTG activation to control-demanding semantic tasks is more variable in location and intensity across participants than the response in left IFG (Vitello et al., 2014). This finding might reflect differences between people in the extent to which pMTG is recruited to support semantic control – i.e., people might universally recruit left IFG but those people who also recruit pMTG might show the most efficient controlled semantic retrieval, and also the strongest structural covariation between pMTG and left aMFG.

Interestingly, the pattern of structural covariation between sites appeared to be a better predictor of performance on semantic control tests than the overall thickness of left pMTG itself, in line with a network view of cognitive functions. Previous studies have found that structural markers of social cognitive ability are also reflected in interregional networks as opposed to anatomical variation within specific regions. For example, the structural covariance network of dorsal anterior insula, but not its thickness, correlated with individual differences in empathic responding (Bernhardt et al., 2014) and structural covariance analysis, not regional thickness mapping, found a double dissociation between empathy and mentalizing (Valk et al., 2017). Structural covariance might reflect persistent cross-talk between regions: brain regions that show stronger correlation in cortical thickness are often part of systems that are known to sub-serve particular cognitive functions (Alexander-Bloch et al., 2013; Evans, 2013). For example, individuals with greater cortical thickness in posterior parts of inferior frontal cortex (Broca's area) typically also have greater cortical thickness in superior temporal cortex (Wernicke's area) (Lerch et al., 2006). We also observed similarities between structural covariance patterns and measures of intrinsic connectivity. The functional connectivity of the regions forming a structural covariance network, i.e., pMTG and aMFG, had similar patterns of functional connectivity at rest. Previous studies have also found that patterns of intrinsic functional connectivity show striking overlap with grey matter co-variance (Seeley, Crawford, Zhou, Miller, & Greicius, 2009; Segall et al., 2012) and give rise to similar network parcellations (Kelly et al., 2012). These findings are consistent with the view that structural covariance might relate to greater cross-talk between regions.

Our results are also consistent with a functional dissociation between semantic and domain-general executive control; however, this is not solely based on the role of specific sites, but instead on their participation in distinct large-scale networks. We found that structural covariance between left pMTG and left aMFG predicted performance on weak associations even after controlling for strong associations (a task comparison that is thought to highlight controlled semantic retrieval; cf. (Badre et al., 2005; Whitney et al., 2011). However, this pattern did not predict performance on a relatively demanding non-semantic task. These findings are consistent with the proposal that interactions between pMTG and anterior parts of prefrontal cortex support relatively abstract or internally-directed aspects of control – i.e., processes that establish which representations to prioritise when an association between two items is weak, as opposed to supporting the capacity to select a relevant response across tasks more generally (Badre & Wagner, 2007; Tomita, Ohbayashi, Nakahara, Hasegawa, & Miyashita, 1999). In a similar way, both left pMTG and anterior aspects of IFG show stronger activation for difficult semantic tasks but not executively-demanding non-semantic tasks (Humphreys & Lambon Ralph, 2017) and inhibitory TMS to both sites disrupts the retrieval of weak associations, yet has no effect on harder perceptual judgements (Whitney, et al., 2011). Both pMTG and anterior parts of inferior and middle frontal cortex lie outside the multiple-demand system implicated in cognitive control across domains (Duncan, 2010; Fedorenko et al., 2013), although they are involved in controlled retrieval from memory (Barredo, Öztekin, & Badre, 2015; Humphreys & Ralph, 2017; Noonan et al., 2013; Whitney et al., 2011).

In contrast, structural covariation between pMTG and pre-SMA predicted performance on a relatively demanding non-semantic task, relative to an easier semantic task probing strong associations. This result suggests that pMTG is not exclusively a semantic control region, but rather can participate in multiple large-scale functional networks – individual differences in structural covariation might reflect which of these networks is dominant in an individual. At the group level, pMTG structurally co-varied with both domain-general control and visual regions, as well as with cortical regions implicated in semantic processing. In line with this observation, previous work has shown that pMTG functionally couples to many different networks at rest (Braga, Sharp, Leeson, Wise, & Leech, 2013). This diverse pattern of connectivity could be crucial to explaining the varied links between structural covariance of pMTG and behaviour in the current study. When pMTG co-varies with left prefrontal regions (implicated in memory control), the capacity for controlled semantic retrieval is high. In contrast, the pre-SMA region showing covariation with pMTG in people who did well at the non-semantic task is implicated in domain-general executive control (Duncan, 2010; Duncan & Owen, 2000; Fedorenko et al., 2013; Thompson & Duncan, 2009). In the meta-analysis of

Noonan et al. (2013), pre-SMA showed a stronger response to control-demanding semantic tasks, but this cluster was also implicated in phonological control. In line with the suggestion that pre-SMA contributes to the multiple-demand system, it shows stronger activation for difficult vs. easy task conditions across domains, including spatial working memory, verbal working memory, maths and music (Fedorenko et al., 2013). Inhibitory TMS to pre-SMA induces deficits related to task switching (Rushworth, Hadland, Paus, & Sipila, 2002), conflict resolution (Mars et al., 2009), response inhibition (Chen, Muggleton, Tzeng, Hung, & Juan, 2009) and complex movement sequencing (Lau, Rogers, & Passingham, 2007). Consequently, although pre-SMA contributes to lexical-semantic tasks (Chee, O'Craven, Bergida, Rosen, & Savoy, 1999; Moore-Parks et al., 2010; Ulrich, Hoenig, Grön, & Kiefer, 2013), its functional role is not constrained to this domain; instead it is thought to contribute to aspects of cognitive control such response selection and switching (Hertrich, Dietrich, & Ackermann, 2016). Our data are consistent with this domain-general role for pre-SMA, although this network-based dissociation requires replication since the pre-SMA cluster did not survive Bonferroni correction for the number of seeds in our analysis.

Left pMTG shows a pattern of intrinsic connectivity that overlaps with the frontoparietal network (Yeo et al., 2011) (see Figure 6). Our finding that pMTG forms structural covariance networks with distinct sites, with diverse consequences for task performance, is consistent with studies showing that this network implements a wide range of task demands by rapidly updating its functional connectivity to suit the circumstances (Cole et al., 2013; Dixon et al., 2018). The frontoparietal network shows stronger shifts in brain-wide functional connectivity patterns across task states than other networks, and these connectivity patterns can be used to identify the current task (Cole et al., 2013). pMTG in particular shows diverse patterns of functional connectivity when compared with other frontoparietal sites (Dixon et al., 2018). These recent observations might relate directly to our findings that pMTG covariation with anterior PFC supports semantic control, while covariation with pre-SMA supports task performance on demanding non-semantic judgements.

Conclusions

In summary, our study documented structural networks that predicted the capacity of individuals to perform well on tests tapping controlled semantic retrieval. The cortical thickness of left pMTG and anterior prefrontal cortex together predicted the capacity to retrieve weak associations. Functionally-significant individual differences in structure were reflected in interregional networks rather than in the anatomy of specific regions.

Chapter 3 : Both default and multiple-demand regions can represent goal information

Declaration:

The study presented in Chapter 3 is a manuscript that is still in preparation for publication (see reference listed below), which contains original work completed by the author under the supervision of Dr.Elizabeth Jefferies and Dr. Jonathan Smallwood.

Wang, X., Gao, Z., Smallwood, J., Jefferies, E., Both default and multiple-demand regions represent goal information. Manuscript in preparation for publication.

Author contributions: X.W., J.S. and E.J. designed research; X.W. performed research; X.W. and G.Z. analyzed data; X.W., J.S. and E.J. wrote the paper.

Abstract

Previous studies have demonstrated that information about current task demands or goal states can be decoded within regions of the multiple demand network (MDN), which is thought to support cognitive flexibility. However, the contribution of the default mode network (DMN), which is frequently associated with automatic aspects of cognition, remains unclear. In this study, we presented a semantic feature matching task, in which participants were asked to focus on specific features of concepts (colour, shape or size) according to the instructions on each trial. In line with previous findings, regions of MDN were found to represent current goal information, as specified by the task instructions; furthermore, we found that regions of DMN, within angular gyrus and posterior cingulate cortex, also represented the goal state. Our results therefore suggest that DMN supports flexible memory retrieval alongside MDN.

Introduction

Human cognition is highly flexible, enabling us to select appropriate external perceptual features or information from memory according to our current goals. This flexibility is supported by the multiple demand network (MDN) (Duncan, 2010; Duncan & Owen, 2000): neurons within MDN regions in prefrontal and parietal cortex show adaptive coding of task-relevant objects, features and categories. In addition, activation patterns in MDN can classify task-relevant information (Bracci, Daniels, & Op De Beeck, 2017; Cole, Ito, & Braver, 2016; Loose, Wisniewski, Rusconi, Goschke, & Haynes, 2017; Qiao, Zhang, Chen, & Egner, 2017; Waskom, Kumaran, Gordon, Rissman, & Wagner, 2014).

While the role of MDN in representing current task demands is relatively uncontroversial, the contribution of default mode network (DMN) is less clear. DMN was originally characterised as "task-negative" (Shulman et al., 1997)(Shulman et al., 1997)(Shulman et al., 1997)(Shulman et al., 1997)(Shulman et al., 1997) as it tends to deactivate during demanding tasks. Regions in this network show a stronger response during more automatic aspects of cognition (Vatansever, Menon, & Stamatakis, 2017). Nevertheless, recent research suggests DMN plays an active role in controlled cognition and adaptive flexibility (Andrews-Hanna, 2012; Crittenden, Mitchell, & Duncan, 2015), especially in tasks that involve memory retrieval (Spreng et al., 2010; Vatansever et al., 2017). It can show a stronger response to memory than perceptual decisions, particularly when these involve meaningful items, and even when the memory task is harder (Murphy et al., 2019). DMN maintains detailed task representations in working memory (Sormaz et al., 2018; Turnbull et al., 2019) and it is engaged when participants are preparing for a task following a cue that specifies the instructions (Crittenden et al., 2015; Smith et al., 2018) and when participants are applying rules from memory during a learned task (Vatansever et al., 2017).

In line with this contribution of DMN to memory-guided cognition, this network overlaps with the semantic network (Humphreys, Hoffman, Visser, Binney, & Lambon Ralph, 2015; Wirth et al., 2011), particularly in left angular gyrus (AG) (Seghier, 2013). Word fluency elicits greater DMN activity and stronger within-network functional connectivity compared with phonemic fluency (Shapira-Lichter, Oren, Jacob, Gruberger, & Hendler, 2013). DMN is significantly less deactivated, relative to rest, for semantic tasks compared to perceptual or phonological tasks (Binder et al., 1999; 2009; Humphreys et al., 2015; Seghier et al., 2010;

Wirth et al., 2011) and shows this pattern when task demands are matched (Wirth et al., 2011) and even when the non-semantic task is easier (Seghier et al., 2010) or when the task demands are regressed out (Binder et al., 2005). These findings suggest the engagement of the DMN in semantic memory processing is not only due to the effects of general difficulty. The involvement in semantic processing of DMN motivated us to explore whether DMN represents goal information during a semantic memory retrieval task.

Previous studies often used perceptual tasks, such as figure feature matching, in which participants rely on information in the environment to drive an appropriate response (Bugatus, Weiner, & Grill-Spector, 2017; Jackson & Woolgar, 2018; Loose et al., 2017; Waskom et al., 2014) or conducted multivariate analysis within regions of MDN (Bracci et al., 2017; Crittenden, Mitchell, & Duncan, 2016; Vaziri-Pashkam & Xu, 2017; Woolgar, Jackson, & Duncan, 2016). Therefore, it remains unknown whether regions outside MDN, also represent goal information when memory retrieval is necessary. In this study, we examined which brain areas can classify goal information, using multivariate fMRI analyses of a semantic feature matching task. We conducted whole brain classification analysis without predefining ROIs, allowing us to reveal all the potential regions that represent goal information. To examine the networks of these regions belong to, we chose these regions as seeds and then conducted resting state functional connectivity analysis. We compared their resting state functional connectivity patterns to large scale networks defined by a resting-state parcellation of 1000 brains (Yeo et al., 2011). We also included our own localizer tasks that were used to define DMN and MDN and examined whether these regions overlap with the localizer results. To examine whether there was any heterogeneity among regions that represent goal information, we examined whether some areas that represent goal information can also represent category information while others do not. Our results indicate that goal information can be decoded in both MDN and DMN and lateral occipital cortex is the only region that represents both goal and category information.

Methods

Participants

The research was approved by the York Neuroimaging Centre and Department of Psychology ethics committees. 31 healthy adults were recruited from the University of York

(26 females; age: mean ± SD = 20.60 ± 1.68, range: 18 – 25 years). All participants were right-handed, native English speakers, with normal or corrected-to-normal vision and no history of psychiatric or neurological illness. All volunteers provided written informed consent. The data of one participant was incomplete (only attended one of two sessions) and was removed. Data in three runs of two participants were removed because of low accuracy (< 3SD).

An independent dataset including 211 participants (129 females; age: mean ± SD = 20.85 ± 2.44, range: 18 – 31 years) was used for the resting-state analysis. This dataset was previously reported by (Ho et al., 2019; Sormaz et al., 2017; Vatansever et al., 2017; Wang et al., 2018).

Procedure

Participants completed two fMRI sessions: in the first session, they performed a semantic feature matching task to locate regions that represent goal information. In the second session, they completed localiser scans designed to identify regions of DMN and MDN, through a contrast of easy and hard spatial working memory and arithmetic tasks (from (Blank, Kanwisher, & Fedorenko, 2014; Fedorenko et al., 2011, 2013). A contrast of the hard versus easy versions of these tasks robustly activates MDN regions (Blank et al., 2014; Fedorenko et al., 2013), while the easy versus hard contrast activates DMN (Fedorenko et al., 2013; Leech et al., 2011; Mckiernan et al., 2003). These data were used to test the hypothesis that regions that represent goal information overlap with multiple demand and default mode areas.

Behaviour tasks

Feature matching task

Participants matched probe and target concepts (presented as words) according to a particular semantic feature (colour, shape or size), specified at the start of each trial in a rapid event-related design (Figure 1). We included three features (i.e. colour, shape and size). All the probe words belonged to one of three categories: animal, plant and tool. This gave generated nine combinations of goal feature and probe category. Unlike the probe words, the target words were drawn from a wider range of categories. Probe and target words were matched on word length (number of letters), word frequency (based on SUBTLEX-UK: Subtitle-based word frequencies for British English) (van Heuven, Mandera, Keuleers, & Brysbaert, 2014)Sub and word concreteness (Brysbaert, Warriner, & Kuperman, 2014) across conditions, respectively. The combination of feature and category led to 216 unique stimulus combinations (3 features × 3 categories × 36 exemplars) which were divided evenly into 4 runs. The order of runs and trials within each run was randomized across subjects. Each run lasted for 600 s. There was no feedback during the main experiment.

In order to maximize the statistical power of the rapid event-related fMRI data analysis, the stimuli were presented with a temporal jitter. The jittered inter-stimulus-intervals (ISIs) were randomized from trial to trial (Dale, 1999). The two inter-stimulus-intervals (between cue and probe, between probe and target) and inter-trial-interval (the jittered fixation at the beginning of each trail) were uniformly distributed across values from 1 to 3s. Each trial started with a jittered fixation. This was followed by the goal instruction period consisting of the presentation of a goal instruction cue at the centre of the screen for 1s followed by a second jittered fixation. This was followed by the probe stimulus period consisting of the presentation of the probe word for 1s followed by a third jittered fixation. Finally, the target was presented at the centre of the screen, triggering the onset of the decision-making period. The target remained visible until the participant responded, or for a maximum of 3s. Participants responded “yes” or “no” in response to each target word, with “yes” indicating that the feature being probed in that trial matched across the probe and target (i.e. the two concepts are typically the same colour). Both response time and accuracy were recorded.

A trial consisted of three events, which were analysed separately below: (1) A goal instruction which indicated the relevant feature for the trial, (2) a probe word, and (3) a target word, which indicated the task-relevant response. Based on these events, we separate each trial into three different time periods: a ‘feature goal instruction period’, a ‘probe word stimuli period’, and a ‘target word stimuli and response mapping period’ which allow us to explore the spatial dynamic of task representation.

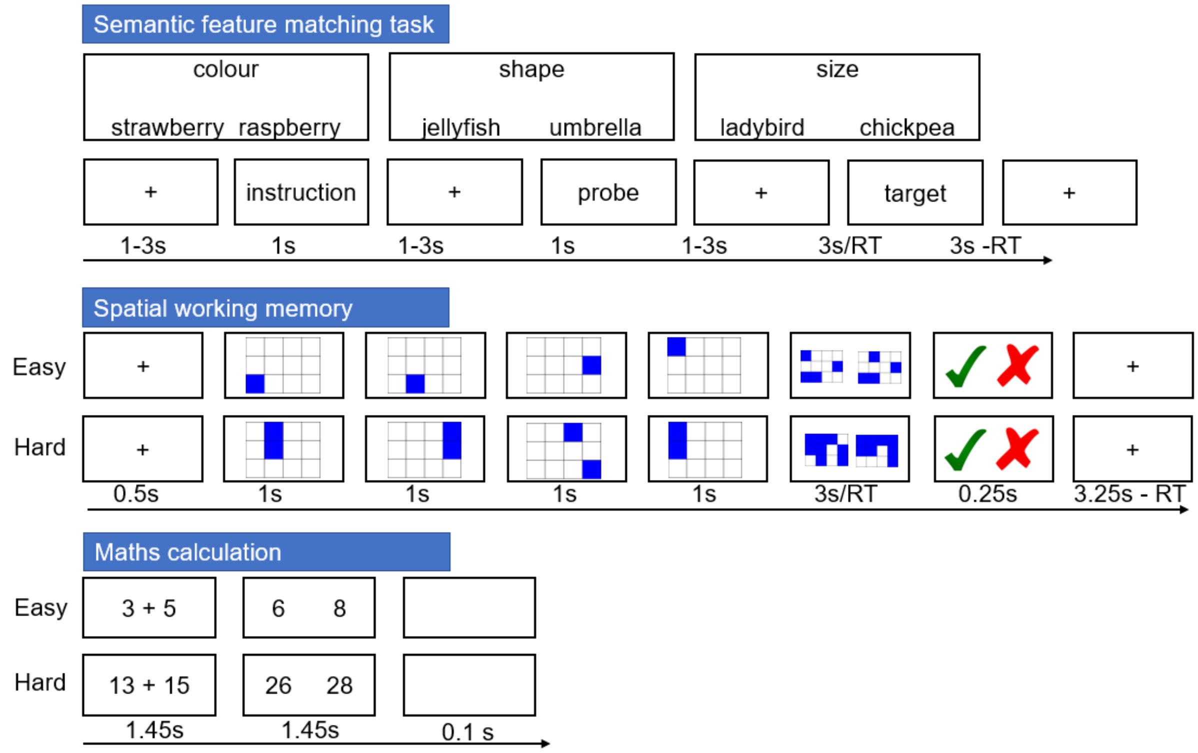


Figure 3-1: Illustration of semantic feature matching task, spatial working memory task and maths task.

Spatial working memory task

Participants had to keep track of four or eight sequentially presented locations in a 3×4 grid (Fedorenko et al., 2011), giving rise to easy and hard spatial working memory conditions. In both conditions, participants performed a two-alternative forced-choice task at the end of each trial to indicate the set of locations they just saw. The hard versus easy contrast has been previously shown to robustly activate MDN regions (Blank et al., 2014; Fedorenko et al., 2013). The reverse contrast, easy versus hard, robustly activates DMN regions (Mckiernan et al., 2003).

