Hemispheric Differences in Semantic Cognition and Their Contribution to Behaviour

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Doctor of Philosophy

University of York

Psychology

December 2019

Abstract

This thesis investigated hemispheric differences in semantic cognition and their contribution to behaviour, using resting-state and task-based fMRI in conjunction with automated meta-analyses and cognitive decoding. The controlled semantic cognition framework proposes that distinct brain regions support the long-term representation of heteromodal conceptual knowledge and semantic control processes that retrieve currently-relevant aspects of knowledge. However, previous studies have not investigated whether these components have distinct patterns of lateralisation. Chapter 2 assessed intrinsic connectivity of four regions implicated in semantic cognition: anterior temporal lobe, angular gyrus, inferior frontal gyrus, and posterior middle temporal gyrus. Semantic sites in the left hemisphere showed connectivity with both control regions and default mode network, whilst their right hemisphere homotopes showed connectivity with control regions and visual and attentional systems. Semantic control regions showed the strongest lateralisation. Chapter 3 examined hemispheric specialisation of the anterior temporal lobes, strongly implicated in semantic representation. It assessed the relationship between differential intrinsic connectivity and behaviour outside the scanner on a semantic categorisation task previously shown to be sensitive to lateralisation. Graded differences in connectivity between left and right anterior temporal lobes, and from right anterior temporal cortex to the visual system related to semantic efficiency. Finally, Chapter 4 tested the specificity of the semantic control system and its relationship to domain-general control. Using a task known to engage domain-general inhibition, but introducing semantic content, this chapter yields evidence that regions implicated in semantic control are not sensitive to challenging tasks that require exercising controlled processing, and instead are specific to semantic processing. Together, these results constitute evidence for a component-process architecture in the semantic cognition system, with different patterns of lateralisation for the semantic representation and control systems. Within these systems, the results confirm the specific nature of semantic control, and fit with the graded-hub architecture of semantic representation.

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Acknowledgements

I dedicate this work to my mother, who believed in me, loved me and showed me the way, even when she did not know it herself (and to my brother, who has so bravely looked after her): mom, everything I am is thanks to you.

To Damian, whom I hope to know how to love and guide as well as I have been loved and guided myself: I will try to leave a better world for you than the one I found, son. And to Kat, who showed me worlds I did not know existed.

Carolina, thank you for your powers of prophecy, love and magic: you never forgot how to dream, and knew how to paint a future when none was at sight. May I someday learn even 1% of your powers.

To Diana, who will never know, and to Lorena, for never letting go.

I would like to extend the most special gratitude to my supervisors. I have been lucky to have worked with really talented people over the years, but you guys take a special place. Beth: Your patience, understanding and kindness are unparalleled. It is a rare treat to find a mind so sharp in such a kind person. Watching you elaborate on thoughts on ideas in front of me, and then so gently and effortlessly share them was always one of my favourite things, as well as the genuine interest you take in fairness and people's well-being. Jonny: It's awesome to find someone who at the same time feels like a mentor and a friend; you exceled in both. It's been a pleasure to witness such intelligence in such a cool and genuine person. You two were, and are, great role models for me. It's been one of the greatest honours (and joys!) of my life to work with you. I am especially indebted to you two and looking forward to a continuous collaboration.

To all the people in the Semantics and Mind Wandering lab, who provided endless hours of scientific and non-scientific chats alike. Thanks for so much help, for so many conversations, shared laughter, great (and not so great) times, nights out and random lab fun. You were truly home away from home.

To all of those who shone a light with their beautiful mind, paved the way with their effort and helped me walk all the way here: To Felipe, Dr. Villa, Juan Valadez, Dr. Sanchez Sosa, Paco, Rosi and Alejandro Herrera. To Juan Lago, Marisol Castaneda, Sarai Vazquez, Alba Garcia (The OG's!), Cecil Ruano, Lore, Sarai Cervantes and the rest of the Anahuac Mayab

group. I grew up as a scientist, and more importantly, as a person, thanks to you all. You taught me we don’t do science to prove we’re right, we do science to become right.

To Alejandro Gonzalez and Betty Canton, who believed in me and gave me the opportunity to prove my worth. I remember being so confused and insecure at the end of the MSc, and getting a great job from you, which turned out to be a place to grow. I owe this too to you.

To my friends from Mexico: Pablo, Diego(s), Vicente, David, Fernando, Omar, Alex(s), Jeros, Hoyos, el Pollo, Gus, Andy, Kuino, Zizi, Luisa, Carmen, Dash, Andrea, Albania, Odette, Cassandra, Aaron, Matos, Maria Jose, Juan, Flor, Gabriel, Tamyko, Roxana, Jasso, Salim, Gemelos, Dante, Edilberto, Mike and so, so many more. Although most of us are spread all over the world now, I still feel we’re one big family and you’re just one call away. Thanks for so, so much life and love: words wouldn’t be enough. Les quiero, banda.

To the friends I’ve made in York (and the rest of Europe). Zdenko, Ruggero, Helen, Simon(s), Vero(s), Gerardo, Julie, Claire, Christianna, Alice, Em(m)a, Bernie, Emily, Adam, Mary, Nathan, Irene, Sara, Lucilla, Theo, Mahiko, Aurelio, Moni, Paola, Renata, Barbara. I don't know half of you half as well as I should like; and I like less than half of you half as well as you deserve. And yes, I stole that quote.

To those of you who helped me and supported me along the way. I literally wouldn’t have made it and be able to stay here without you. Diego, Carolina, Carmen and Emily especially stand out: your kindness will never be forgotten, and hopefully will be repaid in kind.

I would especially like to thank the People of Mexico, who through CONACyT paid for me to have this opportunity. For a country so much in need, betting on science is betting on hope. May your hopes be fulfilled, and may I know how to repay you and not let you down.

Y para América Latina, ese pueblo sin piernas pero que camina (dónde se respira lucha, dónde cantamos porque se escucha): Por mi raza hablara el espíritu.

Author's Declaration

I declare that this thesis is a presentation of original work and I am the sole author. This work has not previously been presented for an award at this, or any other, University. All sources are acknowledged as References.

Two chapters of this thesis have been published as papers in the journal NeuroImage:

Chapter 2:

Gonzalez Alam, T. R. del J., Karapanagiotidis, T., Smallwood, J., & Jefferies, E. (2019). Degrees of lateralisation in semantic cognition: Evidence from intrinsic connectivity. *NeuroImage*, *202*(June), 116089. https://doi.org/10.1016/j.neuroimage.2019.116089

Chapter 4:

Gonzalez Alam, T., Murphy, C., Smallwood, J., & Jefferies, E. (2018). Meaningful inhibition: Exploring the role of meaning and modality in response inhibition. *NeuroImage*, *181*(February), 108–119. https://doi.org/10.1016/j.neuroimage.2018.06.074

Supervisor's Declaration

I declare that this thesis is primarily the work of Tirso Gonzalez Alam. My contribution to the papers listed above was primarily editing and supervision of the research. Tirso Gonzalez Alam completed the analyses, took the primary role in writing scripts, and wrote the first draft of the manuscripts above.

Prof. Elizabeth Jefferies,
PhD supervisor

Chapter 1. Introduction

1.1. Introduction

Hemispheric specialisation is one of the hallmarks of brain function. It was one of the earliest findings of modern neurology, with Broca (and, less known, Dax) challenging the doctrine of symmetrical hemispheric functioning with his case series showing a more detrimental effect of brain damage to language when the damage is left lateralised (Broca, 1865; Manning and Thomas-Anterion, 2011). When Broca described 'the language faculty' as being lateralised to the Left Hemisphere (LH), neurocognitive functions were often thought to be represented in a single brain region, reflecting the localizationist influence of phrenology (Zola-Morgan, 1995). In contrast, we now understand complex cognitive functions as emerging from the interaction between brain regions that are widely distributed across the cortex and organised across cortical gradients dependent on geodesic distance (Bressler and Menon, 2010; Margulies et al., 2016; Medaglia et al., 2015; Yeo et al., 2011). This distributed view of neurocognitive function requires a more nuanced account of lateralisation, as it argues that higher order cognitive functions are often an emergent property of the interaction of multiple processes that are localised in different parts of the brain. This component-process account paints a more complex picture of hemispheric specialisation; one where the lateralisation of a function is not monolithic, but instead functions that were previously described as lateralised can be implemented in a combination of unilateral and bilateral networks that dynamically interact.

Furthermore, although language lateralisation has been investigated in depth, the hemispheric differences in semantic cognition have been subjected to substantially less scrutiny. A Google Scholar search for "lateralization" coupled to "language" yields 67,800 results, whereas the same term coupled to "semantics" yields merely 9,980[1]. The aim of the present body of work is to address both these issues: the thesis aims to update the view on hemispheric differences, focusing on patterns of large-scale connectivity that support semantic cognition.

This introduction examines the evidence for lateralisation within a component-process account of semantic cognition known as the Controlled Semantic Cognition (CSC) framework (Lambon Ralph et al., 2017). First, it will consider evidence pointing to semantic

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[1] As of August 1st, 2019

representations being stored in the bilateral Anterior Temporal Lobes (ATL). Second, it examines the neural basis of control processes that allow the retrieval of currently relevant information as the goal or context changes, even in the absence of strong external constraints on semantic processing. These control processes draw on a domain-general executive control network known as the Multiple-Demand Network (MDN), which is thought to be generally bilateral. Nevertheless, there is evidence that specific functions supported by this network, such as response selection and inhibition, are lateralised. Third, the review discusses brain regions outside of the MDN that have been shown to be important for the control of semantic cognition, including the left anterior Inferior Frontal Gyrus (IFG) and posterior Middle Temporal Gyrus (pMTG). These sites are thought to be key nodes in a network supporting semantic control. This appears to be the most strongly lateralised component within the CSC framework, since both IFG and pMTG are implicated in semantic cognition almost exclusively in the left-hemisphere. The discussion then turns to evidence that shows that the semantic control network and the MDN are partially overlapping, yet functionally distinct networks, before finally considering what might give rise to these patterns of lateralisation within the components of semantic cognition.

1.2. Controlled Semantic Cognition Framework

Semantic cognition helps us make sense of the world around us and helps guide our thoughts and actions. As such, it is essential for intelligent, goal-oriented behaviour. The CSC framework (Lambon Ralph et al., 2017) proposes that semantic cognition involves two interacting components: semantic representations and the capacity to retrieve these in a controlled manner. According to this account, a bilateral network centred on the ATL, serves as a heteromodal semantic ‘hub’ where the perceptual, verbal and emotional features encoded in lower-level ‘spokes’ converge to form semantic representations. When necessary these representations can be retrieved in a more controlled fashion by a lateralised semantic control network, centred on the left IFG and pMTG. This review considers the evidence for the claim that the network for semantic representations is bilateral with graded hemispheric differences, while the controlled retrieval of this information is left-lateralised. Support for this proposal is provided by converging evidence from patients with deficits in semantic cognition, and investigations of healthy participants that use Transcranial Magnetic Stimulation (TMS) and functional Magnetic Resonance Imaging (fMRI).

1.2.1. Semantic representations are instantiated in bilateral ATL

Previous research suggests that heteromodal semantic representations seem to be supported by the bilateral ATL. The CSC account of ATL function suggests that this region forms a semantic “hub” drawing together different features or ‘spokes’ (from visual, hippocampal, valence, language and auditory inputs) to form heteromodal concepts (Patterson et al., 2007). This integration of different aspects of knowledge is thought to occur in a graded fashion, with the most heteromodal semantic responses in ventrolateral ATL (vATL, Lambon Ralph et al., 2017; Visser et al., 2012). Since this view suggests semantic representations reflect interactions between the hub region and the spoke systems, differences in the way various types of concepts or categories are represented and retrieved may emerge from distinct patterns of interaction between the hub and spokes. This introduction now considers the evidence that supports this claim.

1.2.1.1. Patient Evidence

Evidence for a role of bilateral ATL in semantic representations comes from patients with Semantic Dementia (SD). These patients have problems with conceptual knowledge, independently of input/output modality or task used, that impact on virtually all types of concepts —except for numerical knowledge (Cappelletti et al., 2001; Jefferies and Lambon Ralph, 2006). They show a consistent deficit with the same items regardless of the goal or context in which the information must be accessed (Patterson et al., 2007), and little benefit from cues that make retrieval easier suggesting that the problem is not in accessing concepts (Jefferies et al., 2007; Noonan et al., 2010). They also exhibit a frequency/familiarity effect, where the more frequent and familiar items are better preserved, and make errors in picture naming that affect the specific level first (Rogers et al., 2015). These patients present with atrophy and hypometabolism that peaks in ventral bilateral ATL, which hints at the role of this region as a hub that stores heteromodal semantic representations (Jefferies and Lambon Ralph, 2006).

Atrophy in SD is not symmetrical, and is often more severe in the left temporal lobe (Andersen et al., 1997). Using voxel-based morphometry, Mummery et al. (2000) showed that the left temporal pole is the region with greatest neuronal loss in SD, with left sided atrophy also observed in the inferolateral temporal lobe and fusiform gyrus. Adlam et al.

(2006) confirmed these findings of greater left ATL damage; although their patients demonstrated bilateral atrophy, only the left correlated with performance. They conclude that significant bilateral damage to the temporal lobes typically disrupts both verbal and non-verbal semantic memory in SD. Nestor et al. (2006), using combined fMRI and Positron Emission Tomography (PET), also found hypometabolism restricted to the ventral and polar bilateral temporal lobes in SD was associated with semantic memory breakdown.

There is also evidence that the lateralisation of ATL lesions has subtle functional effects. Thompson et al. (2003) found that SD patients with predominantly left-sided atrophy showed word finding and comprehension difficulties, while those with predominantly right-sided atrophy showed difficulties identifying people and other social deficits. Similar findings were described by Lambon Ralph et al. (2001), who noted that SD patients with left greater than right atrophy have more severe anomia compared with patients with more right-hemisphere atrophy, who show similar levels in production and comprehension. Mion et al. (2010) corroborated these findings in a study combining volumetric MRI and PET; they found that performance in expressive verbal tasks like picture naming and category fluency correlated with integrity of the left ATL (specifically, anterior fusiform gyrus), while the right ATL correlated with non-verbal picture-based associative semantic tasks. Snowden et al. (2004) reported a laterality effect, where SD patients with predominantly left atrophy showed better recognition for names than faces, while those with predominantly right-sided atrophy showed the reverse pattern; brain volume correlated with performance for words and pictures in a separate semantic task. Recently, Borghesani et al. (2019) reported a lateralisation effect within face recognition in SD: patients showed a correlation between naming famous people and semantic association for faces with grey matter volume in the left ATL, while the feeling of familiarity correlated with the volume of right anterior MTG.

Is bilateral ATL damage necessary for semantic dysfunction, or does this happen after unilateral damage as well? Evidence derived from other patient groups converges on the importance of the ATLs for semantic representations, and shows that unilateral damage can affect performance, yet there is a degree of resiliency probably afforded by the redundancy of the system. Patients with unilateral temporal damage can perform with normal accuracy on standard semantic assessments, though anomia can be observed after left-lateralised damage in low-frequency concepts (Antonucci et al., 2009; Kemmerer et al., 2012; Lambon Ralph et al., 2010; Tranel, 2009; Tsapkini et al., 2011). Patients with unilateral temporal resection due to epilepsy also perform normally, except for the most demanding items, or in tasks that gauge reaction times, and even then, they match the mildest SD cases (Antonucci et al., 2009; Drane et al., 2008). Patients with fast-growing gliomas in ATL that undergo unilateral resection show reduced semantic accuracy, in contrast with slow-growing gliomas that perform well on semantic tasks, even after temporal resection (Campanella et al., 2009). This suggests that in unilateral lesions, am injury that develops in a brief period that does not allow time for compensation or functional adaptation may be a factor for semantic impairment. In patients with post-stroke left ATL lesions, verbal comprehension correlates with the integrity of functional connectivity between left and right ATLs (Warren et al., 2009), confirming the importance of redundancy for the resiliency of this system. Nevertheless, patients with unilateral ATL damage are less severely affected than SD patients with bilateral atrophy. Lambon Ralph et al. (2012) showed that when patients were assessed with sensitive measures of semantic processing, such as low frequency, more abstract or specific-level concepts, a semantic impairment was found for all patients who had undergone temporal lobectomies, regardless of hemisphere. However, on simple word-picture matching tests that show longitudinal decline in SD, there was little impairment. Rice et al. (2018a) expanded on these findings by studying patients with temporal lobe epilepsy that underwent either left or right ATL lobectomy. The results showed that lesions to either side were associated with problems in receptive and expressive verbal semantics, and deficits in recognising objects and words, perceiving faces and emotions, as well as recognising and naming famous faces. The authors also report graded differences with tasks that required naming or accessing information from written words being more impaired in left-resected patients, whilst right-resected patients showed a poorer performance in recognising famous faces. Rice et al. (2018b) then tested whether compensation in the semantic system following damage to either ATL was implemented through upregulating the rest of the semantic system (i.e. left IFG/pMTG) or the intact ATL. Patients and control participants showed no differences in activation when tasks where picture-based, but when words were presented visually there was a left-lateralised activation pattern, as well as a significant difference across patients: those with left ATL resection upregulated both the right ATL and right IFG, whilst right ATL resected patients only increased activation in left IFG.

Overall, the results of studies on SD patients paint a mixed picture, where bilateral damage to ventral ATL produces severe semantic dysfunction, but with subtle differences between patients with more left-sided and right-sided atrophy. This could result from bilateral heteromodal semantic representations yet graded differential connectivity between hemispheres, with the LH preferring verbal stimuli while the RH makes a more important contribution to visual stimuli including faces (Richard J. Binney et al., 2010). This is in accordance with recent research that has produced a more nuanced hypothesis about ATL function in the form of the graded hub hypothesis (Rice et al., 2015a). This account helps explain the differences between left and right ATL seen in neuropsychological literature. According to this hypothesis, semantic representations are instantiated in bilateral ATL, but with graded functional specialisation arising from differential and asymmetric connectivity between ATL sub-regions and perceptual and limbic spokes. Variations in the strength of connections across and within the ATLs lead to graded specialisation in the types of information represented. Even though the ATLs function as a representational hub as a whole, second-order specialisations emerge as a function of the particular pattern of connections exhibited by different parts of the system. These specialisations are subtle, and overall, the ATLs are not segregated in function. As a consequence, if there is any lateralisation of function in systems that connect to the hub, this will be mirrored to a degree in hemispheric differences in ATL, since each ATL has stronger connectivity to its own hemisphere. This would explain deficits in face and social processing after right ATL damage, and verbal deficits for left ATL. At the same time, the subtle nature of this specialisation would accommodate the fact that it takes bilateral damage to produce a marked semantic deficit, yet unilateral damage can produce subtle dysfunction.

1.2.1.2. Healthy Participants

Making inferences about the localisation of normal cognitive function from patient data can be problematic. A few problems with patient studies are that they assume modularity or localisation of functions; lesions rarely adhere to functional borders in the human brain; they disregard redundancy and functional compensation; individual differences in brain structure and function make inference from overlapping patients dubious; brain regions might be intact but disabled after injury; and lastly, plasticity and diaschisis may cause the way the lesioned brain is functioning to be nothing alike the normal brain (Rorden and Karnath, 2004). Due to these reasons it is important to corroborate these findings in healthy participants. This converging evidence for a role of the ATL in semantic representation comes from inhibitory TMS and fMRI studies of healthy volunteers.

1.2.1.2.1. TMS Evidence

One way to support studies from patients is by generating a ‘virtual lesion’ through TMS. This technique has provided additional evidence supporting the hypothesis that semantic representations are encoded in ATL. Evidence from this method is compatible with the patterns of impairment seen in patients. Applying repetitive TMS (rTMS) to left ATL leads to a pattern of deficit with slowing in both picture naming and word comprehension but not in other equally demanding, non-semantic cognitive tasks regardless of modality (Pobric et al., 2010a). Temporary disruption to neural processing in left ATL using the same method increases naming latencies at the specific level (but not at basic level) and in synonym judgements, while sparing number naming and number quantity decisions (Pobric et al., 2007). Verbal semantic decisions are slowed by applying off-line low-frequency rTMS to disrupt neural processing in either left or right temporal poles (Lambon Ralph et al., 2009). Consistent with the claim that both temporal poles are involved in semantic processing, rTMS to either left or right temporal poles significantly slows synonym judgement (again, sparing number judgement), particularly for abstract items; although accuracy only decreases for abstract items after stimulation to the left, but not right temporal pole (Pobric et al., 2009).

TMS has also replicated the patterns seen in patients regarding the heteromodal nature of these semantic representations within the ATL. Applying off-line low frequency rTMS reduces the efficiency of semantic judgements to words and pictures to the same degree (sparing equally demanding perceptual tasks) regardless of whether stimulation is applied to left or right ATL (Pobric et al., 2010). This suggests that both temporal poles participate in the neural network that supports heteromodal conceptual knowledge.

This method has provided confirmatory evidence not only for the ATL as a semantic hub, but also for other regions acting as lower-level perceptual ‘spokes’ critical for semantic representations. Applying rTMS to ATL in healthy participants causes a category-general impairment, while stimulating the intraparietal cortex induces a category-specific deficit for manipulable objects, which draw on praxis features. In contrast, naming of both living and non-living things is slowed by ATL stimulation (Pobric et al., 2010b). This supports the view that both the ATL heteromodal semantic hub and the modality-specific association ‘‘spokes’’ are necessary for semantic representations.

The relationship of general semantic knowledge with lower level spokes has also been confirmed in the visual system using TMS. One study compared TMS to lateral occipital cortex (LOC) versus ATL while participants performed an object-matching task where they could be instructed to match objects based on either perceptual or conceptual size. The study found that when participants judged perceptual size, performance was disturbed by stimulating LOC but was resilient to ATL stimulation (Chiou and Lambon Ralph, 2016a). In contrast, when participants judged conceptual size, both LOC and ATL stimulation disturbed performance. This adds further evidence that ATL contributes to object size judgements when the context requires semantically based linkage of visual attributes to object recognition. This could be a specific case of the ATL supplementing the visual system with top-down knowledge to aid perceptual processing. A related study using transcranial theta-burst stimulation confirmed this, showing that, when degraded perceptual input makes semantic knowledge necessary for identification, left ATL contributes to discrimination between visual objects, resolving discordance and discerning analogously-coded exemplars (Chiou and Lambon Ralph, 2016b).

Some hemispheric differences in conceptual processing have been documented using brain stimulation methods. Using rTMS, Pobric et al. (2016) found social cognition shows graded interhemispheric differences in superior ATL. While the left superior ATL was necessary for processing both social and nonsocial abstract concepts, the right superior ATL showed a stronger contribution to social conceptual processing. Hemispheric differences have also been found regarding the behavioural output expected for the task; Woollams et al. (2017) showed that picture naming is specifically slowed when applying rTMS to left but not right ATL, with no effect regardless of hemisphere for a number naming control task. Transcranial direct current stimulation to the ATL regardless of hemisphere increases the efficiency of judgements involving the function or manipulation of common tools (Ishibashi et al., 2018). The same technique, however, shows a hemispheric difference in knowledge of faces, with the right vATL being particularly susceptible to disruption for memory of famous faces (Chiou and Lambon Ralph, 2018).

1.2.1.2.2. fMRI Evidence

Research using fMRI has confirmed the role of bilateral ATL in semantic representations. A large-scale Activation Likelihood Estimate (ALE) meta-analysis looked at 97 fMRI studies for ATL involvement in semantic cognition, finding bilateral activations of this region overlapping across all kinds of stimuli, but with subtle gradations both between and within the ATLs. Activations were more likely to be left-lateralised for written words or if word retrieval was needed (Rice et al., 2015b). A separate review suggested that these functional gradations both between and within the ATLs arise from differential connectivity with primary sensory, motor and limbic regions (Rice et al., 2015a).

The functional complexity of this region's graded connectivity has been confirmed in a recent parcellation study. Jackson et al. (2017) acquired resting state scans of 71 participants using dual echo gradient echo planar imaging, which helps overcome the signal dropout usually found near the temporal poles. They performed a connectivity-based parcellation of the temporal lobe and related it to semantic task data, finding that the temporal lobe in general is organised along an axis that progresses from superior temporal gyrus and inferior posterior temporal cortex to ventrolateral ATL. This parcellation found a functional division in posterior and anterior clusters: the posterior (and superior) clusters were modality-specific (posterior inferior regions were involved in visual processes, and superior in audition), and the anterior cluster was heteromodal (centred on vATL proper).

Even constraining examination to the anterior aspect of the temporal lobe highlighted by this parcellation reveals abundant functional complexity. Intra-ATL connectivity within this anterior cluster reveals convergence of information from different modalities, rostrally and laterally, which culminates in vATL (Binney et al. 2012; Lambon Ralph 2014; Rice et al. 2015a). The vATL and anterior MTG connect to areas involved in multimodal semantic cognition, like bilateral ATL, IFG, medial prefrontal cortex, Angular Gyrus (AG), pMTG, and medial temporal lobes. On the other hand, Superior Temporal Gyrus / Superior Temporal Sulcus (STG/STS) connect to a different set of areas, more related to language and audition, including SMA, postcentral and precentral gyri, posterior temporal, bilateral STG, posterior temporal cortex and supramarginal, middle and inferior frontal gyri (Jackson et al., 2016; Murphy et al., 2017). A Psychophysiological Interaction (PPI) analysis using an active semantic task in Jackson et al. (2016) highlighted the same semantic regions outlined above through resting state connectivity (plus vATL's connectivity to occipital and frontal cortex) suggesting a core semantic network active during both rest and task states. More recent research using Independent Component Analysis (ICA) on fMRI data, however, has highlighted the possibility that there are distinct networks involved in cognition during active task states and rest in the ATL. Jackson et al. (2019) showed the Default Mode Network (DMN) and semantic network are two distinct coherent resting-state networks that overlap in the ATL. Assessing the cognitive signature of these spatiotemporally coherent networks directly (and therefore accounting for overlapping networks) showed involvement of the semantic network, but not the DMN, in task-based semantic cognition.

This complex, mosaic-like role of bilateral ATL as a heteromodal hub concurs with fMRI research using methods that focus on the structural connections of this region. A study using Diffusion Tensor Imaging (DTI) and probabilistic tractography (Papinutto et al., 2016) performed a hypothesis-driven parcellation looking at every ATL voxel's ipsilateral connectivity to eight target regions involved in different cognitive networks. The results showed six discrete clusters within each ATL that exhibited preferential connectivity to different networks (spanning occipital, orbitofrontal, posterior temporal and perisylvan language regions) through four major fibre tracts: inferior and middle longitudinal, arcuate and uncinate fasciculi. This study found hemispheric differences in structural connectivity, with stronger connections between the ATL and orbito-frontal areas in the Right Hemisphere (RH), and a more consistent connection between ATL and IFG through the arcuate fasciculus in LH.

A recent study focused on data-driven structural connectivity techniques (Bajada et al., 2019) using three-dimensional Laplacian Eigenmapping (to visualise similarity in a low-dimensional space in terms of distance between data points) to explore vATL's position as a central hub that integrates lower-level spokes in a graded fashion. The findings demonstrated a clear distinction between the connectivity of the medial and lateral portions of the ATL, with the lateral portion showing similarity with both auditory and visual, primary and secondary cortices, eventually converging in vATL. This study shows vATL is the region where the connectivity profiles of all other voxels in temporal cortices converge, and provides further evidence for a graded convergence model of semantic representations in vATL. Integration across all different modalities does not occur within a hard, delineated border in the 'hub' region, like an all-or-none process, but more through gradual convergence of information stemming from different modalities along the course of the semantic network, becoming completely multimodal within the vATL hub.

Regarding a potentially amodal nature of this region, Binney et al. (2016) have shown that the vATL hub is not only limited to representing concepts that have a somatosensory component through the convergence of lower-level spokes, but is also critical to the processing of social and abstract concepts. They also found that, in the case of social relative to non-social concepts, this activation extends to bilateral superior aspects of the ATL; this may be explicable through the graded connectivity hypothesis, due to this region's connections to other limbic regions. A recent set of studies (Rice et al., 2018c) probed this question further, looking at category-selective responses within the ATLs for social versus non-social categories. In accordance with the graded hub hypothesis, they found bilateral vATL showed increased activation to all categories regardless of modality. A second, anterior cluster responded selectively to people (regardless of whether stimuli were presented as faces or spoken names), and a third, more dorsal cluster in anterior STG showed heightened activation for abstract words that were socially relevant, but was insensitive to concrete words of the same type (like written names). Taken together, these results are further evidence of partial specialisation in the ATLs, resulting from graded differences in connectivity across this area.

Relatively few studies have focussed on directly testing potential hemispheric differences between left and right ATL. A recent study (Hoffman and Lambon Ralph, 2018) investigated this question manipulating orthogonally both stimuli (pictures of objects vs written words) and tasks (recognition/naming). It found that whilst objects elicit bilateral activation, words are associated with a left-lateralised hemispheric bias in vATL. It should be noted, however, that more posterior regions did show a rightward bias for objects, but in vATL this was present only for words. Likewise, whilst recognition did not elicit a hemispheric bias engaging bilateral ATL, naming tasks produced left-lateralised activation in vATL. This is further evidence of the bilateral nature of the ATL system in maintaining conceptual representations, whilst at the same time showing graded hemispheric differences associated with differential connectivity with other neural systems (i.e. left ATL would be more active for naming and written words because of connections to the left-lateralised speech system and visual word form area respectively).

In sum, meta-analytic evidence from neuroimaging studies and TMS suggests that although left and right ATL may show subtle functional differences reflecting graded differences in connectivity across hemispheres (mainly, left-lateralisation for verbal material, especially when naming is required, and right-lateralisation for faces and other social stimuli), both hemispheres are often active during semantic retrieval. Together, these lines of evidence provide support for the claim emerging from semantic dementia research that the ATL works in a bilateral fashion to instantiate semantic representations.

1.2.2. Cognitive Control Involves a Bilateral Network

Heteromodal semantic representations are necessary but not sufficient for semantic cognition. Adaptive semantic cognition requires aspects of a representation that are relevant to a particular goal or context be activated in a selective fashion. The section below considers the control of semantic cognition – first by executive mechanisms that operate in a general manner across domains, and then by specific semantic mechanisms.

1.2.2.1. Domain-general cognitive control is implemented in a symmetrical multiple demand network across left and right hemispheres.

An extensive body of research suggests domain-general cognitive control depends on a task-positive network that implements control processes such as inhibition and selection, sometimes termed ‘executive functions’. The Multiple-Demand Network is a task-positive network whose neurons are hypothesised to work by adaptive coding, representing whatever information is relevant for a particular task or achieving a desired goal-state, and hence is activated by many different tasks, in opposition to rest (Cole et al., 2013; Duncan, 2010, 2001; Fedorenko et al., 2013).

When participants perform complex tasks, they engage a network of fronto-parietal and lateral occipital regions including Inferior Frontal Sulcus (IFS), Intraparietal Sulcus (IPS), Anterior Insula/Frontal Operculum (AI/FO), pre-Supplementary Motor Area (pre-SMA) and LOC (Duncan, 2010, 2001; Fedorenko et al., 2013). This system is thought to entail two large-scale networks —the Fronto-Parietal Network (FPN, comprised of IFS, IPS and LOC) and the Cingulo-Opercular Network (including AI/FO and pre-SMA; Dosenbach et al., 2008). These regions are activated in many different conditions required by multiple tasks in common, including planning, organization, decision-making, problem-solving, and logical analysis, shifting and maintaining cognitive set, inhibition of pre-potent responses and selective attention (Duncan, 2010; Fedorenko et al., 2013; Hugdahl et al., 2015). Similar to the ATL hub, the MDN or executive control network seems to be generally bilateral (see evidence above for examples of this), with one crucial exception: FPN (which is the only large-scale network lateralised) splits into left and right subcomponents which are mirror images of each other, despite bilateral task recruitment (Smith et al., 2009).