Stimuli were presented at the centre of the screen across four steps. Each of these steps lasted for 1s and presented one location on the grid in the easy condition, and two locations in the hard condition. Each stimulus was followed by a choice-selection step, which showed two grids side by side. One grid contained the locations shown on the previous four steps, while the other contained an incorrect set of locations, with one or two locations shown in the wrong place. Participants indicated their recognition of these locations in a two-alternative, forced-choice paradigm via a button press and feedback was immediately provided. Each run consisted

12 experimental blocks (6 blocks per condition and 4 trials in a 32 s block) and 4 fixation blocks (each 16s long), resulting in a total time of 448s.

Each task included two runs containing the two conditions, presented in a standard blocked design. Condition order was counterbalanced across runs and run order was counterbalanced across participants for each task.

Maths task

Participants added smaller or larger numbers, giving rise to easy and hard conditions. Participants saw an arithmetic expression on the screen and were given two numbers as choices. Each trial started with an arithmetic expression which lasted 1.45s and the following choices were presented for 1.45s. Each trial ended with a blank screen lasting for 0.1s. Each run consisted of 12 experimental blocks (with 4 trials per block) and 4 fixation blocks, resulting in a total time of 316s. Each task included two runs containing the two conditions, presented in a standard blocked design. Condition order was counterbalanced across runs and run order was counterbalanced across participants for each task. All the stimuli were presented using Psychopy (Peirce, 2007).

fMRI data acquisition

Structural and functional data were collected on a Siemens Prisma 3T MRI scanner at the York Neuroimaging Centre. The scanning protocols included a T1-weighted MPRAGE sequence with whole-brain coverage. The following MRI sequence parameters were used: acquisition matrix of 176 × 256 × 170 and voxel size $1 \times 1 \times 1\text{mm}^3$, repetition time (TR) = 2300 ms, and echo time (TE) = 2.26 ms. Functional data were acquired using an EPI sequence with a 80^0 flip angle and using GRAPPA with an acceleration factor of 2 in 3 x 3 x 4-mm voxels in 64-axial slices. The following parameters were used: 55 3-mm-thick slices acquired in an interleaved order (with 33% distance factor), TR = 3000ms, TE = 15ms, FoV = 192mm.

We used the resting state data from an independent sample (Ho et al., 2019; Vatansever et al., 2017; Wang et al., 2018). A 9-min resting state fMRI scan was collected during which participants were asked to passively view a fixation cross and not to think of anything in particular. Full details of scanning parameters are provided in (Ho et al., 2019).

MRI data pre-processing

Functional and structural data pre-processing was carried out using FMRIB's Software Library (FSL version 6, fsl.fmrib.ox.ac.uk/fsl/fslwiki/FEAT/). The T1-weighted structural brain images were extracted. Structural images were registered to the MNI-152 template using FMRIB's linear image registration tool (FLIRT). fMRI data pre-processing included motion correction, slice-timing correction, and high-pass filtering at 100s. Motion-affected volumes were detected and then were fully removed from the fMRI data (using scrubbing, (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012)).

All pre-processing steps for the resting state data were carried out using the SPM software package (Version 12.0) (https://www.fil.ion.ucl.ac.uk/spm) based on the MATLAB platform (Version 18a) (https://uk.mathworks.com/products/matlab.html). Pre-processing steps included (1) functional realignment and unwarp; (2) head motion correction; (3) slice-timing correction; (4) functional outlier scans detection for scrubbing; (5) functional indirect segmentation and normalization and (6) functional spatial smoothing using a 8mm FWHM of the Gaussian kernel. Full details of this analysis are provided in (Ho et al., 2019).

MRI data analysis

Univariate analysis

In order to do the time-resolved decoding analyses, we first performed a univariate analysis by building the general linear model (GLM) in each participant, fit separate models for each period (goal instruction, probe word and target word), and obtained the β value for each condition, for each period, for each run, in each voxel of the brain. Specifically, the resulting preprocessed unsmoothed data were analysed using first-level FEAT (v6.00; fsl.fmrib.ox.ac.uk/fsl/fslwiki) in each participant's native anatomical space. Parameter estimates of BOLD response amplitude were computed using FILM, with a GLM that included temporal autocorrelation correction, and six motion parameters as nuisance covariates.

Incorrect trials were excluded from all analysis. The univariate analysis was conducted separately in a time-resolved manner, which means only corresponding time points of each period of correct trials were modelled, other time points were included as regressors of no interest. Since there were differences in response time across conditions during target periods, the influence of response time was removed in a trialwise manner by creating the primary regressors in the model using the actual duration of targets of each trial, rather than a fixed duration across trials. The response to each feature was contrasted against rest. To increase the statistic power, we created more data points by randomly but evenly dividing all the correct trials of each feature of each run into 3 sub-datasets and then run the univariate analysis. This resulted in three brain patterns per feature per period per run and then z-scored within each run at each voxel for further classification analysis. We repeated the above analysis to get three brain patterns per category for the probe word per run and then z-scored within each run at each voxel for further classification analysis. Therefore, there were 27 total brain patterns (9 for each of three feature/category classes) to train the classifier and 9 total brain patterns (3 for each of three feature/category classes) to test the classifier each time.

Decoding analysis of goal information

We firstly did a whole brain decoding analysis to investigate which regions represent goal information. We extracted the z-scored β-values for each feature for each period for training and testing. Classifiers were trained and tested on individual subject data transformed into MNI standard space. Classification training and testing were done using a leave-one-run-out cross-validation strategy. We tested the discriminability of patterns for the three features for each period using whole brain searchlight with a radius of 6mm (number of voxels = 123) (Kriegeskorte, Goebel, & Bandettini, 2006) with linear support vector machines (SVMs) (Vapnik & Chapelle, 2000) (LIBSVM, http://www.csie.ntu.edu.tw/~cjlin/libsvm/) implemented within PyMVPA (Hanke et al., 2009). Classification accuracy for each sphere was assigned to the sphere's central voxel, in order to produce accuracy maps. The resulting accuracy maps were then smoothed with a Gaussian kernel (6mm FWHM). We performed a group analysis as a second-level analysis based on pattern-information maps to determine whether accuracy maps were above change-levels (Kriegeskorte et al., 2006). Individual information maps were submitted to a nonparametric one-sample t test to identify regions that support above-chance level classification (accuracy > 0.33) across all participants. Voxel inclusion was set at z = 2.3 with a cluster significance threshold at FWE-corrected p < .05.

Decoding analysis of category information

To examine whether there are any regions that represent goal information also represent category information, we did a whole brain decoding analysis to investigate which regions represent category information and then examined whether they overlap with regions that represent feature information. We extracted the z-scored β-values for each category for only probe period for training and testing because only probe words were chosen from three categories, (e.g., animal, tool and plant). Classifiers were trained and tested on individual subject data transformed into MNI standard space. Classification training and testing were done using a leave-one-run-out cross-validation strategy. We tested the discriminability of patterns for the three categories for the probe period using whole brain searchlight with a radius of 6mm (number of voxels = 123) (Kriegeskorte, Goebel, & Bandettini, 2006) with linear support vector machines (SVMs) (Vapnik & Chapelle, 2000) (LIBSVM, http://www.csie.ntu.edu.tw/~cjlin/libsvm/) implemented within PyMVPA (Hanke et al., 2009). Classification accuracy for each sphere was assigned to the sphere's central voxel, in order to produce accuracy maps. The resulting accuracy maps were then smoothed with a Gaussian kernel (6mm FWHM). We performed a group analysis as a second-level analysis based on pattern-information maps to determine whether accuracy maps were above change-levels (Kriegeskorte et al., 2006). Individual information maps were submitted to a nonparametric one-sample t test to identify regions that support above-chance level classification (accuracy > 0.33) across all participants at threshold p < .05. Voxel inclusion was set at z = 2.3 with a cluster significance threshold at FWE-corrected p < .05.

Localizer task-evoked activation analysis

In the spatial working memory task and maths tasks, we examined the contrast of hard versus easy to define MDN regions and easy versus hard to define DMN regions. A grey matter mask was imposed for all the above analysis and the resulting clusters were corrected for multiple comparisons using Family-Wise Error (FWE) detection at a threshold of z > 3.1, p <

0.05. The whole brain analysis of localizer tasks allowed us to explore whether the regions that represent goal information overlap with DMN and MDN.

Resting state functional connectivity analysis

We conducted seed-based resting state analysis using the Conn functional connectivity toolbox (Version 17.f) (https://www.nitrc.org/projects/conn) (Whitfield-Gabrieli & Nieto-Castanon, 2012). We used brain regions in which the goal information was represented as seeds during each period. The averaged functional connectivity map derived from each seed was generated and the resulting clusters were multiple comparison corrected via FWE detection technique at a threshold $z > 3.1$, $p < .05$. Brain networks were visualized using BrainNet Viewer (Xia, Wang, & He, 2013).

Results

Behaviour results

There was no significant difference in accuracy across trials probing the three feature goals ($F(2, 213) = 1.027$, $p < .360$). However, there were significant differences in response time ($F(2, 213) = 12.444$, $p < .0005$): there was no significant difference between shape and size ($p < .163$), but colour decisions were faster than both shape ($p < .006$) and size decisions ($p < .0005$). There were no significant differences in accuracy ($F(2, 213) = 0.688$, $p < .504$) or response times across categories ($F(2, 213) = 0.742$, $p < .478$) (Figure 3-2).

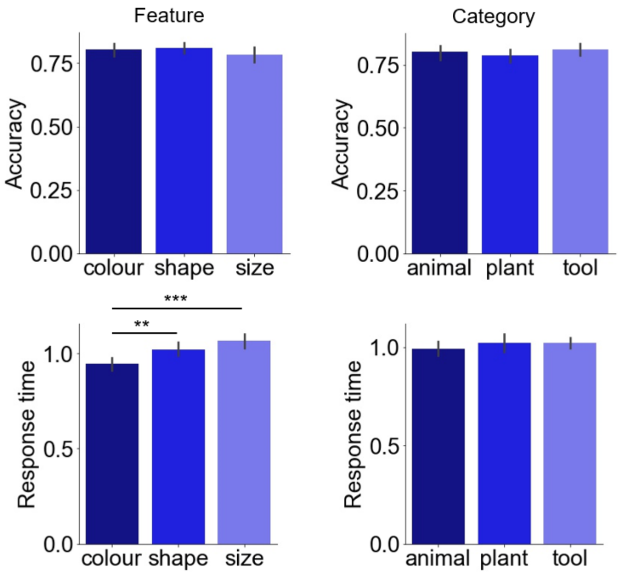


Figure 3-2. The behaviour performance of semantic feature matching task.

Feature decoding results

We did time-resolved decoding analyses. A trial consisted of three events, which were analysed separately below: (1) A goal instruction period (when an instruction word, specifying the feature to match, (2) a probe word stimulus period from the onset to the offset of the probe and (3) a target decision word period, lasting from target onset until a button press response or the maximum time limit (3s).

Goal-related information could be decoded during the instruction phase in bilateral calcarine sulcus and lingual gyrus ($p < .05$) (decoding accuracy: 0.36) (Figure 3-3A). After the probe word was presented, goal-related information could be decoded in left inferior frontal gyrus, left superior parietal lobule (SPL), left inferior parietal sulcus (IPS), AG, left lateral occipital cortex (LOC), and left pMTG ($p < .05$) (decoding accuracy: 0.35) (Figure 3-3B). After the target word was presented, goal-related information could be decoded in bilateral SPL, bilateral IPL, bilateral AG, bilateral precuneus cortex, bilateral posterior cingulate cortex (PCC), left posterior inferior temporal gyrus and left pMTG (decoding accuracy: 0.36) ($p < .05$) (Figure 3-3C).

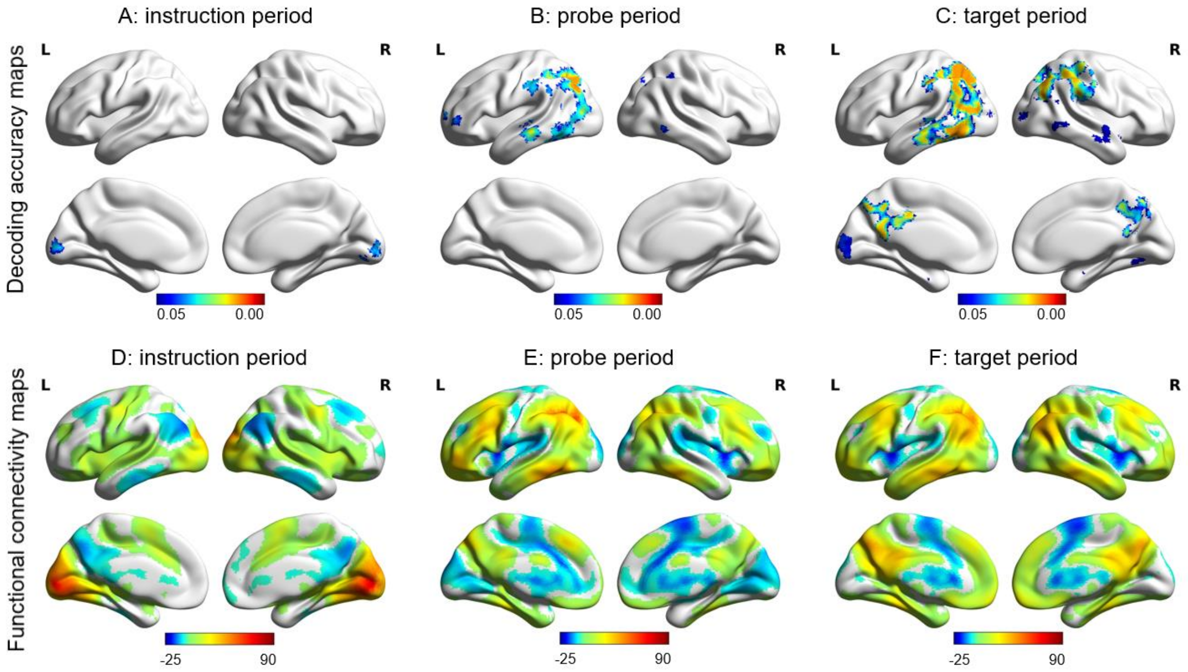


Figure 3-3: Regions that represent feature information for each period (top panel) (FWE-corrected, $z = 2.3$, $p < .05$), and the resting state functional connectivity maps with regions that represent goal information as seeds during each period (bottom panel) (FWE-corrected, $z = 2.3$, $p < .05$).

Regions representing feature information overlap with MDN or DMN

To investigate whether regions that represent goal information overlap with MDN or DMN, we compared regions representing goal information to large scale networks defined by a resting-state parcellation of 1000 brains (Yeo et al., 2011). Regions representing goal information during probe period mainly overlap with dorsal attention, default mode network and frontoparietal network, while during target period mainly default mode, dorsal attention and frontoparietal network (Figure 3-4).

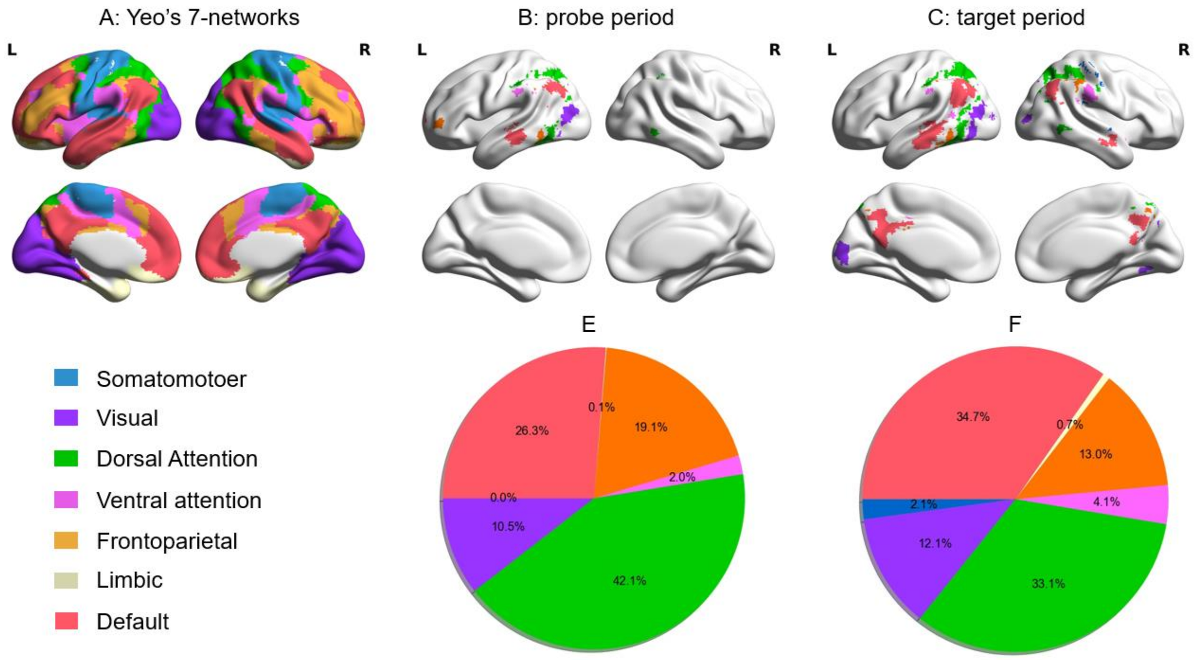


Figure 3-4. Regions representing goal information overlap with DMN and MDN (dorsal attention and frontoparietal) defined by (Yeo et al., 2011). The seven large scale networks identified by (Yeo et al., 2011)(A). The overlapping regions between regions representing goal information and the large scale networks during probe period (B) and target period (C). The pie charts highlight the percentage of voxels within each decoding map fall within each of the seven large scale networks identified by Yeo et al. (2011) during probe period (E) and target period (F).

We also compared feature decoding results to DMN and MDN defined by our own localizer tasks. Regions within DMN and MDN were defined in the same participants using functional localisers. These were contrasts of easy and hard spatial working memory and maths judgements taken from Fedorenko et al. (2011). Consistent with previous findings, DMN regions (showing a stronger response to easy versus hard trials in either task) included posterior cingulate cortex, medial prefrontal cortex, angular gyrus and lateral anterior temporal lobes bilaterally. In contrast, MDN regions (hard versus easy) included inferior frontal sulcus, premotor cortex, intraparietal sulcus, and lateral occipital cortex (FWE-corrected, z=3.1, p<.05) (Figure 3-5A). The regions that represent goal information overlap with MDN and DMN during probe (Figure 3-5C) and target period (Figure 3-5D).

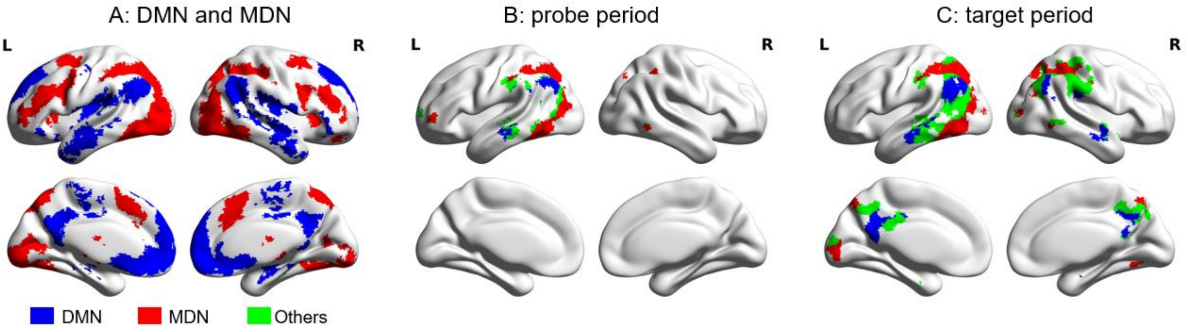


Figure 3-5. Regions representing goal information overlap with DMN and MDN defined by the localizer tasks. DMN and MDN defined using the localizer tasks (A). The overlapping regions between regions representing goal information and DMN and MDN during probe period (B) and target period (C).