Neuropsychological evidence for the implementation of cognitive control through this network is provided by patients with dysexecutive syndrome, a disorder characterised by unregulated behaviour with impaired ability to make decisions, failures in inhibition and other executive functions. This syndrome is often caused by bilateral damage stemming from traumatic brain injury (Baddeley and Wilson, 1988; Levin and Kraus, 1994), and although some components can be dissociated, damage to either LH or RH usually results in some kind of executive control deficit (Tsuchida and Fellows, 2013). Consequently. the contribution of the MDN to the control of behaviour might depend on its bilateral integrity.

TMS evidence has refined our knowledge of the interactions and functional specialisations within this broad, domain-general network. Disrupting one of the MDN's two subnetworks with theta-burst TMS changes connectivity in both, pointing to widespread internetwork communication (Gratton et al., 2013). However, there is also evidence pointing to segregation and specialization of function, showing that targeting specific MDN regions in the right hemisphere can facilitate execution or hinder inhibition, which implies these measures rely on distinct neural processes, despite activating a common cortical network (Chambers et al., 2007). The fact that this study found no effect on homotopic LH sites points to some lateralisation of function. Further evidence for lateralisation was provided by another study, showing that disturbing left or right posterior parietal cortices through off-line rTMS can facilitate or hinder, respectively, visual cueing processing in a working memory attention task (Kiyonaga et al., 2014).

In sum, converging evidence from neuropsychology, TMS and fMRI shows that domain-general control draws on a bilateral network (albeit with some evidence of subtle hemispheric differences) with two distinct sub-networks that can be demonstrated through intrinsic connectivity in fMRI. These networks are active when participants are engaged in almost any task, since most require at least a minimum degree of control.

1.2.2.2. The Multiple Demand Network, although symmetrical in its topography, shows hemispheric differences in function and connectivity.

Although the MDN is broadly bilateral, evidence suggests that there are patterns of lateralisation in terms of specific aspects of executive control including response inhibition and selection, linguistic and attentional processes amongst others, in addition to the studies cited above for the FPN (Diachek et al., 2019; Geddes et al., 2014; Simmonds et al., 2008; Thiebaut De Schotten et al., 2011).

Neuropsychological evidence shows that patients with lesions to the right IFG struggle more with response inhibition, whilst those with lesions to the left have more difficulties with response selection (Aron et al., 2014, 2003; Bellgrove et al., 2006; Chambers et al., 2009, 2006; Cipolotti et al., 2016; Floden and Stuss, 2006; Mostofsky and Simmonds, 2008; Picton et al., 2007; Rushworth et al., 1998, 2003; Scheres et al., 2003; but see Serrien et al., 2006). This pattern has been replicated in healthy participants using TMS (Chambers et al., 2007). A body of fMRI research has also demonstrated this dissociation for these different aspects of response control. Traditional and ALE meta-analyses, critical reviews and various task-based fMRI studies suggest the left prefrontal cortex is more involved with response selection, while inhibition seems to more reliably engage right prefrontal cortex (Criaud and Boulinguez, 2013; Erika-Florence et al., 2014; Garavan et al., 1999; Goghari and MacDonald, 2009; Hampshire et al., 2010; Mostofsky and Simmonds, 2008; Rae et al., 2014; Simmonds et al., 2008; but see Jiang and Kanwisher, 2003, showing evidence for bilateral activation during selection)

Other aspects of cognitive control, like the deployment of attention to unexpected stimuli, also appear to be implemented in an asymmetric fashion in the MDN. While the Dorsal Attention Network (DAN) is distributed bilaterally, the Ventral Attention Network (VAN) shows heightened activation in the RH when it responds to unexpected or rare stimuli, playing a role in bottom-up attention helping in its reorienting to new relevant targets; the DAN, on the other hand, usually shows equal activation in both hemispheres, only showing lateralisation when spatial attention is focused on the contralateral spatial hemifield, as well as greater RH sensitivity to virtual and real lesions (Vossel et al., 2014). In this case, the dynamic interaction of a lateralised and a bilateral network gives rise to naturalistic, high-level flexible cognition in the implementation of attention. These findings concur with research that has shown a rightwards asymmetry in the size of the most ventral tract of the superior longitudinal fasciculus (overlapping with VAN regions), which correlated with behavioural performance on tasks that required visuospatial attention; in contrast, the most dorsal tract (which overlaps with DAN) showed a symmetrical size distribution (Thiebaut De Schotten et al., 2011).

Critically, one of the sub-networks that comprises the MDN –the frontoparietal network – shows a pattern of hemispheric differences in connectivity and interaction with other large-scale networks. Using resting state functional connectivity, Wang et al. (2014) showed that the FPN segregates into LH and RH components (i.e. shows preferential within-hemisphere connectivity), interacting preferentially with DMN and language networks in LH and with attentional networks in the RH; interestingly, these are the classically lateralised functions in neuropsychological literature. The authors suggest this may be one of the mechanisms through which hemispheric specialisation could arise and, in the case of semantics, this LH interaction between large-scale networks might help us understand why the semantic control network is lateralised to the left.

In sum, while the MDN is generally bilateral, there is converging evidence from neuropsychology, TMS and fMRI demonstrating hemispheric specialization for the functions of attention, inhibition and selection. Homotopic regions of the MDN might handle different kinds of response control, with the RH supporting the inhibition of pre-potent responses, and the LH selecting a response amongst several response choices (although such a clear dissociation between these processes is controversial: see, for example, Mostofsky and Simmonds, 2008). Attention potentially shows a more dynamic interplay between two networks, the VAN, which is lateralised, and the more bilateral DAN, to override irrelevant distractors, and to re-orient attention when an unexpected or infrequent biologically relevant stimulus occurs. This lateralisation is not restricted to cognitive functions, being observable at the level of the large-scale intrinsic connectivity networks that comprise the MDN: the FPN, for instance, shows a different pattern in LH, coupling with the DMN and language networks, while in the RH it engages preferentially the VAN and DAN. It should be noted, however, that this trend of hemispheric differences in the MDN is subtle, and usually overshadowed by the symmetrical activation of this network in actual task performance (see, for example, the responses evoked by the multiple tasks reported in Hugdahl et al., 2015). In spite of lateralisation of sub-processes, executive tasks recruit both hemispheres and their functions are likely to be partly overlapping and bilaterally distributed, as opposed to segregated to one hemisphere or the other.

1.2.3. Is semantic control left-lateralised?

While the implementation of domain-general control potentially shows subtle asymmetries, perhaps the most obvious example of lateralisation in control processes emerges during the controlled retrieval of aspects of meaning. When cognitive control has to be applied to semantic content, it relies on a network believed to be left-lateralised, centred on pMTG and IFG, and partially overlapping with, but at the same time distinct to, domain-general control in the MDN (Jefferies, 2013; Jefferies and Lambon Ralph, 2006; Lambon Ralph et al., 2017). This network is thought to interact with the semantic representations stored in the ATL 'hub' to retrieve those aspects that are relevant for our current goals and context, while inhibiting those aspects that are irrelevant. In spite of evidence showing that the activation of these regions is stronger in LH, the lateralisation of the semantic control system has not been formally investigated prior to the work in this thesis. The present section considers the available evidence for this semantic control network.

The heteromodal semantic representations stored in bilateral ATL are extremely rich. In order for them to be used effectively in real-world semantic cognition, we must retrieve those aspects of them that are relevant to the current goal, task or context. For example, the knowledge we have accrued about dogs over the course of our lives far exceeds what we are aware of at any given time. We have visual/spatial knowledge about them, including about the way they look, their size and where to find them; we also have auditory knowledge, about the way they sound, and olfactory knowledge, in the form of the familiar smell of a wet dog. From our experience with them, we also have emotional/valence associations, as well as abstract knowledge (their taxonomy, for instance, or metaphors regarding the use of 'dog'). This vast repository of knowledge about concepts would be relatively useless without the ability to retrieve the relevant part we need to achieve our goal: if we are planning to take our dog on a road trip, we may need to retrieve its size in order to allocate car space accordingly, but when we see a cat dart by while we have our dog on a leash, its size may be irrelevant and we need to quickly retrieve what we know on how dogs behave around cats so we tighten our grip. Semantic control helps us retrieve the aspects of concepts that are pertinent to our current context or goals.

Several different tasks have been developed to measure semantic control. Many require participants to select a response from amongst various potentially correct options: the more distracters there are, the higher the control demands (Wagner et al., 2001). Semantic relatedness judgements that require the retrieval of weak probe-target associations or the inhibition of strong distracters also engage semantic control (Wagner et al., 2001). Asking participants to resolve semantic ambiguity or to retrieve metaphorical over literal word meanings increases the semantic control requirements of the task, as will focusing on a subordinate over a dominant meaning (Whitney et al., 2009; Zempleni et al., 2007a, 2007b). Asking participants to relate concepts using specific features instead of their overall semantic association (i.e. selecting the right target for a probe based on colour or action features) also requires control (Davey et al., 2016). Cyclical naming and matching tasks in which a small set of semantically-related items are recalled or presented repeatedly also increase control demands, as the set of items all become active and generate interference which must be controlled (Thompson et al., 2016).

In sum, when we are operating in a well-practised context where the dominant aspect of the representation at hand fits well, the representation network will suffice. However, when we encounter unpractised contexts, need to suppress strong conceptual competitors, disambiguate an utterance, update conceptual aspects over the development of a task or we need to retrieve a less salient or very specific aspect of meaning to fit our goals, the left-lateralised semantic control network is thought to shape activation within the semantic representation regions to act adaptively. The neuropsychological, TMS and fMRI body of evidence that supports this claim is presently considered.

1.2.3.1. Patient Evidence

Neuropsychological studies of patients with Semantic Aphasia (SA) are a valuable form of information for the function, characteristics and localisation of the semantic control network. The regions impacted by SA that have been identified through lesion studies as critical nodes of the semantic control network are the left IFG and pMTG (Jefferies, 2013; Jefferies and Lambon Ralph, 2006; Lambon Ralph et al., 2017).

Patients with damage to the left IFG and/or pMTG that have SA, in contrast to those with SD, perform most poorly on semantic tasks with the highest control demands and show variable performance between tasks (even if they have the same item set), alongside an effect of the degree of ambiguity or semantic richness of the items (those with more diverse meanings are more impaired), associative errors in naming (in addition to superordinate and coordinate), absence of a frequency/familiarity effect of stimuli, failure to inhibit strong competition or association between items, tendency in fluency tasks to produce associative intrusions/perseverations pertaining to previously tested categories and a strong effect of cueing/miscueing (Corbett et al., 2009; Hoffman et al., 2011; Jefferies et al., 2007; Jefferies and Lambon Ralph, 2006; Lambon Ralph et al., 2017; Noonan et al., 2010, 2013; Riès et al., 2016; Robinson et al., 2010; Rogers et al., 2015). This pattern of deficits in semantic control occurs regardless of the modality of presentation, confirming the heteromodal nature of these semantic control regions (Jefferies and Lambon Ralph, 2006). A recent lesion study using fMRI (Hallam et al., 2018) found evidence for the organisation of these regions together with ATL in a coherent network. Patients with semantic aphasia that had difficulties following left prefrontal damage showed, in comparison to healthy controls, increased recruitment of vATL and pMTG in response to meaningful sentences. In fact, functional coupling between pMTG and anterior temporal regions was associated with better verbal semantic performance in these patients, suggesting functional compensation through pMTG in the case of IFG damage.

The studies reported above show that semantic aphasia is associated with left-lateralised lesions. Classically, it has been considered that patients with right-lateralised lesions typically do not present with substantial semantic deficits (Faglioni et al., 1969; Germani and Pierce, 1995). However, recent studies provide evidence of some potential involvement of RH regions. Thompson et al. (2016), for example, note that activation in fMRI during demanding semantic tasks usually extends to the RH homotope of the left IFG. To investigate the involvement of right IFG in semantic control, they examined left vs. right patients, finding qualitative differences between the groups: While the RH patients presented executive deficits similar to the LH patients, they showed better preserved performance in semantic tests. However, RH patients showed effects that paralleled the documented deficits in LH cases (intrusions/perseverations in cyclical content, sensitivity to cues/miscues) in challenging semantic tasks that are thought to more strongly engage the RH, including those involving facial emotions or the ‘summation’ of meanings across multiple items.

1.2.3.2. Healthy Participants

1.2.3.2.1. TMS Evidence

The importance of left IFG and pMTG in semantic control has been corroborated through TMS. The application of TMS to left IFG or pMTG selectively disrupts executively demanding judgements on semantic tasks regardless of modality, but spares performance on those same tasks when control requirements are low, and on non-semantic tasks (Davey et al., 2015a; Devlin et al., 2003; Hartwigsen et al., 2016; Hoffman et al., 2012; Whitney et al., 2011b, 2012). The application of TMS to either left IFG or pMTG produces similar effects, disrupting picture naming on early cycles of a cyclical task where control demands are high (Krieger-Redwood and Jefferies, 2014). Applying rTMS to left ventrolateral prefrontal cortex in healthy subjects slows reaction times to abstract but not concrete words, but only when these words are presented out of context and hence have high control demands (Hoffman et al., 2010). A study that looked at the temporal unfolding of semantic control found that applying TMS to pMTG during the onset of the second word in a semantic association paradigm disrupts the retrieval of weak, but not strong associations, providing further evidence of this region's involvement in semantic control (Teige et al., 2018). Evidence for the coordinated action of these regions as a network comes from the fact that TMS modulates cortical recruitment within the semantic control network, increasing processing demands on pMTG and pre-SMA if left IFG is stimulated, while at the same time reducing activation on left and right IFG (Hallam et al., 2016). One experiment described laterality effects, finding that rTMS to right posterior superior temporal sulcus disrupts processing of novel, but not conventional metaphors (Pobric et al., 2008).

1.2.3.2.2. fMRI Evidence

A body of fMRI evidence has largely confirmed the findings from patient and TMS studies: semantic tasks with high control demands engage a network with left-lateralised components comprised of IFG, pMTG, AG/IPS and pre-SMA.

The involvement of left IFG in semantic control processes has been established in fMRI for over two decades (Badre et al., 2005; Bedny et al., 2008; Thompson-Schill et al., 1997). There is now strong evidence for other regions besides IFG being organised into a network that subserves semantic control (Noppeney et al., 2004): a large-scale meta-analysis of fMRI studies found left and right IFG, left pMTG and dorsal AG/IPS involvement in semantic tasks with high control demands (Noonan et al., 2013). These regions showed some overlap with domain-general control regions, but the strongest peaks fall outside the multiple-demand network. This semantic control network interacts with, but is distinct to the semantic representation regions discussed above (Whitney et al., 2011a).

This semantic control network shows signs of graded specialisation, with left posterior and mid IFG showing greater activation for words, and right posterior IFG for pictures; left anterior IFG and pMTG show stronger responses to verbal than pictorial associations, with the latter also responding to difficulty across modalities, which could implicate these sites in maintaining context and selecting relevant heteromodal knowledge when required (Krieger-Redwood et al., 2015). Such diverse specialisation might afford this network the chance to implement control for different types of content. Davey et al. (2015b) found that left IFG and pMTG show increased activation for both harder semantic judgements and action judgements. The authors suggest that the co-activation of these regions allows the flexible retrieval of semantic information, appropriate to the current context, which might be needed for semantic control and understanding actions alike. The involvement of these regions in understanding ambiguity, events, actions and thematic associations has also been documented (Chao et al., 1999; de Zubicaray et al., 2013; Martin et al., 1995; Zempleni et al., 2007b).

Recent studies have found structural evidence of these regions' organisation into a network and its functional consequences. Wang et al. (2018) looked at a combination of MRI-based cortical thickness and resting-state connectivity within the semantic control network, and found increased structural covariance between left pMTG and left anterior Middle Frontal Gyrus (aMFG) in participants who were good at semantic control tasks. This relationship was specific to semantics, and was not observed for a contrast involving a demanding non-semantic task. The functional connectivity of these regions overlapped with other semantic control regions, including left IPS, IFG and pMTG, adding further evidence of their organisation in a network.

Chiou et al., (2018) provide a striking demonstration of the dynamics of semantic control characterised through fMRI in a recent study, showing that the semantic control network strengthens its connectivity with relevant components of the representation system in a dynamic fashion to respond to different semantic contents and difficulty levels. The authors used a combination of methods (task-based fMRI, PPI, dynamic causal modelling and novel ROI-vector analyses) which showed that pairing semantic concepts in an atypical/infrequent manner (through a shared colour, compared to more traditional semantic association) engages semantic control and heightens activation within the left-lateralised network that implements it. Furthermore, a PPI analysis revealed increased connectivity between IFG and other control regions (pMTG, IPS) and an occipital 'spoke' when participants performed the more demanding colour-pairing task compared to traditional semantic association (the absence of a link between IFG and vATL as would be expected in the CSC framework might be due to lack of statistical power in the PPI analysis), with information flowing from IFG to occipital regions in a top-down fashion during colour judgements. This study also highlighted an organisational gradient from occipital, through ventral temporal regions culminating in ATL, shifting anteriorly (caudal to rostral) and laterally (medial to lateral) from perceptual to conceptual processing, which fits with tractography evidence and argues against a sharp separation between percept and concept. In sum, this study provides further evidence that semantic cognition is subserved by two components: a bilateral system that stores semantic representations, and a semantic control network probably lateralised to the left. The hub and spokes interact flexibly, mediated by the semantic control network depending on task demands in order to enact semantic cognition.

1.2.4. Multiple Demand and Semantic Control Regions Constitute Partially Overlapping, yet Distinct Networks

There is evidence that semantic control goes beyond the application of domain-general control processes to semantic content. The meta-analysis of Noonan et al. (2013) compared high control tasks that were either semantic or phonological in nature and found overlapping activation in medial and ventral frontal regions. However, a more fine-grained examination reveals a distinction between the areas activated within prefrontal cortex: high-control semantic tasks elicited activation in more ventral parts, while phonological tasks were associated with greater dorsal activation. This is in agreement with previous literature that finds the left IFG is a functionally heterogeneous area, with regions dedicated to semantic versus phonological processing, or to selection versus retrieval (Badre et al., 2005; Badre and Wagner, 2007; Devlin et al., 2003; Gough et al., 2005; Noppeney et al., 2004; Snyder et al., 2007; Thompson-Schill et al., 1997; Zempleni et al., 2007b). Other studies have also found left frontal cortex activation both for semantic and non-semantic control alike (Spreng et al., 2010), as well as in other control regions that extend beyond the semantic control network, like dorsal medial prefrontal cortex (Binder et al., 2009; Duncan, 2010).

In contrast, pMTG was not activated by phonological tasks and only responded to semantic control demands (Noonan et al., 2013). In resting-state studies, the functional connectivity of pMTG correlates with both temporal semantic regions (like ATL) and frontoparietal control regions (Spreng et al., 2010; Vincent et al., 2008). A recent study looking at structural covariation in cortical thickness within the semantic control network found further evidence of this complex pattern of connectivity in pMTG and its consequences for cognitive control (X. Wang et al., 2018). As reviewed in the previous section, this study found that structural covariance between pMTG and aMFG predicted performance in weak semantic associations after controlling for strong associations, but it did not predict performance on a relatively demanding non-semantic task. Both these regions lie outside the MDN, and the conjunction of their intrinsic connectivity showed striking overlap with the left-lateralised semantic control network. This adds further evidence for the specificity of the network formed by these regions to implement control for semantic content. Evidence for a functional dissociation was also observed: the structural covariation of pMTG with pre-SMA predicted performance in a demanding non-semantic task compared to an easier semantic task, suggesting that pMTG can participate in multiple large-scale cortical networks. In this study, left pMTG showed structural covariance with domain-general, visual and semantic regions hinting at its diverse functional roles (Cole et al., 2013; Dixon et al., 2018).

There is also causal evidence, in addition to the meta-analytic and structural evidence of semantic control and MDN being overlapping, yet distinct networks, and of a functional dissociation between semantic and non-semantic control. A TMS study found that stimulating any of three key regions of the semantic control network – left IFG, pMTG or IPS – caused disruption of semantic control (Whitney et al., 2012). However, depending on the site of stimulation, different types of disruption were observed. Stimulating left IFG and pMTG yielded identical results, restricted to disturbing responses to challenging semantic trials. Critically, IPS showed a different behaviour from left IFG and pMTG in that perturbing it hindered performance in both semantic and non-semantic tasks alike, which suggests a role in domain-general control,. This region, unlike IFG/pMTG is coupled to other MDN regions involved in heteromodal domain-general control (Duncan, 2010, 2001; Fedorenko et al., 2013), and is likely to show activation in fMRI when control requirements are high, regardless of semantic content (Noonan et al., 2013). This study provides causal evidence for a dissociation between semantic and domain-general control components, with all three LH areas (IFG, pMTG, IPS) being important for semantic control, but only IPS contributing to domains beyond semantics. This suggests that an interaction between domain-general and semantic-specific networks is necessary in order to implement efficient semantic control.

Further evidence comes from a study that looked directly at the relationship between the DMN, MDN and language networks, testing the correlations in response magnitude across these networks to different, network-specific tasks. Although they did not look specifically into semantic control, the ‘core language network’ the authors identified through a contrast of sentences > non-words included control regions like IFG and pMTG. The authors found that the effect sizes of different regions within each network showed high within-network correlations (i.e. the magnitude of activation of a DMN region correlated with other DMN regions, but did not carry much information about MDN regions’ activation). This was also true for pMTG and IFG: these regions showed higher correlations of effect sizes between themselves during language tasks than they did with other MDN regions, clearly indicating a dissociation between these networks (Mineroff et al., 2018).

In sum, the semantic control network overlaps with aspects of the LH frontoparietal control network, which lies between areas dedicated to visuospatial attention and those engaged in semantic processing, regardless of control demands. Recent evidence suggests that pMTG may play a key role between bridging the gap between two large-scale anti-correlated cortical networks, and in doing so, implement semantic control. Davey et al. (2016) found through structural and functional connectivity analyses that left pMTG is at the nexus of networks recruited in automatic semantic processing —the DMN— and executively demanding tasks (the MDN), and hence is in a privileged position to integrate automatic semantic retrieval and executive control. The following section examines the evidence for differential interactions of large-scale networks between the hemispheres, and how these may give rise to lateralised functions.

1.3. Interactions of large-scale networks in the left and right hemisphere

Higher order cognition arises from the interaction between tertiary association cortices organised in large-scale networks, which have been widely documented functionally and structurally in the literature (Jung et al., 2017; Yeo et al., 2011). Consequently, the pattern of lateralisation for language and semantic processing, especially in the case of the semantic control network, might be understood in the context of differential interactions and organisation of these large-scale networks in the left and right hemispheres.

Some of these networks are intrinsically symmetrical and present very little interhemispheric differences in topography or function, as is the case with visual and somatomotor networks (which deal with a symmetrical field of view, or body, or world). On the other hand, networks including DMN, VAN and DAN show interhemispheric differences, like the ones discussed in the sections above (i.e. greater segregation of DMN in LH, greater VAN activation in RH to unexpected stimuli, as well as greater RH DAN sensitivity to lesions), which may help to explain lateralisation of the components of semantic cognition.

Differences in function observed in neuroimaging and neuropsychological data may arise due to the micro and macro structural differences widely documented in the literature (to cite a few examples: higher cell density in left than right Broca's area, greater spacing across clusters of neurons in left Brodmann area 22, larger planum temporale and deeper posterior temporal sulci in LH, cortical thickness asymmetries in middle frontal, anterior temporal and superior parietal lobes, and white matter asymmetries in major tracts like the arcuate, uncinate and superior longitudinal fasciculi; Amunts et al., 1999; Galuske et al., 2000; Hill et al., 2010; Luders et al., 2005; Ocklenburg et al., 2016; White et al., 1994) and, more importantly, due to differences in connectivity between the hemispheres or networks. Given the gross anatomical symmetry generally observed in the two cerebral hemispheres, how does functional lateralisation emerge in the context of this apparent structural symmetry? Usually, in intrinsic connectivity measured through resting-state fMRI, the timeseries from a seed or Region of Interest (ROI) in one hemisphere is highly correlated with the timeseries in the corresponding location in the opposite hemisphere at rest (Jo et al., 2012). Symmetrical connectivity between homotopic brain regions is the norm, with the degree of symmetry strongest in functional regions that are known to have a bilateral organisation, like visual and motor cortex while exceptions to this norm usually fall within language regions.

This was confirmed by Raemaekers et al. (2018) who analysed hemispheric differences in a seventy-six region whole-brain parcellation (FreeSurfer automatic parcellation scheme: 38 LH and 38 RH regions) in Human Connectome Project (HCP) data, by calculating each region's functional connectivity with all other regions, then 'flipping' that matrix, and subtracting the flipped matrix from the original. They also explored the potential relationship between asymmetric functional connectivity and a language task (stories > maths) from the HCP database. The authors found that 95% of the mean resting state connectivity across the brain was symmetrical, with asymmetrical functional connectivity showing significantly higher correlations between LH language regions than their RH homologues, and higher correlations between DMN in LH with language homologue areas in RH than their homologues. On an individual difference level, there was a correlation between how much a participant exhibited this asymmetry pattern and their language task lateralisation (as well as handedness) which has been reported in previous studies (observed even at the whole-hemisphere level, albeit weaker than with language-specific regions, cfr. Joliot et al., 2016). In conclusion, this study found that the greatest source of asymmetry in whole-brain RS functional connectivity is due to greater connectivity between LH language regions than their RH homologues, and due to an interaction between the lateralisation patterns of the DMN and language networks, and that this lateralisation pattern has functional consequences in the performance of linguistic tasks.

This homotopic functional connectivity of the human brain is related to structural connectivity, mediated through the corpus callosum, and it mirrors macroscopic functional areas (Mancuso et al., 2019): primary cortices, which are connected through fast fibres of the corpus callosum show strong homotopic connectivity, whilst associative cortices which are frequently lateralised and connected by slower fibres show less homotopic connectivity (Stark et al., 2008). In fact, in a recent study using very large-scale novel meta-analytic and voxel mirroring methods to look at homotopic functional connectivity, the results were in agreement with this pattern: the areas with less homotopic connectivity were all associated with memory, language, executive control and working memory, as well as DAN and DMN regions; on the other hand, the areas with more homotopic connectivity were all primary regions (Mancuso et al., 2019). In sum, the areas with less homotopical co-activation are usually involved in higher cognitive functions, and conversely, the more primary functions show higher homotopic co-activation.

The pattern of collaboration between hemispheres revealed through functional homotopy may not be equal in the left and right hemispheres. Using intrinsic connectivity as a metric, Gotts et al. (2013) identified that regions in LH show a ‘segregation’ mode of lateralisation (i.e. they show heightened intrinsic connectivity with other LH regions), while RH regions display an ‘integration’ mode: they communicate with other RH and LH regions equally. Cluster analysis of the whole-brain connectivity matrix revealed stronger segregation in LH language and sensory-motor regions, and stronger integration in RH for visual processing and attentional regions. The strength of segregation/integration in these regions for each participant correlated with their performance in a verbal (vocabulary) and non-verbal (block design) task respectively, showing that these different modes of lateralisation confer behavioural advantages. This might be due to the computational efficiency afforded by these qualitatively different forms of lateralisation: if cortical representations are more focal and spatially restricted in LH, this could optimise systems that necessitate rapid interactions for time-constrained sequential behaviour like language. On the other hand, visuospatial processing may benefit more from the spatial conjunction of multiple inputs from both hemispheres to represent information in space, rather than time, which matches the specialisation of RH (Gotts et al., 2013; although there are other potential explanations for the left-lateralisation of language and right-lateralisation of spatial processing, like causal or statistical complementarity, see Badzakova-Trajkov et al., 2016 for a review).

These two qualitatively different modes of lateralisation seem to occur in a systematic fashion across large-scale cortical networks. Segregation in the form of preferred within-hemisphere interactions in functional connectivity is prominent in heteromodal association cortices, and minimal in sensory-motor cortices (Wang et al., 2014; although this lateralisation pattern might be affected by age and gender, cfr Agcaoglu et al., 2014). Critically, the frontoparietal control network shows strong within-hemisphere interactions, but a different pattern in each hemisphere: while in LH it couples preferentially to the default mode network and language regions, in RH it prefers attentional networks like VAN and DAN (Wang et al., 2014). These particular interactions concur with neuropsychological literature in lateralised functions, as well as other resting-state fMRI studies (e.g. Joliot et al., 2016), hinting at a possible role of these specialised left and right subdivisions of the FPN in facilitating control of processes that are lateralised.

The FPN is situated in a privileged position, between networks that process external input, like the DAN, and internal input like the DMN (Margulies et al., 2016). Furthermore, this network differentially couples with the DAN and DMN depending on the task, strongly suggesting that flexible interactions with other networks are important to implement context-sensitive control in goal-oriented cognition (Niendam et al., 2012; Spreng et al., 2013; Vincent et al., 2008; Wang et al., 2014). If this were the case, having two specialised sub-divisions of this network across the hemispheres makes computational sense, as it would reduce processing time for functions that are lateralised to each hemisphere. This bipartite organisation would also facilitate the implementation of two different modes of regulation, if control has to be computed in different ways: for example, external versus internal, or spatial processes versus processing that evolves over time.

It is possible that semantic control regions in the left hemisphere reflect this type of within-hemisphere interaction, while the homotopic regions in the right hemisphere retain greater separation between the DMN and control networks. By this view, the automatic retrieval of conceptual representations would require a —presumably bilateral— interaction of the ATL with the DMN. On the other hand, the controlled semantic retrieval of these representations would necessitate a more focused network that allows interaction between MDN and ATL, and this might emerge from properties of the left hemisphere. From this perspective, the left pMTG would serve a critical role in semantic processing integrating the bilateral automatic semantic representation system which works in an integrative fashion with the segregated left-lateralised controlled retrieval by being positioned in the middle of both networks (Davey et al., 2016).

In this critical study, Davey et al. (2016) characterised the role of pMTG in semantic processing by looking at its task-related activity for relational semantics (using action > colour and global association > features judgements), task-based connectivity through PPI, intrinsic connectivity (through resting state) and structural connectivity (through DTI). They found that pMTG acts as a functional nexus that integrates the DMN and MDN, which are normally anti-correlated, for the purpose of applying semantic control to the representations stored in ATL. They first identified pMTG functionally through the conjunction of action and global association judgements (which overlapped within the pMTG region identified in Noonan's meta-analysis). Using PPI they showed that in these conditions, pMTG has increased functional coupling with inferior frontal regions that span both DMN and MDN. Through resting-state connectivity in a separate dataset they found that this pMTG region couples both to an IFS area identified in the contrast of hard > easy semantic trials that overlaps with MDN, and to an ATL area identified through the reverse (easy > hard) contrast that is an aspect of DMN. Their DTI analysis revealed that structural connectivity patterns support these findings, through long connections from IFS and ATL that overlapped in white matter adjacent to pMTG. They also found that pMTG couples more to ventral than dorsal aspects of IFG, implicated in controlled retrieval more than selection, with the latter being more active in the hardest trials of their experiment (regardless of the need to establish a spatiotemporal or thematic context). This pattern is consistent with the view that dorsal IFG applies goals to semantic selection, while ventral IFG and pMTG shape retrieval to suit a context that the stimuli demand (i.e. in the absence of an explicit link).

This privileged position spanning the anti-correlated DMN and MDN makes pMTG an ideal candidate to a convergence zone that integrates these networks, which, at the cognitive level would allow it to apply top-down goal-directed cognition to automatic semantic retrieval to shape semantic representations flexibly to meet the current demands.