<u>Resting state functional connectivity results</u>

The regions from feature decoding analysis during each period were used as seeds to construct the whole brain resting state functional connectivity pattern. We found the bilateral calcarine sulcus that represent feature information during clue period showed stronger functional connectivity with extensive regions of other sensory-motor regions, including bilateral visual areas, bilateral auditory areas and bilateral premotor areas (FWE-corrected, p <.05) (Figure 3-3D). Regions that represent feature information during probe period, including left SPL, IPS, LOC, AG showed stronger functional connectivity with extensive regions of MDN, including bilateral MFG, IFS, LOC, SPL, IPS, pre-SMA, and some regions of DMN, including bilateral AG and PCC (FWE-corrected, p <.05) (Figure 3-3E). Regions that represent feature information during target period, including left SPL, IPS, bilateral AG, bilateral PCC, left MTG, showed stronger functional connectivity with extensive regions of DMN, including bilateral AG, PCC, anterior temporal lobe, ACC and extension regions of MDN, including bilateral middle frontal gyrus, inferior frontal sulcus, LOC, SPL, IPS (FWE-corrected, p <.05) (Figure 3-3F).

<u>Category decoding analysis</u>

One tiny clusters in the left hemisphere were found to be sensitive to categories of the probe word: left LOC (Figure 3-6A) (decoding accuracy = 0.36). It overlaps with the regions that represent goal information during target period (Figure 3-6B).

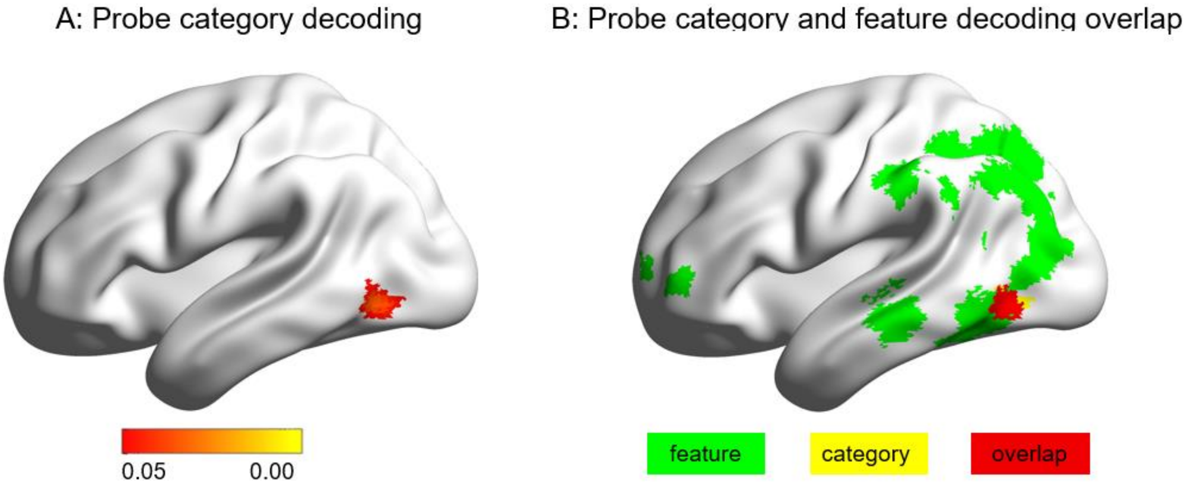


Figure 3-6: Region that represents category information. (FWE-corrected, z = 2.3, p <.05) (A) and it overlaps with regions that represent goal information (B).

Discussion

Prior studies of goal representation typically use stimuli that do not activate long-term memory or limit their analysis within regions of MDN. Few studies have examined the role of DMN in goal representation when memory is relevant to task performance. In this study, we used a semantic feature matching task, in which participants need to integrate external cue and internal memory information. We replicated previous findings that regions of MDN represent goal information. Furthermore, we found that regions of DMN, such as AG and PCC, also represent goal information, suggesting that DMN supports the flexibility of memory retrieval by updating goal information. We also found some regions can only represent goal information while OTC represents both goal information and category information, suggesting that it not only represents invariant visual feature but also is modulated by the task.

It is widely reported that increased activity in the DMN during challenging cognitive-control tasks was related to the intrusion of task-unrelated thoughts that interfere with functioning of the MDN and thus impair performance (Christoff, Gordon, Smallwood, Smith, & Schooler, 2009; Weissman, Roberts, Visscher, & Woldorff, 2006b; Wen, Liu, Yao, & Ding, 2013). However, recent evidence suggests that DMN is important when cognition is guided by representations from memory (Crittenden et al., 2005; Smith et al., 2018; Vatansever et al., 2017). DMN showed stronger activation and stronger within-network functional connectivity during mnemonic word fluency relative to phonemic fluency (Binder et al., 1999; 2009; Humphreys et al., 2015; Seghier et al., 2010; Shapira-Lichter et al., 2013; Wirth et al., 2011). DMN activates more strongly and the transient increases in activity facilitates working memory performance when access to internal mental representations which is congruent with task goals (Spreng et al., 2014). These findings suggest that DMN supports controlled cognition. Our study found that the goal information can be decoded within regions of DMN, providing further evidence that DMN supports controlled cognition.

In line with this view, DMN regions exhibit the greatest geodesic distance along the cortical surface—and are precisely equidistant—from primary sensory/motor morphological landmarks and at the end of the principal gradient revealed by the decomposition of connectivity data in humans and the macaque monkey (Margulies et al., 2016). It has been observed that DMN modulates stimulus-selective visual regions in a way that predict performance (Chadick & Gazzaley, 2011; Heekeren, Marrett, Bandettini, & Ungerleider, 2004). Chadick and Gazzaley (2011) found that DMN (i.e. medial PFC and PCC) was functionally coupled with the visual cortical areas processing irrelevant stimuli, and the coupling was predictive of task performance. Heekeren and colleagues found that activity within the one region of DMN, left dorsolateral prefrontal cortex, covaries with the difference signal between face- and house-selective regions in the ventral temporal cortex and the coupling predicts behavioural performance in the categorization task in which subjects decide whether an image presented is a face or a house (Heekeren, Marrett, Bandettini, & Ungerleider, 2004b). These findings suggest that DMN modulates stimulus-selective visual regions and the dynamic interaction between DMN and feature-selective visual regions might allow DMN represents goal information.

The representation of goal information in DMN might be achieved by its interaction with MDN. DMN and MDN are normally argued to show opposite response patterns (Anticevic et al., 2012), with DMN being involved in automatic information processing (Vatansever et al., 2017) and MDN being involved in demanding tasks (Fedorenko et al., 2013). It has been proposed that DMN is responsible for automatic information processing because DMN often shows stronger activation for easy or highly practiced conditions relative to a harder condition (Mckiernan et al., 2003; Humphreys et al., 2015). MDN often shows stronger activation for hard conditions relative to the easy conditions (Duncan, 2010; Fedorenko et al., 2013). DMN and MDN often show negative functional connectivity at rest (Fox et al., 2005) and during tasks (Fornito, Harrison, Zalesky, Simons, & Analyzed, 2012). Furthermore, greater functional integration within the DMN (Hampson, Driesen, Skudlarski, Gore, & Constable, 2006) and greater anticorrelation between DMN and MDN (Kelly, Uddin, Biswal, Castellanos, & Milham, 2008) are both associated with improved behavioural performance when attention is directed externally. This evidence suggests that the functions of DMN and MDN are in opposition. However, recent evidence revealed that DMN and MND do not always show anticorrelation at rest and DMN and MDN can reconfigure their functional architecture in a context-dependent manner (Beaty, Benedek, Kaufman, & Silvia, 2015; Kelly, Uddin, Biswal, Castellanos, & Milham, 2008; Elton & Gao, 2015; Krieger-Redwood et al., 2016). For example, at rest, the dorsal PCC, a core region of DMN, shows functional connectivity with both the DMN and MDN (Leech et al., 2011). One subnetwork of MDN shows stronger intrinsic connectivity with DMN (Dixon et al., 2018). PCC, one of core DMN hubs (Zhao et al., 2017), showed increased connectivity with left medial temporal lobe memory system during more automated information processing, while increased connectivity with MDN during tasks that depend on the maintenance or extended evaluation of information (Andrews-Hanna, Smallwood, & Spreng, 2014; Dixon et al., 2017; Spreng et al., 2010; Vatansever, Menon, Manktelow, Sahakian, & Stamatakis, 2015; Vatansever et al., 2017), in a way that predicted performance (Beaty et al., 2015; Elton & Gao, 2015; Fornito et al., 2012; Krieger-Redwood et al., 2016). DMN showed increased cooperation with frontoparietal network when memory retrieval is required (Fornito et al., 2012; Spreng et al., 2010) and the increased cooperation facilitates rapid memory recollection (Fornito et al., 2012). In addition, higher task-state DMN-MDN dynamic functional connectivity associates with greater cognitive flexibility (Douw, Wakeman, Tanaka, Liu, & Stufflebeam, 2016). This enhanced cooperation is facilitated by dynamic, context-dependent reconfiguration of the DMN into core and transitional modules, with the latter supporting greater functional integration between the DMN core and frontoparietal areas. In facilitating these dynamic shifts of functional network architecture, the PCC seems to act as a critical information processing bottleneck, representing a major hub of the transitional DMN module while also retaining high functional integration with other regions. This is consistent with the finding that PCC is a hub and then flexibly switches its connectivity pattern. Ventral PCC showed high interaction with other DMN regions at low task demands, while high interaction with MDN at high task demands, which is consistent with its role in modulating the dynamic interaction between these two networks and controlling the efficient allocation of attention (Leech et al., 2011; Utevsky, Smith, & Huettel, 2014). This may explain why we found bilateral PCCs represent goal information. The dynamic interaction between DMN and MDN might allow DMN represents goal information like MDN.

Our finding that both DMN and MDN can represent goal information suggests that there might not be a sharp functional distinction between DMN and MDN. Following previous studies that have demonstrated that MDN represents task information (Bracci et al., 2017; Cole et al., 2016; Loose et al., 2017; Qiao et al., 2017; Waskom et al., 2014), recent evidence (Smith, Mitchell, & Duncan, 2018a) reveals that DMN can represent task information when the instructions of the tasks are complex and participants need to memorize them before the tasks and then retrieve them when starting the corresponding task. Our current study reveals that DMN can represent task goals when participants have to maintain the goal after the goal disappears and then apply the goal, suggesting that these networks may support overlapping functions (at least in some contexts). This evidence suggests DMN and MDN can show functional similarity, allowing the flexible interactions between the DMN and MDN under different task conditions to cope with changing environmental demands.

It is widely known that most regions of MDN can extract salient task-relevant visual information to produce a timely and appropriate action. However, whether OTC represents task, or object, or both is under debate. One point is that OTC is an invariant visual processing system which more faithfully reflect the quality of visual input that is general as well as context and task invariant (Xu, 2018a, 2018b). This point is supported by OTC encodes task-independent object properties or category, and task has small effects on the overall object information (Bracci et al., 2017; Bugatus et al., 2017). However, other studies found that behavioural goals directly impact object representations in the ventral visual pathway, producing reduced object decoding across tasks and strongly supporting a recurrent interactive view of visual object processing (Harel, Kravitz, & Baker, 2014). To resolve the debate, we investigated whether it was the same visual processing region represents goal information and category information using the same stimuli. We found that both goal and category information could be decoded in OTC, supporting the interactive view of visual object processing.

To sum, by using a semantic feature matching task and doing the multivariate analysis at the whole brain level, we found that goal information could be decoded in regions of both MDN and DMN, suggesting that DMN plays an important role in flexible semantic memory retrieval. We investigated whether it was the same visual processing region represents goal information and category information. We found that both goal and category information could be decoded in OTC, supporting the interactive view of visual object processing.

Chapter 4 : A gradient from memory-based to novel cognition: graded transitions from default mode to executive cortex

Declaration:

The study presented in Chapter 4 is a manuscript that is still in preparation for publication (see reference listed below), which contains original work completed by the author under the supervision of Dr.Elizabeth Jefferies and Dr. Jonathan Smallwood.

Wang, X., Margulies, D., Smallwood, J., Jefferies, E., A functional gradient for semantic cognition: graded transitions from default mode to executive cortex. Manuscript in preparation for publication.

Author contributions: X.W., M.D., J.S. and E.J. designed research; X.W. performed research; X.W. analyzed data; X.W., M.D., J.S. and E.J. wrote the paper.

Abstract

Human cognition is flexible, ranging from highly familiar situations (when cognition is supported by long-term memory) to novel scenarios (when cognition is driven by current goals). Traditionally, these aspects of cognition are ascribed to dichotomous neural systems supported by default mode (DMN) and multiple-demand (MDN) networks. In reality, however, most situations are neither completely familiar, nor entirely novel, highlighting the need to understand how cognition is constrained in a graded fashion. A contemporary account proposes a connectivity gradient along the cortical surface that captures the transition from heteromodal DMN, through MDN regions, to unimodal regions. We asked whether brain responses changed linearly along the connectivity gradient as we parametrically varied the match between task demands and global semantic similarity within a feature matching task. At one end of this 'task gradient', probe and target words shared both goal-relevant and irrelevant features, such that task requirements were well-aligned with long-term memory; at the other end, items only shared the goal-relevant feature. We found the brain's response to the semantic task varied systematically with the task gradient along the connectivity gradient. This graded functional change was seen in multiple brain regions and in individual runs within individual brains, suggesting it was not a product of spatial averaging. The peak response for semantic control in previous studies fell midway between DMN and MDN, showing these graded functional transitions capture the layout of networks involved in semantic processing.

Introduction

At the heart of adaptive cognition is flexibility – the capacity to focus on particular mental representations and to utilise distinct processes at different points in time, in a way that is appropriate for the circumstances. This flexibility allows us to efficiently deal with a spectrum of situations – from those which occur commonly, to others which we have not encountered previously. Although long-term memory can efficiently guide familiar decisions, in novel situations, cognition must be shaped by dynamically-varying representations of current goals (Kahneman, 2003; Tversky & Kahneman, 1974). Traditionally, these different facets of cognition have been ascribed to dichotomous neural systems. Regions within the lateral anterior temporal lobe and angular gyrus, allied to the default mode network (DMN), are important when the knowledge required by a task is readily available within long-term memory (Badre & Wagner, 2007; Bemis & Pylkkänen, 2013; Davey et al., 2016; Humphreys & Lambon Ralph, 2015; Humphreys & Ralph, 2017; Lau, Gramfort, Hämäläinen, & Kuperberg, 2013; Teige et al., 2018; Wagner, Paré-Blagoev, Clark, & Poldrack, 2001). In contrast, novel decisions are supported by the multiple demand network (MDN), including the inferior frontal sulcus, intraparietal sulcus, and pre-supplementary motor area, which are thought to maintain current goals (Duncan, 2010; E. Fedorenko, Duncan, & Kanwisher, 2013).

Many of the decisions we face are neither completely familiar, nor entirely novel, highlighting the need to understand how cognition is constrained in a graded manner. Semantic cognition extends along the length of this psychological continuum, from the efficient and largely automatic retrieval of strongly-encoded aspects of long-term memory, to controlled goal-driven semantic retrieval tailored to the task-demands. At the same time, contemporary accounts of cortical organisation suggest that intrinsic connectivity and functional organisation may change gradually and systematically along the cortical surface (Huntenburg, Bazin, & Margulies, 2018; Margulies et al., 2016). Margulies et al. (Margulies et al., 2016) recently described the principal gradient of the human brain, recovered through diffusion embedding techniques that decompose connectivity into its spatial components; this extends from primary sensorimotor areas at one end, through attention and executive areas of MDN, to heteromodal DMN regions at the opposite end. This principal gradient correlates with physical distance along the cortical surface from sensory-motor regions. Moreover, since there are multiple DMN peaks in the brain, there are multiple spatial gradients extending along the cortical surface from the DMN, through regions of the MDN, to sensory-motor regions – with previous studies describing this pattern within temporal, medial and lateral prefrontal cortex (Badre &

Nee, 2018; Jackson, Bajada, Ralph, & Cloutman, 2019; Margulies et al., 2016; Nee & D'Esposito, 2016; Ralph, Jefferies, Patterson, & Rogers, 2017). In this way, the principal connectivity gradient is thought to explain the topographical organisation of the brain, with transitions between networks in multiple cortical zones following the same orderly sequence.

Motivated by these insights, we considered whether functional variation along the cortical surface, captured by the principal connectivity gradient (Margulies et al., 2016), would relate to a task gradient corresponding to the extent to which current goals align with, or deviate from, the structure of semantic knowledge. Semantic tasks recruit both DMN and MDN regions, yet the peak response during semantic decisions often falls within regions in between these networks associated with semantic control, such as the left inferior frontal gyrus, posterior middle temporal gyrus and dorsal anterior cingulate cortex (Noonan, Jefferies, Visser, & Lambon Ralph, 2013). These peaks typically fall outside the MDN, and are adjacent to, yet distinct from, the DMN (Gonzalez Alam, Murphy, Smallwood, & Jefferies, 2018; Humphreys & Ralph, 2017; Noonan et al., 2013; Wang et al., 2018). Semantic control regions also show structural and functional connectivity to regions implicated in conceptual representation (anterior temporal lobes) and domain-general executive control (inferior frontal sulcus), suggesting that integration of long-term conceptual knowledge with currently-relevant goals might support flexible patterns of semantic retrieval (Davey et al., 2016). This raises the possibility that there might be an orderly arrangement of networks related to semantic cognition along the connectivity gradient described by Margulies et al. (Margulies et al., 2016), from DMN, through semantic control regions, to MDN.

We created a task gradient that parametrically varied the extent to which goal-driven semantic retrieval was aligned with the structure of long-term semantic knowledge. Participants were asked to decide if two words, presented successively, shared a specific feature (colour, shape or size). We varied the number of features that the two items shared parametrically, from situations where only the goal-relevant feature was shared (e.g., colour: tomato and post-box) to trials in which nearly all features were shared (e.g., colour: raspberry and strawberry), even though these features were largely irrelevant to the goal. We measured neural activity in thirty participants using functional magnetic resonance imaging (fMRI) to establish whether there is a graded change in the neural response along the connectivity gradient described by Margulies et al. (Margulies et al., 2016), such that globally-related feature matching tasks generate stronger responses in regions of the DMN, while feature matching judgements that require the retrieval of specific visual features generate stronger responses in MDN and sensorimotor regions. In a separate session, we used task localisers to characterise the spatial organisation of DMN and MDN and to assess whether semantic control peaks are located at the juxtaposition of these networks in a way that is captured by the connectivity and task gradients.

Methods

Participants

The research was approved by the York Neuroimaging Centre and Department of Psychology ethics committees. 31 healthy adults were recruited from the University of York (26 females; age: mean ± SD = 20.60 ± 1.68, range: 18 – 25 years). All participants were right-handed, native English speakers, with normal or corrected-to-normal vision and no history of psychiatric or neurological illness. All volunteers provided written informed consent. The data of one participant was incomplete (only attended one of two sessions) and was removed.

Design and tasks

Participants completed a semantic feature task, in which they had to match probe and target concepts (presented as words) according to particular features (colour, shape or size), specified at the start of each trial in a rapid event-related design. The degree of feature overlap between the probe and target was parametrically manipulated: there were some trials in which there was little need to constrain retrieval, since the items shared many features in addition to the goal-relevant feature (e.g., strawberry and raspberry), while others had higher control requirements because they only shared the critical feature (e.g. tomato and postbox in a colour trial) (Figure 4-2). The global similarity in features between probe and target (i.e. global feature similarity rating) was rated by an independent group (N=30) on a 5-point Likert Scale and the resulting global similarity ratings were evenly distributed from 1 to 5.