Based on the literature reviewed above, this thesis presently advances a speculative framework to formulate hypothesis to guide the research work. Perhaps this integration between MDN and DMN occurs in the left hemisphere due to the qualitatively different segregation mode this hemisphere exhibits (Gotts et al., 2013). The LH FPN sub-network might be more integrated with DMN and language regions in the semantic control network taking advantage of the preferential within-hemisphere interactions of the left side of the brain, allowing it to perform sequential, time-constrained operations, explaining the left-lateralisation of this system, and giving the semantic control network the characteristics outlined by Davey et al. (2016) – namely strong connectivity to both DMN and control regions. On the other hand, these same regions in RH might capitalise on the integrative (i.e. bilateral) nature of this hemisphere to handle functions like visuospatial processing and spatial attention that, by their very nature, require dealing with a symmetrical, bilateral representation of space (Gotts et al., 2013; Z. Liu et al., 2009; Seydell-Greenwald et al., 2017). This would allow the bilateral representation system to instantiate a rich array of content, capitalising on the different modes of each hemisphere: visuospatial concepts, for example, might be easier to represent in RH. The three studies undertaken in this PhD seek to investigate whether qualitatively different modes of organisation between the hemispheres produce a left-lateralised semantic control system that acts to constrain the activation of bilateral semantic representations which show more subtle graded differences in connectivity. The following section outlines the scope of these PhD studies.

1.4. Aims, Scope and Outline of the Present PhD Project

This project investigates hemispheric differences in the key components of semantic cognition posited by the CSC framework (Lambon Ralph et al., 2017). It uses a range of methods to explore the hemispheric specialisation of these components and the networks and brain regions that support them. The first analysis contrasts patterns of intrinsic connectivity in left and right-hemisphere regions and examines individual differences in these patterns, which are then related to performance on semantic assessments. The PhD also includes other complementary work employing task-based fMRI to examine activation of left and right brain regions during semantic and matched non-semantic tasks, in conjunction with resting state functional connectivity analysis to probe the effects of differences in connectivity between regions identified in task-based fMRI on the performance of semantic tasks, from a hemispheric differences perspective. This is complemented using automated meta-analytic techniques and cognitive decoding to interpret results of intrinsic connectivity wherever relevant (Gorgolewski et al., 2015; Yarkoni et al., 2011).

The overarching hypothesis states there will be meaningful differences in the way semantic sites overlap with different large-scale cortical networks tied to higher-order heteromodal cognitive processes in LH compared to RH. Concretely, LH sites are expected to bring together control and attentional networks with regions implicated in automatic semantic cognition like the DMN, whereas in RH these same regions are expected to engage visuospatial networks (Chapter 2). These differences are anticipated to give rise to a control network dedicated to shaping semantic representations through control processes to flexibly suit different contexts and goals; this control network will be specific to semantics and will not be just a special case of domain-general control processes applied to semantic content (Chapter 4). Finally, although the system in charge of storing semantic representations is bilateral and largely symmetrical, in keeping with the graded hub hypothesis (Rice et al., 2015a), it is hypothesised that the left and right components will differ in terms of the type and modality of stimuli they are better suited to represent, as a function of their connectivity to visual or other semantic regions (Chapter 3).

Chapter 2 starts by exploring the intrinsic connectivity patterns of four key ROIs that have been linked to different components of semantic cognition in the CSC framework. Left IFG and pMTG were examined as semantic control sites given that recent meta-analytic evidence found peaks in these regions (Noonan et al., 2013) and ATL for semantic representations, based on a recent large-scale meta-analysis that found bilateral ventral peaks of activation in these regions (Rice et al., 2015b). Left AG was considered in this analysis due to a body of literature that has linked it to semantic cognition (see Humphreys and Lambon Ralph, 2015 for a review), although whether it is specifically involved in semantics or just deactivates less for semantic tasks is controversial (Humphreys et al., 2015). The LH intrinsic connectivity patterns of these seeds were compared to those of their RH homotopes to describe differences in connectivity. These were then interpreted through automated large-scale meta-analysis and cognitive decoding techniques, and through how these connectivity patterns (both at the level of individual seeds, as well as pairs of seeds that constitute different components of semantic cognition) interact with different large-scale networks derived from a widely-accepted parcellation (Yeo et al., 2011) in LH versus RH. Lastly, the examination addressed whether individual differences in the strength of intrinsic connectivity from these ROIs to LH and RH relate to differences in performance of semantic tasks outside the scanner, to investigate whether lateralisation has functional relevance.

Chapter 3 examines hemispheric differences in the bilateral semantic representation system in the context of the graded hub hypothesis for left and right ATL. Although this system is known to be largely bilateral and symmetrical, recent meta-analytic evidence suggests that the type and modality of semantic representations it stores show laterality effects as a function of graded differences in connectivity (Rice et al., 2015b). An experiment was designed to test whether individual differences in the strength of intrinsic connectivity from left and right ATL relate to the efficiency of semantic performance as a function of type and modality of stimuli presented on a task undertaken outside the scanner. The hypothesis states that, whilst left ATL connectivity to other regions involved in language / semantics might predict efficiency as other studies have shown (Hurley et al., 2015), right ATL's connectivity to visual regions might be differentially associated to semantic performance in accordance with this hemisphere's preference for visual / spatial processes and the graded hub hypothesis.

Finally, Chapter 4 examines the semantic control system. Two experiments address the specificity of this system and investigate whether it is a case of cognitive control applied to semantic content or, conversely, shows a dissociation with domain-general control processes. This work consists of a task-based fMRI experiment complemented by a second resting state fMRI experiment using a go/no-go task: a paradigm known to evoke a robust response in MDN domain-general control regions in RH (Criaud and Boulinguez, 2013; Simmonds et al., 2008). The structure of the paradigm was manipulated in such a way that in half the trials, inhibition was driven by a merely perceptual signal, while in the other half it was driven by semantics. If the activation tied to semantic control regions in previous studies reflected the responsiveness of this network to any challenging tasks with semantic content, then introducing meaning to a process classically mediated by domain-general control should elicit this same left-lateralised activation. Alternatively, if the semantic control system is functionally distinct from the MDN, then adding semantic content as the basis of go/no-go decisions, but without requiring meaning itself to be controlled, should not change the nature of the neural response to inhibition demands.

These studies, taken together as a whole, will elucidate the extent to which differential interactions between large-scale networks in LH and RH might relate to the left-lateralisation of semantic control, and/or to the hemispheric differences previously described within the bilateral semantic representation system supported by ventral ATL. Furthermore, the PhD will investigate whether individual differences in the strength of intrinsic connectivity, and connectivity differences between the cerebral hemispheres, have associated differences in behaviour – for example, in the efficiency of performance on semantic tasks.

Chapter 2. Degrees of Lateralisation in Semantic Cognition: Evidence from Intrinsic Connectivity

In this first empirical chapter, we explored patterns of intrinsic connectivity for four left hemisphere regions thought to be critical for semantic cognition. We compared connectivity patterns for these sites with their right-hemisphere homotopes, identifying differences between the hemispheres in the strength of their connectivity with large-scale cortical networks (characterised by Yeo et al., 2011). We characterised this overlap both at the level of individual seeds, and in terms of pairs of regions that implement different components of semantic cognition (e.g. semantic control vs. heteromodal semantic store). We interpreted these differences through automated meta-analytic techniques and cognitive decoding using Neurosynth. Finally, we showed that individual differences in the strength of intrinsic connectivity from these left hemisphere semantic sites are associated with behavioural performance on semantic tasks outside the scanner.

The results indicate that two distinct components of semantic cognition - regions supporting semantic representation and semantic control - have different patterns of lateralisation as measured through intrinsic connectivity. A site implicated in semantic representation in the anterior temporal lobes (ATL) showed bilateral and symmetrical connectivity (with left and right ATL showing the highest similarity across all pairs of seeds). In contrast, the connectivity of regions within the semantic control network was strongly left-lateralised. The strength of this left-lateralisation was related to participants' efficiency in performing semantic tasks outside the scanner: participants with stronger within-hemisphere connectivity for posterior middle temporal gyrus (pMTG), a key semantic control site, had more efficient retrieval of strong associations, while cross-hemispheric connectivity from the same site predicted worse performance for weak associations requiring greater control. We also observed differences in overlap with the canonical Yeo networks: in general, left-sided sites coupled more with lateral default mode network regions, and less with dorsal attention regions. This is consistent with stronger integration of Default Mode Network and Multiple-Demand Network regions in the left-hemisphere, supporting semantic control.

Acknowledgements: This chapter was accepted for publication in the journal NeuroImage on August 8, 2019 (https://doi.org/10.1016/j.neuroimage.2019.116089). Elizabeth Jefferies,

Jonathan Smallwood and the author developed the experimental design and the main ideas in this manuscript. Theodoros Karapanagiotidis provided technical advice on the implementation of the analyses. The author was responsible for the majority of the work, including study design, implementation of analyses, interpretation of the results and writing of the text. The data were collected prior to the start of the PhD by the research team led by Jonathan Smallwood and Elizabeth Jefferies and have been described in previous publications (see Methods Section).

2. Degrees of Lateralisation in Semantic Cognition: Evidence from Intrinsic Connectivity

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Abstract

The semantic network is thought to include multiple components, including heteromodal conceptual representations and semantic control processes that shape retrieval to suit the circumstances. Much of this network is strongly left-lateralised; however, work to date has not considered whether separable components of semantic cognition have different degrees of lateralisation. This study examined intrinsic connectivity of four regions implicated in heteromodal semantic cognition, identified using large scale meta-analyses: two sites which have been argued to act as heteromodal semantic hubs in anterior temporal lobe (ATL) and angular gyrus (AG); and two sites implicated in semantic control in inferior frontal (IFG) and posterior middle temporal gyri (pMTG). We compared the intrinsic connectivity of these sites in left hemisphere (LH) and right hemisphere (RH), and linked individual differences in the strength of within- and between-hemisphere connectivity from left-lateralised seeds to performance on semantic tasks, in a sample of 196 healthy volunteers. ATL showed more symmetrical patterns of intrinsic connectivity than the other three sites. The connectivity between IFG and pMTG was stronger in the LH than the RH, suggesting that the semantic control network is strongly left-lateralised. The degree of hemispheric lateralization also predicted behaviour: participants with stronger intrinsic connectivity *within* the LH had better semantic performance, while those with stronger intrinsic connectivity *between* left pMTG and homotopes of semantic regions in the RH performed more poorly on judgements of weak associations, which require greater control. Stronger connectivity between left AG and visual cortex was also linked to poorer perceptual performance. Overall, our results show that hemispheric lateralisation is particularly important for the semantic control network, and that this lateralisation has contrasting functional consequences for the retrieval of dominant and subordinate aspects of knowledge.

Keywords: Hemispheric differences; lateralisation, semantic cognition, semantic control, fMRI, resting state, intrinsic connectivity

2.1. Introduction

Semantic cognition allows us to understand the meanings of words, images, sounds, actions and events, and to flexibly use our knowledge to drive thoughts and behaviours that are appropriate to our goals and the current context (Jefferies, 2013; Lambon Ralph et al., 2017). Since we know many features and associations for any given concept, semantic cognition is thought to reflect the interaction of at least two separable neurocognitive components: (i) long-term heteromodal semantic representations and (ii) control processes that focus retrieval on aspects of knowledge that are currently relevant, even when these are non-dominant (Chiou et al., 2018; Hoffman et al., 2017; Jefferies, 2013; Lambon Ralph et al., 2017; Noonan et al., 2013). Contemporary accounts of semantic cognition, such as the Controlled Semantic Cognition framework, propose that these interacting elements are supported by dissociable cortical regions within the semantic network, which is largely left-lateralised (Lambon Ralph et al., 2017; Davey et al., 2016). However, the degree of lateralisation might vary across the neurocognitive components that support semantic representation and control.

Heteromodal concepts are thought to be represented bilaterally, in ventral aspects of the anterior temporal lobes (ATL; Hub and Spoke model, Lambon Ralph et al., 2017; Patterson et al., 2007; Rogers et al., 2006). This site is thought to act as a “hub” allowing the integration of diverse features, including visual, auditory, motor, linguistic, praxis and valence information (stored within “spokes”). Semantic dementia, which is associated with marked degradation of conceptual knowledge across modalities, follows bilateral atrophy of ventral ATL; cases with unilateral ATL lesions have less pronounced semantic deficits (Lambon Ralph et al., 2010; Rice et al., 2018a), suggesting that conceptual knowledge is distributed across both hemispheres. Nevertheless, even within a bilateral system, there can be some degree of lateralisation. Patients with more left than right-sided ATL damage often show greater difficulties with verbal semantic access, while those with the converse pattern can show greater impairment on pictorial and social semantic tasks (Lambon Ralph et al., 2001; Mion et al., 2010; Rice et al., 2018a; Snowden et al., 2004; Thompson et al., 2003). Similarly, while neuroimaging meta-analyses show bilateral ATL activation across word and picture semantic tasks (see Figure 3), this response is more strongly left-lateralised for tasks involving written words and language production (Rice et al., 2015b).

In contrast to the bilateral response in ATL, other sites in the semantic network typically show little or no response in the RH. Left but not right AG is implicated in semantic cognition (Binder et al., 2009)– with a recent meta-analysis linking AG with ‘automatic’ aspects of semantic retrieval (Davey et al., 2015a; Humphreys and Lambon Ralph, 2015), although its contribution to semantic cognition remains unclear (Humphreys et al., 2015). ATL and AG are commonly implicated in processing coherent conceptual combinations (Bemis and Pylkkänen, 2013; Davey et al., 2015a; Price et al., 2015; Teige et al., 2018) and both are argued to act as heteromodal ‘hub’ regions (Reilly et al., 2016; Seghier, 2012). AG also shows relatively strong intrinsic connectivity to lateral parts of ATL (Bellana et al., 2016; Davey et al., 2016, 2015a; Hurley et al., 2015; Jackson et al., 2017) and both sites show a pattern of intrinsic connectivity allied to the default mode network (DMN) – at least when contrasted with semantic regions that support control processes. However, there are functional subdivisions in both regions: the ventral ATL site, thought to act as a heteromodal hub, is *not* a core region within DMN (Jackson et al., 2019).

Other left-lateralised parts of the semantic network – namely left IFG and pMTG – are thought to support semantic control processes (Badre et al., 2005; Hallam et al., 2016; Noonan et al., 2013; Thompson-Schill et al., 1997; X. Wang et al., 2018). Neuroimaging studies show consistent activation of left IFG and pMTG in control-demanding semantic tasks involving weak associations, ambiguous words or strong distractors (Noonan et al., 2013), across both verbal and non-verbal tasks (Krieger-Redwood et al., 2015). Damage or inhibitory stimulation to either left IFG or pMTG elicits difficulty in semantic tasks with high but not low control demands (Davey et al., 2015a; Jefferies and Lambon Ralph, 2006; Whitney et al., 2011b), while disruption of left IFG elicits compensatory increases in pMTG recruitment (Hallam et al., 2018, 2016). Right IFG also shows some activation in contrasts tapping semantic control, although this response is weaker and less extensive than in left IFG (Noonan et al., 2013), and activation in right pMTG is rarely observed. Interestingly, although sites activated in semantic control partially overlap with bilateral multiple-demand network (MDN) regions (Davey et al., 2016; Noonan et al., 2013), the peak semantic response in left IFG and pMTG is outside the executive network (Gonzalez Alam et al., 2018). We recently suggested that LH semantic control regions sit at the juxtaposition of DMN and multiple-demand cortex, suggesting they might help to integrate processes supported by these networks, which are normally anti-correlated (Davey et al., 2016). Yet these large-scale networks (DMN and MDN) are bilateral and largely symmetrical, raising the question of why semantic cognition is left-lateralised.

This study examined connectivity differences for LH semantic regions and their homotopes in the RH, to see if this can explain semantic lateralisation. Previous work has already shown stronger intrinsic connectivity in left than right ATL to other LH semantic sites (Hurley et al., 2015). Left IFG and pMTG have strong intrinsic connectivity, consistent with the view they form a left-lateralised network for semantic control (Davey et al., 2016; Hallam et al., 2018; Hurley et al., 2015; X. Wang et al., 2018), although the comparison with RH connectivity has been little explored. Left AG also shows stronger connectivity than right AG to semantically-relevant lateral temporal regions during memory retrieval (Bellana et al., 2016). This study extends this research to characterise hemispheric differences across four key semantic sites, within the same participants, allowing us to compare the degree of lateralisation for semantic representation and control sites for the first time.

We first examine the connectivity profiles of four key sites – ventral ATL, AG, pMTG and IFG – which are implicated in heteromodal semantic cognition by neuroimaging meta-analyses. We characterise the intrinsic connectivity of these LH sites and their RH homotopes in 196 participants who completed a resting-state scan, and quantify (i) simple differences in connectivity across hemispheres (by computing contrasts between LH and RH seeds, which are largely symmetrical); and (ii) regions in which left-lateralised and right-lateralised patterns of connectivity show topographic differences. We also examine overlap in the connectivity patterns of these semantic sites within each hemisphere to establish whether regions thought to support semantic control (i.e. IFG and pMTG) show stronger connectivity to each other than other semantic sites (ATL and AG), and whether this pattern varies across the hemispheres. We use meta-analytic decoding to examine the likely functional consequences of asymmetries in connectivity.

Next, we investigate how individual differences in the intrinsic connectivity of the four left-lateralised semantic sites is related to individual variation in the efficiency of semantic retrieval, relative to perceptual judgements. In order to test the multiple component account of semantic cognition, in which different patterns of connectivity might be critical for heteromodal conceptual representation and control, we contrast different semantic tasks, involving the comprehension of words and pictures, as well as the retrieval of strong and weak associations that differ in their semantic control demands. We test the hypothesis that within-hemisphere connectivity from left-sided seeds may be associated with good semantic performance, while controlled semantic retrieval may be weaker in participants who have more cross-hemisphere connectivity, since the semantic control network is thought to be strongly left-lateralised. To anticipate, we also observe distinct patterns of connectivity, which are associated with semantic and language processing in LH, and visual perception and spatial processing in the RH. We find that ATL has more symmetrical intrinsic connectivity than the other sites. In contrast, the semantic control network is more strongly left-lateralised, and this pattern of lateralisation is associated with efficient semantic retrieval.

2.2. Methods

2.2.1. Overview

This study was approved by the local research ethics committees. The data were obtained as part of a large cohort study, consisting of resting state fMRI and a battery of cognitive assessments in 207 healthy young adult volunteers (137 females; age: mean ± SD = 20.21 ± 2.35, range: 18 – 31 years). Elements of this cohort study have been described previously in papers focussing on mind-wandering (Poerio et al., 2017; Sormaz et al., 2018; Turnbull et al., 2018; H. T. Wang et al., 2018a, 2018b), the functional consequences of hippocampal connectivity (Karapanagiotidis et al., 2017; Sormaz et al., 2017), patterns of semantic performance linked to individual differences in connectivity within LH semantic sites falling in different networks (Vatansever et al., 2017) and cortical thickness (X. Wang et al., 2018). No previous studies using this cohort have examined semantic performance in relation to hemispheric differences.

The analysis was divided into three steps. (i) We compared the intrinsic connectivity of four heteromodal semantic ROIs in the LH (ATL, AG, IFG, pMTG) with RH homotopes. The ROIs were identified using activation likelihood estimation meta-analytic maps of semantic processing (Humphreys and Lambon Ralph, 2015; Noonan et al., 2013; Rice et al., 2018c). We compared patterns of connectivity across pairs of seeds implicated in semantic control (pMTG and IFG) and not implicated in semantic control (ATL and AG). (ii) We also quantified the extent to which LH seeds and their RH homotopes showed symmetrical patterns of connectivity. We performed meta-analytic decoding using Neurosynth (Gorgolewski et al., 2015; Yarkoni et al., 2011) to identify psychological terms associated with LH vs. RH connectivity from these individual seeds. (iii) We then assessed whether individual differences in the intrinsic functional connectivity of the LH seeds would predict variation in performance on semantic and non-semantic tasks. Our semantic battery allowed a comparison not only of semantic and non-semantic decisions, but also of different types of semantic judgement (strong and weak thematic associations, which differ in their requirement for controlled semantic retrieval, and word vs. picture-based judgements). If semantic control is strongly left-lateralised, we might expect within-hemisphere connectivity to show an association with better performance, while cross-hemisphere connectivity from LH seeds to semantic homotopes in the RH might relate to poorer control over retrieval. We elected to focus on LH seeds since all four LH seeds are implicated in semantic processing, while this is not the case for all the RH seeds. This decision also allowed us to avoid the inflation of type I error which would arise from examining many seeds. Since bilateral ATL is implicated in semantic processing, we also examined behavioural associations with right ATL connectivity in a supplementary analysis, but found no significant effects.

2.2.2. Participants

The analysis was based on 196 participants out of 207 (126 females; mean ± SD age = 20.1 ± 2.3 years), recruited from the undergraduate and postgraduate student body at the University of York. The participants were right handed, native English speakers with normal/corrected vision. None of them had a history of psychiatric or neurological illness, severe claustrophobia, drug use that could alter cognitive functioning, or pregnancy. We excluded eleven participants: two due to missing MRI data and nine due to missing behavioural data. All volunteers provided written informed consent and were either paid or given course credit for their participation.

2.2.3. Procedure

The participants first took part in a neuroimaging session, where we acquired structural images and a resting-state scan. Participants then completed numerous cognitive assessments across three sessions, each lasting around two hours, with the order of the sessions counterbalanced across participants. This study provides an analysis of the semantic battery administered as part of this protocol.

2.2.4. Tasks

We manipulated decision type (semantic/non-semantic), modality (words/pictures) and strength of association (weak/strong associates). All tasks employed a three-alternative forced-choice design: participants matched a probe stimulus on the screen with one of three possible targets, and pressed buttons to indicate their choice.

We compared semantic relatedness judgements to words and pictures to verify whether patterns of connectivity from heteromodal LH seeds predicted performance across modalities (Rice et al., 2015b). We also manipulated strength of association in a picture-word matching task. Strength of association is thought to modulate the ‘controlled retrieval’ demands of semantic judgements; weak associations elicit stronger activation in the semantic control network, in both left pMTG and IFG (Badre et al., 2005; Davey et al., 2016; Noppeney et al., 2004; Wagner et al., 2001). In contrast, semantic control demands are minimised during the retrieval of strong associations, since the target is a dominant associate of the probe. Consequently, individual differences in intrinsic connectivity from LH semantic control seeds might relate to performance differences between weak and strong associations. Finally, we included a non-semantic task involving perceptual judgements. Participants were asked to select which scrambled picture was an exact match to a probe image.

In all tasks, each trial consisted of a centrally-presented probe presented with a target and two unrelated distractors, 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 (with the three options aligned horizontally, and the target in each location equally often). Finally, the probe was presented at the top of the screen. 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, and an efficiency score was calculated for each participant in each condition by dividing response times by accuracy (note: in brain analyses, this efficiency score was inverted to aid the interpretation of the results, such that a higher score corresponded to better performance). Figure 2.1 illustrates the tasks and summarises the behavioural results.

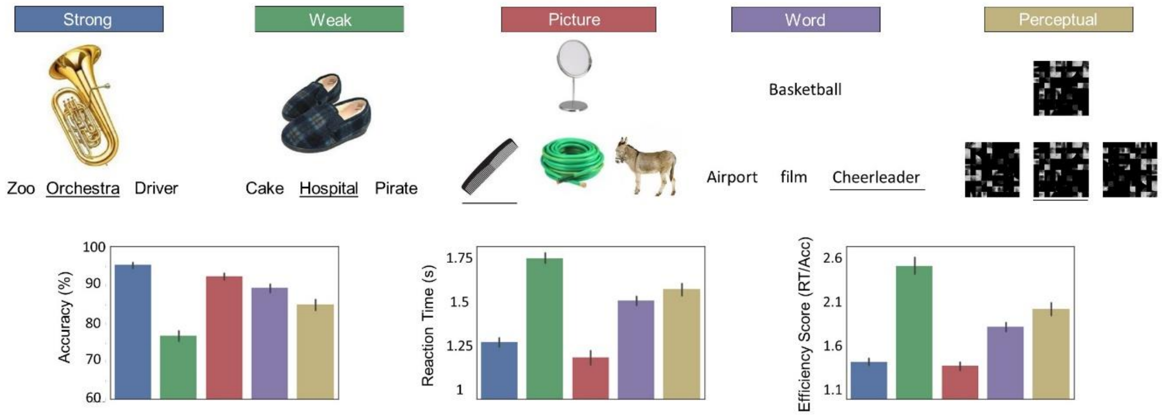

Figure 2.1. Top row: Illustration of the behavioural tasks. For all the tasks, correct answers are underlined. The weak and strong associations involved Picture-Word matching. The layout of the Word-Word and Picture-Picture conditions was identical, except all the stimuli were either words or pictures. The perceptual matching task required participants to identify a complex item that was visually identical to the probe. Bottom row: Plots depicting the mean accuracy, reaction time and efficiency score (not reversed) for each task. The colour of each bar corresponds to the names of the tasks in the top row. Error bars represent 95% confidence intervals. All conditions were significantly different to each other in average efficiency score (p < .001, see Results section below).

The stimuli employed in the tasks were selected from a larger dataset of words and photographs used in previous experiments (Davey et al., 2015a; Krieger-Redwood et al., 2015). The pictures were coloured photographs collected from the internet and re-sized to fit the trial structure (200 pixels, 72 dpi). All the coloured pictures and words were rated for familiarity using 7-point Likert scales, and imageability (>500) from the MRC psycholinguistic database (Coltheart, 1981; Wilson, 1988). Lexical frequency for the words was obtained by the SUBTLEX-UK database (van Heuven et al., 2014) to allow matching on psycholinguistic properties. Specific details for each task are provided below.

2.2.4.1. Word-Picture Matching Manipulating Strength of Association

Participants were asked to select the target word that was most strongly associated with a probe picture. The probe list included 60 coloured pictures (e.g., dog) which were paired with 60 strongly related (e.g., bone) and 60 weakly related targets (e.g., ball), presented as written words. The strength of association between probe-target pairs was assessed using a 7-point Likert scale and differed significantly between conditions (Table 2.1). There were no differences between strong and weak associations in word length, familiarity, imageability or lexical frequency (Table 2.1). These 120 trials were presented in four blocks of thirty trials each, and both strong and weak associations were presented in each block. The order of trials within the blocks was randomized across subjects. The presentation of the blocks was interleaved with blocks of the other semantic and non-semantic judgements.

	Strength of association				Modality			
	Strong	Weak	t	Sig.	Word	Picture	t	Sig.
	Mean (Standard errors)				Mean (Standard errors)			
Word Length	6.43 (.39)	6.6 (.34)	-.16	.873	6.08 (.31)	6.4 (.32)	-.69	.490
Lexical Frequency	13564.8 (1887)	11233.6 (1805)	.89	.374	4619.8 (823.1)	6458.7 (827.5)	-1.56	.122
Familiarity	6.02 (.09)	6.12 (.08)	-.88	.381	6.04 (.1)	5.98 (.1)	.40	.688
Imageability	5.16 (.13)	4.96 (.13)	1.07	.287	4.96 (.13)	4.97 (.12)	-.07	.948
Semantic Association	6.02 (.07)	3.32 (.10)	21.74	.000	4.80 (.14)	4.95 (.15)	-.76	.447

Table 2.1. Psycholinguistic variables for our semantic battery by strength of association and modality.

2.2.4.2. Input Modality: Picture-Picture vs. Word-Word Association Matching

Additional judgements of semantic association were presented using only written words, or coloured pictures (60 trials for each). In these trials, the probe and the response options were all presented in the same modality (i.e., word probes were presented with word responses). The two sets of target concepts did not differ in terms of mean word length, familiarity, imageability, lexical frequency and strength of association (Table 2.1). The task was split in four blocks of 30 trials each. The order of trials within the blocks was randomized across subjects. The presentation of the blocks was interleaved with the blocks of the other tasks.

2.2.4.3. Non-semantic Perceptual Matching Task

This perceptual control task had decision-making demands that were similar to the semantic judgments (cf. Visser et al., 2012). The stimuli were 60 pixelated and scrambled black-and-white photographs of faces. Participants were asked to select the target that was identical to the probe; the distractors were the same images rotated by 180° or 270° (see Figure 2.1 for an example). The task was split in two blocks of 30 trials each. The presentation of the blocks was interleaved with the blocks of the other tasks.

2.2.5. Neuroimaging

2.2.5.1. 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.

2.2.5.2. Pre-Processing

All pre-processing of resting-state data used FMRIB Software Library (FSL version 4.1, http://fsl.fmrib.ox.ac.uk/fsl/). The Brain Extraction Tool (BET) was used to extract individual FLAIR and T1 weighted structural brain images (Smith, 2002). Structural images were linearly co-registered to the MNI 152 standard template using FMRIB's Linear Image Registration Tool (FLIRT, Jenkinson et al., 2002; Jenkinson and Smith, 2001). FMRI Expert Analysis Tool (FEAT Version 5.98, part of FSL) was used to perform the following standard analysis steps: (1) correcting for head movement using MCFLIRT (Jenkinson et al., 2002); (2) slice timing correction using Fourier space time-series phase-shifting; (3) spatial smoothing with a 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).

2.2.5.3. ROI Selection

Figure 3 (top row) shows an automated meta-analysis for the term “semantic”. There is a strongly left-lateralised response to semantic tasks in four key regions: ATL, AG, IFG and pMTG, which we investigated in this study. Semantic cognition also elicits a response in dorsal anterior cingulate; however, since our focus was on hemispheric asymmetry, we excluded this medial region.

We identified co-ordinates for our ROIs from three neuroimaging meta-analyses of semantic cognition. (i) We selected an ATL seed from an average of peaks across eight studies that included a semantic > non-semantic contrast (Rice et al., 2018c), providing a peak response in left ventral ATL (MNI coordinates -41, -15, -31). (ii) Left AG also commonly shows activation during semantic tasks, when contrasted with non-semantic decisions that are at least as difficult (Binder et al., 2009). Our AG seed was taken from an ALE meta-analysis of 386 studies (Humphreys and Lambon Ralph, 2015), which identified a peak for automatic semantic retrieval in left AG (MNI -48, -68, 28). (iii) To identify ROIs associated with semantic control, we used an ALE meta-analysis of 53 studies (Noonan et al., 2013), which manipulated the control demands of semantic judgements in diverse ways (strength of association, ambiguous words, strength of distractors). This identified activation peaks in left IFG (MNI -47, 21, 18) and pMTG (MNI -58, -49, -9). To create ROIs, we placed a binarised spherical mask with a radius of 3mm, centred on the MNI coordinates of the peak response in each site. We generated right-hemisphere homotopic spheres for each seed by following the same procedure, but flipping the sign of the x coordinate in MNI space from negative to positive. An advantage of this sign-flipping method is that it allowed us to generate symmetrical seeds for all sites in a comparable way, even for sites that typically do not show a semantic response in the RH (e.g. for pMTG). However, there is good evidence of bilateral engagement of ATL in semantic cognition. Moreover, Rice et al. (2018c) identified a right ATL peak (MNI 44, -11, -36), which was not in an identical location to that in the LH. We replicated all of our analysis in the pipeline using this RH seed, instead of the sign-flipped homotope, in Supplementary Analysis S1. The results across the two ATL seeds were similar.

2.2.5.4. Analysis of intrinsic connectivity of ROIs

In a first-level analysis, we extracted the time series from each ROI. These were used as Explanatory Variables (EVs) in separate connectivity analyses for each seed (eight seeds in total: four LH seeds and their RH homotopes). 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 et al., 2007). These masks were generated from each individual's structural image (Zhang et al., 2001). We did not perform global signal regression which has been reported to introduce spurious anti-correlations (Murphy et al., 2009).

At the group level, analyses were carried out using FMRIB's Local Analysis of Mixed Effects (FLAME1) with automatic outlier detection (Beckmann et al., 2003; Woolrich, 2008; Woolrich et al., 2004). Significant clusters ($p < .05$) were defined using Gaussian random field theory with a voxel inclusion threshold of $z = 3.1$ to define contiguous clusters (Eklund et al., 2016).

2.2.5.5. Characterising hemispheric similarities and differences in intrinsic connectivity

Having characterised the whole-brain intrinsic connectivity of each site, we directly compared connectivity across the hemispheres. We took the intrinsic connectivity of single seeds at the individual level and defined a second level analysis including the LH and RH seeds as two EVs, including two contrasts: left > right seed connectivity and the reverse. Significant clusters at the group level were defined as above.

This direct comparison of LH and RH seeds yielded largely left-lateralised regions for the left > right connectivity contrast and largely right-lateralised regions for the reverse contrast. These two lateralised maps had similar shapes, although there were some asymmetries. In order to identify regions in which these patterns of differential connectivity varied across the hemispheres, we performed a second difference analysis. We projected the RH connectivity map into LH coordinate space for each participant (using the tool 'fslswapdim' in FSL 4.1. specifying as the only transformation the inversion of the x axis). This allowed us to perform a direct comparison of the shapes of the connectivity patterns for

LH and RH. This is akin to the ‘Flip Method’ described in Baciu et al., 2005. At the group level, we again defined two contrasts: left > right flipped hemisphere connectivity and the reverse. The flip method therefore identified regions where LH seeds showed heightened connectivity, compared to the expected pattern from RH. Figure 2.2 provides a summary of the analysis pipeline.

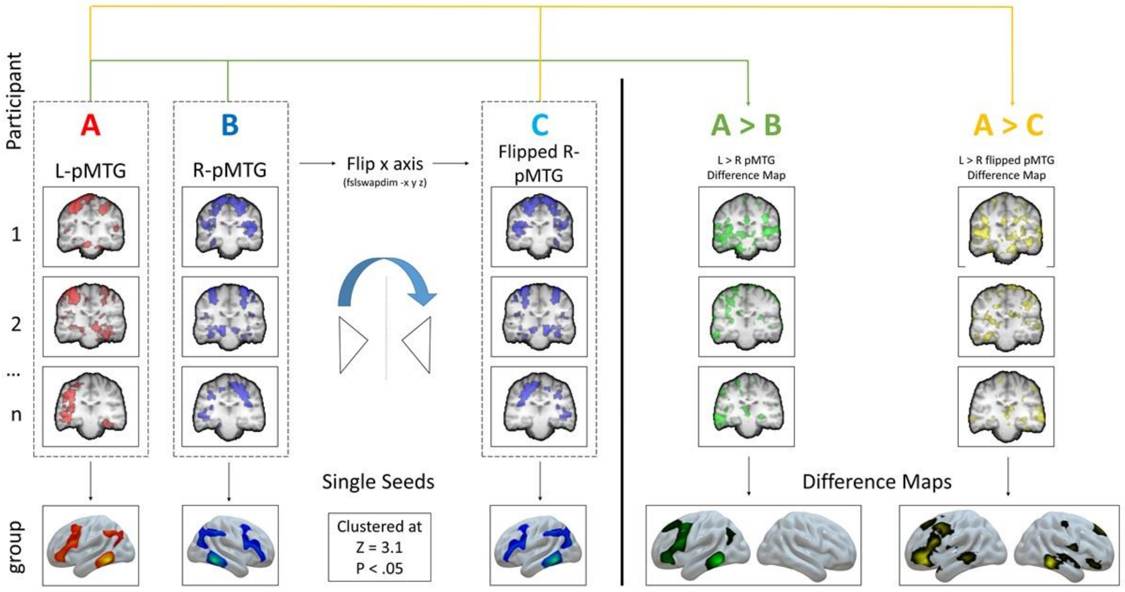

Figure 2.2. Analysis pipeline for the single seed correlation analysis and for the difference analyses using posterior middle temporal gyrus as an example. The A and B columns illustrate our single seed analyses, while A>B and A>C show our direct and flipped difference analyses respectively. The green arrow describes our pipeline for the direct comparison difference maps, which highlight the differences in the topography of connectivity for left and right seeds, while the yellow shows the one for the flipped difference maps, which reveal differences in the shape of these topographies for left and right seeds.

We examined the conjunctions for pairs of seed regions allied to (i) the semantic control network (IFG and pMTG) and (ii) not implicated in semantic control (ATL and AG), to identify voxels connected to both regions using the ‘easythresh_conj’ tool in FSL (Z=3.1, p=.05); we did this for the LH and RH group maps resulting from 2.2.5.4 separately. We then computed voxels that were common for each conjunction in both hemispheres performing a binarised multiplication of the LH and the RH conjunction maps for each conjunction separately. Supplementary Analysis S2.3 provides the shared connectivity of each LH seed and its RH homotope; these maps are also available on NeuroVault (https://neurovault.org/collections/4683/).

2.2.5.6. Cognitive decoding and automated meta-analysis using Neurosynth

Connectivity maps were uploaded to Neurovault (Gorgolewski et al., 2015, https://neurovault.org/collections/4683/) and decoded using Neurosynth (Yarkoni et al., 2011). Neurosynth is an automated meta-analysis tool that uses text-mining approaches to extract terms from neuroimaging articles that typically co-occur with specific peak coordinates of activation. It can be used to generate a set of terms frequently associated with a spatial map (as in Figures 2.5 and S2.3). The results of cognitive decoding were rendered as word clouds using R. We manually excluded terms referring to neuroanatomy (e.g., “inferior” or “sulcus”), as well as repeated terms (e.g., “semantic” and “semantics”). The size of each word in the word cloud relates to the frequency of that term across studies.

Neurosynth can also generate ‘reverse inference’ maps associated with a particular term, such as “semantic”. This approach highlights regions that are more likely to be activated for that particular term than for others (as in Figure 2.3).

2.2.5.7. Associations between connectivity and behavioural performance

In a final step, we considered whether individual differences in intrinsic connectivity from our LH seeds correlated with behavioural performance. We elected to focus on LH seeds since all four LH seeds are implicated in semantic processing, while this is not the case for all the RH seeds. This decision also allowed us to avoid the inflation of type I error which would arise from examining many seeds. However, seeding the LH semantic sites still allows us to test the hypothesis that lateralisation of connectivity has functional consequences, since we can consider individual differences in the extent to which these LH seeds couple with other LH semantic and language sites, vs. homologous regions in the RH. We might expect for a highly-lateralized seed like pMTG, connectivity to other LH regions might be associated with good performance, while strong intrinsic connectivity to RH homologues of semantic regions might be associated with poor performance. Since bilateral ATL is implicated in semantic processing, we also examined behavioural associations with right ATL connectivity in a supplementary analysis (following reviewers’ comments), but found no significant effects. In each analysis, we included as EVs the efficiency scores corresponding to the four semantic conditions (Weak and Strong associations, Picture and Word modalities of presentation), the non-semantic perceptual matching task as a control, and a motion regressor using the mean (across time/frames) of the absolute values for framewise displacement for each participant. We z-scored the behavioural data, and imputed all outliers exceeding $z > 2.5$ with the cut-off value (except for the motion regressor). The resulting data was mean-centred and entered into a model where we defined as contrasts of interest: group intrinsic connectivity for the seed, semantic > perceptual matching (with semantic performance estimated as the average of the four semantic conditions), weak > strong associations, picture > word modality and the reverse contrasts. Significant clusters were identified using the methods above, with the addition of a Bonferroni correction to account for the one-tailed nature of our tests and the fact that we initially examined four seeds (ATL, AG, IFG, pMTG)[2]. We therefore accepted $p = .0063$ ($p = .05/8$) as reaching the threshold for significance. Since the average efficiency scores were significantly different across conditions, we included two extra contrasts to control for difficulty: Given that the weak and strong associations conditions were the hardest and easiest respectively, and the perceptual task was midpoint between the two, we contrasted strong > perceptual and perceptual > weak, to establish if effects could be attributed to difficulty.

2.2.6. Data and Code Availability Statement

Neuroimaging data at the group level are openly available in Neurovault at https://neurovault.org/collections/4683/. The conditions of our ethical approval do not permit public archiving of the raw data because participants did not provide sufficient consent. Researchers who wish to access the data and analysis scripts should contact the Research Ethics and Governance Committee of the York Neuroimaging Centre, University of York, or the corresponding author, Beth Jefferies. Data will be released to researchers when this is possible under the terms of the GDPR (General Data Protection Regulation).

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[2] We did not correct for the additional RH ATL seed, reported in Supplementary Materials, since it was added following the reviewers' comments.

2.3. Results

2.3.1. Intrinsic Connectivity of LH and RH Seed Regions

Figure 2.3 shows the intrinsic connectivity maps for the four LH seeds and their RH homotopes. The connectivity maps and all results discussed in this section can be found in Neurovault (https://neurovault.org/collections/4683/). All LH seeds showed intrinsic connectivity with other left-lateralised semantic regions (i.e. ATL, AG, IFG, pMTG), as well as with their RH homotopes (Figure 2.3, rows 2-5). The intrinsic connectivity of these regions showed clear overlap with an automated meta-analysis for the term ‘semantic’ performed using Neurosynth (row 1). Left ATL showed relatively strong connectivity to other temporal lobe regions and IFG (see Jackson et al., 2016 for similar results – although unlike that study, we did not observe strong intrinsic connectivity between left ATL and dorsomedial prefrontal cortex; see also Supplementary Figure S2.1). AG showed strong connectivity to all other semantic seeds and to medial default network regions in posterior cingulate and medial prefrontal cortex. Left pMTG and IFG showed highly similar patterns of connectivity, consistent with the proposal that these brain areas form a distributed network underpinning semantic control. Along with left-lateralised semantic regions, both pMTG and IFG showed strong connectivity to dorsal medial prefrontal cortex, bordering preSMA, and to lateral prefrontal regions in the RH, which are implicated in the control of memory (Noonan et al., 2013).

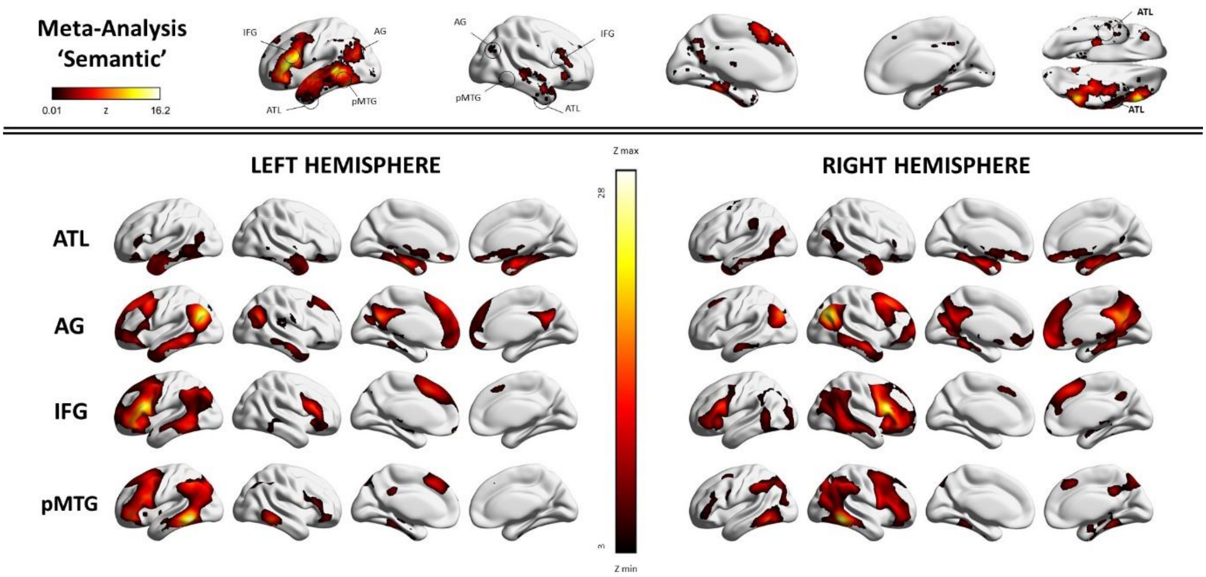

Figure 2.3. The top row depicts the meta-analytic map for the term 'semantic' extracted from Neurosynth, with the location of the LH and RH seeds indicated. The bottom panel shows the group mean intrinsic connectivity maps for these LH and RH seeds, projected to the surface using BrainNet. These connectivity maps present Z values (unthresholded).

We next quantified the degree to which patterns of intrinsic connectivity are similar across pairs of seeds implicated in semantic control (IFG and pMTG) or not associated with control (ATL and AG; see Figure 2.4). We correlated the intrinsic connectivity of each seed with the three other seeds within the same hemisphere (for example, we compared left IFG-pMTG with left IFG-AG and left IFG-ATL) and tested for significant differences between these correlations using the Fisher r-to-z transformation. Table 2.2 shows the correlations between all the different pairs of intrinsic connectivity maps.

There was extensive shared connectivity for pMTG and IFG, in both hemispheres. Overlap between IFG and pMTG was seen within these two seed regions, but also within other regions implicated in executive control, such as intraparietal sulcus and pre-supplementary motor area, in both hemispheres (see Figure 2.4). The intrinsic connectivity patterns of IFG and pMTG showed higher correlations with each other than with other semantic sites. In both hemispheres, IFG was significantly more correlated with pMTG than with either AG (LH: $z = 7.72$, $p < .001$; RH: $z = 5.33$, $p < .001$) or ATL (LH: $z = 9.57$, $p < .001$; RH: $z = 7.91$, $p < .001$). Likewise, pMTG was more correlated with IFG than with AG (LH: $z = 5.48$, $p < .001$; RH: $z = 3.15$, $p = .002$) and ATL (LH: $z = 7.68$, $p < .001$; RH: $z = 5.01$, $p < .001$). These results demonstrate that the semantic network is not homogeneous: LH sites implicated in semantic control are more connected to each other than to other semantic regions, and the same pattern is seen for their RH homologues.

ATL and AG are not implicated in semantic control and Figure 2.4 shows that these sites overlap with DMN sites – including within ATL, medial prefrontal cortex, AG and hippocampus. However, comparisons of the correlations in Table 2.2 suggest that ATL and AG are not always more connected to each other than to other semantic sites, and in this way, they do not appear to form a strong sub-network within the semantic system. In the LH, there was a difference between AG-ATL and AG-IFG coupling which approached significance ($z = -1.73$, $p = .08$), while in the RH, there was no evidence that AG was more correlated with ATL than IFG ($z = -0.58$, $p > .1$). In both hemispheres, AG showed stronger intrinsic connectivity with pMTG (a nearby site) than with ATL (LH: $z = -3.94$, $p = .0001$; RH: -2.77, $p = .0056$). The LH correlation for ATL-AG was not statistically different from ATL-IFG ($z = -0.12$, $p > .1$), although in the RH, we found a marginally stronger correlation for ATL-AG than AG-IFG ($z=2.0$, $p = .05$). Finally, there was no evidence that ATL-AG correlations were stronger than ATL-pMTG correlations, in both LH (where there was a trend in the opposite direction; $z = -1.74$, $p = 0.8$) and RH ($z = 0.90$, $p > .1$).

In a final step, we compared the patterns of shared connectivity for IFG-pMTG (implicated in semantic control) and for ATL-AG (not implicated in control) in the LH and RH, with canonical networks derived from a parcellation of resting-state connectivity (Yeo et al., 2011; Figure 2.4). The left-lateralised semantic control sites (IFG and pMTG) showed a high degree of overlap with both DMN and control networks, supporting the view that these regions sit at the intersection of networks that are typically anti-correlated yet recruited together during semantic tasks (Davey et al., 2016). The RH homologue regions showed a high degree of overlap with control networks (frontoparietal and dorsal attention network) but not with DMN. The connectivity patterns of LH non-control semantic regions (AG and ATL) showed high overlap with lateral default mode regions, not core DMN regions, such as posterior cingulate cortex. The RH homologue regions showed a similar degree of overlap with lateral, core and medial DMN networks, and also strong overlap with the dorsal attention network.

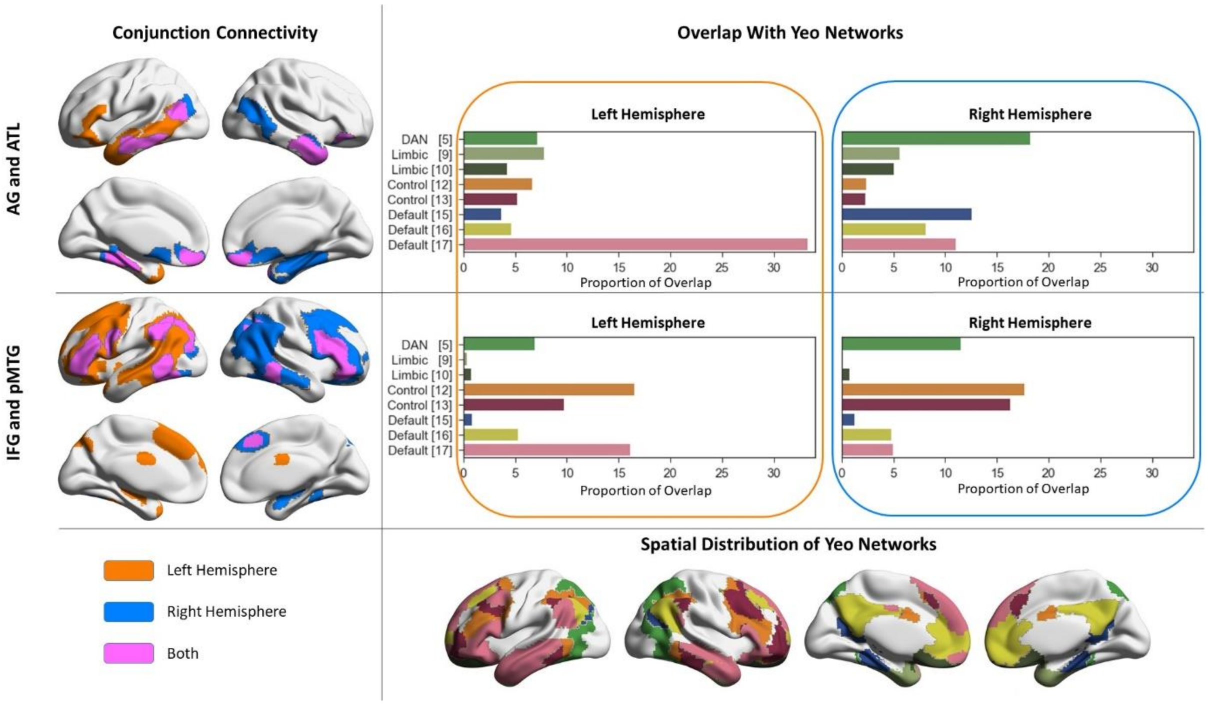

Figure 2.4. The maps in the left-hand column depict conjunctions of group mean intrinsic connectivity for pairs of ROIs located in distant parts of cortex (semantic control sites, IFG and pMTG; and sites outside the semantic control network, in AG and ATL). Orange shows regions of overlap between LH seeds while blue shows overlap between RH seeds (pink shows regions of overlap between pairs of semantic seeds that were present for both LH and RH conjunctions). The bar plots adjacent to each conjunction map show the proportion of voxels of this map that overlap with networks from the 17-network parcellation described by Yeo et al. (2011, depicted in the bottom row, colour-coded to match the bar plots; the network names and colour codes for these maps and the corresponding bar plots above can be consulted in detail in Shinn et al., 2015). To simply this figure, we only show those networks for which at least 5% of the voxels in at least one connectivity map showed overlap. Connectivity maps are projected to the surface and plotted using BrainNet.

2.3.2. Similarities and differences in intrinsic connectivity across hemispheres

The left and right hemisphere maps were largely symmetrical (see Figure 2.3 and Supplementary Figure S2.1). We tested for any significant differences in the strength of the correlation between particular pairs of seeds in the LH and RH using the Fisher r-to-z transformation. We also tested for equivalence between the correlations in each hemisphere using the Two One-Sided Tests (TOST) approach as implemented by Lakens (2017). ATL showed the most symmetrical pattern of connectivity (Pearson's r: ATL = 0.85, AG = 0.46, IFG = 0.43 and pMTG = 0.52, all $p < .001$): this site had a significantly higher correlation across LH and RH seeds than all of the other sites (using a Fisher to z transform, $z > 6.68$, p <

.001). The strength of cross-hemisphere correlations for the other seeds were not significantly different from each other (z < 1.15, p > .2; all statistically equivalent, p < .05).

We also compared the strength of correlation between different pairs of seeds in LH and RH. The correlation between IFG and pMTG was significantly higher in the LH than the RH (results of analysis shown in Table 2.2), consistent with the hypothesis that the semantic control system is particularly left-lateralised. The strength of correlations across other seeds was not significantly different in the LH and RH, and in most cases they were statistically equivalent (with one exception: ATL to IFG showed a numerically higher correlation in the LH, which was not statistically equivalent to RH). All correlations were positive except between IFG and ATL in the RH, which showed a negative correlation.

	LH	**RH**	**LH vs. RH: Fisher r to z**	**Equivalence test for difference in r (TOST)**
IFG to pMTG	.795	.640	**z=3.21, p=.001**	**r(194)=0.16, p=.223**
IFG to AG	.293	.212	z=0.85, p>.1	r(194)=0.08, p=.036
IFG to ATL	.113	-.047	z=1.58, p=.1	**r(194)=0.16, p=.245**
pMTG to AG	.483	.412	z=0.87, p>.1	r(194)=0.07, p=.026
pMTG to ATL	.294	.243	z=0.54, p>.1	r(194)=0.05, p=.013
ATL to AG	.125	.155	z=-0.30, p>.1	r(194)=-0.03, p=.006
Average intra-hemispheric correlation	.351	.269		

Table 2.2 Within-hemisphere correlations for our four ROIs group mean connectivity maps. All correlations are significant at p < .001. Correlations that are different between LH and RH, and those that are not statistically equivalent across hemispheres, are highlighted in bold. The correlations reported here are not corrected for multiple comparisons, although applying Bonferroni correction does not change the outcome.

In summary, the analysis so far shows (i) the semantic system is not homogeneous, with higher similarity between the intrinsic connectivity patterns of the semantic control sites (IFG and pMTG); (ii) ATL shows a more symmetrical pattern of connectivity than other sites, in line with the view this site is a bilateral semantic hub; (iii) the connectivity pattern underpinning the semantic control network is highly lateralised to the LH.

2.3.3. Differences in network topography between hemispheres

To characterise any differences in the topographical organisation of connectivity from left lateralised semantic regions and their homotopes in RH, we directly contrasted the connectivity of LH and RH for each seed location. In a basic analysis, we computed the simple difference maps between LH and RH seeds. The contrasts of LH>RH and RH>LH produced largely symmetrical maps, which are provided in the Supplementary Materials (Supplementary Analysis S2.2, Figure S2.3). All LH sites showed strong connectivity to semantic sites, while right-lateralised seeds showed strong connectivity to the homotopic sites in the RH (indicated by the symmetry of the red and blue regions). In order to compare the shapes of connectivity patterns directly, we flipped the connectivity map of the RH seeds into LH space, and subtracted one map from the other, to identify regions of stronger and weaker connectivity in LH, relative to the pattern for the RH. For example, a region like left IFG might show stronger intrinsic connectivity to left ATL than would be expected from the pattern of connectivity between right IFG and right ATL. This difference in network topography can be highlighted through a comparison of the connectivity maps for left and right IFG by flipping the RH seed map along the x axis (see Figure 2.2, which illustrates this method). The results are shown in Figure 2.5. We then compared these connectivity difference maps with the network parcellation provided by Yeo et al. (2011). In Figure 2.5, we show differences in network overlap for regions with stronger than expected connectivity to the LH seed given the pattern for the RH seed, and the reverse. Networks overlapping with both L>R and R>L maps to an equal degree fall at the zero point of these charts, since our focus is on network differences.

Left ATL showed stronger connectivity to medial temporal cortex, right ATL, left ventral IFG/insula and left intraparietal sulcus, relative to the connectivity of right ATL flipped into LH space. This is consistent with the low correlation between right ATL and IFG reported above. The right ATL (flipped into LH space) showed stronger connectivity to AG and dorsomedial prefrontal cortex, relative to the pattern of connectivity seen for left ATL. The regions with stronger left-lateralised ATL connectivity showed more extensive overlap with lateral DMN and limbic networks, while the regions with stronger right-lateralised ATL connectivity overlapped to a greater extent with multiple control and attention networks.

Left AG showed stronger connectivity to left and right lateral occipital-temporal cortex, right ATL, left and right IFG, left and right dorsal medial prefrontal cortex and portions of somatomotor cortex, relative to right AG flipped into LH space. The right AG (flipped into LH space) showed stronger connectivity to precuneus and posterior cingulate cortex, plus medial temporal lobe regions. The regions with stronger left-lateralised AG connectivity showed more extensive overlap with lateral DMN and the ventral attention network. The regions with stronger right-lateralised AG connectivity showed greater overlap with visual, control and core/medial DMN networks.

Left IFG showed stronger connectivity to left motor cortex, extending into left dorsal medial prefrontal cortex, and to left inferior frontal cortex. Left pMTG showed a similar pattern, extending further into left IFG, right pMTG and left and right lingual gyrus/cuneus. LH IFG and pMTG seeds also showed weaker connectivity to parietal-occipital fissure, intraparietal sulcus, precuneus, posterior cingulate and medial prefrontal cortex, both within and across hemispheres, compared with right-hemisphere seeds (indicated by the presence of blue in Figure 2.5). Regions with stronger left-lateralised IFG connectivity showed more extensive overlap with control, ventral attention, medial visual and somatomotor networks, while sites with more right-lateralised IFG connectivity showed greater overlap with core DMN and lateral visual regions. Regions with stronger left-lateralised pMTG connectivity showed greater overlap with lateral DMN, while sites with more right-lateralised pMTG connectivity showed greater overlap with dorsal attention and lateral visual networks.

We applied cognitive decoding to these maps using Neurosynth (see word clouds in Figure 2.5). The set of brain regions showing stronger connectivity with LH seeds were associated with semantic and language terms (pMTG and ATL) and somatomotor processing (for IFG and AG). Brain regions showing stronger connectivity to RH seeds were associated with terms relating to visual-spatial processing. This association between left-lateralised connectivity and somatomotor processing as well as semantics and language has previously been reported by Gotts et al. (2013). To quantify these differences, we obtained meta-analytic maps from Neurosynth for key terms thought to show strong lateralisation (terms with presumed LH lateralisation: semantic, language, words; terms with presumed RH lateralisation: visual, spatial, attention) and we computed their correlation with our connectivity difference maps. We found that brain regions showing stronger connectivity with LH seeds had positive correlations with these left-lateralised terms (average for the four seeds: $r = .13$) and negative correlations with right-lateralised terms (average: $r = -.11$); the reverse was true for regions with stronger connectivity to RH seeds (average correlation with right lateralised terms: $r = .1$; with left-lateralised terms: $r = -.14$). These findings are consistent with the view that different patterns of connectivity from homotopic regions in left and right hemisphere relate to functional distinctions observed in neuropsychological investigations (where spatial neglect is more associated with right-lateralised lesions, and semantic-language dysfunction with left-lateralised lesions).

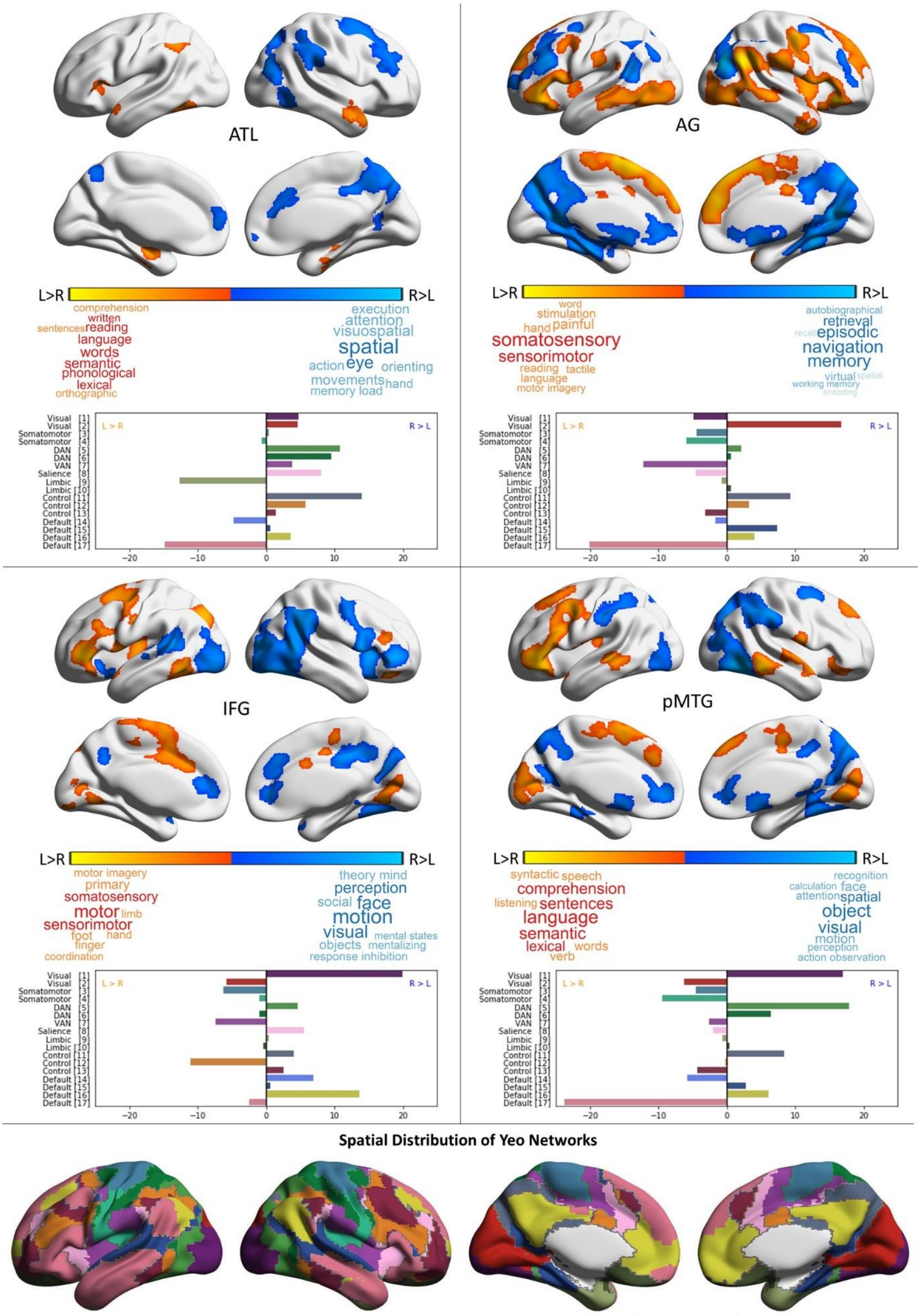
ATL
L>R
R>L
comprehension
written
sentences
reading
language
words
semantic
phonological
lexical
orthographic
execution
attention
visuospatial
spatial
action
eye
orienting
movements
hand
memory load
AG
L>R
R>L
word
stimulation
hand
painful
somatosensory
sensorimotor
reading
tactile
language
motor imagery
autobiographical
retrieval
recall
episodic
navigation
memory
virtual
spatial
working memory
encoding
IFG
L>R
R>L
motor imagery
primary
somatosensory
motor
limb
sensorimotor
foot
hand
finger
coordination
theory mind
perception
social
face
motion
visual
mental states
objects
mentalizing
response inhibition
pMTG
L>R
R>L
syntactic
speech
comprehension
listening
sentences
language
semantic
lexical
words
verb
recognition
calculation
face
attention
spatial
object
visual
motion
perception
action observation
Visual [1]
Visual [2]
Somatomotor [3]
Somatomotor [4]
DAN [5]
DAN [6]
VAN [7]
Salience [8]
Limbic [9]
Limbic [10]
Control [11]
Control [12]
Control [13]
Default [14]
Default [15]
Default [16]
Default [17]
L > R
R > L
−20
−10
0
10
20
Spatial Distribution of Yeo Networks

Figure 2.5. Intrinsic connectivity group maps showing differences in the network topography (shape/magnitude) of connectivity patterns for left and right hemisphere seeds. The connectivity patterns for right hemisphere seeds were 'flipped' into left hemisphere space, and the maps therefore characterise differences in the shapes and magnitudes of largely symmetrical patterns of connectivity for the two hemispheres ($z = 3.1$, $p < .05$); these patterns are depicted in Figure S3. The results of cognitive decoding using Neurosynth (Yarkoni et al., 2011) are shown in the word clouds below the colour bars. The charts for each seed show a comparison of these spatial maps with the Yeo et al. (2011) 17 networks (depicted in the bottom row, colour-coded to match the bar plots). Each chart plots the difference in overlap for each network from Yeo et al., comparing the LH > RH and RH > LH connectivity maps. A left-facing bar corresponds to more extensive overlap with the left-lateralised connectivity map, while a right-facing bar corresponds to more extensive overlap with the right-lateralised connectivity map. The network names and colour codes are taken from Shinn et al., 2015.