We used established localiser tasks to define functional networks of interest, which involved comparisons of visually-presented words and nonwords to identify the semantic network, and comparisons of easy and hard spatial working memory and maths decisions to define DMN and MDN (from (Fedorenko et al., 2011, 2013)) (Figure 4-1). Full details about these tasks are provided in the SI materials. All the stimuli were presented using Psychopy (Peirce, 2007).

Semantic feature matching task

Participants were asked to match probe and target concepts (presented as words) according to a particular semantic feature (colour, shape or size), specified at the start of each trial in a rapid event-related design. In this task, we parametrically manipulated the extent to which semantic knowledge must be shaped to suit the demands of the task to establish if there was a shift in the univariate response along the gradient as the pattern of semantic retrieval required by the task deviated more substantially from the structure of conceptual knowledge. Specifically, we parametrically varied the featural overlap between the probe and target, according to global feature similarity ratings as assessed by ratings from a separate group of participants. For example, in colour-matching, strawberry – raspberry share many features (not just colour), while tomato – postbox share few features besides colour. This parametric design allowed us to model the effect of global feature similarity on the BOLD response during the semantic feature matching task and examine if there are orderly or abrupt transitions in patterns of cortical recruitment as the global feature similarity rating decreases.

Each word referred to an object that was associated with a typical feature. The global similarity in features between probe and target (i.e. global feature similarity rating) was rated by an independent group on a 5-point Likert Scale. The global similarity ratings were evenly distributed from 1 to 5. This group of participants also rated whether the probe and target shared the specific similar feature, such as colour. We controlled for word length (number of letters), word frequency (based on SUBTLEX-UK: Subtitle-based word frequencies for British English) and word concreteness according to a recent large-scale study in which subjects rated words on a 5 point scale (Brysbaert, Warriner, & Kuperman, 2014) to ensure the difficulty effect is mainly driven by the global similarity of probe and target. We used a behaviour efficiency metric that combined response time with accuracy to account for potential speed-accuracy trade-offs: i.e., the mean RT for correct responses was divided by the proportion of correct responses (Townsend and Ashby., 1983) and we reversed this measure so that higher efficiency scores would correspond to better performance like other researchers did (Wang et al., 2018; Wei et al., 2012). There were no correlation between behaviour performance and word length ($r = -0.15$, $p = 0.07$) and word frequency ($r = 0.14$, $p = 0.11$). There was significant correlation between word concreteness and behaviour performance ($r = 0.19$, $p = 0.03$). However, the global similarity ratings were significantly correlated with behaviour performance after regressing out these control variables (r = 0.32, p = 0.0001), indicating global feature similarity ratings are a good predictor of the difficulty of semantic retrieval in this task context.

In order to maximize the statistical power of the rapid event-related fMRI data analysis, the stimuli were presented with a temporal jitter and the jittered inter-stimulus-intervals (ISIs) were randomized from trial to trial (Dale, 1999). The two ISIs and inter-trial-interval (ITI) were uniformly distributed across values from 1 to 3s. Each trial started with a fixation which was followed by a clue presented at the centre of the screen for 1s. Then the clue disappeared and the second fixation was presented. After that the probe was presented at the centre of the screen for 1s and then the probe disappeared and a fixation was presented again. Finally, the target was presented at the centre of the screen, triggering the onset of the decision-making period. The target remained visible until the participant responded, or for a maximum of 3 s. Both response time and accuracy were recorded.

There were 216 trials in total, presented in 4 runs of 54 trials each. Each run lasted for 600 s. The global feature similarity was evenly distributed in each run. For each run, there were 18 trials for each feature and the probe and target of 12 trials shared similar feature. The order of runs and trials within each run was randomized across subjects.

Localizer tasks

To examine whether the orderly transitions between DMN, semantic control and MDN reflect a large-scale functional gradient which explains the macro-organisation of the cortex, three localizer tasks, for semantic processing, spatial working and maths were included to define the semantic network, DMN and MDN (adapted from Fedorenko et al., (2011)). We presented a spatial working memory task and a maths task, each with an easy and a hard condition to define the DMN and MDN (from (Fedorenko et al., 2011, 2013)). Regions showing stronger activation during hard trials of either task were defined as ROIs comprising the MDN network. Regions responding more strongly during easy trials in either task were defined as ROIs within DMN. A semantic control mask from a meta-analysis of task contrasts manipulating semantic control demands from Noonan et al. (2013) was chosen to define the semantic control network.

Each localizer task included two runs and two conditions, presented in a standard blocked design. Condition order was counterbalanced across runs and run order was counterbalanced across participants for each task.

Semantic localizer task

Subjects read sentences and lists of pronounceable nonwords, each followed by a probe test of recognition memory (present/absent judgment on a single probe word/nonword). The sentences versus nonword lists contrast has been previously shown to reliably activate semantic and syntax language regions and to be robust to the materials, task, and modality of presentation (Fedorenko et al., 2011; Fedorenko, Hsieh, Nieto-Castañón, Whitfield-Gabrieli, & Kanwisher, 2010; Mahowald & Fedorenko, 2016). Stimuli were presented at the centre of the screen, one word/nonword at a time, at the rate of 450ms per word/nonword. Each stimulus was preceded by a 100ms blank screen and followed by a probe word where subjects needs to decide whether the word has been presented within 2 s, for a total trial duration of 7.5s. Each run included 16 experimental blocks with 3 trials per block and 5 fixation blocks lasted for 14s. Each run lasted a total of 430 s.

Spatial working memory task

Participants had to keep track of four or eight sequentially presented locations in a 3×4 grid (Fedorenko et al., 2011), giving rise to easy and hard spatial working memory conditions. In both conditions, participants performed a two-alternative forced-choice task at the end of each trial to indicate the set of locations they just saw. The hard > easy contrast has been previously shown to robustly activate MDN regions (Blank et al., 2014; Fedorenko et al., 2013). The reverse contrast, easy versus hard, robustly activates DMN regions (Fedorenko et al., 2013; Leech et al., 2011; Mckiernan et al., 2003).

Stimuli were presented at the centre of the screen across four steps. Each of these steps lasted for 1s and presented one location on the grid in the easy condition, and two locations in the hard condition. Each stimulus was followed by a choice-selection step, which showed two grids side by side. One grid contained the locations shown on the previous four steps, while the other contained an incorrect set of locations, with one or two locations were shown in the wrong place. Participants indicated their memory for these locations in a two-alternative, forced-choice paradigm via a button press and feedback was immediately provided. Each run consisted 12 experimental blocks (6 blocks per condition and 4 trials in a 32 s block) and 4 fixation blocks lasted for 16s and lasted a total of 448 s.

Maths tasks

Participants saw an arithmetic expression on the screen and were given two numbers as choices. The hard condition incudes two greater numbers while the easy condition two smaller numbers. Each trial started with an arithmetic expression lasted 1.45s and the following choices were presented for 1.45s. Each trial ended with a blank screen lasted for 0.1s. Each run consisted 12 experimental blocks (with 4 trials per block) and 4 fixation blocks and lasted a total of 316s.

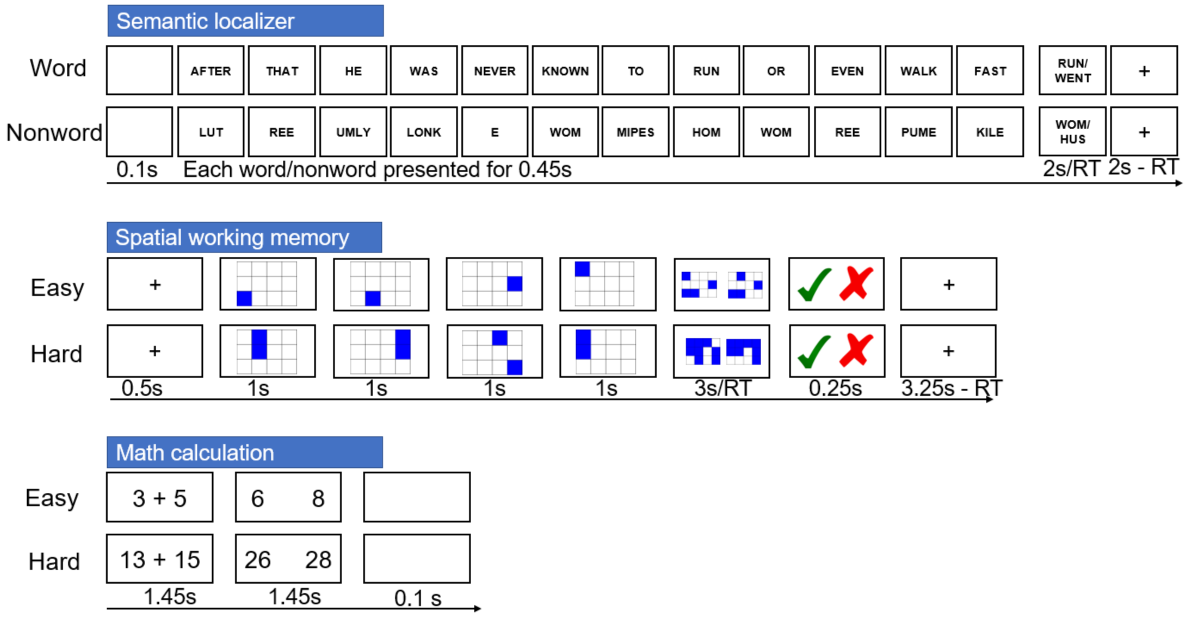


Figure 4-1: Illustration of localizer tasks.

fMRI data acquisition

Structural and functional data were collected on a Siemens Prisma 3T MRI scanner at the York Neuroimaging Centre. The scanning protocols included a T1-weighted MPRAGE sequence with whole-brain coverage. The following MRI sequence parameters were used: acquisition matrix of 176 × 256 × 170 and voxel size 1 × 1 × 1mm^3, repetition time (TR) = 2300 ms, and echo time (TE) = 2.26 ms. Functional data were acquired using an EPI sequence with a 80^0 flip angle and using GRAPPA with an acceleration factor of 2 in 3 x 3 x 4-mm voxels in 64-axial slices. The following parameters were used: 55 3-mm-thick slices acquired in an interleaved order (with 33% distance factor), TR = 3000ms, TE = 15ms, FoV = 192mm.

MRI data pre-processing

Functional and structural data pre-processing was carried out using FMRIB's Software Library (FSL version 6, fsl.fmrib.ox.ac.uk/fsl/fslwiki/FEAT/). The T1-weighted structural brain images were extracted. Structural images were registered to the MNI-152 template using FMRIB's linear image registration tool (FLIRT). fMRI data pre-processing included motion correction, slice-timing correction, spatial smoothing with a 5mm FWHM Gaussian filter and high-pass filtering at 100s. Motion-affected volumes were detected and then were fully removed from the fMRI data (using scrubbing, (Power et al., 2012)).

MRI Data Analysis

Parametric modulation analysis

To examine whether incrementing the number of shared features between probe and target produced concomitant linear changes in BOLD signal, we modelled the parametric effect of global feature similarity. The demeaned global feature similarity ratings for each probe and target word pair, for all the matching trials leading to a YES response, were entered as the parametric regressor. The resulting parameter estimates of the regressor indicated the correlation between the observed BOLD signal and global feature similarity ratings. We also modelled the main effect of the task, and a further six regressors for the clue period, two inter-stimulus interval periods, probe period, negative trials in which there was no match between probe and target on the basis of the current goal, and trials in which participants made mistakes.

Correlations between connectivity gradient values and psychological gradient at the group level

To examine whether the psychological gradient we found is similar to the connectivity gradient identified by Margulies et al., 2016, we examined the correlation between connectivity gradient and the psychological gradient value reflecting the effect of global feature similarity. We defined a space relevant for semantic processing by choosing the voxels within the semantic mask from Neurosynth (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011). We also defined several anatomical regions, in lateral frontal, medial frontal, temporal, and parietal areas, which have been associated with semantic processing. We used the Harvard-Oxford cortical structural atlas and removed voxels with < 5% probability of gray matter. For the left lateral frontal cortex, we included frontal orbital cortex, frontal pole, inferior frontal gyrus (IFG) pars opercularis, pars triangularis, middle frontal gyrus, superior frontal gyrus and frontal operculum cortex, excluding medial prefrontal regions beyond $x > 53$. For the left medial frontal, we included lateral medial cortex, frontal pole, supplementary motor area and superior frontal gyrus and chose voxels where $x < 53$, to exclude more lateral regions. For the left temporal area, we included temporal pole, anterior and posterior inferior temporal gyrus, middle temporal gyrus, superior temporal gyrus and temporal fusiform cortex. For the parietal area, we included angular gyrus, anterior and posterior supramarginal gyrus, and superior parietal lobe. We excluded voxels with a high probability of falling in the temporal lobe by employing the cut-off $z > 41$. We extracted the value of each voxel on the connectivity gradient and the psychological gradient. We tested whether these values were significantly correlated, both across the whole brain, and within specific semantic regions.

Linear contrast analysis

To examine the possibility of a continuous functional gradient in within the semantic mask from Neurosynth (Yarkoni et al., 2011), voxels were assigned into ten decile bins according to their values on the connectivity gradient (Margulies et al., 2016). Parameter estimates for the psychological gradient (i.e., the effect of global feature similarity) were extracted from each bin for each subject in each run in order to avoid averaging across runs and across subjects. We investigated whether there is a linear relationship between connectivity gradient bin and the effect of the task manipulation by building a linear mixed effects model which retained all of the information and variability in the data (Shek & Ma, 2011). The mixed effects model can be expressed as follows: $Y = \beta_0 + \beta_1 * \text{Bin} + r$. Y is the beta value modulated by the global similarity rating, β_0 is intercept, β_1 is the linear rate of change across gradient bins and r is the residual in the beta value. To allow for individual differences in the effect of psychological gradient and in the overall BOLD response, we allowed for random intercepts and slopes within the model, with variance components used as the covariance structure for the residuals. A quadratic and cubic model were also tested and -2 log likelihood was used to select the best model. Analyses were performed using the mixed model procedure in IBM SPSS Statistics Software for Windows, Version 25.0.

Correlations between gradient values and effects of semantic similarity within individuals

Emerging evidence shows that analysing group-level data potentially obscures meaningful individual differences in cortical organization(Braga & Buckner, 2017; Gordon et al., 2017; Laumann et al., 2015; Poldrack, 2017). We therefore examined the data from single participants to establish how many participants would show a gradient-like pattern. For each voxel, we extracted its value on the connectivity gradient value and psychological gradient value reflecting the effect of global feature similarity. We tested whether these values were significantly correlated in each participant within the semantic mask and for each region. We did permutation testing to examine whether the correlation coefficients are significantly greater than zero.

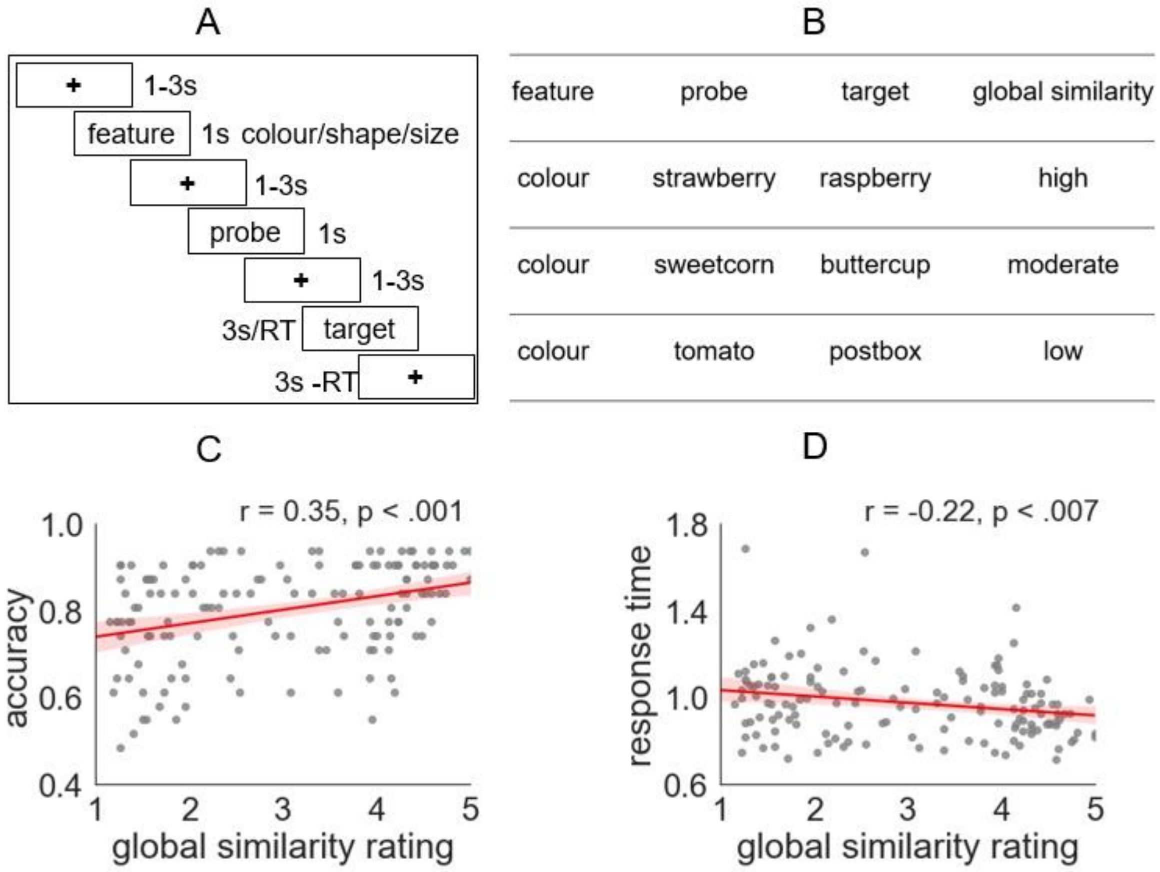
Localizer task-evoked activation analysis

To assess differential BOLD activity in the semantic localiser task, we examined the contrast of words > pronounceable non-word task blocks and confirmed that the task activated brain regions involved in semantic processing. In the spatial working memory task and maths tasks, we examined the contrast of hard > easy to define MDN regions and easy > hard to define DMN regions. A grey matter mask was imposed for all the above analysis and the resulting clusters were multiple comparison corrected via Family-Wise Error (FWE) detection technique at a threshold $z > 3.1$, $p < 0.05$. Brain networks were visualized using BrainNet Viewer (Xia et al., 2013). The whole brain analysis of localizer tasks allowed us to examine whether semantic control recruits cortical regions that fall between default and multiple demand areas across cortical lobes. To examine whether the psychological gradient and connectivity gradient capture the organization of these networks, we extracted the beta value modulated by the global similarity rating and connectivity gradient value and examined whether there is orderly decrease in the beta value from DMN to MDN.

Results

Semantic feature matching performance

Participants saw two words in succession and judged whether they shared a specific feature (colour, shape or size; Fig 4-2B). We parametrically varied the global semantic similarity of these two concepts (Fig 4-2A), while eliminating concurrent variation with psycholinguistic variables. One third of the trials were ‘no match’ trials, and these also varied from globally semantically-related to unrelated. Global feature similarity ratings correlated with both accuracy (r = 0.35, p < .001; Fig 4-2C) and response times (r = 0.22, p <.007; Fig 4-2D), indicating that participants could more readily judge that items matched on the current goal feature when task-irrelevant characteristics were also shared.



feature	probe	target	global similarity
colour	strawberry	raspberry	high
colour	sweetcorn	buttercup	moderate
colour	tomato	postbox	low

Figure 4-2: A – Task structure: first, the feature to be matched was specified (e.g. colour), then the probe word was presented (e.g. strawberry), followed by the target word (e.g. raspberry). Participants indicated if the probe and target shared the specified feature through a button press. B – Parametric manipulation of global semantic similarity within a semantic feature matching task creates a 'task gradient' varying from strong to weak alignment between task requirements and long-term memory. C and D show correlations between ratings of global semantic similarity and average performance across 30 participants (each trial is shown as a data point).