2.3.4. Intrinsic connectivity of semantic seeds regions predicts behavioural efficiency

We analysed the behavioural results of our tasks using repeated-measures ANOVAs with Greenhouse-Geisser correction to test for significant differences between conditions. There was an effect of condition for both accuracy ($F(2.92, 574.24) = 303.33$, $p = .000$) and RT ($F(2.74, 540.08) = 420.85$, $p = .000$). Speed and accuracy may be traded off in different ways across tasks and individuals. We overcame this issue by using inverse response efficiency to capture global performance (RT divided by accuracy, multiplied by -1; high scores reflect good performance). We have successfully used this approach in other recent studies (Gonzalez Alam et al., 2018; Lanzoni et al., 2019; Murphy et al., 2018; Poerio et al., 2017; Vatansever et al., 2017; H. T. Wang et al., 2018b; X. Wang et al., 2018). There was a difference in response efficiency across conditions ($F(2.64, 519.45) = 398.05$, $p = .000$). Bonferroni corrected t-tests revealed participants were less efficient for weak than strong associations ($t(195) = 30.02$, $p = .000$), and less efficient for word than picture decisions ($t(195) = 17.95$, $p = .000$). Participants were also more efficient in three of the four semantic tasks relative to perceptual judgements ($t(195) = 5.58 – 19.01$, $p = .000$), yet less efficient for weak associations relative to perceptual trials ($t(195) = 10.28$, $p = .000$).

We examined the relationship between the intrinsic connectivity of each of our four LH ROIs and task performance outside the scanner, to test the hypothesis that stronger connectivity *within* LH cortical regions is associated with efficient semantic retrieval, while stronger connectivity *between* LH seeds and RH regions disrupts semantic control. The results are summarised in Figure 2.6. Supplementary analyses to confirm that these effects did not solely reflect differences in task difficulty are shown in Table 2.3.

We found a significant relationship between the strength of intrinsic connectivity of two semantic seeds – AG and pMTG – and individual differences in participants' efficiency when performing semantic and perceptual tasks, in whole-brain analyses. Connectivity from left AG to bilateral medial occipital regions was associated with differential performance on perceptual and semantic tasks (Figure 2.6; dark blue). Participants with poorer performance on perceptual decisions, relative to semantic decisions, showed stronger connectivity from left AG to bilateral occipital cortex. An overlapping cluster predicted weak performance on perceptual trials (Figure 2.6; light blue). Since the perceptual decisions were more difficult than the semantic decisions overall, it is possible that this contrast reflected poorer performance on harder decisions in general, in participants with weaker connectivity from left AG to occipital cortex. As a control analysis, we compared weak associations (a harder semantic task) with perceptual matching and found the same positive correlation, suggesting that irrespective of difficulty, participants with poorer perceptual than semantic performance have stronger connectivity from left AG to occipital cortex.

Patterns of connectivity from pMTG – a key semantic control site – also predicted the capacity to retrieve weak associations, relative to strong associations, and therefore the retrieval of non-dominant aspects of knowledge in a controlled fashion to suit the circumstances. Stronger within-hemisphere coupling to left pSTG and supramarginal gyrus, implicated in language (Figure 2.6, green), was associated with the efficient retrieval of strong associations. In contrast, cross-hemisphere connectivity with right aSTG was associated with poorer performance on weak relative to strong associations (Figure 2.6, red and orange). Since weak associations are harder than strong associations, we performed a supplementary analysis to test the effect of this cross-hemispheric connectivity pattern on demanding tasks in general. There was no correlation between this pattern of connectivity (defined by the strong vs. weak association contrast) and performance on easy semantic vs. harder perceptual decisions, suggesting that the association between connectivity and performance was specific to demanding semantic judgements.

Seed	Connectivity to:	Behavioural control	r	p
pMTG	Strong > Weak (RH)	Strong - Perceptual	0.04	0.62
AG	Weak > Strong (Cerebellum)	Weak - Perceptual	0.09	0.2
	Semantic > Perceptual (Occipital)	Weak - Perceptual	0.91	< 0.001

Table 2.3. Correlations to control for possible difficulty confounds in our behavioural regressions. In these supplementary analyses, we took patterns of connectivity defined by the main analysis and computed correlations with different task effects.

There was an additional effect which did not survive Bonferroni correction. AG's connectivity to a left cerebellar cluster (Figure 2.6, brown) was positively associated with participants' efficiency in retrieving weak associations (relative to strong associations), consistent with a role for the cerebellum in semantic cognition. No patterns of connectivity predicted differences between word and picture performance. This null result perhaps reflects the heteromodal nature of the seeds we selected. Finally, in order to increase our confidence that the results obtained were not specific to a particular cluster-forming threshold, we conducted additional analyses using Threshold-Free Cluster Enhancement (Smith and Nichols, 2009). All of the results shown in Figure 2.6 replicated for 5,000 permutations. Full results from this supplementary analysis are provided in NeuroVault (https://neurovault.org/collections/4683/).

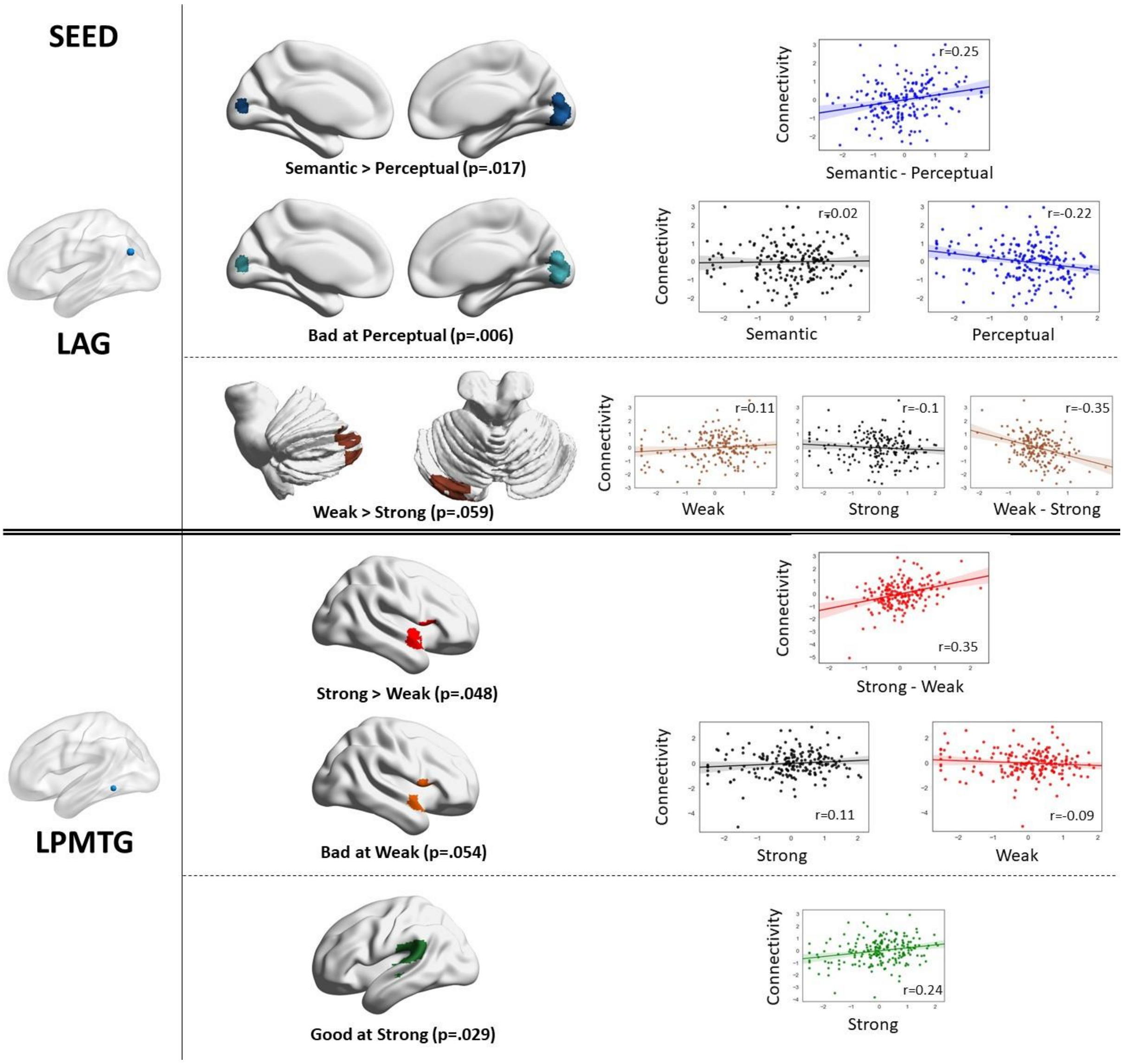

Figure 2.6. Regions associated with behavioural performance in semantic tasks as a function of their connectivity with left angular gyrus and posterior middle temporal gyrus. The scatterplots show the mean connectivity of the seed to the cluster for each participant as a function of their behavioural efficiency score in the task condition depicted in the brain images. The top panel shows results by type of stimulus, and the bottom panel by strength of association. We found no significant results for ATL and IFG. The results were projected to the surface and displayed using SurfIce for ease of viewing (non-projected results can be seen in Neurovault: https://neurovault.org/collections/4683/ and their peaks can be consulted in Table 2.4). The scatterplots were produced using FSL's featquery to extract the mean strength of connectivity between the seed and cluster. The effects survived Bonferroni correction for four seeds and the two-way nature of our tests, with the exception of the AG-cerebellar cluster (p = 0.059) and the pMTG-right aSTG cluster for the main effect of poor weak associations (p = 0.054). The *p* values in the figure are Bonferroni corrected for 8 multiple comparisons.

In summary, when connectivity from left pMTG to other LH language regions is relatively strong, participants tend to be good at retrieving strong associations. In contrast, when this region shows stronger connectivity to RH homologues of semantic processing, the retrieval of weak associations is less efficient. These results are consistent with the view that the semantic control system is strongly left-lateralised. We also found that when left AG has stronger intrinsic connectivity to visual cortex, participants tend to perform perceptual judgements less efficiently, suggesting that semantic and perceptual information might compete for processing in left AG.

Seed	**Contrast**	**Hem.**	**Connectivity**	**Voxels**	**p**	**z**	**x**	**y**	**z**
AG	Semantic > Perceptual	L	Lingual Gyrus	497	.018	4.2	12	-86	-4
	Bad at Perceptual	L	Lingual Gyrus	606	.006	4.2	12	-86	-4
	Weak > Strong	L	Cerebellum Crus I	380	.059, n.s	4.27	-36	-78	-26
pMTG	Strong > Weak	R	Planum Polare	396	.048	4.94	46	0	-8
	Bad at Weak	R	Planum Polare	385	.054, n.s	4.63	46	0	-8
	Good at Strong	L	Parietal Operculum	443	.029	4.96	-54	-34	20

Table 2.4. Peak coordinates for behavioural regression results. p values are reported after applying Bonferroni correction for 8 multiple comparisons (to account for 4 seed regions and the two-tailed nature of our tests). For completeness, all results where p < .1 are shown, including two non-significant results. The coordinates are given in MNI (mm) and the labels were obtained from the Harvard-Oxford Cortical Structural Atlas and Cerebellar Atlas in MNI152 space after normalisation with FLIRT. Full maps are provided on Neurovault (https://neurovault.org/collections/4683/).

2.4. Discussion

This study characterised similarities and differences in intrinsic connectivity between LH sites implicated in semantic cognition, and their RH homotopes, and explored the functional significance of individual differences in these connectivity patterns. Since distinct neurocognitive components are thought to underpin semantic representation and control processes, we focussed on whether there are differences in the lateralisation of these components. We found that intrinsic connectivity analyses were consistent with the view that the semantic system is not homogeneous: sites implicated in semantic control – IFG and pMTG – were more strongly connected to each other than they were to other semantic sites (ATL and AG). The semantic control network was also strongly left-lateralised, since the connectivity between IFG and pMTG was stronger in the LH than RH – and this lateralisation in connectivity was unique to this pair of seeds. Conversely, ventral ATL implicated in semantic representation showed the most symmetrical connectivity, consistent with the view that this site is a bilateral 'hub'. Cognitive decoding of differences in the topology of connectivity across LH and RH found semantic, language and motor terms for LH semantic seeds, and terms related to visual attention, spatial processing and navigation for RH seeds, suggesting that distinct patterns of connectivity across the hemispheres relates to the lateralisation of semantic cognition in the LH, and potentially the right lateralised nature of other functions such as spatial attention.

Individual differences in intrinsic connectivity also predicted task performance: participants who had stronger connectivity between left pMTG and LH regions tended to have more efficient retrieval of strong associations. Conversely, stronger connectivity from left pMTG to right IFG/aSTG (homologous to the LH conjunction site) was related to poorer controlled retrieval of weak associations. This finding is consistent with the view that left-lateralised connectivity within the semantic control network is associated with better semantic control. We also found that when left AG was more connected to visual cortex, people were poorer at perceptual tasks. Left AG is implicated in semantic retrieval and understanding meaningful conceptual combinations (Davey et al., 2015a; Humphreys and Lambon Ralph, 2015; Murphy et al., 2018). More widely, inferior parietal cortex is implicated in stimulus-driven visual attention, as well as reflexive attention to memory (Cabeza et al., 2008) and multimodal feature integration in memory (Bonnici et al., 2016). Consequently, there may be individual differences that reflect a trade-off between perceptual and memory-based cognition in AG (see also Sormaz et al., 2017). When this site in the LH connects more to visual regions that are allied to right-lateralised patterns of connectivity, the network implicated in visual attention (e.g. by cognitive decoding) may be weakened. There was one further behavioural regression effect – stronger connectivity from AG to a left cerebellar cluster, which predicted better semantic control – however, this effect did not pass Bonferroni correction for the number of analyses. Since cerebellar lateralisation is opposite to that in the cortex, this result could indicate that semantic control is better in people with less lateralised connectivity from AG. This pattern would potentially give rise to a left-lateralised semantic network that is more strongly dominated by semantic control regions, and less dominated by DMN. However, the evidence for this pattern was weak and it requires replication.

Our methodology, which compared patterns of intrinsic connectivity from LH seeds and RH seeds flipped into LH space, resembles the approach of Raemaekers et al. (2018). This recent study found that resting-state connectivity was symmetrical in around 95% of regions, yet asymmetrical in language regions, and this predicted the BOLD response to a story versus a maths task (see also Gotts et al., 2013; Hurley et al., 2015; Jo et al., 2012; Karolis et al., 2019; Raemaekers et al., 2018; Wang et al., 2014). The current study adds to this body of work by specifically assessing connectivity differences for four key heteromodal semantic nodes, as opposed to language sites, and by differentiating between sites implicated in heteromodal conceptual representation (ventral ATL) and semantic control (IFG; pMTG). We found strong left-lateralisation similar to that reported by Raemaekers et al. (2018) for semantic control sites, but not for ventral ATL. Moreover, we used a fine-grained semantic battery examining different modalities (words; pictures) and semantic control demands (strong vs. weak associations). As well as stronger lateralisation of intrinsic connectivity for the semantic control sites in resting-state fMRI, we found poor controlled retrieval of weak associations was associated with more right-lateralised connectivity from a key LH site implicated in semantic control. However, we did not observe differences between verbal and non-verbal tasks, potentially consistent with the heteromodal nature of our seeds.

These findings fit broadly with several key predictions of the Controlled Semantic Cognition framework. According to this theory, semantic representation draws on a semantic ‘hub’ in bilateral ATL, with some relatively subtle functional specialisation for verbal and non-verbal semantic tasks in left and right ATL respectively (Rice et al., 2018a, 2015a, 2015b). We found highly symmetrical connectivity maps for left and right ventral ATL, in line with other recent studies (Jackson et al., 2017). We found no evidence that connectivity patterns from left ATL were associated with different performance on word and picture matching tasks – although we cannot rule out the possibility that connectivity patterns from left and right ATL would differentially predict performance on tests requiring specific identities to be retrieved, such as names and faces (Rice et al., 2018a, 2015b, 2015a). The CSC framework envisages that semantic representations (supported by the ATL hub interacting with sensory-motor spokes) are shaped by control processes supported by a different network, including IFG and pMTG. It is interesting to speculate about why semantic activation is left-lateralised, given that ATL is assumed to represent concepts bilaterally. Given the CSC framework proposes at least two interacting components – namely bilateral semantic representations and control processes – we might anticipate that the semantic control system is the most lateralised component, but this prediction has rarely if ever been tested. We found evidence for a lateralised semantic control network both in terms of patterns of intrinsic connectivity at rest and lateralisation predicting behavioural performance on weak vs. strong associations.

The patterns we observed may be explicable in terms of different interactions between large-scale networks in LH semantic regions, relative to their RH counterparts. The frontoparietal network is the most segregated network across the hemispheres, coupling more to DMN in LH and more to attention networks in RH (Dixon et al., 2018; Wang et al., 2014). For our two heteromodal semantic seeds which showed relatively high connectivity to FPN regions (IFG; pMTG), there appeared to be greater connectivity to LH lateral DMN regions than would be expected from intrinsic connectivity in the RH (particularly in LH lateral DMN). Moreover, for our semantic DMN seeds in LH (AG; ATL), there was greater connectivity to ventral LOC and anterior insula sites implicated in attention/control. These findings are consistent with Davey et al.'s (2016) proposal that semantic cognition in the LH involves the integration of DMN and executive networks. One interesting observation is that the conjunction of the intrinsic connectivity maps of all four LH semantic seeds showed strong connectivity to the lateral regions of DMN, which have been previously implicated in semantic cognition – regions such as lateral temporal cortex and angular gyrus – and weak connectivity to medial default mode regions, such as posterior cingulate cortex, medial prefrontal cortex and hippocampus, which are not strongly implicated in semantic cognition. In contrast, the RH seed conjunction showed stronger connectivity to medial core default mode regions. Consequently, lateralised patterns of connectivity that support semantic cognition may reflect a particular form of interaction between DMN and control regions (Davey et al., 2016; Dixon et al., 2018; Wang et al., 2014), and this pattern of interaction might play an important role in functional subdivisions within DMN (e.g. Andrews-Hanna et al., 2010).

Chapter 3. Individual Differences in Left and Right ATL Connectivity Relate to Modality and Category Effects in Semantic Categorisation

Having established hemispheric differences in intrinsic connectivity for all the regions of the semantic system, and that these differentially engage the Yeo networks across hemispheres with functional significance in offline tasks, the next study specifically examined the bilateral semantic representation system. Although we found no behavioural association with ATL intrinsic connectivity in Chapter 2, we reasoned that this might be because the tasks were not well-suited to detecting hemispheric differences in function that have been documented previously.

In this second empirical chapter, we used a task designed to be sensitive to hemispheric differences in semantic representation in order to test the graded semantic hub hypothesis (Rice et al., 2015a), which proposes that graded differences in connectivity between left and right ATL give rise to hemispheric differences in the type of stimulus that each ATL is best suited to represent. We first characterised the patterns of connectivity of left ATL, as well as two right ATL seeds determined by sign-flipping and functional meta-analytic evidence respectively. This was necessary given that ATL is the only semantic site that has a right functional peak in meta-analyses of semantic cognition, and for consistency with our previous chapter we also decided to test the sign-flipped homotopic seed. We described the commonalities and differences in these patterns of connectivity, and related them to the efficiency in performing a semantic task outside the scanner, where we manipulated the type of stimulus (famous faces versus landmarks) and modality of presentation (visual versus verbal) in accordance with known interhemispheric differences. We aimed to characterise whether individual differences in the strength of intrinsic connectivity to lower-level perceptual ‘spokes’ from the left and right ATL heteromodal ‘hub’ regions helped explain more efficient behaviour for stimuli more dependent upon these regions for their representation.

We found that people with greater connectivity between left and right ATL were more efficient at categorising landmarks, especially when these were presented visually. In addition, participants who showed stronger connectivity from right than left ATL to medial occipital cortex — a visual spoke region — were more efficient at all semantic tasks, particularly those involving the names of famous people. We conclude that individual differences in the intrinsic connectivity of left and right ATL are associated with different effects of category and modality in semantic categorisation. In the context of the graded hub hypothesis, these effects can be interpreted in terms of graded differences in the strengths of inputs from ‘spoke’ regions, such as regions of visual cortex, to a bilateral yet partially segregated semantic ‘hub’, encompassing left and right ATL.

Acknowledgements: Elizabeth Jefferies, Jonathan Smallwood and the author developed the experimental design and main ideas in this manuscript. Katya Krieger-Redwood and Megan Evans helped with the implementation of the analysis (concretely with generating the final pipeline for CONN). Megan Evans additionally helped with data collection. The author developed the majority of the work, including study design, data collection, final design and implementation of analyses, interpretation of the results and writing of the text. Grace Rice provided the behavioural paradigm.

3. Individual Differences in Left and Right ATL Connectivity Relate to Modality and Category Effects in Semantic Categorisation

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Abstract

Neuropsychological and neuroimaging studies suggest that the ventral anterior temporal lobes (ATL) provide a bilateral heteromodal semantic hub, with graded functional differences between the hemispheres. Individual differences in connectivity from bilateral ATL and between left and right ATL might give rise to differences in function within this bilateral system. Here, we investigated the possibility that the relative strength of intrinsic connectivity from left and right ATL relate to different patterns of performance in semantic tasks. We measured resting-state fMRI in more than 70 participants and, in a separate session, examined semantic categorisation, manipulating the type of stimuli (famous faces versus landmarks) and modality of presentation (visual versus verbal). We found that people with greater connectivity between left and right ATL were more efficient at categorising landmarks, especially when these were presented visually. In addition, participants who showed stronger connectivity from right than left ATL to medial occipital cortex were more efficient at all semantic tasks – particularly those involving the names of famous people. We conclude that individual differences in the intrinsic connectivity of left and right ATL are associated with different effects of category and modality in semantic categorisation. These effects can be interpreted in terms of graded differences in the strengths of inputs from 'spoke' regions, such as regions of visual cortex, to a bilateral yet partially segregated semantic 'hub', encompassing left and right ATL.

Keywords: Hemispheric Differences, Semantic Representations, Modality, Anterior Temporal Lobes, fMRI, Intrinsic connectivity.

3.1. Introduction

Semantic cognition allows us to understand the world around us – including the meaning of words and objects, locations and people (Lambon Ralph et al., 2017; Patterson et al., 2007). Conceptual representations that underpin semantic performance across input modalities (e.g., words and pictures) and across different tasks are thought to be supported by the bilateral ventral anterior temporal lobes (ATL; Binney et al., 2010; Rice et al., 2015a, 2015b). An influential account of ATL function suggests that this region forms a semantic "hub" drawing together different features represented within 'spokes' (capturing visual, hippocampal, valence, language and auditory inputs) to form heteromodal concepts (Patterson et al., 2007). This integration of different aspects of knowledge is thought to occur in a graded fashion, with the most heteromodal semantic responses in ventrolateral ATL (Lambon Ralph et al., 2017; Visser et al., 2012). Since this view suggests semantic representations reflect interactions between the hub and spokes, individual differences in the way people represent and retrieve different types of concepts or categories may emerge from distinct patterns of interaction between the hub and spokes.

Substantial neuropsychological and neuroimaging literatures show that the involvement of the ATL in semantic representation is bilateral. Patients with bilateral ATL atrophy in the context of semantic dementia have severe degradation of conceptual knowledge, while other aspects of cognition are largely intact. These deficits are most severe for semantic tasks that probe specific-level knowledge – including knowledge of unique entities such as people, and highly-specific concepts, such as types of car (Rogers et al., 2015). In contrast, patients with unilateral lesions following resection for temporal lobe epilepsy have measurable yet much milder semantic deficits (Rice et al., 2018b). This might reflect functional compensation by the intact ATL (Jung and Lambon Ralph, 2016). Neuroimaging studies with healthy participants have found bilateral responses to semantic tasks in ATL (Visser et al., 2009), irrespective of whether words or pictures are presented for meaning-based decisions (Vandenberghe et al., 1996). Moreover, inhibitory transcranial magnetic stimulation (TMS) delivered to either left or right ATL disrupts both picture and word-based semantic tasks, mimicking the pattern in semantic dementia (Pobric et al., 2010a, 2007). In line with expectations for a single semantic hub distributed across two hemispheres (cf. Schapiro et al., 2013), inhibitory TMS to left ATL leads to an increase in the response within right ATL, suggesting the non-stimulated hemisphere may compensate for functional disruption within the stimulated hemisphere (Binney and Lambon Ralph, 2015; Jung and Lambon Ralph, 2016).

Nevertheless, there is also strong evidence that the left and right ATL are not functionally identical. There may be differences in the extent to which the two ATLs connect to visual, auditory-motor, social or emotional networks, which give rise to a degree of functional specialisation (Rice et al., 2015a). By one account, there is a modality difference between left and right ATL – with left ATL showing stronger engagement for verbal tasks, and right ATL showing a preference for non-verbal tasks. This suggestion has some support from studies of patients with semantic dementia who have more left-sided or right-sided atrophy (Gainotti, 2012). For example, Snowden et al. (2004) found that patients with more left-lateralised atrophy had greater impairment for people's names, while patients with more right-sided atrophy had greater difficulty on semantic tasks employing faces. Similarly, several studies have shown that atrophy in right ATL correlates with difficulties on picture semantic tasks, while damage to left ATL is more strongly correlated with verbal semantic task performance (Butler et al., 2009; Mion et al., 2010). A variant of this modality view suggests that output modality is also important – damage to left ATL is associated with problems in naming concepts, and therefore with deficient lexical access from semantic knowledge, while right ATL is linked to poor object recognition (Damasio et al., 2004). This pattern might reflect differential connectivity from left and right ATL to motor speech regions.

An alternative account of functional specialisation across left and right ATL suggests it is not the input/output modality that is critical, but instead the nature of the conceptual information itself – right ATL has been argued to play a larger role than left ATL in understanding social concepts and retrieving conceptual information about specific people (Olson et al., 2013, 2007; Ross and Olson, 2010; Zahn et al., 2007). Patients with damage to right ATL often have difficulties recognising faces, but there is an ongoing debate about whether these difficulties reflect impairment for faces per se (i.e. difficulty when the task involves both social stimuli and picture inputs) or a wider problem with social concepts (Gainotti, 2013; Gorno-Tempini et al., 1998). A recent fMRI study (Rice et al., 2018c) directly compared the neural response in ATL during semantic decisions about specific entities that were social (people) and non-social (landmarks). The social and non-social stimuli were presented as both words (i.e., people's names) and as pictures (i.e., of faces). This study found that clusters within right ventral ATL showed stronger activation to people vs. landmarks (particularly towards the temporal pole). In contrast, left ventral ATL responded more equally across categories and verbal/visual modalities.

A recent neuroimaging meta-analysis of 97 functional neuroimaging studies (Rice et al., 2015b) confirmed the view that the left and right ATLs are more similar than they are different, and yet confirmed some degree of functional heterogeneity. Both left and right ATL were activated across verbal and non-verbal stimuli, and social and non-social tasks. However, activation likelihood estimation revealed that studies involving word retrieval are more likely to report unilateral left ATL activation, while social semantic studies are more likely to observe bilateral ATL activation (with non-social tasks more likely to give rise to unilateral left ATL activation). Given that Rice and colleagues suggested these functional differences reflect differential connectivity between left and right ATL and other brain networks – for example, stronger connectivity between right ATL and regions associated with social cognition, or between left ATL and language regions – we might anticipate that individual differences in intrinsic connectivity at rest would relate to performance on social vs. non-social, or verbal vs. non-verbal semantic tasks.

In a recent study (Gonzalez Alam et al., 2019), we compared the connectivity of four heteromodal semantic sites across hemispheres (ATL, angular gyrus, posterior middle temporal gyrus and left inferior frontal gyrus), and found that ATL had the most symmetrical pattern (i.e. the highest correlations between connectivity patterns generated from left and right-hemisphere seeds). However, some subtle differences in connectivity were still observed. Left ATL was more connected with other sites implicated in semantic cognition, including left inferior frontal gyrus, posterior middle and inferior temporal cortex, posterior dorsal angular gyrus/intraparietal sulcus and medial temporal lobe. Right ATL was more connected to extensive regions of default mode network, including angular gyrus and dorsomedial prefrontal cortex. We might also envisage that individual differences in these patterns of connectivity from left and right ATL would affect the efficiency of semantic decisions for different kinds of stimuli. To address this issue, in the current study we acquired resting-state fMRI from more than 70 participants, who completed semantic decisions about social and non-social stimuli, presented as written words and pictures (using the task from Rice et al., 2018c). We then assessed relationships between connectivity and behavioural performance – with particular focus on whether right ATL connectivity would predict social vs. non-social performance, or the performance on trials presented through different modalities (pictures vs. words).

3.2. Methods

3.2.1. Participants

This study was approved by the local research ethics committees. The data were obtained as part of a large cohort study, consisting of resting state fMRI and a battery of cognitive assessments in 207 healthy young adult volunteers (137 females; age: mean ± SD = 20.21 ± 2.35, range: 18 – 31 years). Elements of this cohort study have been described previously in papers focussing on mind-wandering (Poerio et al., 2017; Sormaz et al., 2018; Turnbull et al., 2018; H. T. Wang et al., 2018a, 2018b), the functional consequences of hippocampal connectivity (Karapanagiotidis et al., 2017; Sormaz et al., 2017), patterns of semantic performance linked to individual differences in connectivity within LH semantic sites falling in different networks (Vatansever et al., 2017; Gonzalez Alam et al., 2019) and cortical thickness (X. Wang et al., 2018).

Participants were invited to come back for further behavioural testing, in which we presented an additional battery of semantic tasks, including the task reported here which manipulated modality and category. This subset consisted of 83 participants (19 male, 64 female, mean age=19.69, range=18-26). Two participants were removed before pre-processing due to missing resting-state scans, and a further three due to not having full brain coverage. Another two were excluded during pre-processing because they exceeded our quality assessment measures of (i) motion greater than 0.3mm, (ii) invalid scans greater than 20%; and/or (iii) global mean signal change greater than z=2. Finally, two more participants were excluded because they performed at least one behavioural task at chance level, leaving us with a final sample size of 74 participants recruited from undergraduate and postgraduate students at the University of York. All participants were right handed, native English speakers with normal/corrected vision. None of them had a history of psychiatric or neurological illness, severe claustrophobia, drug use that could alter cognitive functioning, or pregnancy. All volunteers provided written informed consent and were either paid or given course credit for their participation.

3.2.2. Procedure

The participants first took part in a neuroimaging session, where we acquired structural images and a resting-state scan. We invited participants back for a behavioural session where they were tested on five tasks. The duration of the full testing session was approximately 1.5 hours. To control for order effects, each participant completed the tasks in the same order. The task used in the current study was presented towards the end of this session.

3.2.3. Task

We adapted a task from Rice et al. (2018c). Participants were presented with different categories of stimuli (animals, landmarks and people) as either images or written words. They had to judge whether the stimuli were European or non-European. They were also presented with a non-semantic perceptual control condition, in which participants were shown a scrambled image (generated by taking the pixels from the images in the other conditions and randomising their location so they were devoid of meaning) an asked to judge whether it was presented higher or lower on the screen. Examples of the stimuli in each condition are shown in Figure 3.1.

Stimuli were taken from Rice et al. (2018c), and reduced to only include trials with 85% accuracy or above in Rice's data, providing 60 stimuli per category. Blocks consisted of 30 trials each (480 trials in total), randomly sampled with replacement from the stimulus pool. The task consisted of sixteen blocks (four conditions by two modalities; each combination presented twice), pseudorandomised in four possible sequences to which participants were randomly assigned.

Each trial lasted 3000ms, consisting of a 500ms fixation cross followed by 2500ms stimulus presentation (see Figure 3.1). Participants indicated their response using the '1' key on a computer keyboard for European/higher location and '2' for non-European/lower location. Before the task commenced, an instruction slide was presented which remained on screen until the participant indicated they were ready to begin via key press. At the beginning of each block, a cue screen indicating the condition was presented for 500ms. Every four blocks participants were presented with a rest screen until they indicated they were ready to continue via key press. Both response time (RT) and accuracy were recorded, and an efficiency score was calculated for each participant in each condition by dividing median response times by accuracy (note: in brain analyses, this efficiency score was inverted to aid the interpretation of the results, such that a higher score corresponded to better performance). The duration of the whole task was 15-20 minutes. The task was implemented in E-prime 2.0.

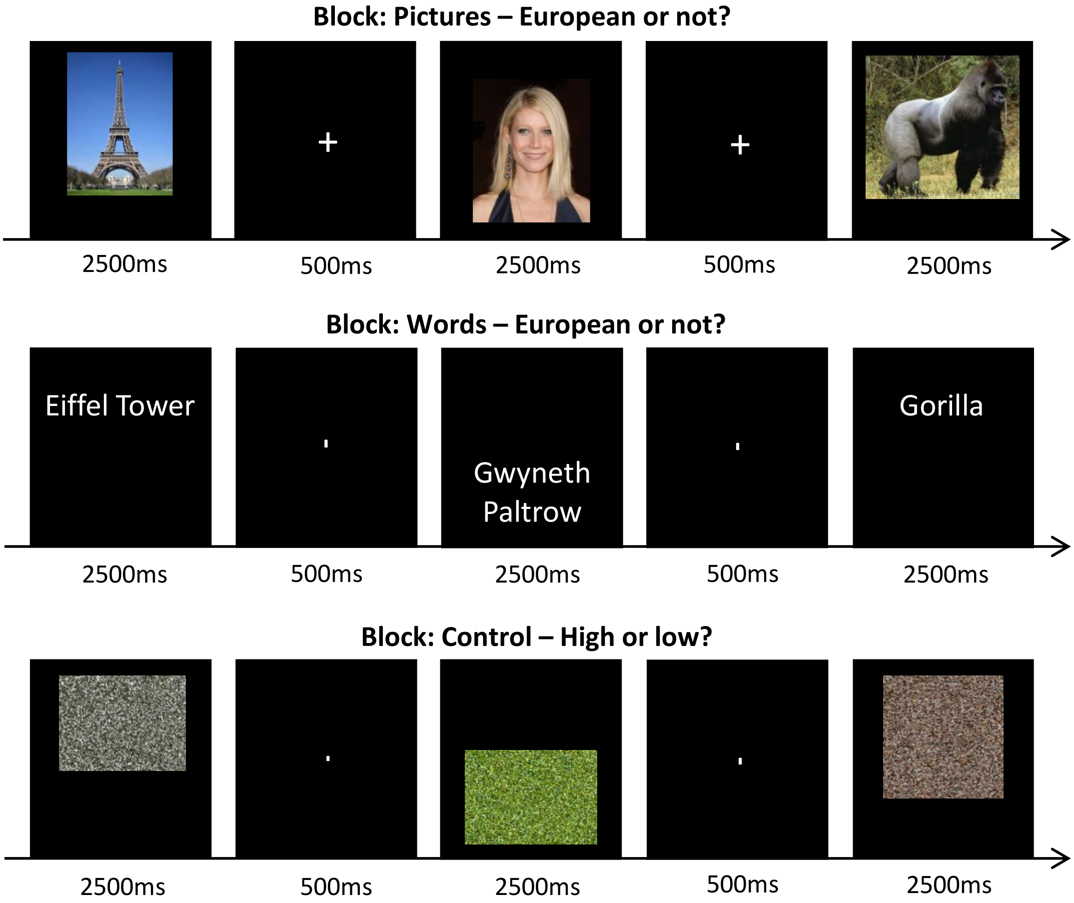


Figure 3.1. Example stimuli and trial structure for each condition in the semantic representation task and non-semantic control task. This is a simplification of the actual structure of the task, where the stimuli were not only blocked by modality of presentation, but also by category of stimuli (i.e. “pictures of landmarks” would be a block).

3.2.4. Neuroimaging

3.2.4.1. 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 = 7.8s, 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 = $3 \times 3 \times 3$ 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.

3.2.4.2. Pre-Processing

All pre-processing of resting-state data was performed using the CONN functional connectivity toolbox V.18a (http://www.nitrc.org/projects/conn; Whitfield-Gabrieli & Nieto-Castanon, 2012). MRI data pre-processing and statistical analyses were carried out using the SPM software package (Version 12.0), based on the MATLAB platform (Version 17a) implemented in CONN. For pre-processing, functional volumes were slice-time (bottom-up, interleaved) and motion-corrected, skull-stripped and co-registered to the high-resolution structural image, spatially normalized to the Montreal Neurological Institute (MNI) space using the unified-segmentation algorithm, smoothed with a 6 mm FWHM Gaussian kernel, and band-passed filtered (0.008 – 0.09 Hz) to reduce low-frequency drift and noise effects. A pre-processing pipeline of nuisance regression included motion (twelve parameters: the six translation and rotation parameters and their temporal derivatives), scrubbing (all outlier volumes were identified through the artifact detection algorithm included in CONN, with conservative settings: scans for each participant were flagged as outliers based on a composite metric with parameters set to scan-by-scan change in global signal z-value threshold = 3, subject motion threshold = 5mm, differential motion and composite motion exceeding 95% percentile in the normative sample) and CompCor components (the first five) attributable to the signal from white matter and CSF (Behzadi et al., 2007), as well as a linear detrending term, eliminating the need for global signal normalization (Chai et al., 2012; Murphy et al., 2009).

3.2.4.3. ROI Selection

We used an average of left ATL peaks reported by Rice et al. (2018c) for semantic > non-semantic contrasts across eight studies using distortion-corrected fMRI, providing a peak response in left ventral ATL (MNI coordinates -41, -15, -31). We generated a right-hemisphere homotopic sphere for this seed by following the same procedure, but flipping the sign of the x coordinate in MNI space from negative to positive. Since there is good evidence of bilateral engagement of ATL in semantic cognition and Rice et al. (2018c) identified a right ATL functional peak (MNI 44, -11, -36), which was not in an identical location to that in the LH, we also included this seed in our investigation. To create ROIs, we placed a binarised spherical mask with a radius of 3mm, centred on the MNI coordinates of the peak response in each seed of interest. The BOLD time series extracted for each seed region was an average for all voxels making up the 6mm diameter sphere.

3.2.4.4. Resting-State fMRI Analysis

This analysis examined individual differences in the connectivity of left and right ATL to the rest of the brain, measured through resting-state fMRI, and related these differences to behavioural efficiency on semantic tasks (measured outside the scanner in a separate session).

In a first-level analysis, we extracted the time series from each ROI for each participant. These were used as Explanatory Variables (EVs) in separate whole-brain connectivity analyses for each seed (three seeds in total: left ATL, its right hemisphere homotope and the right hemisphere functional peak). In each analysis, the nuisance regressors detailed in section 2.5.2. were removed and we computed the seed to voxel correlations for each of our seeds.

At the group level, our analysis focused on associations between hemispheric similarities and differences in ATL connectivity and effects of the category of the stimuli and the modality of presentation on the efficiency of semantic categorisation. We entered into a GLM the mean-centred efficiency scores (with outliers +/-2.5 SD imputed to +/-2.5) of five task conditions (excluding the Animal Verbal condition, which showed chance performance, and the non-semantic Control condition, which showed ceiling performance), together with a nuisance regressor containing mean motion (measured in framewise displacement) for each participant as EVs.

We performed functional connectivity weighted GLM seed-to-voxel analyses convolved with a canonical haemodynamic response function (HRF). There were seven analyses: three models for the single seeds (left ATL, the right ATL homotope site and right ATL's functional peak – which did not yield significant effects, and are therefore not discussed further); two models examining the common connectivity of both left and right ATL (examining seed regions that encompassed both hemispheres – with one model for the conjunction of left ATL and the homotopic region in right ATL, and another examining the conjunction of left and right functional peaks); and finally two models that examined the difference between left and right ATL (examining left versus right homotopes, and left versus right functional peaks). We applied Bonferroni correction to the FWE values resulting from two-sided t-tests in the models to determine significant clusters (correcting for these seven models). Besides the mean group connectivity for each seed, we defined the following contrasts of interest: category (People > Landmarks and vice-versa), modality (Verbal > Visual and vice-versa), modality by category interaction (the effect of modality for people versus landmarks) and the main effects for five tasks conditions (i.e. Verbal Landmark, Verbal People, Visual Landmark, Visual People and Visual Animals).

At the group-level, analyses were carried out using CONN with cluster correction ($p < .007$, corresponding to $p < .05$ with Bonferroni correction), and a threshold of $z=3.1$ (p-FWE=0.001) to define contiguous clusters (Eklund et al., 2016). This analysis included the behavioural regressors described above (as mean-centred inverse efficiency scores for each condition) to evaluate whether performance correlated with individual differences in intrinsic connectivity. The connectivity maps resulting from these analyses were uploaded to Neurovault (Gorgolewski et al., 2015, URL: https://neurovault.org/collections/5687/). As a confirmatory analysis, to verify that the results were not dependent on an arbitrary significance threshold, we carried out non-parametric permutation testing as implemented on CONN for each significant result that survived Bonferroni correction. Most but not all clusters were replicated by permutation testing (with non-replicating results clearly indicated in the figures).

In order to interpret the results that survived Bonferroni correction, we used the significant clusters as binarised masks to extract the global-scaled mean connectivity for each seed per participant to each cluster using REX implemented in CONN. These values were then related to each participant's mean-centred inverse efficiency score for the relevant EV, and plotted as scatterplots using Seaborn in Python 2.7, colour coded so that red scatterplots show connectivity stemming from the left ATL seed and blue scatterplots show connectivity from the right ATL seeds.

3.3. Results

3.3.1. Behavioural Results

Figure 3.2 shows the median reaction times, accuracy and efficiency scores of our sample in the semantic task adapted from Rice et al. (2018c). A two-way repeated measures ANOVA on reaction time data with category and modality as factors revealed no main effect of modality, a significant main effect of category and a category by modality interaction [Category: F(2,144) = 56.07, p < .001; Interaction: F(2,144)=69.1, p < .001]. Post-hoc tests using Bonferroni correction showed no difference between people and landmarks, but significant differences between animals and all other conditions, with participants performing more slowly for animals (p < .001). Post hoc testing with Bonferroni correction also confirmed the interaction was driven by a difference in reaction time for the modality condition, with participants being significantly slower for verbal than visual animal judgements (p < .001). The same analysis for accuracy found significant effects of category, modality and a category by modality interaction [Category: F(2,144) = 174.39, p < .001; Modality: F(2,144) = 487.39, p < .001; Interaction: F(2,144)=41116.11, p < .001]. Post-hoc tests revealed that participants showed equivalent accuracy for landmark and people judgements, but both of these significantly differed from animal judgements, where participants made more errors (p < .001). Likewise, participants were significantly less accurate in verbal than picture judgements (p < .001). Post-hoc tests revealed that the interaction was driven by participants being significantly less accurate for verbal than visual judgements of animals.

Speed and accuracy may be traded off in different ways across tasks and individuals. To address this issue we calculated response efficiency scores which adjusted reaction times by accuracy to capture global performance (reaction time divided by accuracy, inverted for neuroimaging analyses, so that high scores reflect good performance in the scatterplots depicted in Figures 3.3 – 3.10). A two-way repeated measures ANOVA of participants' efficiency scores with Greenhouse-Geisser correction using category and modality as factors showed significant effects of category, modality and an interaction for efficiency [Category: F(1.7,122.6) = 63.22, p < .001; Modality: F(1,72) = 136.08, p < .001; Interaction:

F(1.8,130)=478.47, p < .001]. Post-hoc tests once more found no difference between landmark and people judgements in participants' efficiency scores, and a significant difference between both of these and the animal condition, where participants performed more poorly (p < .001). Participants performed significantly less efficiently in verbal than visual judgements (p < .001). Again, the interaction was driven by participants being less efficient in verbal than visual judgements about animals (p < .001).

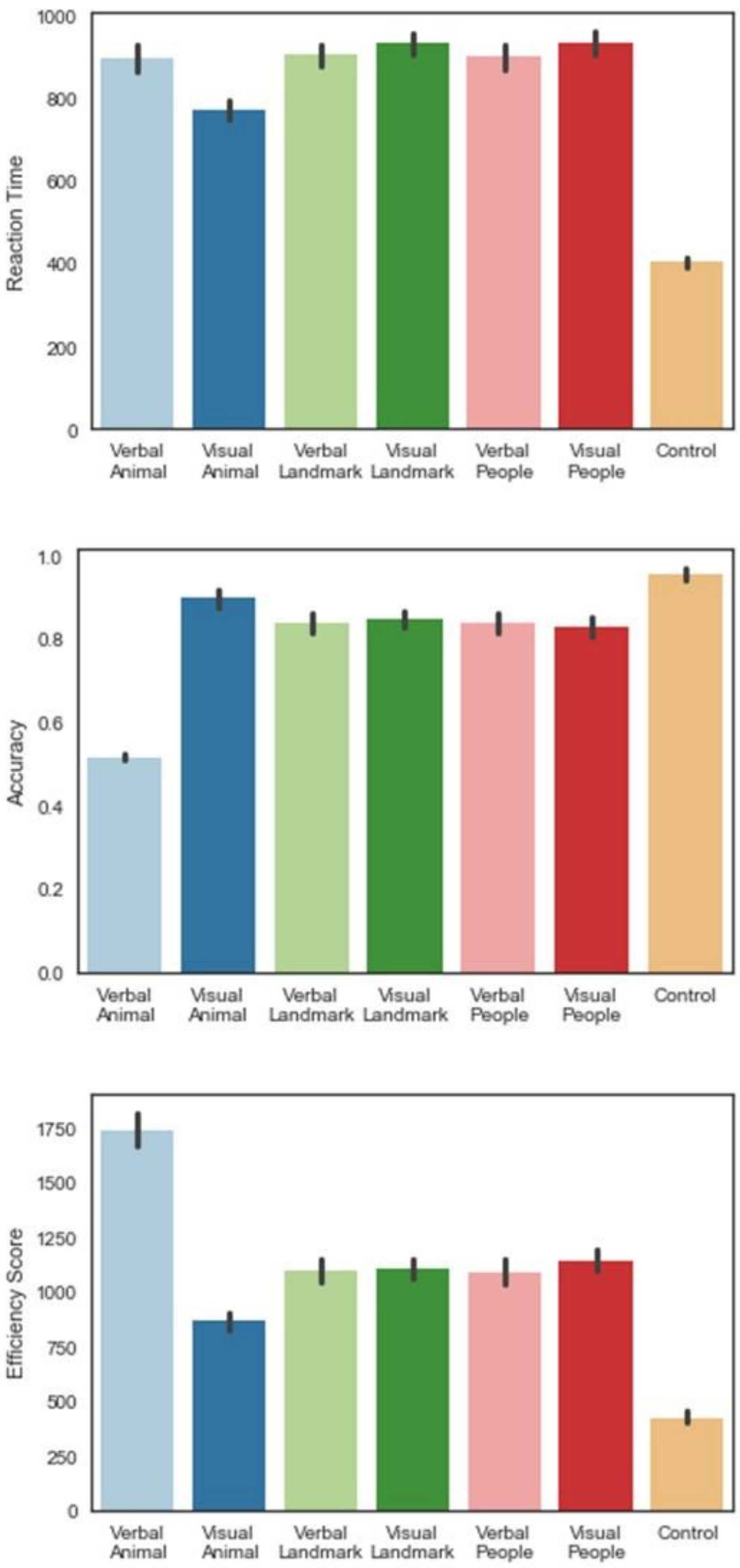


Figure 3.2. Median reaction time (milliseconds), accuracy (proportion correct) and efficiency scores (reaction time divided by accuracy) for the semantic categorisation task. Error bars show the standard error of the mean.

3.3.2. Mean connectivity of left and right ATL

We first examined the mean functional connectivity of left ATL and its right homotope as measured through resting-state fMRI. We examined the single seed mean connectivity for each ATL, as well as differential left and right connectivity, and the conjunction of left and right mean connectivity. The results are shown in Figure 3.3. The left ATL showed a pattern of bilateral functional connectivity overlapping with the semantic cognition network in the left hemisphere, including medial and lateral aspects of the temporal lobe extending posteriorly to the angular gyrus bilaterally, as well as parts of the inferior frontal gyrus (extending more anteriorly in the LH) and central sulcus, posterior cingulate cortex and frontal poles (Figure 3.3, top row). This pattern was similar for the RH homotopic seed (Figure 3.3; second row): it showed temporal lobe connectivity, albeit less continuous in the LH and more restricted to the ventral temporal lobes, with a separate cluster for angular gyrus that extended more posteriorly than for the left ATL; unlike left ATL, the RH homotope did not show connectivity to the central sulcus, but it did to the superior frontal gyrus and medial orbitofrontal cortex extending posteriorly to the posterior cingulate cortex; it also showed negative connectivity to medial occipital, paracingulate and right insular/orbitofrontal regions (Figure 3.3, second row). This pattern is similar to that described by Gonzalez Alam et al. (2019). A conjunction analysis giving equal weight to both left and right ATL seeds captured this similarity between the maps (Figure 3.3, third row). A difference between the maps was only observed in the ventral regions centred around our seeds (Figure 3.3, bottom row).

Since the right ATL’s functional peak was not in an identical location to that in left ATL, we also took the right-lateralised functional peak determined by Rice et al. (2018c) and conducted the same analyses. The results are depicted in Figure 3.4. The right ATL’s functional peak showed positive connectivity to ventral aspects of the left temporal lobe and right temporal pole. It also showed positive connectivity to left angular gyrus, inferior frontal and posterior middle temporal gyri, frontal pole, bilateral superior frontal gyrus and medial aspects of the temporal lobe; plus negative connectivity to bilateral occipital lobes. Again, the conjunction of left and right ATL’s functional peak connectivity included bilateral temporal regions extending into angular gyrus, as well as inferior and superior frontal gyri, posterior cingulate and orbitofrontal cortex, with common negative connectivity in medial occipital cortex. The differential connectivity comparing right ATL's functional peak with the left ATL seed showed stronger connectivity between the left ATL seed and left dorsal ATL and bilateral dorsal central sulcus, and stronger connectivity between the right ATL seed in left middle frontal gyrus, orbitofrontal and ventral ATL. Lastly, a direct comparison between the homotopic and functional right ATL seeds revealed stronger connectivity with bilateral LOC, lingual, posterior cingulate and medial temporal cortex for right ATL, and bilateral ventral ATL, right frontal pole and left temporo-parietal junction for left ATL.

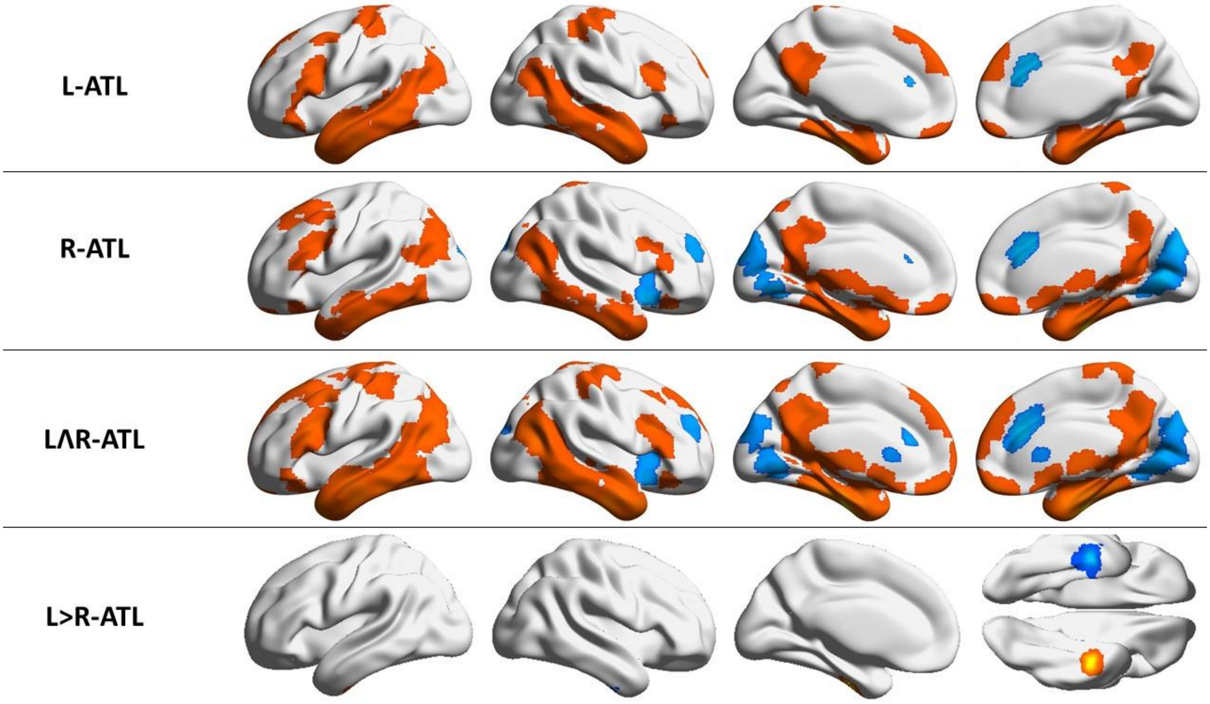


Figure 3.3. Resting state connectivity for left and right (homotopic) anterior temporal lobe, their differential and common connectivity. For the single seeds, the warm and cool colours represent the positive and negative maps respectively, while for the difference analysis the warm and cool colours represent left and right connectivity respectively, and for the conjunction warm represents left and right connectivity, and cool represents neither left nor right connectivity. The group maps are thresholded at z=3.1, p=0.05.

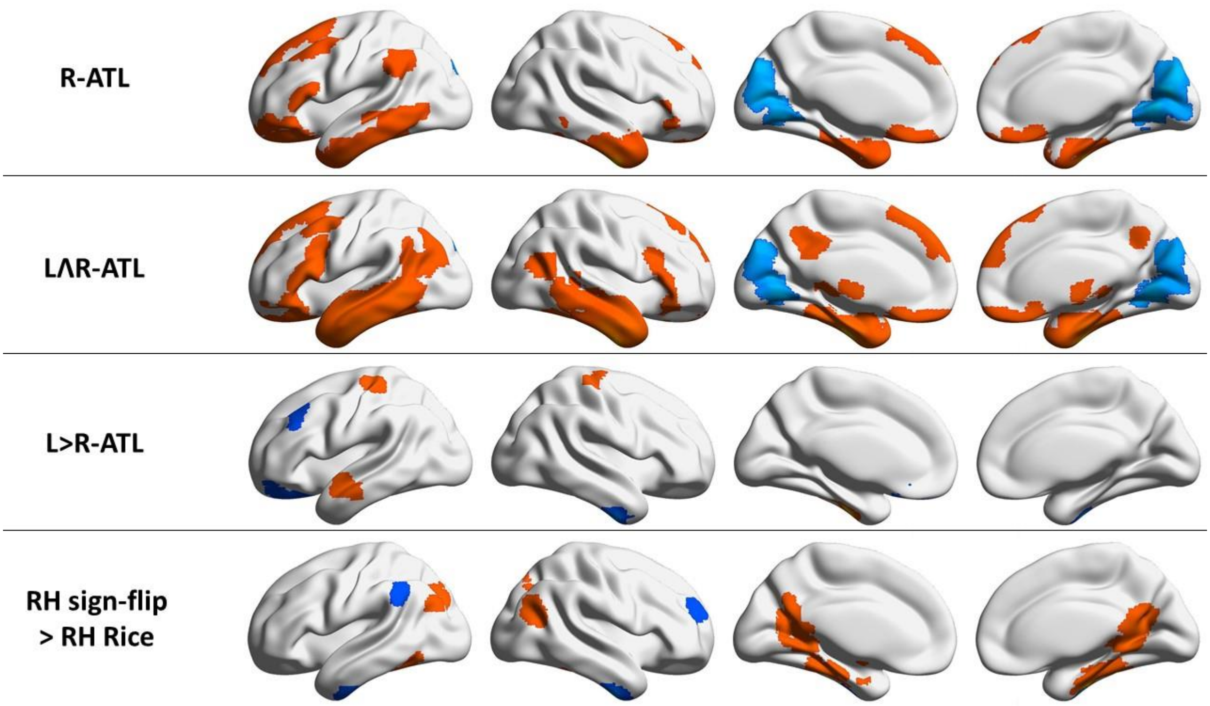


Figure 3.4. Resting state connectivity for the functional peak for right ATL from Rice et al. (2018c), its differential and common connectivity with left ATL, and a comparison with the right ATL seed determined through sign-flipping (presented in Figure 3.3). For the single seeds, the warm and cool colours represent the positive and negative maps respectively, while for the difference analysis the warm and cool colours represent left and right connectivity respectively, and for the conjunction warm represents left and right connectivity, and cool represents neither left nor right connectivity; in the last row, stronger connectivity for the homotopic seed is represented by warm colours while stronger connectivity for the functional seed is depicted in cool colours. The group maps are thresholded at z=3.1, p=0.05.

3.3.3. Behavioural consequences of single seed connectivity – overview

We performed whole brain resting-state functional connectivity analysis using the behavioural performance in five conditions of our semantic representation task as covariates, to probe for possible associations between single-seed connectivity and categorisation efficiency. We did not include the verbal animal condition due to chance-level performance. For each significant result found using a cluster-forming threshold of z=3.1, we ran non-parametric analysis using CONN to confirm whether the result was robust irrespective of this particular cluster-forming threshold. Most results were replicated across these analyses, with exceptions indicated in the figures and text. Below, we first present the analyses for combined left and right ATL seeds, followed by analyses of differences between left and right ATL connectivity. There were no results from single seeds that survived Bonferroni correction for the number of analyses, and consequently these findings are not discussed further. The results converged on two main findings – behavioural associations relating to the strength of connectivity between the left and right ATLs (stronger bilateral ATL connectivity was linked to better performance on picture landmark trials), and results relating to connectivity between right ATL and medial occipital cortex (stronger connectivity was linked to better categorisation of people's names). We show the overlap of different results relating to these effects in Figures 3.11 and 3.12.

3.3.4 Common bilateral ATL connectivity and associations with behaviour

We examined the equally weighted connectivity of both left and right ATL by taking both hemispheres as a seed. We found no results when left and the sign-flipped right ATL homotope were used as the seed; however, we found three significant results when left and right ATL functional peaks were used.

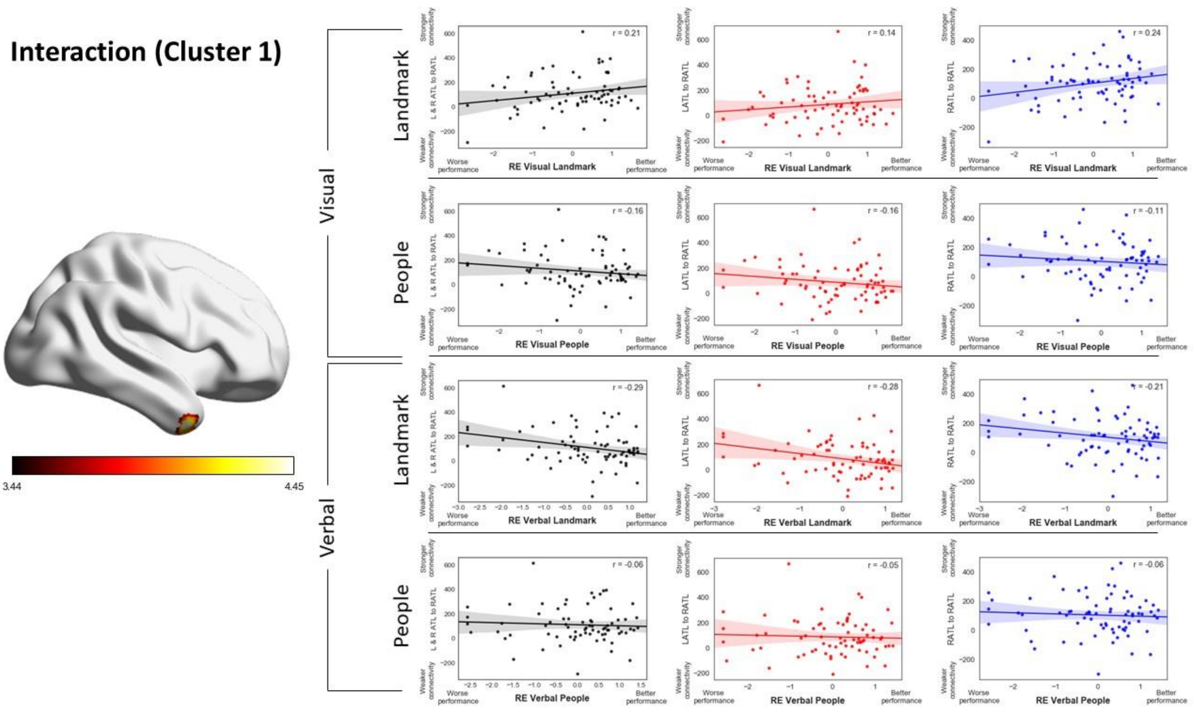
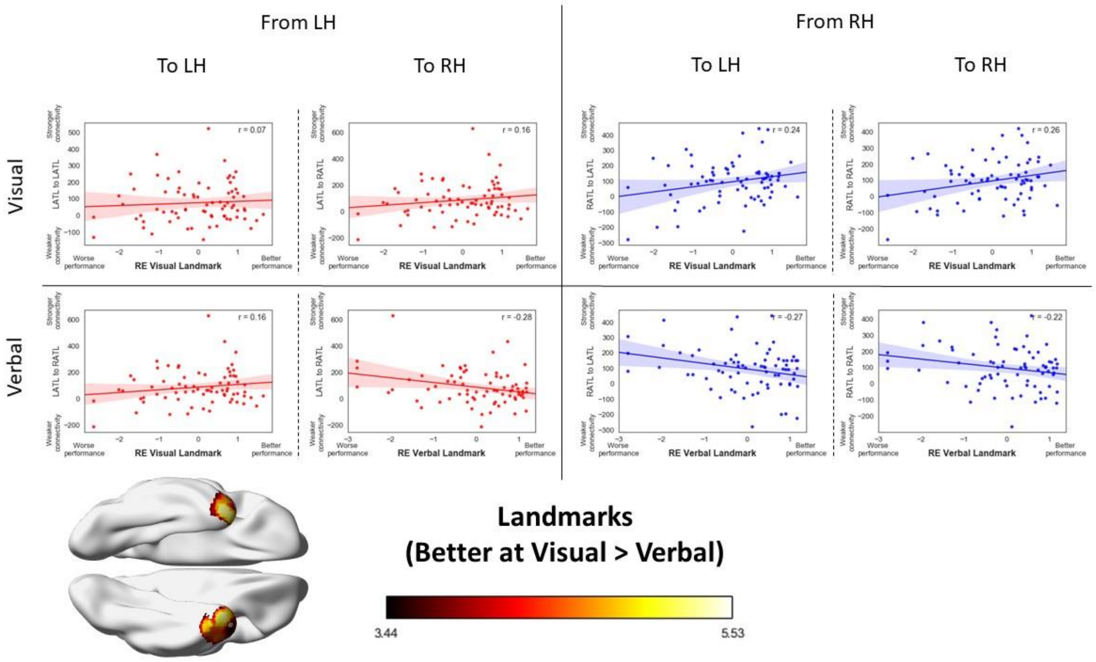


Figure 3.5. A right ATL cluster whose common connectivity to a seed region encompassing both left ATL and (functional) right ATL seeds showed a modality by category interaction (Z=3.1, p=.05, Bonferroni-corrected for 7 models). The scatterplots depict the mean-centred efficiency scores plotted as a function of the normalised (scaled to the global mean) functional connectivity from left ATL (red), right ATL's functional peak (blue) and common (black) to the right ATL cluster depicted in the figure. All units are given in z-scores.