The parametric effect of semantic control demands

To characterise whole-brain spatial patterns relating to the parametric effect of semantic control demands (i.e. the task gradient), we modelled the parametric effect of global feature similarity by entering the demeaned global semantic similarity ratings for correct matching trials as a parametric regressor. Fig 4-3A shows the unthresholded effect of the parametric manipulation of global feature overlap in the semantic feature matching task. Positive effects of this variable (i.e., a stronger BOLD response when items share more features) are seen within lateral anterior-to-mid temporal cortex, angular gyrus and medial and superior frontal regions - regions associated with DMN (Raichle, 2015). Negative effects of this variable (i.e., a stronger BOLD response when items share few features) are seen in temporal-occipital cortex, intraparietal sulcus, inferior frontal sulcus and pre-supplementary motor area within the right hemisphere – regions that fall largely in MDN (Duncan, 2010; E. Fedorenko et al., 2013) (see below for network analysis).

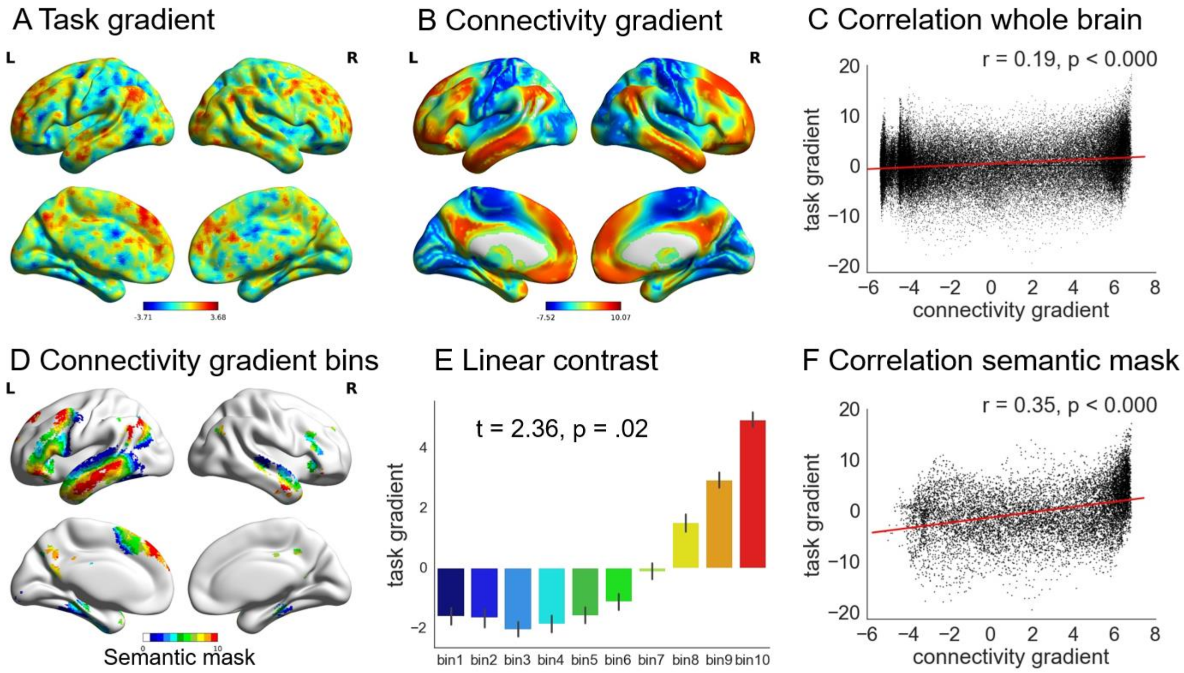


Figure 4-3: A – Unthresholded map of the task gradient: i.e. parametric manipulation of global semantic similarity. Warm colours = positively correlated activity [stronger response when task-irrelevant semantic features were shared between probe and target]. Cool colours = negatively correlated activity [stronger response when only the goal feature was shared between probe and target]. B – The principal gradient of intrinsic connectivity from Margulies et al. (Margulies et al., 2016). C – Correlation between the task gradient and the connectivity gradient (Margulies et al., 2016) across the whole brain. D – The connectivity gradient (Margulies et al., 2016) within a semantic mask defined using Neurosynth, divided into decile bins according to gradient value: Bin 1 is located towards the unimodal end, while bin 10 is at the heteromodal end of the principal gradient. E – The effect of the task gradient in each bin of the connectivity gradient within the semantic mask, showing that the response to the task changes in an orderly way. F – Correlation between the task gradient and the connectivity gradient (Margulies et al., 2016) within the semantic mask defined using Neurosynth.

<u>Correlation between task gradient and connectivity gradient</u>

Margulies and colleagues found the principal gradient of connectivity (Fig 4-3B) was anchored at one end by heteromodal DMN regions, and at the other end by unimodal sensory-motor cortex (Margulies et al., 2016). This connectivity gradient was able to explain the topographical organisation of large-scale networks in multiple cortical zones. We found a significant correlation between this connectivity gradient and the task gradient corresponding to the effect of global semantic overlap. This correlation was significant across the whole brain (Fig 4-3C) and was stronger when only voxels associated with semantic processing (falling within a semantic mask from Neurosynth) were included (Fig 4-3F; there was a significant difference between these two correlation coefficients; z = 16.7, p < .001), suggesting the relationship between the task gradient and the connectivity gradient may be influenced by the specific task.

Next, to test whether a similar functional organisation was present in multiple cortical zones, we calculated the correlation between the connectivity gradient (Margulies et al., 2016) and the task gradient created through our parametric manipulation of global feature overlap. We focussed on four anatomically-defined regions: left lateral frontal, left medial frontal, left lateral temporal, and left lateral parietal cortex, since these sites are extended across the connectivity gradient and they are also broadly implicated in semantic processing (Margulies et al., 2016; Ralph et al., 2017). We found a significant correlation between the task gradient and the connectivity gradient in all four zones (Fig 4-4).

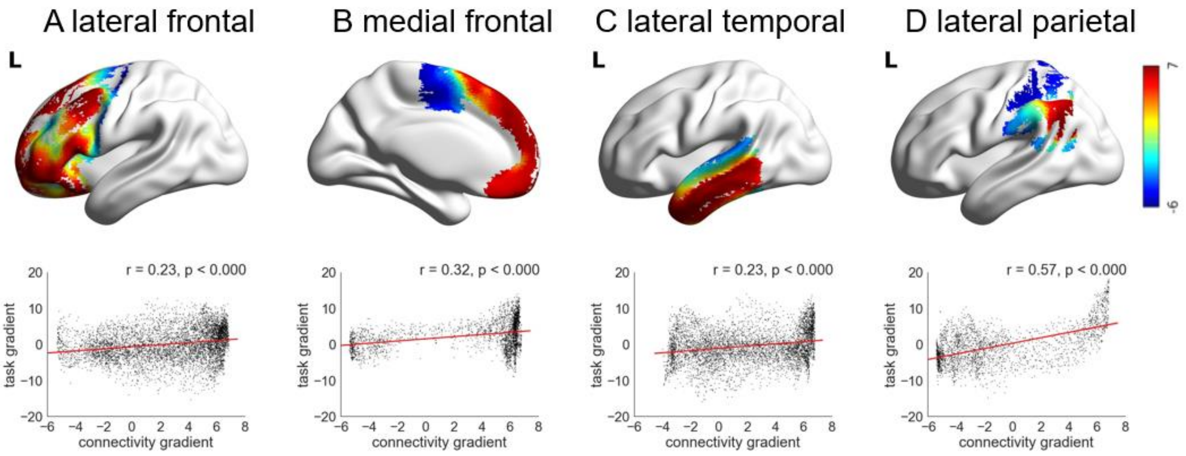


Figure 4-4: The correlation between task gradient and connectivity gradient in lateral frontal (A), medial frontal (B), lateral temporal (C) and lateral parietal (D) cortex. The colour represents each voxel’s value on the connectivity gradient defined by Margulies et al. (Margulies et al., 2016).

Linear change along the connectivity gradient

To establish if the response to the task gradient changed in a systematic way along the connectivity gradient within the semantic mask, we extracted the beta values corresponding to the effect of global semantic similarity within successive bins along the connectivity gradient (Fig 4-3D) and examined whether the task response showed a linear change across these bins (Fig 4-3E). Since the connectivity gradient varies with physical distance from the DMN (Margulies et al., 2016), a linear trend would suggest that the response to the semantic task changes gradually along the cortical surface. There were ten bins based on deciles, which contained voxels falling within 10% bands along the connectivity gradient, from bin 1 located towards the sensory-motor end of the gradient, through to bin 10 at the heteromodal end overlapping with the DMN (shown in Fig 4-3D). We characterised the effect of the task gradient within each bin, for each run and for each participant separately, and performed a linear contrast analysis within a linear mixed effects model, including participant as a random effect. This analysis showed an orderly relationship between the task gradient and the connectivity gradient. There was a linear change along the connectivity gradient in the effect of global feature similarity: positive parameter estimates, corresponding to a stronger BOLD response for trials with high global feature similarity in the DMN, gradually reduced in magnitude and became negative at the sensorimotor end of the gradient, reflecting a stronger response for trials with lower global feature similarity ($t = 2.36$, $p = .02$, Fig 4-3E). None of the high order effects, such as quadratic and cubic effects, improved model fit over the linear effect at $p < .05$.

Table 4-1: Relationship between connectivity and task gradient recovered through linear mixed effects modelling using 10 bins. Table of fixed effects.

Parameter	Estimate	Standard Error	t	p
Intercept	-3.69	2.24	-1.65	.11
Connectivity gradient linear effect	0.55	0.23	2.36	.02

Table 4-2: Relationship between connectivity and task gradient recovered through linear mixed effects modelling using 10 bins. Table of random effects.

Groups	Variance	SD
Subject intercept	87.34	9.35
Subject slope	0.25	0.50

Run intercept	1.32	1.15
Residual	443.70	21.06

Individuals show the association between the connectivity gradient and task gradient

Individual participants are known to show differences in cortical organisation which can be obscured at the group level (Braga & Buckner, 2017; Gordon et al., 2017; Laumann et al., 2015; Poldrack, 2017). A particular concern here was the possibility that non-graded functional changes in a multitude of different locations across participants could give rise to an apparent functional gradient in group analyses. We therefore examined the voxel-wise correlation between the task gradient and connectivity gradient value in each individual participant. More than half of the participants showed a significant correlation between the connectivity gradient values and effects of global feature similarity across the whole brain (17/30 participants) at p = .05. The same participants showed correlations that exceeded the null distribution based on permutation of the connectivity gradient values (Margulies et al., 2016). Correlations between connectivity and task gradients were observed in lateral frontal cortex (in 17/30 participants), in medial frontal cortex (in 14/30 participants), in temporal cortex (in 16/30 participants) and in lateral parietal cortex (in 19/30 participants) at p = .05. Two-thirds of the sample showed a significant correlation between the task and connectivity gradients within the semantic mask generated using Neurosynth (21/30 participants) at p = .05. The correlation can be found in individual brains, indicating the effect we found is not a product of group-level spatial averaging.

Semantic control peaks are located at the juxtaposition of DMN and MDN

Regions within DMN and MDN were defined in the same participants using non-semantic functional localisers. These were contrasts of easy and hard spatial working memory and maths judgements taken from Fedorenko et al. (E. Fedorenko, Behr, & Kanwisher, 2011). Consistent with previous findings, DMN regions (showing a stronger response to easy versus hard trials in either task) included posterior cingulate cortex, medial prefrontal cortex, angular gyrus and lateral anterior temporal lobes bilaterally. In contrast, MDN regions (hard versus easy) included inferior frontal sulcus, premotor cortex, intraparietal sulcus, and lateral occipital cortex (Family-Wise Error (FEW) -corrected, z=3.1, p<.05) (Fig 4B).

Noonan et al. (Noonan et al., 2013) found left inferior frontal gyrus, left posterior middle temporal gyrus and dorsal anterior cingulate were the most reliably activated sites across different manipulations of semantic control in a neuroimaging meta-analysis. We compared the location of these semantic control sites with DMN and MDN, as defined by the localiser tasks (Fig 4B). The semantic control sites overlapped with MDN in lateral and medial prefrontal regions, in line with the view that MDN is recruited whenever task demands are high. However, two of these sites (left inferior frontal gyrus and middle temporal gyrus) also responded to a semantic localiser, showing stronger activation during the maintenance of strings of words than pronounceable nonwords (FWE-corrected, z=3.1, p<.05) (Fig 4A). The word condition was easier than the nonword condition and consequently these semantic control regions did not show the functional profile of MDN. Instead, in left inferior frontal gyrus, left posterior middle temporal gyrus and dorsal anterior cingulate, the response to semantic control demands, defined by (Noonan et al., 2013), was observed at the juxtaposition of DMN and MDN. This observation was particularly striking in posterior middle temporal gyrus (Fig 4A), where the semantic control response was largely located in between these two canonical networks. These results suggest an orderly arrangement of the networks involved in semantic cognition along the cortical surface.

The psychological and connectivity gradient captures the orderly transitions between DMN, semantic control and MDN

The final analysis examined whether DMN, semantic control and MDN networks are located at distinct points along the task and connectivity gradients described above. We defined the following cortical regions within the Neurosynth semantic mask: (i) Regions within DMN, (ii) semantic control regions from the meta-analysis of Noonan et al. (Noonan et al., 2013) that fell outside MDN, (iii) semantic control regions within MDN and (iv) MDN regions not implicated in semantic control (Fig 4-5C). MDN and DMN were defined using the functional localisers described above. We found that the task gradient values decreased in an orderly fashion across these networks: voxels within DMN had the highest task gradient values, voxels in the semantic control network had lower values, while voxels that fell only in MDN had the lowest beta values (Fig 4-5D). One-way ANOVA found significant differences in task gradient values (F(3,10987) = 899.97, p < .0001). Post hoc tests using Tukey HSD criterion for significance indicated significant differences between every network pair (p < .05).

To examine whether the connectivity gradient also captured the order of these networks, we extracted the connectivity gradient value within each network. We found the same decreasing pattern revealed by the task gradient (Fig 4-5E). One-way ANOVA found significant differences in connectivity gradient values (F(3, 4990) = 673.57, p < .0001). Post hoc analysis using the Tukey HSD post hoc criterion for significance indicated significant differences between each pair (p < .001) except between DMN and semantic control regions outside MDN (p=.309). These findings suggest both the task gradient and connectivity gradient capture the orderly transitions between DMN, semantic and MDN.

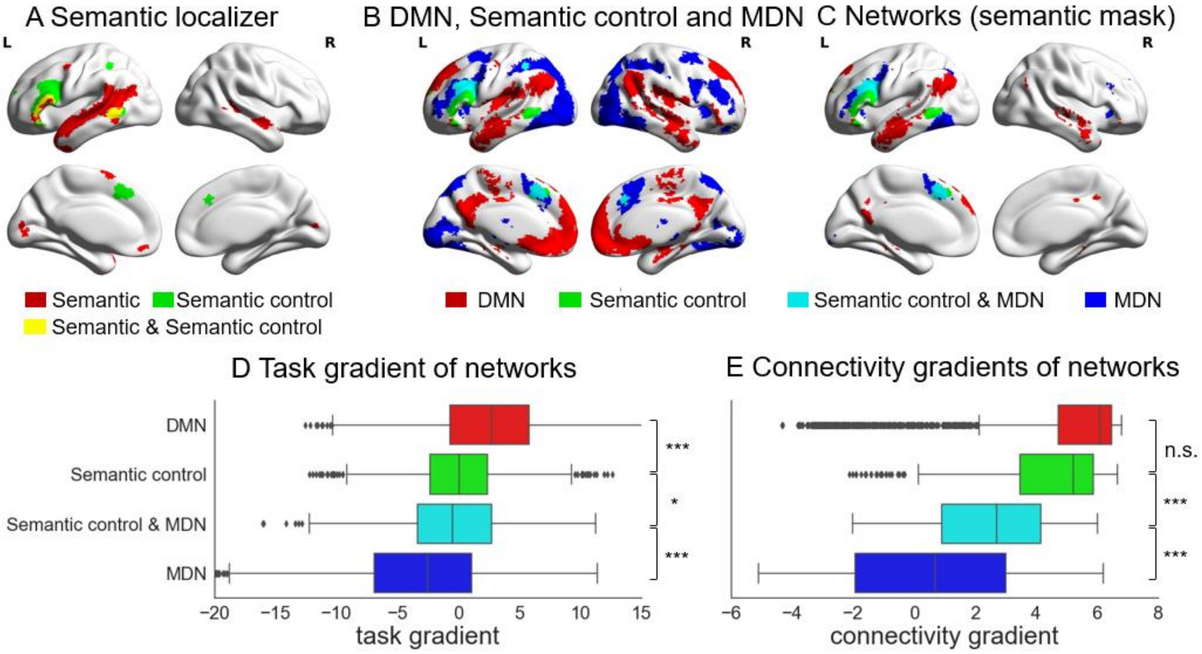


Figure 4-5: A – Semantic regions defined by the semantic localizer task (in red), regions implicated in semantic control by an activation likelihood meta-analysis (Noonan et al., 2013) (in green), and their overlap (in yellow). This highlights the critical role of left inferior frontal gyrus and posterior middle temporal gyrus in controlled semantic processing. B – Networks used in the analysis, including DMN (in red) and MDN (in blue), defined by the localizer tasks, together with semantic control regions from the meta-analysis of semantic control (Noonan et al., 2013) (in green). C – The same networks masked by semantically relevant regions, defined using Neurosynth. D – The task gradient values of each network. E – The connectivity gradient values of each network.

Discussion

This study manipulated the global semantic similarity of probe and target words parametrically in a feature matching task, creating a task gradient. At one end of this task manipulation, items shared both goal-relevant and irrelevant features, such that the goal was well-aligned with conceptual knowledge, while at the other end, items had little conceptual overlap beyond the goal feature. We demonstrated that functional recruitment changed systematically along the cortical surface, such that strong global semantic similarity elicited more activation towards heteromodal DMN regions, and weaker global semantic similarity produced more activation within regions linked to executive control and unimodal processing. These topographical changes in the effect of the task gradient were linked to the principal gradient of intrinsic connectivity in the human brain (Margulies et al., 2016), which captures the gradual transition between heteromodal DMN regions and unimodal sensorimotor regions. There was a correlation between the task gradient and the principal connectivity gradient across the whole brain and in multiple cortical regions associated with semantic cognition, indicating that our data relate to the macroscale functional organisation of the cortex, with parallel patterns of systematic functional change in different lobes. The gradient pattern was also seen in individual brains, suggesting it is not driven by spatial averaging. Finally, we found that the task gradient and connectivity gradient both captured the layout of networks related to semantic processing, including the observation that the semantic control network falls mid-way between DMN and MDN.

The correspondence between the task gradient and the connectivity gradient: The principal gradient of connectivity is consistent with a hierarchical view of brain organisation, in which heteromodal processing emerges from the gradual integration of unimodal sensory-motor representations. This view has been described previously within the temporal lobes by the ‘graded hub account’, which proposes that different modalities (visual, auditory, valence) are gradually integrated within the anterior temporal lobes, with heteromodal conceptual responses falling within ventrolateral regions that are maximally distant from these different inputs (Chiou, Humphreys, Jung, & Lambon Ralph, 2018; Connolly, Gobbini, & Haxby, 2018; Ralph et al., 2017). The whole-brain nature of the principal gradient suggests that a similar gradual abstraction of heteromodal representations occurs across the brain (Guell, Schmahmann, Gabrieli, & Ghosh, 2018). Moreover, the principal gradient of connectivity captures the sequence of large-scale networks on the cortical surface, which show orderly transitions from primary visual/auditory/motor systems, through attention networks, to fronto-parietal control regions, to default mode regions, in multiple locations (Margulies et al., 2016).