First, we found a significant interaction between modality and category (see Figure 3.5). Stronger connectivity from the combined left and right ATL seed to right ATL was associated with better performance in the visual than verbal modality for landmarks, whilst the reverse pattern was observed for trials involving people knowledge (relatively better performance in the verbal than visual modality). We also found two significant results for the landmarks task, consistent with this interaction. Connectivity of the bilateral seed to left and right ventral ATL was associated with better visual than verbal categorisation for landmarks (see Figure 3.6, top panel). People who were better at categorising visual landmarks overall also had stronger connectivity between the bilateral ATL seed and right temporal pole (Figure 3.6, bottom panel). In order to confirm that these findings pattern reflected cross-hemispheric connectivity, we plotted the results for ATL seed regions within left and right hemisphere separately. These plots show that left and right-lateralised parts of the seed were both associated with better categorisation for the picture landmark condition.



Good at Landmarks (Visual)

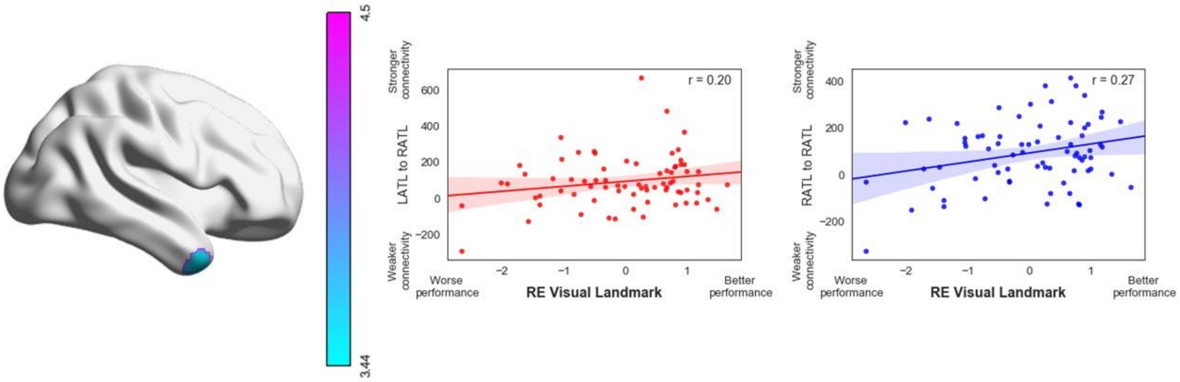


Figure 3.6. Top panel: Bilateral temporal clusters whose connectivity to the conjunction of left ATL and right ATL's functional peak is significantly associated with being better at visual landmark relative to verbal landmark judgements. Bottom panel: a right ATL cluster whose connectivity to the conjunction of left ATL and right ATL's functional peak is significantly associated with being good at visual landmarks (both results are thresholded at Z=3.1, p=.05, Bonferroni-corrected for 7 models). The scatterplots depict the mean-centred efficiency scores in the relevant condition plotted as a function of the normalised (scaled to the global mean) functional connectivity from both, left ATL (red) and right ATL's functional peak (blue) seed to the clusters depicted in the figure. All units are given in z-scores.

3.3.5. Differential ATL connectivity between hemispheres and associations with behaviour

In a second set of analyses, we examined whether differences in connectivity between left and right ATL related to performance on our semantic tasks. A whole-brain difference analysis contrasting left ATL with the homotopic seed in right ATL revealed three significant results, all of them located in medial occipital lobe. First, we identified two clusters reflecting an association between connectivity and performance that was common to all tasks (Figure 3.7). Stronger connectivity from the right ATL homotopic seed was associated with better performance in all tasks, while left ATL connectivity was associated with poorer performance. Next, we observed an interaction effect: this benefit for right-lateralised connectivity was stronger for people's names than for other conditions (Figure 3.8). Finally, there was a significant effect of modality for the categorisation of people (Figure 3.9). Better verbal than visual categorisation of people was associated with differential right versus left ATL connectivity to a relatively large bilateral occipital cluster. The scatterplots show that participants with stronger connectivity from the right homotopic versus left ATL seed to occipital cortex had better performance for people's names.

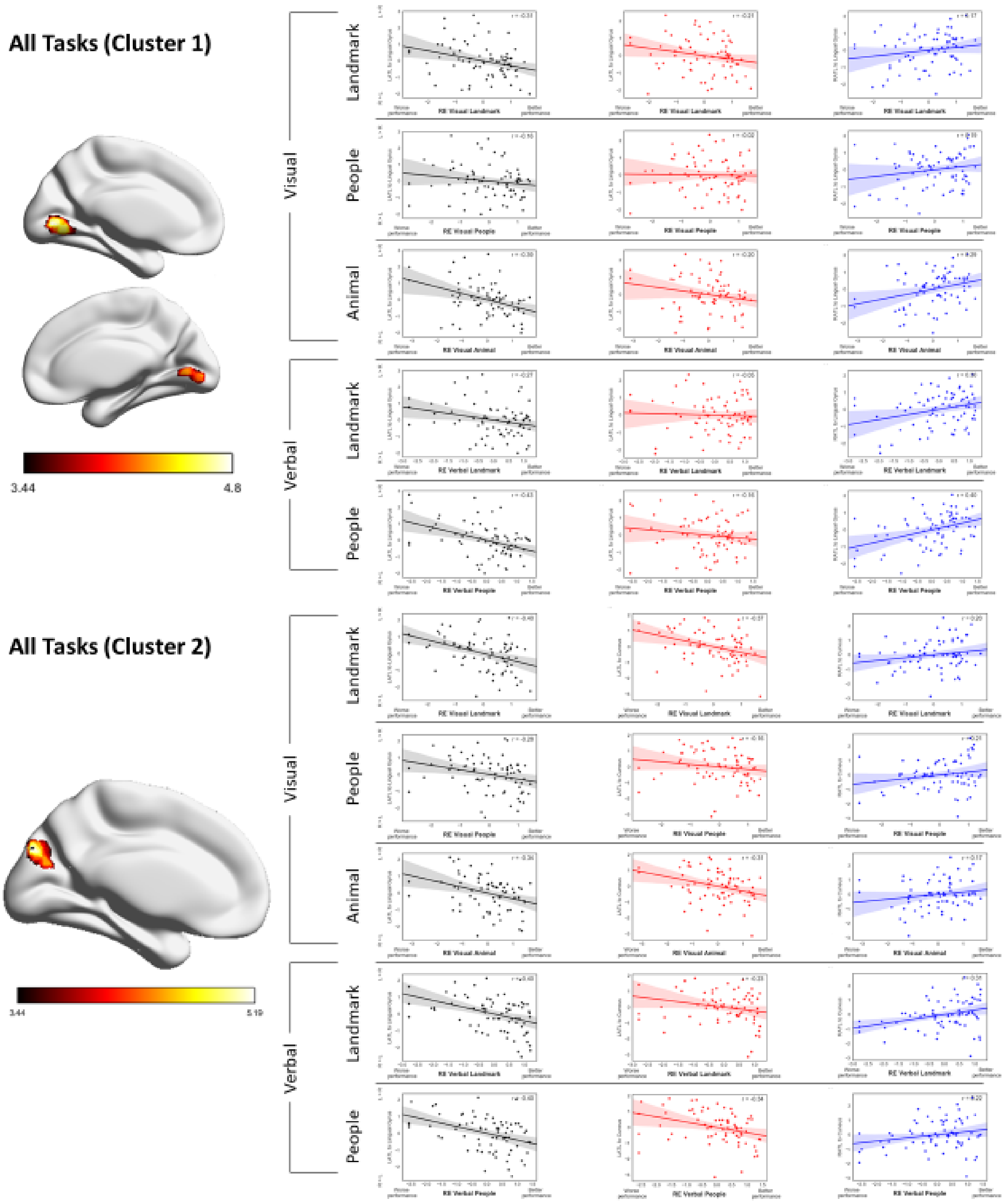


Figure 3.7. Top panel: A ventral occipital cluster whose differential connectivity to right vs. left ATL was significantly associated with being good at all tasks. Bottom panel: A dorsal occipital cluster showing the same pattern (results are thresholded at Z=3.1, p=.05, Bonferroni-corrected for 7 models). The scatterplots depict mean-centred efficiency scores plotted against the normalised (scaled to the global mean) functional connectivity from the differential left versus right ATL (black), left ATL (red) and right ATL's homotopic (blue) seed to the clusters depicted in the figure. All units are given in z-scores.

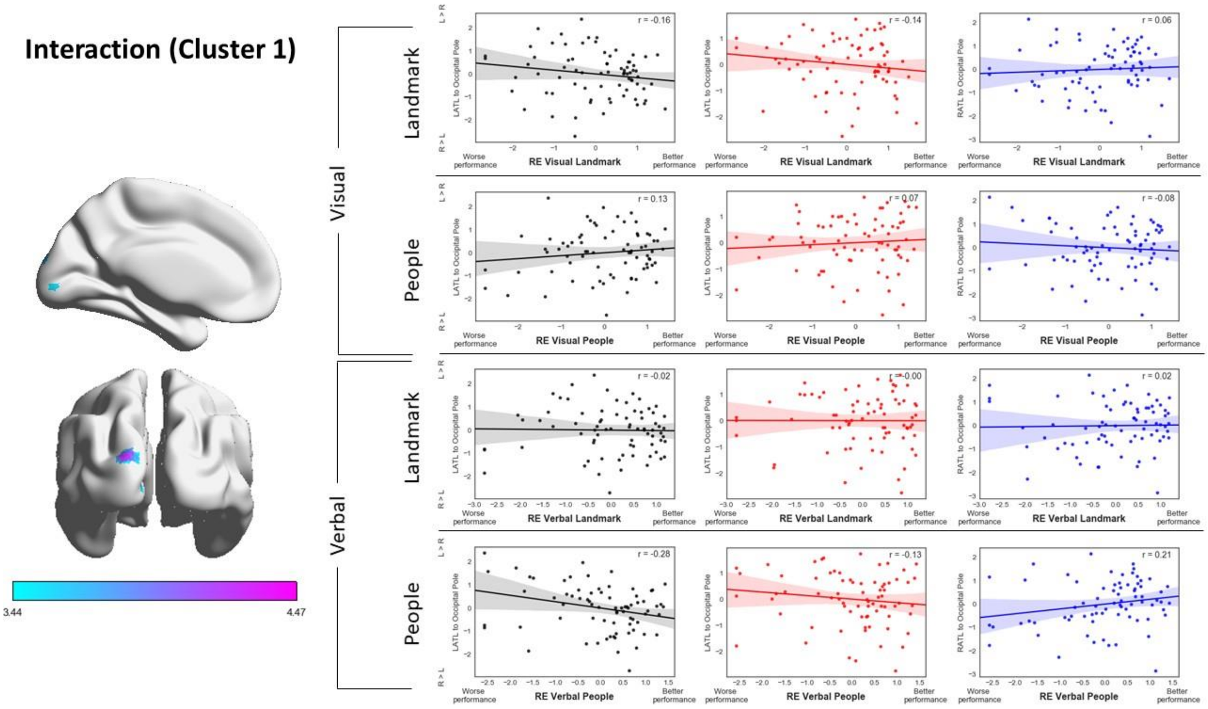


Figure 3.8. A polar occipital cluster whose differential connectivity to left ATL and right ATL's homotopic seed is significantly negatively associated with a modality by category interaction (Z=3.1, p=.05, Bonferroni-corrected for 7 models). The scatterplots depict the mean-centred efficiency scores in the relevant condition plotted as a function of the normalised (scaled to the global mean) functional connectivity from the differential (black), left ATL (red) and right ATL (blue) seed to the cluster depicted in the figure. All units are given in z-scores.

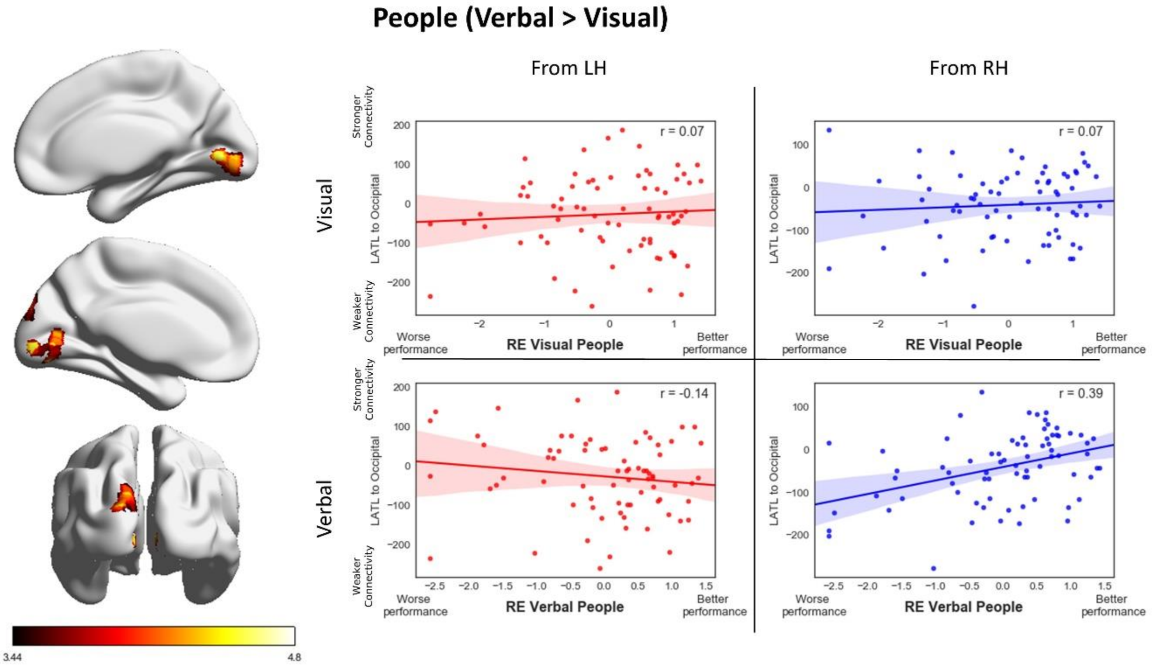


Figure 3.9. A bilateral occipital cluster whose differential connectivity to left ATL and right ATL's homotopic seed is significantly associated with being better at verbal than visual judgements of people (Z=3.1, p=.05, Bonferroni-corrected for 7 models). The scatterplots depict the mean-centred efficiency scores in the relevant condition plotted as a function of the normalised (scaled to the global mean) functional connectivity from the left ATL (red) and right ATL (blue) seed to the cluster depicted in the figure. All units are given in z-scores.

A second whole-brain difference analysis, this time contrasting left ATL with right ATL's functional peak, found one occipital pole result relating to performance for landmarks, regardless of modality (Figure 3.10). Participants with right more than left ATL connectivity to this occipital pole cluster showed better performance for landmarks.

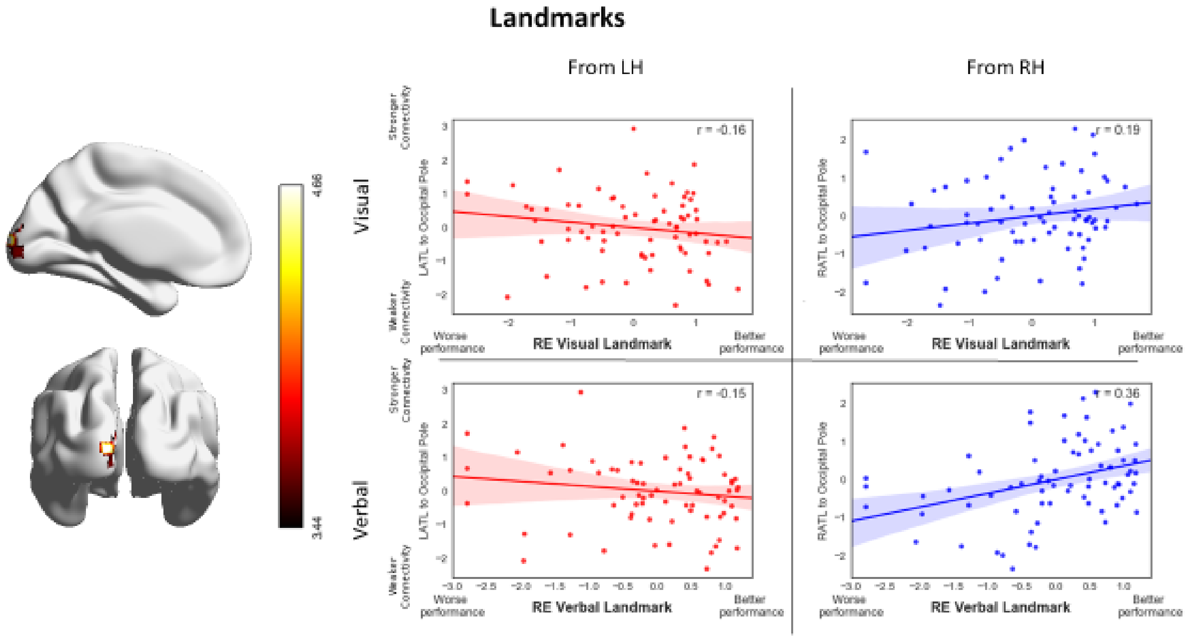


Figure 3.10. A polar occipital cluster whose differential connectivity to left ATL and right ATL's functional peak is significantly associated with landmarks performance (Z=3.1, p=.05, Bonferroni-corrected for 7 models). The scatterplots depict the mean-centred efficiency scores in the relevant condition plotted as a function of the normalised (scaled to the global mean) functional connectivity from the left ATL (red) and right ATL's functional peak (blue) seed to the cluster depicted in the figure. All units are given in z-scores.

3.3.6. Summary of results

There were two sets of results. The first related to higher connectivity between left and right ATL, which was associated with better categorisation of landmarks, especially for the visual modality (Figure 3.11). These results were generated by taking both left and right functional ATL peaks as the seed region. There was a main effect reflecting an association between stronger connectivity and better performance on the picture-based landmark condition, a significant effect of modality for landmarks and an interaction between category and modality that reflected the same pattern.

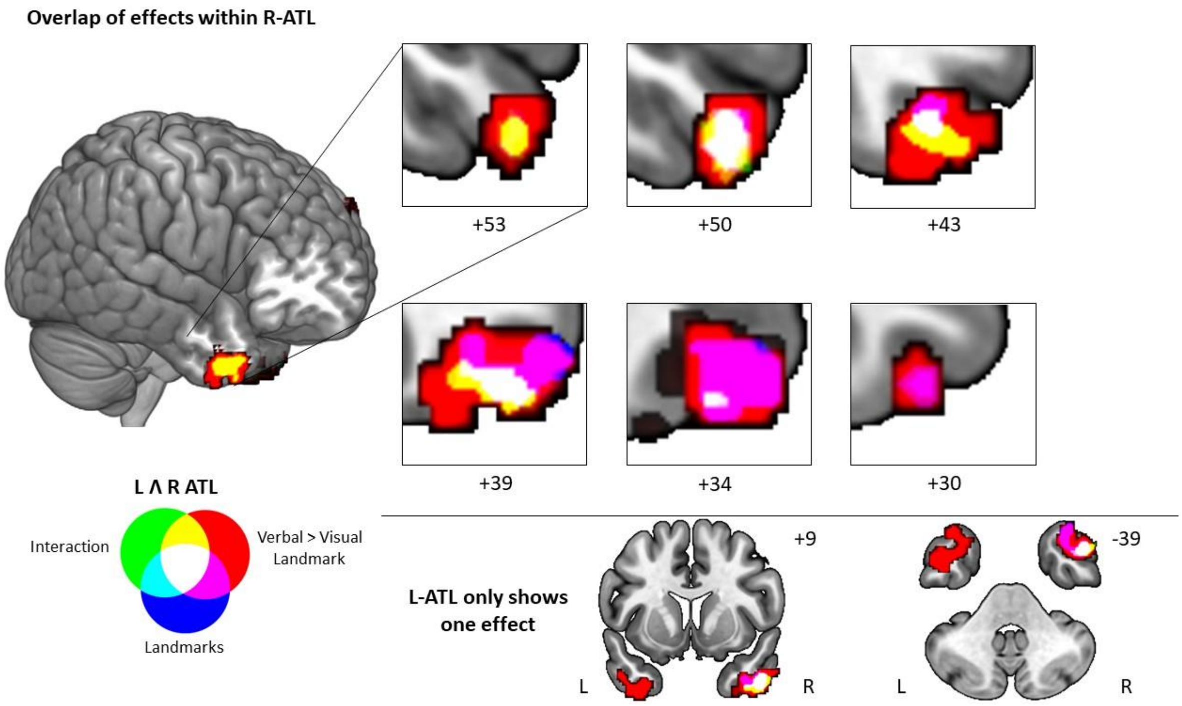


Figure 3.11. Results of our analysis that fell within left and right ATL; all of these come from common left and functional right ATL connectivity and relate to better processing of landmarks, especially in the visual modality. Top panel: Landmarks results that fell in the right temporal lobe and sagittal slices that highlight their topography. Bottom panel: Selected coronal and axial slices that allow comparison between the only effect observed in left ATL with the ones observed in right ATL.

The second set of findings concerned asymmetric connectivity from ATL to medial occipital cortex. These results were primarily related to the comparison of left ATL with the homotopic site in right ATL. Stronger connectivity from right compared with left ATL was associated with better performance across all tasks, although there were some nuances: stronger right ATL connectivity with a ventral occipital cluster was associated with better semantic performance, while stronger left ATL connectivity with a more dorsal occipital cluster was associated with poorer performance. There was a significant interaction between category and modality, and a modality effect for the people category, reflecting a bigger benefit of right ATL connectivity for the categorisation of people’s names. Distinct from these effects, greater right than left hemisphere connectivity to occipital pole (this time from functionally-defined right ATL) was associated with better performance on landmarks, regardless of modality (Figure 3.12).

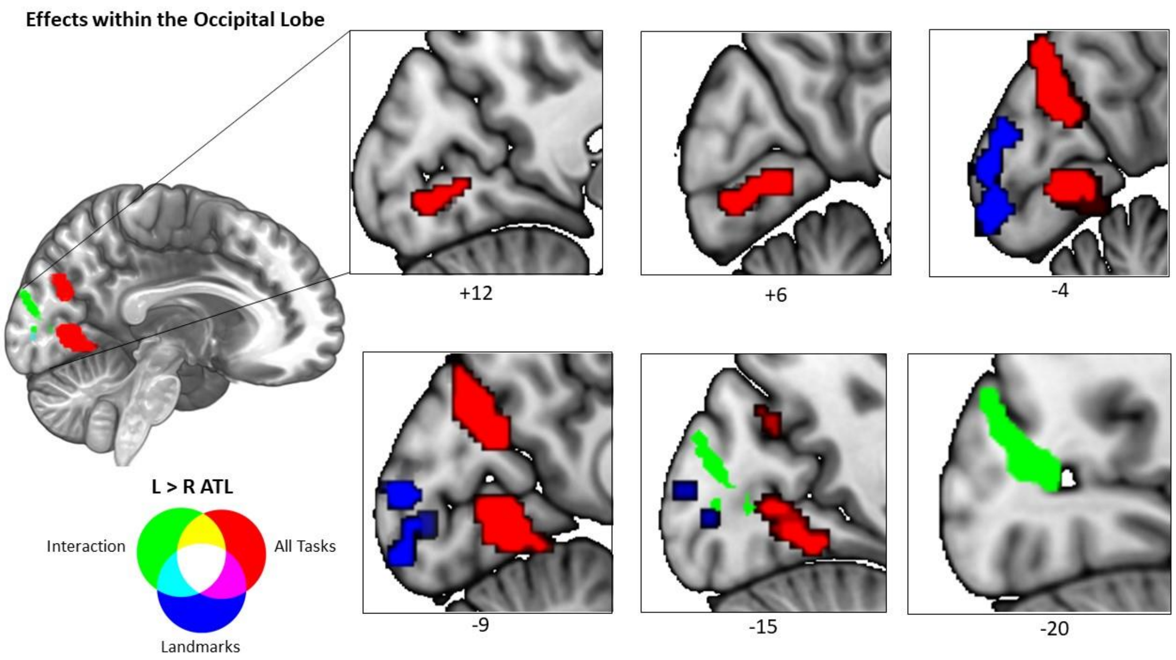


Figure 3.12. Results of two differential analyses that fell in the occipital lobe depicted in selected slices to highlight their relation. These results capture two general effects: being differentially good or bad at tasks as a function of right or left ATL connectivity to these clusters, and an effect of being good at landmark judgements regardless of modality. Taken together, these clusters span a large part of the medial occipital lobe and show minimal overlap between themselves. The landmarks result stems from the left > right functional seed analysis, whilst the interaction and all tasks effects come from the left > right homotopic seed analysis.

3.4. Discussion

This study examined the relationship between individual differences in the intrinsic connectivity of left and right ATL and performance on semantic tasks that involved (i) different modalities of presentation (pictures vs. words) and (ii) knowledge of people vs. landmarks. Previous work has suggested that while the functions of left and right ATL are more similar than they are different, there is some subtle hemispheric specialisation – with research suggesting that right ATL might be disproportionally important for non-verbal tasks and/or for social concepts. We identified two key behavioural associations with intrinsic connectivity. (i) We found that when functionally-defined left and right ATL seeds showed strong connectivity to each other (i.e., the system was strongly bilateral), participants were more efficient at retrieving semantic information about famous landmarks, such as the Eiffel Tower, when these items were presented as pictures instead of words. (ii) We also found that stronger connectivity from right ATL to medial visual cortex was associated with more efficient semantic retrieval in general, but especially in semantic tasks involving people's names (this time using a homotopic site identified by flipping the left-lateralised ATL semantic peak into the right hemisphere). As well as better categorisation in individuals with stronger connectivity from right ATL to ventromedial visual cortex, left ATL connectivity to dorsomedial visual regions was associated with poorer performance on all tasks. These effects are discussed below.

The first of these findings suggests that there are some functional benefits that result from strong intrinsic connectivity between the two ATLs. This pattern might be expected for a bilateral semantic representation system: patients with bilateral ATL atrophy who have semantic dementia show more substantial semantic deficits than patients with unilateral ATL lesions following resection for temporal lobe epilepsy (Lambon Ralph et al., 2012; Rice et al., 2018b), perhaps because the two ATLs show a high degree of connectivity (Gonzalez Alam et al., in press) and consequently the semantic store is only partially divided between left and right hemispheres. This neuropsychological data is accommodated by a model of ATL with strong bilateral connections, as well as somewhat distinct connections from left and right ATL to other brain regions (Schapiro et al., 2013). However, this benefit of bilateral connections between the two ATLs was shown in the current study to be unequal across tasks. Strong cross-hemispheric connectivity particularly benefits tasks which probe knowledge of places and that also use pictorial inputs – perhaps because, in these circumstances, right-lateralised visual-spatial representations (H. Liu et al., 2009; Stevens et al., 2012) need to be integrated with a left-lateralised semantic network (including IFG and posterior temporal regions), shown to activate more strongly to landmarks than to people in an on-line fMRI study employing the same tasks (Rice et al., 2018c). Figure 3.13 shows the neural network engaged in the contrast of landmarks vs. people in Rice's study, and confirms that this network overlaps with regions showing stronger intrinsic connectivity to left than right ATL in a recent study (Gonzalez Alam et al., 2019). This network includes regions of bilateral fusiform and parahippocampal cortex thought to be critical for scene processing (Hodgetts et al., 2016). Participants with more efficient retrieval of semantic information for pictures of landmarks may integrate this network, biased towards left ATL, with right ATL. According to the graded hub account, each ATL receives its strongest inputs from proximal regions within the same hemisphere, and consequently visual-spatial and stimulus-driven attention networks which are right-lateralised (H. Liu et al., 2009) in posterior temporal and parietal cortex might have privileged access to the right ATL (Gonzalez Alam et al., 2019). We also found that participants who show more efficient categorisation of landmarks showed stronger intrinsic connectivity between right ATL and occipital pole, consistent with the suggestion that visual processes are important for knowledge of landmarks. One yet untested hypothesis emerging from this analysis is the possibility that patients with semantic dementia might have more severe difficulties in retrieving conceptual information from visual landmark pictures (compared with the categorisation of famous faces and names, and the names of landmarks), reflecting their highly bilateral atrophy.

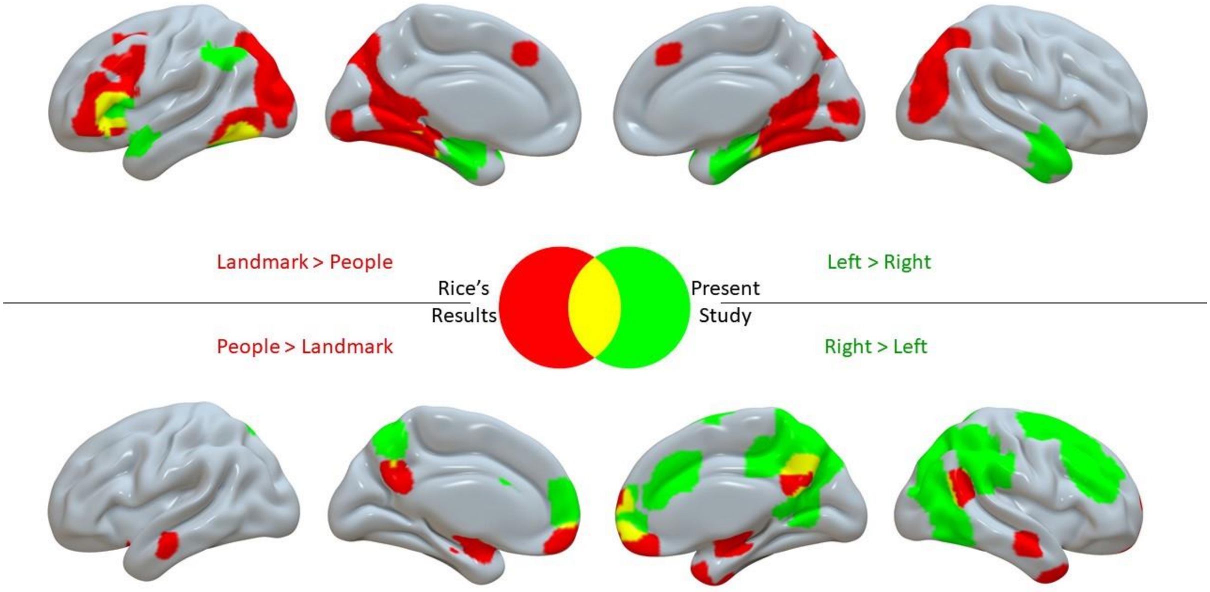


Figure 3.13. Relationship between Rice et al. (2018c) behavioural results (shown in green) and a large sample resting state differential connectivity analysis of the anterior temporal lobe (in red; Gonzalez Alam et al., 2019). The top panel compares the Landmark > People contrast in Rice's study with Gonzalez Alam left > right ATL connectivity, while the bottom panel compares People > Landmark with right > left ATL connectivity.