We were able to demonstrate this macroscale pattern of functional transitions within a single task. When many features of the concepts were consistent with the task demands, trials elicited greater engagement of the heteromodal end of the gradient, presumably because the integrated concept was sufficient to support ongoing goal-driven cognition. In contrast, for trials in which only the goal feature was shared by the two concepts, heteromodal concepts would not provide an appropriate similarity structure for the task, and the functional response moved along the gradient towards control and unimodal regions.

Systematic functional transitions in multiple zones: We found correspondence between the task gradient and the connectivity gradient in multiple cortical zones, including ventral ATL to auditory cortex, ventromedial to dorsomedial prefrontal cortex, angular gyrus to intraparietal sulcus and inferior frontal gyrus to inferior frontal and precentral sulcus. Although our task involved decisions based on visual features – namely colour, shape and size – functional transitions were observed in regions far from visual cortex. This suggests that the functional gradient is a general principle of whole brain organisation that captures multiple local gradients. These findings are consistent with several local gradients that have been described in isolation (Chiou et al., 2018; Connolly et al., 2018; Ralph et al., 2017; Visser, Jefferies, Embleton, & Lambon Ralph, 2012). Jackson et al. (Jackson et al., 2019) identified graded change in the structural and functional connectivity of the ventral medial prefrontal cortex, from DMN to sensory-motor cortex, in line with functional transitions observed in this region (Denny, Kober, Wager, & Ochsner, 2012; Sul et al., 2015). Similarly, Badre et al. (Badre & D’Esposito, 2009) proposed a rostrocaudal gradient in lateral frontal cortex, with rostral frontal areas supporting more abstract forms of control than caudal areas. We observed more complex spatial transitions in lateral frontal cortex, with high gradient values in anterior, ventral and dorsal regions. This is in line with the revised framework of Badre et al. (Badre & Nee, 2018), which suggests that although the frontal lobes are organized hierarchically, there is no unidimensional spatial gradient of abstraction or global difficulty in this region (Badre & D’Esposito, 2009; Badre & Nee, 2018; Koechlin, Le Ody, & Kouneiher, 2003).

The task gradient was captured in individual analysis. Averaging data across individuals can mischaracterize the functional organization of the brain because people exhibit distinct functional topographies (Braga & Buckner, 2017; Gordon et al., 2017; Poldrack, 2017). At the single-subject level, regions engaged by a contrast of words over nonwords can lie adjacent to multiple-demand regions – and, critically, the location of this functional transition is different across individuals (Evelina Fedorenko, Duncan, & Kanwisher, 2012). Systematic and gradual changes in function could potentially be observed in group-level analyses, even if individuals show abrupt functional change between two discrete response profiles, as long as these transitions occur at different locations on the cortical surface in different people (Evelina Fedorenko, Hsieh, Nieto-Castañón, Whitfield-Gabrieli, & Kanwisher, 2010). To investigate this possibility, we examined the correlation between the task gradient and the connectivity gradient in individual participants. We found that single subjects showed this correlation, suggesting that the functional gradient is a stable organising principal across people, instead of a product of group-level spatial averaging.

The large-scale task gradient explains the spatial arrangement of networks that support semantic cognition. We found that networks that support semantic cognition are organised in a systematic way along the gradient. Multiple networks with distinct connectivity profiles are recruited in semantic tasks – including DMN regions (such as angular gyrus and lateral middle temporal gyrus) (Humphreys, Hoffman, Visser, Binney, & Lambon Ralph, 2015; Wirth et al., 2011)(Wirth et al., 2011), areas specifically implicated in semantic control (Noonan et al., 2013), and MDN regions implicated in domain-general executive control (Chiou et al., 2018; E. Fedorenko et al., 2013); however, the topographical organisation of these networks has not been previously investigated. On both the connectivity and task gradients, the semantic control network had intermediate values – falling in between DMN and MDN in terms of patterns of connectivity and task response. The spatial adjacency of the semantic control network to both DMN and the MDN might allow semantic control regions to integrate long-term conceptual knowledge with more adaptive representations of currently-relevant goals, supporting flexible patterns of semantic retrieval (Davey et al., 2016). This is consistent with recent evidence that DMN and MDN cooperate when memory is controlled (Elton & Gao, 2015; Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010; D. Vatansever, Menon, Manktelow, Sahakian, & Stamatakis, 2015; Deniz Vatansever et al., 2017).

Graded transitions in the BOLD response from DMN to executive cortex might reflect the shift from intrinsically-guided retrieval based on representations in memory, to goal-driven cognition instantiated by cues in the environment (which, in this experiment, were the instruction slides specifying the feature type for each trial). DMN regions show stronger activation when semantic tasks are guided by memory (Humphreys & Lambon Ralph, 2015; Lau et al., 2013; Wirth et al., 2011). In contrast, when task requirements are not a good match with the information in memory, a complementary strategy is needed in which intrinsic cognition is temporarily suppressed. MDN is thought to dynamically alter semantic processing by coding for information relevant to the current decision (Duncan, 2010) and by changing its pattern of connectivity according to task demands (Cole et al., 2013).

A single study cannot fully specify the critical aspects of the task which gave rise to the functional gradient. This research does not address the question of whether the same spatial relationships would be observed for parametric manipulations of non-semantic goals, and/or other semantic tasks that vary in difficulty but in the absence of an explicit goal. We found that the correlation between the task gradient and the connectivity gradient was maximal within brain regions recruited during semantic tasks, suggesting that if there are similar patterns for non-semantic tasks, these might be strongest in different cortical regions. Future studies that parametrically manipulate other types of semantic and non-semantic tasks can examine the specificity of our findings. The unique contribution of the current study is to show that functional recruitment within a single task can show systematic variation in a way that follows graded changes in intrinsic connectivity.

Chapter 5 : Thesis summary and discussion

This thesis sought to investigate the neural basis of flexibility in semantic retrieval. While previous research has uncovered many regions involved in semantic representation and semantic control (for a review, see Lambon Ralph, Jefferies, Patterson, & Rogers, 2017), the thesis work focused on using structural MRI metrics (i.e. cortical thickness) and task fMRI to explore the regions and networks that support semantic cognition and their the organizational principle of networks. The empirical work delineates regions whose structural covariance predicts behavioural performance on tests of controlled semantic retrieval (Chapter 2); and identifies regions across multiple large-scale networks that represent goal information using a semantic feature matching task (Chapter 3). Finally, the thesis uses a parametric design to explore the organization principle of networks that support semantic cognition (Chapter 4). In this way, this research interrogates the neural basis of flexibility in semantic retrieval with regards to three major themes, described below.

Theme 1. The neural network underpinning controlled semantic retrieval

A major aim of the thesis was to delineate the neural network underpinning controlled semantic retrieval. We examined the structural basis of controlled semantic retrieval (Chapter 2); the regions that represent goal information in a demanding semantic task (Chapter 3); and examined how the BOLD response to a semantic task changes as the control demands increase (Chapter 4).

In Chapter 2, we were interested in elucidating the structural basis of controlled semantic retrieval. fMRI, TMS and lesion studies have identified regions that are important for controlled semantic retrieval. However, little is known about individual differences in these abilities – i.e., what are the structural and functional markers of efficient semantic cognition, even in the face of high control demands, in healthy participants? This question is important for several reasons: (1) although most research in cognitive neuroscience focusses on commonalities across individuals, inter-individual differences can be exploited to understand the neural basis of human cognition (Kanai & Rees, 2011); (2) regions that are commonly activated in task-based fMRI may not relate to variation in controlled retrieval; (3) patients with semantic aphasia show variation in semantic control but tend to have large lesions encompassing inferior frontal gyrus (IFG), posterior middle temporal gyrus (pMTG) and angular gyrus (AG) rather than focal damage. Therefore, neuropsychological evidence alone is insufficient to establish the extent to which each of these regions individually contributes to semantic control. By examining the biological basis of individual differences in semantic control using cortical thickness metrics, we can examine (1) whether seed regions involved in semantic control show structural covariance with other regions involved in semantic control; (2) whether this structural covariance is modulated by behavioural performance; (3) whether the modulation is specific for demanding semantic tasks but not demanding non-semantic tasks; (4) whether the structural covariance between regions is a more sensitive index than the cortical thickness of individual sites implicated in semantic control. Chapter 2 reported the combined analyses of MRI-based cortical thickness with resting-state fMRI connectivity to identify structural markers of individual differences in semantic control.

In Chapter 3, we identified the regions that represent goal information in a demanding semantic task. Previous studies of goal representation have often used perceptual tasks, such as perceptual feature matching, in which participants have to control their processing of information provided on the screen, as opposed to information in memory (Bugatus, Weiner, & Grill-Spector, 2017; Jackson & Woolgar, 2018; Loose et al., 2017; Waskom et al., 2014). Many previous studies have also conducted multivariate analysis within pre-specified regions of multiple demand network (MDN) (Bracci et al., 2017; Crittenden et al., 2016; Vaziri-Pashkam & Xu, 2017; Woolgar et al., 2016). Therefore, it remains unknown whether regions outside MDN also represent goal information, and how goals for memory retrieval are maintained. In Chapter 3, we examined which brain areas can classify goal and category information, using a semantic feature matching task in which participants were asked to decide whether the probe and target word were similar in terms of a specific feature – colour, shape and size. We divided each trial into three events: a goal instruction period, probe word and target period in which participants reached a decision. We conducted whole brain classification analysis for each period without predefining regions of interest (ROIs), allowing us to reveal all the potential regions that represent goal information. In this way, we revealed the regions/networks that support controlled semantic retrieval.

In Chapter 4, we identified how the semantic response changes along the cortical surface depending on the demands of the semantic task. We used a feature matching task in which participants were asked to match words on the basis of a specific semantic feature, such as colour, while parametrically varying other features. This created a ‘psychological gradient’ varying from strong to weak convergence between long-term memory and the current goal. At one end of this ‘psychological gradient’, probe and target words shared both goal-relevant and irrelevant features, such that task requirements were well-aligned with long-term memory; at the other end, items only shared the goal-relevant feature. This allowed us to examine how the BOLD response to a semantic task changes as the control demands increase. Chapter 4 provides converging evidence for the neural network underpinning controlled semantic retrieval.

Theme 2. Organizational principles of networks involved in semantic cognition

The thesis work revealed the neural network underpinning controlled semantic retrieval and then considered the relationship between this network and others that are involved in semantic cognition. The aim was to uncover organizational principles for the networks that support flexible semantic retrieval. In Chapter 2, the structural covariance of pMTG and anterior middle frontal gyrus (aMFG) modulated the performance of controlled semantic retrieval, rather than the cortical thickness of each region alone, suggesting that there is a network which is more than the sum of its parts. In Chapter 3, both default mode network (DMN) and MDN regions were found to represent goal information in a demanding semantic task, suggesting that at least aspects of both networks are involved in controlled semantic retrieval. Next, Chapter 4 investigated how human cortex is organised to produce a spectrum of semantic cognition, from efficient memory-based decisions to more flexible novel patterns of semantic retrieval. Human cognition is flexible, allowing us to efficiently deal with diverse situations – ranging from highly familiar tasks (when cognition is supported by long-term memory) to novel scenarios (when cognition is driven by current goals). Traditionally, these aspects of cognition have been ascribed to dichotomous neural systems supported by the DMN and MDN. In reality, however, most situations are neither completely familiar, nor entirely novel, highlighting the need to understand how cognition is constrained in a graded fashion by these networks working together. One possibility is that there are graded functional changes within brain regions from DMN regions, through semantic control to more domain-general control regions. Graded functional changes have been reported for specific regions, such as anterior temporal lobe (ATL), lateral and medial prefrontal cortex. Here we wanted to investigate graded functional transitions at the whole brain level. We parametrically manipulated the global semantic similarity of words in a semantic feature matching paradigm, to create a ‘psychological gradient’ ranging from decisions in which goal-relevant features were well-aligned with the structure of long term memory, to decisions in which the items to be matched only shared the goal-relevant feature. The research tested the predictions of a recent study which proposes a connectivity gradient along the cortical surface capturing the transition from unimodal regions concerned with perception and action, through MDN, to DMN. Chapter 4 asked whether brain responses change linearly along the connectivity gradient in a way that reflects the match between task demands and long-term memory.

For more than a century, neuroscientists have studied the cerebral cortex by delineating individual cortical areas and mapping their function. To complement the description of individual cortical areas, we propose an inquiry into the significance of their spatial arrangement, asking the question: Why are cortical areas located where they are? To examine whether these graded transitions capture the layout of networks involved in semantic processing, we defined DMN and MDN and examined whether the peak response for semantic control in previous studies fell midway between these networks in temporal and frontal cortex.

Interpreting the main findings of each study

Chapter 2

Chapter 2 combined analyses of MRI-based cortical thickness with resting-state fMRI connectivity to identify structural markers of individual differences in semantic control. It mainly revealed the regions that support controlled semantic retrieval and explored whether these regions work as a network to support controlled semantic retrieval. We also explored whether the controlled retrieval is specific for semantic by comparing demanding semantic tasks with demanding non-semantic tasks. We combined cortical thickness with resting-state fMRI connectivity to explore the convergence between these structural and functional networks.

Chapter 2, Finding 1. pMTG supports semantic control

The structural covariance of pMTG with other semantic control regions is particularly important for predicting individual differences in controlled semantic retrieval ability, in line with previous studies which found that pMTG activation to control-demanding semantic tasks is more variable in location and intensity across participants than the response in left IFG (Vitello et al., 2014). Our current findings support the view that pMTG supports semantic control, although the role of pMTG is controversial, with multiple theories proposed to explain its function, including thematic association, action understanding and lexical access.

Traditionally, temporal lobe regions were not thought to contribute to the executive control of behaviour (Binder & Desai, 2011). However, there is compelling research showing that pMTG contributes to semantic control. A meta-analysis of task-based fMRI studies identified pMTG as the second most reliably activated region across diverse manipulations of semantic control, after left IFG (Noonan et al., 2013), and numerous individual studies have reported responses in both left IFG and pMTG for the contrast of weak over strong associations (James Davey et al., 2016; Gold et al., 2006); ambiguous words (with multiple meanings) compared with unambiguous words (Bedny, McGill, & Thompson-Schill, 2008; Rodd et al., 2005); associations based on specific semantic features (i.e., colour, shape) as opposed to associations based on global semantic relatedness (Chiou et al., 2018) and decisions involving many versus few response options (Badre et al., 2005; Badre & Wagner, 2007). However, the interpretation of these effects has remained unclear since greater activation in pMTG could arguably reflect increased activation of conceptual knowledge in more demanding tasks. Studies have shown that inhibitory stimulation of pMTG disrupts the retrieval of weak associations more than strong associations (Davey et al., 2015; Whitney et al., 2011), suggesting that this region does play a critical role. This is consistent with a recent MEG study that found pMTG showed a more substantial oscillatory response in weak association trials (Teige et al., 2019). Our current results showed that if pMTG co-varies in cortical thickness with a region in aMFG, participants tend to be more efficient at retrieving weak associations, confirming that pMTG contributes to individual differences in semantic control.

The role of pMTG is highly controversial. One of the proposed functions is thematic association. However, the finding that pMTG is involved in thematic association might not weaken the account that pMTG support semantic control because there might be different sub-regions, with one being responsible for semantic control while another supports thematic association. Task fMRI studies found that pMTG showed stronger activation for thematic processing than taxonomic processing (de Zubicaray, Hansen, & McMahon, 2013; Kalénine et al., 2009b), even with difficulty matched (Teige et al., 2019); pMTG showed stronger activation for thematic association than size judgment even when the latter was more difficult (Davey et al., 2016). Converging evidence is provided by semantic aphasia patients with prefrontal or temporal-parietal infarcts, who make associative errors during picture naming tasks (Jefferies & Lambon Ralph, 2006). Using voxel-based symptom-lesion mapping, Schwartz et al. (2011) found that voxel damage in left temporoparietal junction, including left pMTG, was associated with a higher rate of association/thematic errors. These findings are consistent with the view that pMTG supports thematic knowledge. However, patients tend to have large lesions encompassing both AG and pMTG (Schwartz et al., 2011). Therefore, it is difficult to establish from neuropsychological evidence alone the extent to which each of these regions individually shows the characteristics of a thematic hub. Furthermore, the region of pMTG that showed a greater engagement for thematic than taxonomic relationships also showed a greater engagement for weak than strong thematic relationships (Teige et al., 2019), which is consistent with the possibility that pMTG supports both knowledge of thematic relations and semantic control processes, in line with previous observations using fMRI (Davey et al., 2015). However, since MEG lacks the spatial resolution to separate proximal sources, there could be distinct regions of pMTG associated with processing thematic relations (irrespective of difficulty) and semantic control. This possibility is consistent with the observation that the effects of thematic judgements and difficulty were non-overlapping in time-frequency. The thematic > taxonomic contrast occurred within the beta band, which has been associated with the retrieval of action semantics and syntactic binding processes -- aspects of cognition which may relate to thematic processing (for a review, see Weiss & Mueller, 2012). In contrast, the effect of difficulty across taxonomic and thematic judgements occurred within the alpha band, which has been linked to controlled access to semantic information and to sustained patterns of focussed retrieval (for a review, see Klimesch, 2012). The proposal that pMTG supports controlled semantic cognition but not thematic matching per se is supported by a TMS study. TMS to pMTG disrupted thematic judgments for weak but not strong associations (e.g., a picture of an Alsatian with razor wire) (Davey et al., 2015), suggesting that there is a specific region for semantic control but not thematic association. In our current study, we used the contrast of weak versus strong associations and found that the structural covariance between pMTG and aMFG is modulated by the weak associations after controlling for strong associations, suggesting thematic association alone cannot explain this effect.

pMTG has also been proposed to support action/event understanding, tool recognition and verb processing. One possibility is that semantic control might be more heavily taxed by event > object contrasts. Events often have complex behavioural structures and require structured mental programs, which might be supported by the MDN (Duncan 2010). It has long been noted that, after major frontal lobe damage, the structure of complex behaviour is impaired, with important parts omitted, irrelevant parts introduced, and the whole failing to achieve its ends (Fuster, 2001). In line with this viewpoint, patients with semantic control deficits show ideational apraxia, irrespective of whether they have lesions in left temporoparietal or inferior prefrontal cortex (Corbett et al., 2011). Ideational apraxia is characterised by difficulty using objects in a meaningful way, especially in the context of complex multi-step actions like making a cup of tea: patients produce errors such as selecting coffee instead of tea, or adding sugar twice. This kind of errors might be caused by (1) the damaged knowledge of event structures; they have difficulty to consciously represent sequences of speech or behaviour, especially if they are novel or complex; or (2) deficits in cognitive control which is critical for multi-step actions; they have difficulty to initiate them and execute them in orderly manner (Fuster, 2001). However, patients tend to have large lesions encompassing both AG and pMTG. Therefore, it is difficult to establish from neuropsychological evidence alone the extent to which each of these regions individually supports actions and events.

Strong converging evidence for the role of pMTG in the comprehension of actions and events across modalities is provided by fMRI and TMS studies of healthy participants. For example, Wurm & Caramazza (2019) used multi-voxel pattern analysis of fMRI data to show that pMTG represents actions in a similar way across observed scenes and written descriptions. This site also activates in response to action understanding (Chen, Garcea, Jacobs, & Mahon, 2018), tool recognition (Ishibashi, Pobric, Saito, & Lambon Ralph, 2016) and to verbs more than nouns (Peelen, Romagno, & Caramazza, 2012). Causal evidence for a role of pMTG in verb processing is provided by inhibitory TMS (Papeo et al., 2015). Interestingly, the role of pMTG in verb processing cannot be entirely explained in terms of its role in understanding actions: pMTG supports the processing of both action and non-action verbs (Bedny, Caramazza, Grossman, Pascual-Leone, & Saxe, 2008). These observations suggest that pMTG might support event structures or aspects of contextually-guided semantic retrieval, which are important even for non-motoric verbs. It remains unclear whether this contribution reflects heteromodal long-term representations of action/event/thematic knowledge in pMTG, or instead processes that are particularly important for understanding events. However, in our current study reported in Chapter 2, many associations do not involve action, suggesting that structural covariance between pMTG and aMFG is not underpinned only by action.

Another possibility is that there might be different regions for action/event understanding and semantic control. Recent studies found that the pMTG area that supports high level language processing (i.e., semantic and/or syntactic processing) does not overlap with the region that is involved in action observation/imitation (Pritchett, Hoeflin, Koldewyn, Dechter, & Fedorenko, 2018). pMTG has been proposed to support action understanding and tool recognition. It has been reported that pMTG responded more strongly to verb relative to noun processing, even in the absence of a task difficulty difference between conditions (Papeo et al., 2015). One concern is that existing evidence is indirect, relying on group analyses or reverse inference. Pritchett and colleagues (2018) defined high level language regions (i.e., semantic and syntactic) functionally in each individual participant and they found that pMTG showed little or no response during action observation/imitation (Pritchett et al., 2018), suggesting that pMTG as a language processing area does not overlap with the region that is involved in action observation/imitation, excluding the possibility that the same sub-region in pMTG supports semantic control and action observation.

It has also been proposed that pMTG might be the best candidate for lexical access to meaning (Hickok & Poeppel, 2007; Lau, Phillips, & Poeppel, 2008). However, pMTG mediates lexical access to meaning but only when control demands are high. fMRI studies using semantic tasks consistently showed activity in this region (Binder et al., 2009). Left pMTG showed word-specific but not pseudowords repetition suppression effect (Gagnepain et al., 2008), and this priming effect modulated activity in pMTG across all stimulus onset asynchrony (Gold et al., 2006); studies using distorted speech stimuli found that MTG activation was correlated with intelligibility (Davis & Johnsrude, 2003; Giraud et al., 2004). These findings suggest that pMTG support lexical access to meaning. However, pMTG showed stronger activation for the weak than strong associations (Davey et al., 2016; Gold et al., 2006); inhibitory stimulation of pMTG disrupts the retrieval of weak associations more than strong associations (Davey et al., 2015; Whitney, et al., 2011); a recent MEG study found that pMTG showed a more substantial oscillatory response in weak association trials (Teige et al., 2019). The converging evidence suggests that the access to meaning in pMTG is modulated by the control demands. In our current study reported in Chapter 2, lexical access is required for both strong and weak associations, suggesting that structural covariance between pMTG and aMFG is not underpinned only by lexical access.

Our current results showed that if pMTG co-varies in cortical thickness with a region in aMFG, participants tend to be more efficient at retrieving weak associations, confirming that pMTG contributes to semantic control. In our current study, we used the contrast of weak versus strong associations, which both involve thematic associations. Therefore, the structural covariance cannot reflect a difference between thematic and non-thematic knowledge. Since most weak and strong associations do not involve actions, it seems unlikely that the findings in Chapter 2 can be explained in terms of a role of pMTG in action understanding. Similarly, since both weak and strong associations require lexical access, the relationship between structural covariation and task performance is not readily explained by the lexical access hypothesis. Our study provided further evidence to support the role of pMTG in semantic control, using the index of cortical thickness and individual differences. However, pMTG may sustain representations of the currently-meaningful context, which is necessary for semantic control, thematic association and action observation – since actions take place in a meaningful context, suggesting that there might be parallel or proximal networks that underpin aspects of cognition that have similarities in the way that information must be maintained over time and shaped according to the context.

Chapter 2, Finding 2. A network view of cognitive functions

The pattern of structural covariation between sites was a better predictor of performance on semantic control tests than the overall thickness of left pMTG itself, in line with a network view of cognitive functions. Structural covariation between regions forming large-scale functional networks has previously been shown to be more sensitive to behavioural differences than regional thickness metrics (Bernhardt et al., 2014; Valk et al., 2017). For example, the structural covariance network of dorsal anterior insula, but not its thickness, correlated with individual differences in empathic responding (Bernhardt et al., 2014) and structural covariance analysis, not regional thickness mapping, found a double dissociation between empathy and mentalizing (Valk et al., 2017). The results in Chapter 2 provide further evidence supporting the view that it is necessary to use a network view to characterise the neural basis of high-level cognitive functions.

For more than a century, neuroscientists have studied the cerebral cortex by delineating individual cortical areas and mapping their function. Experiments aiming to localize regions that are differentially activated across tasks are complemented by observations of anatomical and functional relationships among such regions. Evidence from both anatomical and physiological studies supports the view that that interactions among distributed neuronal populations and brain regions are important for virtually all domains of cognition processes. For example, Betti et al. (2013) found that viewing natural scenes alters the dynamics of functional connectivity in the human brain; Simony et al. (2016) found the inter-subject functional correlation within DMN only appears when listening to an intact story; Ekman and colleagues, using a colour-or-motion judgment task, demonstrated that when perceptual areas were recruited for their specialized functions (for example, V4 for colour perception), they were tightly integrated into large-scale network topology (Ekman, Derrfuss, Tittgemeyer, & Fiebach, 2012). These results are compatible with findings that global functional connectivity can be used to decode what the stimuli participants are viewing (Wang et al., 2016), and what tasks they are performing (Cole et al., 2013; Hermundstad et al., 2013).

Structural covariance might reflect persistent cross-talk between regions: brain regions that show stronger correlation in cortical thickness are often part of systems that are known to sub-serve particular cognitive functions (Alexander-Bloch et al., 2013; Evans, 2013). For example, individuals with greater cortical thickness in posterior parts of inferior frontal cortex

(Broca's area) typically also have greater cortical thickness in superior temporal cortex (Wernicke's area) (Lerch et al., 2006).

More flexible patterns of memory retrieval occurred when pMTG co-varied in cortical thickness with a distant region in aMFG, as opposed to nearby visual, temporal or parietal lobe regions; suggesting long-range intra-hemispheric connections are important for memory retrieval. The importance of long-range intra-hemispheric connections has been reported in task fMRI studies. For example, long-range intrahemispheric connections are often found in task-dependent reconfiguration of functional connectivity (Hermundstad et al., 2013; Park & Friston, 2013). These are compatible with complex network theory which suggests that, for optimal information processing, functional networks must simultaneously enable local segregation and global integration, thereby allowing for the interplay between specialization and integration of function (Sporns, Tononi, & Edelman, 2000a, 2000b; Tononi, Sporns, & Edelman, 1994). To strike an adaptive balance between integration and segregation, task-dependent reconfiguration of functional networks would require flexible functional connectivity that is not biased by the distance between areas. According to this hypothesis, changes in long-range functional connections will have important implications for integration (Mišić et al., 2014).

Our current study revealed the pattern of structural covariation between sites was a better predictor of performance on semantic control tests than the overall thickness of left pMTG itself, providing further evidence to support the view that it is necessary to use a network view to characterise the neural basis of high-level cognitive functions, such as semantic control. More flexible patterns of memory retrieval occurred when pMTG co-varied in cortical thickness with a distant region in aMFG, as opposed to nearby visual, temporal or parietal lobe regions, suggesting long-range intra-hemispheric connections are important for controlled patterns of memory retrieval.

Chapter 2, Finding 3. Semantic control versus domain general control

This pattern of structural covariance was specific to semantic control and did not predict performance when harder non-semantic judgements were contrasted with easier semantic judgements, in line with the purported functional dissociation between semantic and domain-general executive control. Our results provide further evidence that semantic control is at least partially separable from domain-general executive control, although this separation might not solely reflect the role of specific sites, but instead on their participation in distinct large-scale networks.

Although regions of MDN show stronger activation for demanding tasks across modalities, there might be differences in domain preference across regions of MDN (Nee & D'Esposito, 2016). For example, it has been suggested that anterior frontal areas are domain general while posterior frontal areas are sensitive to stimulus domain, with middle ventral areas demonstrating verbal sensitivity and middle dorsal areas demonstrating spatial sensitivity (Lara & Wallis, 2015; Nee & D'Esposito, 2016; Wilson, Scalaidhe, & Goldman-Rakic, 1993). Potential differences in the degree of domain generality may be driven by differences in connectivity patterns. Dorsal frontal cortex tends to connect with posterior dorsal parietal regions supporting spatial representations, while ventral frontal areas connect with ventral temporal regions that process objects and verbal–semantic information (Wilson et al., 1993). Thus, these connectivity patterns generally align with the observation that posterior areas of prefrontal cortex (PFC) are relatively more domain specific because they have closer distance to the corresponding input (Courtney, Petit, Haxby, & Ungerleider, 1998; Nee & D'Esposito, 2016). The graded specialisation for modality in inferior frontal cortex was revealed by another study. Krieger-Redwood and colleagues found inferior frontal cortex showed graded specialisation for pictures and words using the word and picture versions of association tasks. They found that left middle IFG (BA45) showed equivalent response to picture and words while anterior IFG (BA44) showed a stronger response to verbal than pictorial associations and the posterior site supported demanding phonological tasks which are beyond the semantic domain (Krieger-Redwood et al., 2015). The above evidence suggests the heterogeneity in functions of MDN.

This heterogeneity in connectivity patterns and functions of MDN has been observed in multiple studies. Yeo and colleagues (2011) found that frontal parietal control network (FPCN) can be divided into three sub-networks. Inspired by Yeo et al. (2011), Dixon et al. (2018) identified two distinct subsystems within the FPCN, $\mathrm{FPCN_A}$ and $\mathrm{FPCN_B}$, exhibiting distinct patterns of functional connectivity with DMN and the dorsal attention network (DAN). This twofold FPCN differentiation was observed across four independent datasets, across nine different conditions (rest and eight tasks), at the level of individual-participant data, as well as in meta-analytic coactivation patterns, providing strong evidence that FPCN is heterogeneous. Both subsystems showed high loadings to general executive function topics, including working memory, switching, and conflict. However, there were also distinctions. FPCN_A was associated with "mentalizing" and "emotion" topics; FPCN_B was associated with "attention," "action," "reading" and "semantics". The frontal area of FPCN_B overlaps with the ventral frontal areas that prefer objects and verbal–semantic information (Nee & D'Esposito, 2016) and the temporal area of FPCN_B overlaps with the left pMTG that showed a stronger response overall to verbal stimuli (Krieger-Redwood et al., 2015), suggesting that FPCN_B might be specific for verbal control.

Left IFG and pMTG are specific for semantic control, even though both of these regions lie adjacent to regions implicated in domain-general executive control. Using a series of tasks, Fedorenko and colleagues (2011) found that IFG and pMTG demonstrate high level language sensitivity (i.e. semantic and syntax) using the contrast of words versus pronounceable nonwords. These two regions activated more during high-level language processing and same areas process semantic and syntactic information (Mollica et al., 2018). Recent evidence suggests that they are only sensitive to difficulty of semantic tasks rather than other non-semantic tasks. This is evidenced by that left IFG and pMTG are specifically activated by demanding semantic tasks but not demanding non-semantic tasks (Humphreys & Lambon Ralph, 2017; Noonan et al., 2013) and inhibitory stimulation of these two regions disrupt demanding semantic but not non-semantic tasks (Whitney et al., 2011). The semantic control peak lies outside the multiple demand network regions. By contrast, MDN regions, such as MFG, lack stimulus domain-sensitivity and therefore enable us adaptively implement a wide variety of tasks (Cole et al., 2013; Nee & D'Esposito, 2016). In a recent study, Alam and colleagues (2018) found right intraparietal sulcus, right inferior frontal sulcus, and bilateral lateral occipital cortex are the regions of MDN because they show common neural activity for semantic and perceptual inhibition. Our results provide further evidence that semantic control is at least partially separable from domain-general executive control. We found that structural covariance between left pMTG and left aMFG predicted performance on weak associations even after controlling for strong associations (a task comparison that is thought to highlight controlled semantic retrieval); (cf. Badre et al., 2005; Whitney et al., 2011). However, this pattern did not predict performance on a relatively demanding non-semantic task, suggesting this modulation is specific for semantic control.

Chapter 2, Finding 4. Convergence between structural and functional networks

We observed similarities between structural covariance patterns and measures of intrinsic connectivity, further supporting the interdependence of the organization of functional and structural networks. Left MFG and left pMTG, which formed a structural covariance network, had similar patterns of functional connectivity at rest, which overlapped with previously-described semantic control regions, including bilateral IFG and inferior parietal sulcus (IPS), and left posterior temporal cortex. These findings are consistent with the view that, at least to some extent, structural covariance might relate to greater cross-talk between regions.

Functional connections are at least partially determined by the underlying structural connectivity. How do functional brain networks emerge from structural brain connectivity? We can investigate how much of the pattern of functional connectivity is determined by underlying structural networks by comparing the resting state functional connectivity network with structural connectivity network. Convergent experimental and computational data suggest that there is interdependence in the organization of functional and structural networks. Patterns of intrinsic functional connectivity show striking overlap with grey matter co-variance (Seeley et al., 2009; Segall et al., 2012) and give rise to similar network parcellations (Kelly et al., 2012). The convergence between structural and functional networks can be found using other modalities and/or indexes. For example, Greicius and colleagues combined diffusion tensor imaging (DTI) tractography with resting-state fMRI to test the hypothesis that resting-state functional connectivity reflects white-matter connectivity. Using seed regions of DMN from the functional connectivity maps, they found robust structural connections between regions of DMN (Greicius, Supekar, Menon, & Dougherty, 2009). Furthermore, the topology, synchronizability and other dynamic properties of functional networks are strongly affected by small-world and other metrics of structural connectivity. Simulation studies of the human brain network show that white matter connectivity can predict resting-state functional connectivity (Dupriest, 2005). A study based on macaque brain connectivity also demonstrated that anatomical connectivity derived from axonal tract tracing provided a good explanation for resting-state functional connectivity (Shen et al., 2012). Inferring structural connectivity from resting-state functional connectivity may also be possible within subgroups of structural connections (Hermundstad et al., 2013). The results demonstrate that resting-state functional connectivity reflects structural connectivity and structural connectivity places constraints on which functional interactions occur in the network.

However, structural connectivity cannot account for all the variance in functional connectivity. Honey et al. (2009) measured resting state functional connectivity (using fMRI) and structural connectivity (using diffusion spectrum imaging tractography) in the same individuals at high resolution. They observed (i) that strong functional connections commonly exist between regions with no direct structural connection; (ii) that some of the variance in functional connectivity that was unexplained by direct structural connectivity can be accounted for by indirect connections and interregional distance. These results are in accordance with an interpretation that regions which are clearly directly linked by white matter fibre tracts should show high functional connectivity, but that the inverse need not be true as functional connectivity may also be indirectly mediated via more distant grey matter regions (Koch, Norris, & Hund-Georgiadis, 2002). Indirect interactions can account for additional functional linkages. Such indirect connections can lead to discrepancies between structural and functional connectivity; therefore combining modalities can enrich our understanding of these canonical brain networks. The regions whose structural covariance is modulated by semantic control performance show similar functional connectivity, suggesting the interdependence between structural and function.

Chapter 2, Conclusion

In summary, Chapter 2 revealed the regions that support controlled retrieval and these regions work as a network to support controlled retrieval. Our current study revealed the pattern of structural covariation between sites was a better predictor of performance on semantic control tests than the overall thickness of left pMTG itself, providing further evidence to support the view that it is necessary to use a network view to characterise the neural basis of high-level cognitive functions, such as semantic control. Chapter 2 also revealed that semantic control is partially different from domain general control, as evidenced by the structural covariance between pMTG amd aMFG is modulated by the demanding semantic task but not demanding non-semantic task. The regions whose structural covariance is modulated by semantic control performance show similar functional connectivity, suggesting the interdependence between structural and function.

Chapter 3

Chapter 3 examined brain areas/networks that supports demanding semantic task, especially the contribution of the default mode network (DMN), which is frequently associated with automatic aspects of cognition. We answered this question by exploring regions that classify goal information, using multivariate fMRI analyses of a semantic feature matching task. In line with previous findings, regions of MDN were found to represent current goal information, as specified by the task instructions; furthermore, we found that regions of DMN, within angular gyrus and posterior cingulate cortex, also represented the goal state. Our results therefore suggest that DMN supports flexible memory retrieval alongside MDN. Our results also suggested DMN and MDN show functional similarity rather than being opposite networks.

Chapter 3, Finding 1. DMN supports controlled cognition and flexibility

Converging evidence suggests that regions of DMN represent goal information. We replicate the well-established finding that goal-related information can be decoded in regions of MDN during a probe period when goal information needed to be maintained. Goal-related information could also be decoded in regions of MDN and DMN during the target period, showing that both DMN and MDN can represent goal information. Regions representing goal information during the probe period mainly overlapped with dorsal attention and frontoparietal networks, while regions representing the goal information during the target period included default, dorsal attention, and frontoparietal networks. Regions that represented feature information during the probe period showed stronger functional connectivity with extensive regions of MDN and some regions of DMN. Regions that represented feature information during target period also showed functional connectivity with extensive regions of DMN and MDN. All these results suggest that DMN represents goal information in a controlled semantic task, providing further evidence to support the view that DMN supports controlled cognition and mental flexibility rather than simply being a task negative network, reflecting the default function of the brain or automatic information processing.

We found that DMN represents goal information when using a demanding feature matching task, suggesting that DMN is not a task negative network or a default mode of brain function. DMN was originally characterised as "task-negative". Shulman et al., (1997) first noted that a constellation of areas in the human cerebral cortex consistently reduced its activity while performing various novel, non-self-referential, goal-directed tasks when these tasks were compared with a resting state (Binder et al., 1999; Raichle, et al., 2001). Furthermore, the magnitude of the DMN deactivation is related to the degree of task demand (Humphreys et al., 2015; Leech et al., 2011; Mckiernan et al., 2003; Singh & Fawcett, 2008). Lower DMN activity on a trial-by-trial basis is associated with better cognitive performance (Anticevic, Repovs, Shulman, & Barch, 2010; Daselaar, Prince, & Cabeza, 2004), indicating that DMN suppression is functionally important. However, the interpretation of BOLD deactivation of DMN is highly controversial since rest periods that are frequently used as the baseline are contaminated by self-generated thought which draws on semantic processing (Binder, 2012). Semantic tasks might elicit deactivation in DMN when the baseline contains strong semantic generation. Deactivation might also reflect the suppression of task-irrelevant inputs, allowing greater 'tuning' of the neural response to suit the ongoing task – in this context, deactivation or reduced activation would be seen in the context of increased engagement in a task. These perspectives suggest that task-related deactivation cannot be straightforwardly interpreted as lack of task engagement. In our study, we used a semantic feature matching task which was control demanding and participants had to retrieve semantic information according to an external goal, contradicting the view that DMN is a task negative network or a default mode of brain.

The demanding feature matching task we used also suggests that DMN is not only responsible for automatic information processing. It has been proposed that DMN is responsible for automatic information processing because DMN often shows stronger activation for easy or highly practiced conditions relative to harder conditions (Mcvay & Kane, 2010; Smallwood & Schooler, 2006). However, this stronger activation might be explained by the account that easier and more practiced tasks often yield a greater percentage of spontaneous thoughts (reviewed in Mcvay & Kane, 2010; Smallwood & Schooler, 2006) as well as more pronounced default network activity (e.g., (Mason et al., 2007; McKiernan, D'Angelo, Kaufman, & Binder, 2006)). While applying learned rules, the default mode network shows both greater activity and connectivity (Vatansever et al., 2017). However, this period that applying learned rules corresponds to the period that participants need to retrieve information from memory or participants yield a greater percentage of spontaneous thoughts which result in stronger activity in DMN. The evidence suggests that automatic information processing alone may not explain the stronger activation in DMN.

Our results confirmed that the DMN supports the controlled cognition and flexibility when memory retrieval is necessary, in line with recent research suggesting that DMN plays an active role in controlled cognition and adaptive flexibility (Andrews-Hanna, 2012; Crittenden, Mitchell, & Duncan, 2015). DMN increases its activity during various goal-directed tasks, especially tasks that involve memory retrieval (Spreng et al., 2010; Vatansever et al., 2017), even when they are cognitively demanding (Murphy et al., 2019; Crittenden et al., 2015; Smith et al., 2018). For example, studies indicate that the DMN can play an important role in maintaining detailed representations of task-relevant information in working memory (Sormaz et al., 2018; Turnbull et al., 2019). DMN can be engaged when participants are preparing for a task following a cue – presumably when they are retrieving the task instructions and the task information could be decoded during this instruction period (Crittenden et al., 2015; Smith et al., 2018). In other contexts, activity within DMN increases when participants have acquired the rules and must apply them – again, when memory can guide cognition (Vatansever et al., 2017). Inhibitory TMS to regions of DMN, such as AG, disrupts semantic processing, suggesting that DMN has an active engagement (Davey at al. 2016). Our results confirm that DMN supports controlled semantic cognition and flexibility by representing goal information when memory retrieval is necessary, rather than acting as a task negative network, supporting only default functions of the brain or automatic information processing.

Chapter 3, Finding 2. DMN and MDN can show functional similarity.

Our finding that both DMN and MDN can represent goal information suggests that there might not be a sharp functional distinction between DMN and MDN. DMN and MDN are normally argued to show opposite response patterns (e.g. Anticevic et al., 2012), with DMN being involved in automatic information processing (Vatansever et al., 2017) and MDN being involved in demanding tasks (Fedorenko et al., 2013). It has been proposed that DMN is responsible for automatic information processing because DMN often shows stronger activation for easy or highly practiced conditions relative to a harder condition (Mcvay & Kane, 2010; Smallwood & Schooler, 2006; Humphreys et al., 2015). MDN often shows stronger activation for hard conditions relative to the easy conditions (Duncan, 2010; Fedorenko et al., 2013). DMN and MDN often show negative functional connectivity at rest (Fox et al., 2005) and during tasks (Fornito et al., 2012a). Furthermore, greater functional integration within the DMN (Hampson, Driesen, Skudlarski, Gore, & Constable, 2006) and greater anticorrelation between DMN and MDN (Kelly, Uddin, Biswal, Castellanos, & Milham, 2008) are both associated with improved behavioural performance when attention is directed externally. This evidence suggests that the functions of DMN and MDN are in opposition. However, the dynamic interaction between DMN and MDN can change under different conditions. As task difficulty increases, the ventral posterior cingulate cortex (PCC) shows reduced integration within the DMN and less anticorrelation with the MDN activated by the task. DMN and MDN can work together to support demanding tasks (Beaty et al., 2015; Elton & Gao, 2015; Krieger-Redwood et al., 2016; Smallwood et al., 2012; Spreng et al., 2010). Furthermore, higher task-state DMN-MDN dynamic functional connectivity associate with greater cognitive flexibility (Douw et al., 2016). At rest, the dorsal PCC, a core region of DMN, shows functional connectivity with both the DMN and MDN (Leech et al., 2011). One subnetwork of MDN shows stronger intrinsic connectivity with DMN (Dixon et al., 2018). Following previous studies that have demonstrated that MDN represents task information (Bracci et al., 2017; Cole et al., 2016; Loose et al., 2017; Qiao et al., 2017; Waskom et al., 2014), recent evidence (Smith, Mitchell, & Duncan, 2018a) reveals that DMN can represent task information when the instructions of the tasks are complex and participants need to memorize them before the tasks and then retrieve them when starting the corresponding task. Our current study reveals that DMN can represent task goals when participants have to maintain the goal after the goal disappears and then apply the goal, suggesting that these networks may support overlapping functions (at least in some contexts). This evidence suggests DMN and MDN can show functional similarity, allowing the flexible interactions between the DMN and MDN under different task conditions to cope with changing environmental demands.

Chapter 3, Conclusion

In summary, Chapter 3 revealed the networks that support controlled semantic retrieval. The main finding is both DMN and MDN support controlled cognition and flexibility by representing current goals in a demanding semantic task, suggesting that these two networks can show functional similarity rather than being opposite networks.

Chapter 4

Chapter 4 explored the organization principle of networks that support semantic cognition. Chapter 4 investigated how human cortex is organised to produce a spectrum of cognition, from efficient memory-based decisions to more flexible novel patterns of thought. We addressed this question by asking participants to match words on the basis of a specific semantic feature, such as colour, while parametrically varying other features. This created a ‘psychological gradient’ varying from strong to weak convergence between long-term memories and evolving task demands. We then investigated whether this psychological gradient co-varied with a previously-described connectivity gradient which captures transition along the cortical surface from perception and action, through executive control areas, to regions of the so-called default mode network. To examine whether these graded transitions capture the layout of networks involved in semantic processing, we defined DMN and MDN and established that the peak response for semantic control in previous studies fell midway between these networks in temporal and frontal cortex. We found that there is a functional gradient of semantic cognition and this functional gradient can explain the spatial layout of networks that are related to semantic cognition.

Chapter 4, Finding 1. Functional gradient of semantic cognition

The functional gradient might be a general principle of whole brain organisation. We found a correspondence between the psychological gradient and the connectivity gradient in multiple cortical zones, including medial PFC which is not a visual processing area, suggesting the functional gradient is a general principle of whole brain organisation that captures multiple local gradients, instead of reflecting the retrieval of specific visual features. The association between the connectivity gradient and the psychological gradient was apparent in data from individual runs within individual brains, suggesting it is not a product of spatial averaging. This evidence suggests that the functional gradient might be a general principle of whole brain organisation and the functional gradient might be driven by the connectivity gradient.

A gradient principle can explain the topological organization of primary and association cortex. Functional localization in some domains appears to follow gradients across the cortical landscape. For instance, cortical visuotopic maps organize into a supra-areal structure such that visual topography varies smoothly across areal boundaries (Rosa, 2002). Multiple local gradients in the association cortical regions have been revealed, including ventrolateral ATL (Lambon Ralph et al., 2017), lateral PFC (Badre & D'Esposito, 2009) and medial PFC (Chester & DeWall, 2019; Denny et al., 2012; Sul, Tobler, Hein, et al., 2015). Recent evidence suggests that whole-brain gradients can explain the topological organization of association cortical regions. Margulies et al. (2016) used a diffusion embedding algorithm and produced an axis that represents relative differences in connectivity patterns by a region's position on the axis. Their results demonstrate that the axis describing the most variance forms a functional gradient; sensory and motor regions load on one end while regions of DMN load on the other, including the medial prefrontal, middle temporal, and dorsal prefrontal cortex and the dorsal and anterior cingulate cortex. The functional gradient is related to the spatial configuration of functional regions across the cortex. Margulies et al., (2016) showed that regions within the default network tend to lie spatially furthest away from primary sensory and motor regions. Specifically, a region's loading on the principal gradient is strongly predicted by its distance to peak locations within the default network. In other words, regions that tend to be maximally dissimilar from these higher-order association zones in terms of their connectivity also tend to lie furthest from them spatially. This evidence suggests that there might be a macroscale principal gradient of cortical organization.

A similar topographic gradient from sensory motor cortex to association cortex has been revealed using other indexes. Lerner and colleagues revealed a topographic mapping of a hierarchy of temporal receptive windows, which is the length of time before a response during which sensory information may affect that response, using a narrated story. They found that temporal receptive windows increase gradually from sensory areas with short temporal receptive windows up to higher-order areas with long temporal receptive windows (Lerner, Honey, Silbert, & Hasson, 2011). This effect was replicated in different methods. Simony and colleagues found that the inter-subject functional correlation (ISFC) over the course of the narrative in the auditory network is driven by transient features of the story because mean ISFC in the auditory network was similar for each paragraph, regardless of whether that paragraph had been presented in the scrambled context or in the intact context. However, in the DMN, the ISFC time course was qualitatively different when the order of the paragraphs had been scrambled, suggesting that the changes in inter-regional correlations in the DMN depend on the previous history and context of each moment within the narrative (Simony et al., 2016). Gonzá Lez-García and colleagues compared the representational similarity of visual images across different regions and networks and found that neural representations of visual stimuli were structured in a hierarchy that remained stable across conditions, with early visual areas and DMN anchored at the two extremes. Two large-scale cortical gradients occur along this hierarchy: first, the dimensionality of the neural representational space increased along the hierarchy; second, the prior's impact on neural representations was greater in higher-order areas (Gonzá Lez-García, Flounders, Chang, Baria, & He, 2018). These studies provide converging evidence to support a macroscale principal gradient of cortical organization.

We found a correspondence between the psychological gradient and connectivity gradient, suggesting that the functional gradient might be related to the connectivity gradient. As the functions of the PFC rely closely on its connections with a vast array of other cerebral structures. None of its cognitive functions can be understood if taken out of a broad connectionist context (Fuster, 2001). In line with this view, regions that show local gradients often show connectivity gradients. The local gradients in ATL (Lambon Ralph et al., 2017), PFC (Badre & D'Esposito, 2009) and medial PFC (Chester & DeWall, 2019; Denny et al., 2012; Sul et al., 2015; Jackson, Bajada, Ralph, & Cloutman, 2019) have been previously described. The corresponding connectivity gradients in each region have also been revealed. Nakae et al. (2019) found a connectivity gradient along the anterior-posterior axis of IFG, with the more anterior part of the IFG connecting to the more anterior part of the lateral temporal area, and the more posterior IFG connecting to the more posterior temporal area. Jackson and colleagues accessed the structural and functional connectivity of each voxel in the ventral medial prefrontal cortex to delineate changes in the pattern of connectivity across this region. They identified a highly graded change in both the structural and functional connectivity of the ventral medial PFC, with regions with distinct connectivity being distinguished at either end of this gradient (Jackson, Bajada, Ralph, & Cloutman, 2019). The multiple local gradients and corresponding connectivity gradients in ATL, PFC and ventral medial PFC suggests that whole-brain gradients might be a general principle of brain organization which are related to the connectivity gradient. We found that our psychological gradient correlates with the connectivity gradient at the whole brain level and in multiple zones, providing further evidence to support to view that there is a functional gradient related to distance between DMN and primary regions. Our study revealed a psychological gradient which did not use the method – diffusion embedding – that can only produce gradient patterns, suggesting that the psychological gradient is independent of the specific research method.

Chapter 4, Finding 2. The psychological gradient can explain the spatial arrangement of semantic related networks.

In line with the connectivity gradient, our findings show gradual transitions between multiple networks supporting semantic cognition, which are organised along a functional gradient – with activation towards the DMN reflecting patterns of conceptual retrieval when current goals closely align with the structure of long-term knowledge, and activation towards MDN reflecting the need to identify a match from goal representations when conceptual knowledge is not shared. This functional gradient can explain the spatial layout of networks related to semantic cognition, with the semantic control network falling in-between DMN and MDN. We found that the psychological gradient values decreased gradually from DMN to MDN, suggesting the psychological gradient explains the spatial layout of networks supporting semantic cognition, with semantic control regions falling between DMN and MDN on the cortical surface. A similar network transition is captured by the connectivity gradient (Margulies et al., 2016), providing further support for the correspondence between these two gradients.

Chapter 4, Conclusion

Chapter 4 explored the organization principle of networks that support semantic cognition and investigated how human cortex is organised to produce a spectrum of cognition, from efficient memory-based decisions to more flexible novel patterns of thought. We found that there is a functional gradient of semantic cognition and this functional gradient can explain the spatial layout of networks that are related to semantic cognition. Graded transitions in the BOLD response from DMN to executive cortex might reflect the shift from intrinsically-guided retrieval based on representations in memory, to goal-driven cognition instantiated by cues in the environment (which, in this experiment, were the instruction slides specifying the feature type for each trial). DMN regions show stronger activation when semantic tasks are guided by memory (Humphreys & Lambon Ralph, 2015; Lau et al., 2013; Wirth et al., 2011). In contrast, when task requirements are not a good match with the information in memory, a complementary strategy is needed in which intrinsic cognition is temporarily suppressed.

Future directions

This thesis provides evidence for the neural basis of flexibility in semantic retrieval. Naturally, there are questions which remain to be answered in view of the findings presented here. Firstly, we need to replicate our findings from Chapter 2, using matched semantic tasks and non-semantic tasks. The current Chapter 2 used the contrast of hard versus easy semantic judgements to investigate semantic control and the contrast of hard non-semantic judgements with an easy semantic task to investigate general executive control. Since the contrast between semantic control and general executive control is not well matched, conclusions about the dissociation between semantic control and general executive control is weakened. In the future, we can adopt an easy and a difficult non-semantic task and then examine whether the structural covariance between pMTG and aMFG is modulated by general executive control performance after controlling for the easy condition. We can adopt another paradigm that explores semantic control, such as retrieving dominant versus subordinate meanings to explore whether our findings are replicable to rule out the possibility that the original results are due to idiosyncrasies of the original stimulus sample.

Secondly, in Chapter 3, we found that regions of DMN, PCC and AG, represent goal information when retrieving information from memory. However, since we lacked a matched non-semantic task that does not require memory retrieval, we cannot establish whether the goal representation in DMN is specific for a memory retrieval task, or would be found in other non-semantic executively-demanding tasks. Using a perceptual feature matching task and then conducting a similar classification analysis, we could examine whether memory retrieval is necessary for goal representation in DMN. If the goal information can be decoded during a perceptual feature matching task, it indicates that memory retrieval is not necessary for goal representation in DMN. Otherwise, it supports the theory that memory retrieval is an important function of DMN, in line with the view that DMN supports external task processing when behaviour depends on pre-existing representations guiding cognition (Margulies & Smallwood, 2017; C. Murphy et al., 2018; Nathan Spreng et al., 2014; Smallwood et al., 2013).

Thirdly, in Chapter 3, we found that regions of DMN and MDN represent goal information. However, we cannot reveal what they exactly represent: abstract goal representations (i.e., colour as an organising principle) or specific feature information (i.e., the colour of strawberries). We could conduct another fMRI experiment, using the same feature matching task combined with pairwise feature similarity ratings for all the probe words. We could ask participants to do the pairwise feature similarity ratings for all the probe words and then build a representational dissimilarity matrix (RDM) for these ratings. Then we present each trial multiple times when scanning participants to get a steady activation pattern for each trial, allowing us to build a RDM for the neural activation pattern of the probe words and to do single-trial analysis. Finally, we would calculate the correlation of these two RDMs. If there was a significant correlation within the regions that represent goal information, it would indicate these regions represent specific goal information. Otherwise, it would suggest these regions represent abstract goal information.

Fourthly, in Chapter 3, there might be at least two possibilities to explain why DMN can represent goal information. One is driven by the functional connectivity between DMN and MDN. Although DMN and MDN often show anticorrelated activity across a range of experimental paradigms, they can reconfigure their functional architecture in a context-dependent manner. This is consistent with recent evidence that PCC, one of core DMN hubs (Zhao et al., 2017), showed increased connectivity with left medial temporal lobe memory system during more automated information processing, and increased connectivity with MDN during tasks that depend on the maintenance or extended evaluation of information (Andrews-Hanna et al., 2014; Dixon et al., 2017; Spreng et al., 2010; Vatansever et al., 2015; Vatansever, et al., 2017) in a way that predicted performance (Elton & Gao, 2015; Fornito, Harrison, Zalesky, Simons, & Analyzed, 2012b; Krieger-Redwood et al., 2016). This effect has been replicated. DMN shows increased cooperation with the frontoparietal network when memory retrieval is required (Fornito et al., 2012; Spreng et al., 2010) and the increased cooperation facilitates rapid memory recollection (Fornito et al., 2012). The dynamic interaction between DMN and MDN might allow DMN to represent goal information like MDN. Another possibility is that the representation of goal information in DMN might be achieved by modulating feature-selective visual regions (colour, shape, size). It has been observed that DMN modulates stimulus-selective visual regions in a way that predict performance. Chadick & Gazzaley, (2011) found that DMN (i.e. medial PFC and PCC) was functionally coupled with the visual cortical areas processing irrelevant stimuli, and the coupling was predictive of task performance. Heekeren and colleagues found that activity within the one region of DMN, left dorsolateral prefrontal cortex, covaries with the difference signal between face- and house-selective regions in the ventral temporal cortex and the coupling predicts behavioural performance in the categorization task in which subjects decide whether an image presented is a face or a house (Heekeren et al., 2004). These findings suggest that DMN modulates stimulus-selective visual regions and the dynamic interaction between DMN and feature-selective visual regions might allow DMN represents goal information. We could perform classification analysis using functional connectivity or use dynamic causal modelling to explore how DMN represents goal information.

Fifthly, in Chapter 4, we found that the functional gradient from DMN to MDN corresponds to the psychological gradient: from memory-based to novel cognition by varying the global feature overlap in a semantic feature matching task. However, a single study cannot fully specify the critical aspects of the task which gave rise to the psychological gradient. We do not know whether a similar functional gradient appears when manipulating the difficulty of semantic tasks in other ways, such as via varying the association strength of word pairs. In addition, we do not yet know if a similar pattern emerges for a parametric manipulations of difficulty within non-semantic tasks, such as a perceptual task. Therefore, future studies that parametrically manipulate other types of semantic tasks and non-semantic tasks should provide a great opportunity to examine the generalization/specificity of the functional gradient.

Sixthly, in Chapter 4, we focused on analysing data averaged across groups rather than studying individual brains. This might be problematic because averaging small amounts of data from larger groups of individuals which may mischaracterize some aspects of the functional organization of the brain because individuals exhibit distinct brain network topography and topology (Gordon et al., 2017; Poldrack, 2017; Braga and Buckner, 2017). Therefore, an fMRI study that scan the participants multiple times when performing tasks and at rest would give us the opportunity to examine the psychological gradient patterns at the individual level. We can create the steady psychological gradient and connectivity gradient of each participant by averaging each participant's multiple task and resting state data, respectively. Then we examine the convergence and differences in gradient across modalities. It also allows us to examine whether the functional gradient we found correlates with physical distance along the cortical surface on each individual. We can define the peaks of DMN, MDN and the peak that is modulated by the difficulty in each individual. We can calculate the physical distance along the cortical surface between these peaks. Therefore, the individual study would also allow us to examine whether the functional gradient is related to its functional connectivity gradient.

Conclusion

This thesis partially reveals how flexible semantic cognition emerges. Firstly, we revealed the regions and networks that support controlled semantic retrieval and then we found there is a psychological gradient that can explain the spatial arrangement of these networks that support controlled semantic retrieval. We found that the flexible semantic cognition emerges through the combined action of multiple regions and multiple networks, DMN, semantic control and MDN. There is a principle gradient can explain the spatial arrangement of these networks. Semantic control regions fall at the intersection of DMN and MDN, with these networks showing a systematic arrangement along the gradient.

We found the regions (pMTG, a critical region of semantic control network) and networks (DMN, semantic control and MDN) that are important for controlled semantic retrieval. Then we found a psychological gradient can explain the spatial arrangement of these networks to support flexible semantic retrieval. Our findings show systematic transitions between multiple networks supporting semantic cognition, which are organised along a functional gradient – with activation towards the DMN reflecting patterns of conceptual retrieval that closely align with the structure of long-term knowledge, and activation towards MDN reflecting more adaptive coding of current conceptual demands. This functional gradient can explain the spatial layout of networks related to semantic cognition, with semantic control network falling in the middle way of DMN and MDN.

In conclusion, this thesis partially reveals how flexible semantic cognition emerges – e.g. through the combined action of multiple regions; through the action of heteromodal regions in both DMN and MDN, with semantic control regions falling at their intersection; with these regions showing a systematic arrangement along the gradient.

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