Our second key finding was that stronger intrinsic connectivity from right ATL to ventromedial visual cortex was associated with more efficient categorisation, with this pattern especially associated with better retrieval of conceptual information about people from their names. This better semantic performance was associated with a stronger pattern of connectivity from right ATL, relative to left ATL, to visual cortex – which was found to be the typical pattern for ATL in Gonzalez Alam et al. (2019; Chapter 2). In other words, this finding is an example of an exaggeration of average connectivity asymmetries being beneficial to performance. A role of the right ATL in knowledge about people is anticipated by previous studies (Gainotti, 2007a, 2007b; Olson et al., 2013; Rice et al., 2015b; Snowden et al., 2004). Using the same paradigm as in the current study, Rice et al. (2018c) found a cluster in right ventral ATL for people versus landmark categorisation (see Figure 2, top row in their paper). In addition, the wider network of regions activated by this contrast is quite similar to brain regions that show stronger connectivity to right than left ATL (see Figure 3.13). Rice et al. (2018c) also reported a ventromedial visual cluster for the contrast of social words vs. non-social abstract terms. These findings taken together are consistent with the view that right ATL does not specifically support visual semantic cognition; instead connectivity from right ATL to ventromedial visual cortex may play an important role in social cognition, as opposed to face recognition per se. Accessing conceptual information about people from their names as opposed to their faces might entail more visual imagery, thought to be supported by medial aspects of visual cortex (Kosslyn et al., 1999, 1995). Overall, our findings do not fit well with the hypothesis that left ATL differentially supports verbal tasks, while right ATL supports picture-based tasks. Our results are more compatible with the view that right ATL plays a central role in knowledge of people, and that integration of conceptual processes with visual cortex particularly supports the ability to recall someone from their name.

The analysis in the current study employed two right ATL seeds: (i) a functional peak derived from a meta-analysis of semantic task data, and (ii) a homotopic site in the same location as the left ATL peak but sign-flipped to the right hemisphere. These two ATL seeds yielded the two different behavioural associations discussed above – strong intrinsic connectivity from the right ATL functional seed to left ATL was associated with more efficient conceptual retrieval about landmarks, while strong intrinsic connectivity from the right ATL homotopic seed to ventromedial visual cortex was associated with more efficient conceptual retrieval from people’s names. This difference between seeds requires further exploration but might reflect the complex functional organisation of ATL (Jackson et al., 2017, 2016; Rice et al., 2015a). An example of this complex organisation can be seen when we contrasted the intrinsic connectivity of the homotopic versus functional seed (Figure 3.4, bottom row); even the small distance between these seeds was enough to engage different networks, with the homotopic (more posterior) seed showing greater connectivity with parts of the ventral visual stream and occipital cortex.

In conclusion, this study shows that individual differences in intrinsic connectivity of left and right ATL are associated with effects of category and modality on semantic efficiency. These effects can be interpreted in terms of graded differences in the strengths of inputs from ‘spoke’ regions, such as regions of visual cortex, to a bilateral yet partially segregated semantic ‘hub’, encompassing left and right ATL.

Chapter 4. Meaningful Inhibition: Exploring the Role of Meaning and Modality in Response Inhibition

Having examined the semantic system as a whole (in Chapter 2), and then hemispheric asymmetries in the anterior temporal lobes thought to support heteromodal semantic representations (in Chapter 3), we turned our focus to the semantic control system, to examine its relation with domain-general cognitive control in the left and right hemisphere.

In the first study in this chapter, we utilised a go/no-go paradigm that reliably engages right-lateralised prefrontal regions when participants have to inhibit a prepotent behaviour based on a no-go signal. Since we know semantic control (which includes inhibition) is left-lateralised, but domain-general inhibition (which is usually tested through perceptual paradigms) is right-lateralised, we manipulated the no-go signal to be perceptual in nature in half the trials, and semantic in the other half. We aimed to test whether inhibition guided by semantics elicits a left-lateralised response or, alternatively, the right-lateralised multiple-demand network regions in charge of domain-general inhibition are engaged regardless of the semantic content of the stimuli. We found support for the latter, adding further evidence that the left-lateralised semantic control network is functionally dissociated from the bilateral multiple-demand network, since it is not recruited just by difficult tasks with a semantic component like the one used in the present study.

In the second study in the current chapter, we examined behavioural consequences of individual differences in intrinsic connectivity from the regions implicated in inhibition by on-line task-based fMRI. We took common regions for response inhibition across perceptual and conceptual decisions as a seed region for this analysis. Participants with stronger connectivity from these multiple-demand areas to limbic medial temporal and subgenual ACC were better at inhibition tasks driven by meaning. Additionally, a region of ventral lateral occipital cortex showing a heightened response in visual compared to verbal inhibition in the on-line study was used as a second seed. Increased connectivity from this lateral occipital region to thalamus/caudate was linked to better inhibition guided by pictures in the offline task. These results show that the capacity to appropriately withhold action depends on interactions between common control regions, which are important across multiple types of input and decision, and other brain regions linked to specific inputs (i.e., visual features) or representations (e.g., memory).

Acknowledgements: This chapter was accepted for publication in the journal NeuroImage on June 27, 2018 (https://doi.org/10.1016/j.neuroimage.2018.06.074). Elizabeth Jefferies, Jonathan Smallwood and the author developed the experimental design and main ideas in this manuscript. Charlotte Murphy helped with adapting the task for fMRI and offered general advice on fMRI analysis. The author developed the majority of the work, including study design, data collection, final design and implementation of analyses, interpretation of the results and writing of the text.

4. Meaningful Inhibition: Exploring the Role of Meaning and Modality in Response Inhibition

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Abstract

We frequently guide our decisions about when and how to act based on the meanings of perceptual inputs: we might avoid treading on a flower, but not on a leaf. However, most research on response inhibition has used simple perceptual stimuli devoid of meaning. In two Go/No-Go experiments, we examined whether the neural mechanisms supporting response inhibition are influenced by the relevance of meaning to the decision, and by presentation modality (whether concepts were presented as words or images). In an on-line fMRI experiment, we found common regions for response inhibition across perceptual and conceptual decisions. These included the bilateral intraparietal sulcus and the right inferior frontal sulcus, whose neural responses have been linked to diverse cognitive demands in previous studies. In addition, we identified a cluster in ventral lateral occipital cortex that was sensitive to the modality of input, with a stronger response to No-Go than Go trials for meaningful images, compared to words with the same semantic content. In a second experiment, using resting-state fMRI, we explored how individual variation in the intrinsic connectivity of these activated regions related to variation in behavioural performance. Participants who showed stronger connectivity between common inhibition regions and limbic areas in medial temporal and subgenual anterior cingulate cortex were better at inhibition when this was driven by the meaning of the items. In addition, regions with a specific role in picture inhibition were more connected to a cluster in the thalamus / caudate for participants who were better at performing the picture task outside of the scanner. Together these studies indicate that the capacity to appropriately withhold action depends on interactions between common control regions, which are important across multiple types of input and decision, and other brain regions linked to specific inputs (i.e., visual features) or representations (e.g., memory).

Keywords: Inhibition, multiple demand, semantic control, fMRI, resting state, intrinsic connectivity

4.1. Introduction

The emergence of adaptive human behaviour requires the co-ordinated action of multiple brain regions to achieve complex goals. When our goals require stimulus-response contingencies that align well with our past experiences, representations in memory may be sufficient to guide action. For example, we know stinging nettles hurt if they are touched – and processing along the ventral visual to semantic pathway allows us to apparently effortlessly avoid these plants when picking berries. In other situations, successful execution of our goals requires us to diverge from the response that was typical in the past. For example, if we decide to deliberately pick stinging nettles in order to clear a path, we must over-ride our pre-potent response based on our past experience with these plants. These different types of behavioural control are likely to rely to differing degrees on the multiple-demand network – a set of distributed brain regions which show a common pattern of activation across a broad range of tasks that require cognitive control (Duncan, 2010, 2001). The multiple-demand network includes inferior frontal sulcus (IFS), intraparietal sulcus (IPS) and pre-supplementary motor area (pre-SMA) bilaterally. These regions respond across multiple domains and paradigms when there is a requirement to produce flexible patterns of behaviour not supported by long-term memory; for example, when we follow arbitrary stimulus-response mappings provided in the task instructions, or when we change or inhibit a response that is already established.

While multiple-demand regions show patterns of common activation across diverse tasks (Cole et al., 2013; Crittenden et al., 2016; Crittenden and Duncan, 2014; Fedorenko et al., 2013), less is known about the degree of functional specialization within this network (see Banich and Depue, 2015, for a review). Distinctions between multiple-demand regions can reflect different processes, such as the distinction between goal-driven attention (dorsal attention network) and stimulus-driven attention (ventral attention network) (Corbetta and Shulman, 2002), or the distinction between a fronto-parietal network (inferior frontal sulcus and intraparietal sulcus) and a separate cingulo-opercular network engaging the dorsal anterior cingulate, anterior insula and the anterior prefrontal cortex (Crittenden et al., 2016; Dosenbach et al., 2008). Evidence for heterogeneity also comes from the degree of lateralization in neural processing linked to the application of control to different domains. The inhibitory control of behaviour, for example, is linked to right-lateralised multiple-demand areas and bilateral pre-SMA (Aron et al., 2014, 2004; Criaud and Boulinguez, 2013; Garavan et al., 1999). The importance of right-hemisphere structures in response inhibition is supported by clinical and lesion studies (Aron et al., 2003; Bellgrove et al., 2006; Chambers et al., 2006; Floden and Stuss, 2006; Mostofsky and Simmonds, 2008; Picton et al., 2007). In contrast, the application of control to semantic information engages a strongly-left lateralised network that involves left inferior frontal gyrus (IFG), posterior middle temporal gyrus (pMTG) and dorsal angular gyrus/intraparietal sulcus (AG/IPS, Lambon Ralph et al., 2017; Noonan et al., 2013). Neuroimaging studies show recruitment of this left-lateralised network across multiple tasks when controlled semantic decisions are contrasted with more automatic semantic retrieval (Badre et al., 2005; Krieger-Redwood et al., 2015; Noonan et al., 2013; Thompson-Schill et al., 1997). The role of left hemisphere regions in controlled semantic retrieval is also supported by evidence that infarcts in these regions lead to problems in shaping semantic activation to suit the task or context (Jefferies, 2013; Jefferies and Lambon Ralph, 2006; Noonan et al., 2010). Finally, regions that support cognitive control may also be functionally segregated by their association with particular input modalities (Duncan, 2010). For example, lateral occipital complex in the multiple-demand network is activated by difficult tasks, yet this region is also important for object recognition and shape processing (Cant and Goodale, 2007; Grill-Spector et al., 2001; Kim et al., 2009). This region might support difficult tasks by maintaining task-relevant visual features. Nonetheless, intrinsic connectivity measures show coupling between lateral occipital cortex and other multiple-demand network regions, suggesting that these regions form a network even in the absence of a task (Crittenden and Duncan, 2014; Stiers et al., 2010).

The present study explored the functional heterogeneity of the multiple-demand network in two experiments using functional magnetic resonance imaging (fMRI). In both studies, we used a Go/No-Go paradigm in which participants were asked to withhold their responses to infrequent targets. In some blocks the No-Go targets were defined based on the meaning of the stimulus (whether it was an animal or a man-made object), while in other blocks No-Go targets were defined by perceptual features (the degree of slant of a box). We searched for regions that showed a different response to inhibition demands depending on the nature of the decision (semantic vs. perceptual) or the modality of the input (words vs. pictures). Since the categorisation of pictures is typically faster than the categorisation of words (Bajo, 1988; Kiefer, 2001; Potter and Faulconer, 1975), the control blocks varied in difficulty, to provide a more balanced design. Experiment 1 measured neural activity online using task-based fMRI, while Experiment 2 explored whether individual differences in behavioural performance across conditions were related to patterns of intrinsic connectivity using resting-state fMRI. Experiment 1 allows us to characterise the neural response that supports response inhibition as it varies with respect to the relevance of meaning and the modality of presentation. Experiment 2 allows us to identify the patterns of intrinsic connectivity at rest that support variation in how effectively these different processes can be engaged.

4.2. Methods

This study was approved by the University of York Neuroimaging Centre and by the Department of Psychology ethics committees. All volunteers provided informed written consent.

4.2.1. Design

Experiment 1 used on-line fMRI to characterise the neural response to Go/No-Go tasks based on different types of decisions (semantic vs. perceptual) and inputs (words vs. pictures). Participants were scanned whilst performing a Go/No-Go task lasting for 26 minutes. We examined contrasts of No-Go over Go events for semantic and non-semantic trials, to identify a commonly-recruited network. We also computed interactions between the Go/No-Go contrast and the role of meaning (semantic vs. non-semantic decisions), plus the effect of stimulus type (words vs. pictures).

Experiment 2 focused on resting-state functional connectivity. In this experiment, a group of participants for whom we had already collected resting state data were invited to come into the laboratory to perform the same inhibitory control tasks. We investigated whether the functional connectivity of the regions activated in Experiment 1 would predict individual variation in performance on these tasks. Participants took part in a 9 minute functional MRI resting state scan where they viewed a central fixation cross on a grey screen. On a separate session, they performed the Go/No-Go task outside the scanner for 26 minutes. Individual differences in intrinsic connectivity were then related to behavioural performance on the Go/No-Go task measured outside the scanner. For this experiment, we used activation maps from Experiment 1 as seed regions (details of this approach are provided in Sormaz et al., 2017).

4.2.2. Participants

For Experiment 1, we tested 34 right-handed, native English-speakers with normal or corrected to normal vision, with no history of neurological or psychiatric illness. One participant was excluded due to not understanding the instructions and performing the task incorrectly, another two were excluded due to excessive motion artefacts (> 5mm in at least one run)[3], and four due to problems during MRI acquisition (failure to record the onset time for stimuli), leaving a final sample size of 27 (mean age = 20.7, 19 females). For Experiment 2, an additional 60 participants (14 of whom had already performed the first experiment) were recruited (mean age = 20.2, 37 females). We used a separate sample of 145 participants (mean age = 20.5, 96 females) in whom we recorded structural MRI and intrinsic connectivity at rest (for details of acquisition see Sormaz et al., 2017), to examine the intrinsic connectivity of regions identified in Experiments 1 and 2. This sample did not overlap with the participants in Experiment 1 and 2.

4.2.3. Materials

4.2.3.1. Go/No-Go Paradigm

The participants took part in a Go/No-Go task designed to probe semantic inhibition. Each trial consisted of a fixation cross, followed by the stimulus. The duration of the fixations and stimuli were jittered between 0.5-1s and 0.75-1.25s for fixation and stimulus respectively. The stimuli consisted of pictures/words framed by a box that was slanted to different degrees (slight slant, medium slant or pronounced slant).

The task was divided into three blocks: in the ‘Word’ blocks, the participants saw a series of words referring to either animals or man-made objects, while in the ‘Picture’ blocks, they saw pictures depicting these same categories; their task was to press a button every time they saw a word or picture referring to a man-made object (Go event), and refrain from pressing when they saw an animal (No-Go event). In the ‘Perceptual’ (non-semantic) blocks, stimuli were scrambled images generated from the word and picture stimuli ensuring that

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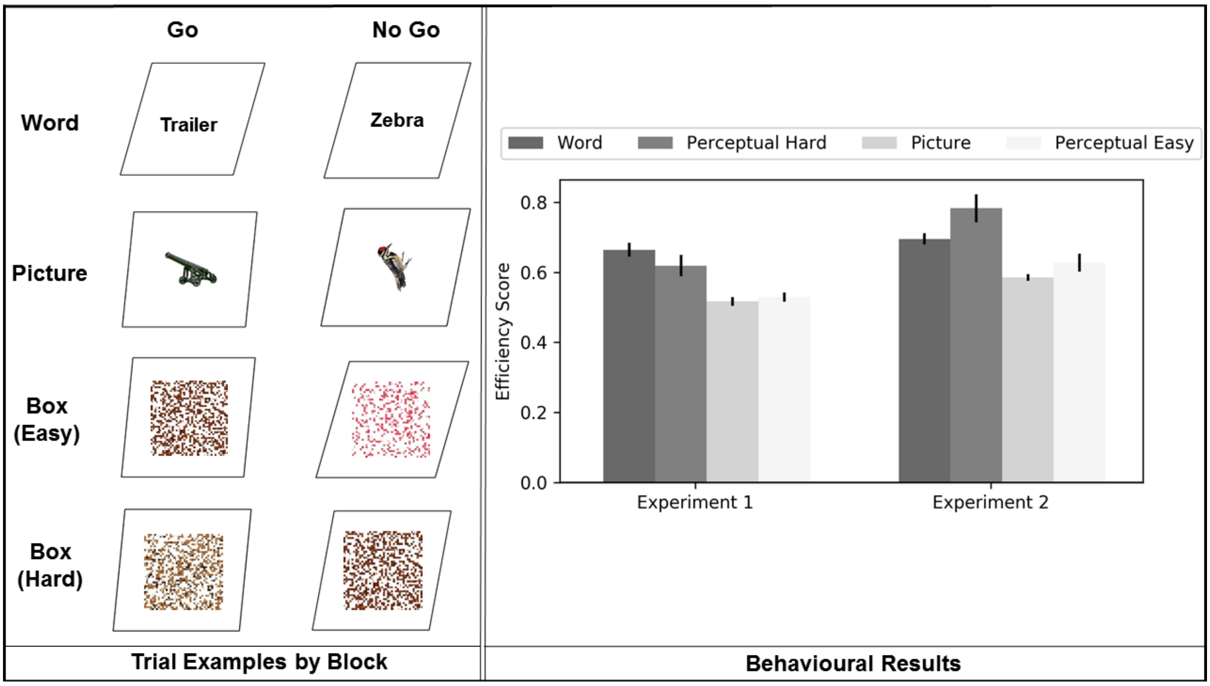
[3] At the request of a reviewer, we re-analysed the data excluding all runs where a participant showed an absolute mean displacement greater than 1mm. The results of this re-analysis are similar: there was one additional cluster for the Picture > Word interaction term in left fusiform gyrus – i.e., this effect became bilateral. No other clusters deviated in important ways from the previous analysis. The results of this re-analysis are publically available in Neurovault (https://neurovault.org/collections/3158/).

basic features like luminance were constant across the experiment (See the ‘Stimuli Generation’ section for details). In this condition, participants were asked to inhibit responses when they saw that the framing box was more slanted than usual (No-Go event) and to press the button for the usual, slight degree of slant (Go event). This last condition was further subdivided in Easy and Hard trials based on the degree of slant: The Easy trials involved discriminating between slight and pronounced slants, while the Hard trials involved discriminating between the slight and medium slants (this was harder to do, as there was only a slight difference between them). This manipulation was included to provide perceptual decisions that matched in difficulty to both word and picture semantic trials. Examples of the Go and No-Go trials, as well as the behavioural results from the paradigm are presented in Figure 4.1.



Trial Examples by Block

Behavioural Results

Figure 4.1. The left-hand panel depicts example stimuli per block. In WORD blocks, participants pressed for words denoting man-made objects and withheld this response for words denoting animals. In PICTURE blocks, participants pressed for pictures of man-made objects and withheld this response for pictures of animals. In BOX blocks, participants pressed for slightly slanted boxes and withheld this response for more strongly slanting boxes. Difficulty in the BOX trials was manipulated by adjusting the size of the slant. The right-hand panel shows behavioural results for the Go/No-Go paradigm expressed as efficiency scores (a proportion of reaction time divided by accuracy). The error bars depict the standard error of the mean. In Experiment 1, the task was performed inside the scanner, while in Experiment 2 it was performed outside.

For Experiment 1, neural data was recorded in six blocks (two for each condition) containing 46-54 stimuli each, with the order of blocks counterbalanced across participants. Each block contained 80% Go events and 20% No-Go events. We divided these into two 3-block runs, each lasting 13 minutes. The distribution of Go and No-Go events within the blocks was pseudorandomised, with 1-6 Go events between No-Go events. Each block started with a cue to inform the participant which type of stimuli to expect, and ended with a screen informing the participant they had a 5 second break before the next block. In Experiment 2, participants performed these same 6 blocks, but in a single 26-minute session. Our design made it necessary to trade off the number of No-Go events with the strength of the inhibition effect (which is maximised by having predominately Go events and relatively few No-Go events). We opted for approximately 20 No-Go events against 80 Go events per condition.

4.2.3.2. Stimuli Generation

In order to ensure the stimuli could be clearly distinguished as man-made or animal, we presented images from the *Bank of Standardized Stimuli* (Brodeur et al., 2014, 2010) to four native British English speakers, who provided as many names as possible for each picture, and decided if the item belonged to the category of animal or man-made object. Based on this, we chose a subset of pictures given a single non-ambiguous word as a name (i.e., with a single meaning). This provided 174 pictures of man-made objects and 51 of animals. Subsequently, we used independent samples t-tests to verify that the names assigned to the man-made objects and animals did not differ significantly in lexical frequency and letter length using Celex implemented in N-Watch (Davis, 2005). There were no significant differences in lexical frequency (man-made objects: M = 13.1 counts per million, SD = 22.6; animals: M = 12.0, SD = 27.5; t(219) < 1), or letter length (man-made objects: M = 6.2, SD = 2.1; animals: M = 6.1, SD = 2.2; t(219) < 1). The scrambled images were derived from these selected picture and word trials. We submitted the original pictures to a scrambler that broke them down in 160 equilateral ‘tiles’, and then randomly assigned a place to each tile to create a scrambled image of 40 x 40 tiles where no meaning was discernible. We did the same for the visually-presented words used in the word condition. The resulting scrambled pictures constituted the stimuli of the Perceptual trials.

4.2.4. Image Acquisition

Structural and functional data were acquired using a 3T GE HDx Excite MRI scanner utilising an eight-channel phased array head coil (GE) 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 ms, TE = minimum full, flip angle 20°, matrix size = 256 x 256, 176 slices, voxel size = 1.13 x 1.13 x 1 mm). Task-based and resting-state activity was recorded using single-shot 2D gradient-echo echo planar imaging (EPI) with a flip angle = 90°, TE = minimum full, voxel size = 3 x 3 x 3 mm^3. Other scan parameters slightly varied for task-based fMRI (field of view (FOV) = 192 mm^2, TR = 2000 ms, matrix size = 64 x 64 x 38 slices, 376 volumes per run, for a total of 2 runs) and resting-state fMRI (whole brain, TR = 3000 ms, matrix size = 64 x 64 x 60 slices 180 volumes). An intermediary FLAIR scan with the same orientation as the functional scans was collected to improve the co-registration between subject-specific structural and functional scans.

4.2.5. Data Pre-processing and Analysis

4.2.5.1. Task-based fMRI

Analyses were conducted at the first and higher level using FSL-FEAT version 6.0, part of FSL (FMRIB’s Software Library, www.fmrib.ox.ac.uk/fsl, Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009). Pre-processing included slice timing correction using Fourier-space time-series phase-shifting (interleaved), motion scrubbing (using the fsl_motion_outliers tool) to identify volumes that exceeded a threshold of 0.9 using framewise displacement as the metric, which then were entered as confounds, motion correction using MCFLIRT (Jenkinson et al., 2002), high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 50s), brain extraction (Smith, 2002), linear co-registration to the corresponding T1-weighted image followed by linear co-registration to MNI152 standard space using FLIRT (Jenkinson et al., 2002; Jenkinson and Smith, 2001), spatial smoothing using a Gaussian kernel with full-width-half-maximum (FWHM) of 5mm and grand-mean intensity normalisation of the entire 4D dataset by a single multiplicative factor.

Pre-processed time series data were modelled using a general linear model, using FILM correcting for local autocorrelation (Woolrich et al., 2001). We used an event-related design – the linear model included ten Explanatory Variables (EV): Button presses and Instruction screens, which were modelled to control and exclude from the contrasts of interest, and Go and No-Go events for each of the three conditions: Word, Picture and Perceptual (i.e., non-semantic control), which was subdivided into Easy and Hard.

Our analysis focused on the comparison of inhibition events involving different types of judgements (semantic and perceptual) and different modalities of presentation (pictures and words). We examined the main effect of inhibition for the tasks separately: Semantic No-Go > Go (collapsing across word and picture trials), and Perceptual No-Go > Go (collapsing the easy and hard trials). We were then able to identify common inhibition regions via a formal conjunction analysis, using FSL's 'easythresh_conj' tool (Nichols et al., 2005). We also examined main effects of task type: Semantic > Perceptual; Words > Pictures and the reverse. Most importantly, we defined interaction terms to examine differential effects of the No-Go > Go contrast between words and pictures, and between matched sets of semantic and perceptual conditions (Picture and Perceptual Easy, Word and Perceptual Hard). At the group-level, analyses were carried out using FMRIB's Local Analysis of Mixed Effects (FLAME1) stage 1 with automatic outlier detection (Beckmann et al., 2003; Woolrich, 2008; Woolrich et al., 2004), using a (corrected) cluster significance threshold of $p = 0.05$, with a z-statistic threshold of 3.1 (Eklund et al., 2016) to define contiguous clusters.

While the analyses below focus on whole-brain contrasts, in Supplementary Analyses, we also examined regions of interest defined by prior studies. First, we examined the same contrasts within the semantic control network, defined by the meta-analysis of Noonan et al. (2013; Supplementary Analysis 4.1). Secondly, we examined activation within spherical regions of interest (3mm in radius) placed at key sites in the multiple-demand system defined by Duncan (2010; Supplementary Analysis 4.2).

4.2.5.2. Resting-state fMRI

Analyses were conducted at the first and higher level using FSL-FEAT version 5.98, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl, Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009). Pre-processing steps were as for task-based fMRI, except for Gaussian low-pass temporal filtering, with sigma = 2.8s, high-pass temporal filtering

(Gaussian-weighted least-squares straight line fitting, with sigma=100.0s), no motion scrubbing, and spatial smoothing using a Gaussian kernel with FWHM of 6mm. Regions of Interest (ROI) were taken from the task-based fMRI results (see Results section), and binarised using FSL Maths. We extracted the time series from each ROI mask and used these as explanatory variables in connectivity analyses at the single subject level. In each analysis, we entered 11 nuisance regressors; the top five principal components extracted from white matter (WM) and cerebrospinal fluid (CSF) masks based on the CompCor method (Behzadi et al., 2007) and six head motion parameters. WM and CSF masks were generated from each individual's high resolution structural image (Zhang et al., 2001). No global signal regression was performed, following the method implemented in Murphy et al. (2009). At the group-level, analyses were carried out using FMRIB's Local Analysis of Mixed Effects (FLAME1) with automatic outlier detection (Beckmann et al., 2003; Woolrich, 2008; Woolrich et al., 2004), using a cluster correction ($p < .05$), and a threshold of $z=3.1$ to define contiguous clusters at the group level. This analysis included behavioural regressors (efficiency scores for each condition, i.e. No-Go accuracy / Go RT) to evaluate whether performance correlated with individual differences in intrinsic connectivity, and a motion regressor using the mean (across time/frames) of the absolute values for framewise displacement for each participant. The connectivity maps resulting from these analyses were uploaded to Neurovault (Gorgolewski et al., 2015, URL: https://neurovault.org/collections/3158/) and decoded using Neurosynth (Yarkoni et al., 2011), allowing us to extract key terms associated with each connectivity pattern.

4.2.5.3. Decoding and automated meta-analysis using Neurosynth (Yarkoni et al., 2011)

Neurosynth is an automated meta-analysis tool that associates spatial activation maps with descriptive terms from the neuroimaging literature. It uses text-mining tools to extract high frequency terms taken from the abstract and main body of neuroimaging articles and associates them with peak coordinates of activation (following certain criteria, such as only including terms used in at least 20 studies). In this way, it can generate ‘reverse inference’ maps associated with a particular term, such as “semantic”. These maps show regions that are more likely to be activated for that particular term than for others (this approach was used in Figure 4.9, Step 3). It can also be used to generate a set of terms frequently associated with a spatial map. This approach is used in Figure 4.9, Steps 1 and 2. In presenting these results as word clouds, we manually excluded terms referring to neuroanatomy (e.g., “inferior” or “sulcus”), as well as repeated terms (e.g., “semantic” and “semantics”). The size of each word in the word cloud relates to the frequency of that term across studies.

4.3. Results

4.3.1 Behavioural Results

We combined reaction time (RT) on Go events and the accuracy of participants’ responses on No Go events into an efficiency score (a ratio of a participant’s RT divided by accuracy) for each condition. Table 4.1 provides descriptive statistics for RT and accuracy, while response efficiency is shown in Figure 4.1 (see Methods section).

	Experiment 1 (n=27)		Experiment 2 (n=60)	
Condition	RT	Accuracy	RT	Accuracy
Word	0.43 (0.04)	66.27 (12.51)	0.51 (0.05)	75.65 (11.97)
Picture	0.42 (0.07)	81.33 (12.35)	0.51 (0.06)	87.77 (8.87)
Perceptual Easy	0.41 (0.05)	79.05 (9.06)	0.49 (0.07)	81.06 (16.19)
Perceptual Hard	0.42 (0.06)	71.12 (17.98)	0.50 (0.07)	70.22 (17.87)

Table 4.1. Response time and accuracy for the behavioural data. Note. Means with standard deviations in parentheses. RT on Go trials (i.e., when a response was required) is shown in seconds. Accuracy on No-Go trials (i.e., the successful suppression of a pre-potent response) is given as a percentage of trials.

In Experiment 1, the Word trials were more demanding than the Picture trials $t(26) = 8.83$, $p < 0.0001$ (see Figure 4.1). Behavioural performance was matched for Word and Perceptual Hard conditions ($t(26) = 1.68$, $p = 0.11$), and Picture and Perceptual Easy conditions (t(26) = -0.84, p = 0.41). This pattern was mostly replicated in Experiment 2. There was a significant difference in the efficiency score for Word and Picture conditions (t(59) = 9.37, p < 0.0001). Again, there were no significant differences between the Picture and Perceptual Easy conditions (t(59) = -1.77, p = 0.082), but the difference between the Word and Perceptual Hard conditions was significant (t(59) = -2.52, p < 0.05).

4.3.2 fMRI Results

Our fMRI analysis was performed in three separate steps. We first conducted task-based fMRI analysis, identifying areas that were involved in semantically and perceptually-guided inhibition, as well as any differences between semantic and perceptual processing, and any interactions between the Go/No-Go contrast and modality (Word and Picture) and/or difficulty (Perceptual Hard and Easy). Next we conducted resting-state functional connectivity analysis using the results from the task-based fMRI analysis as seeds, in order to identify regions whose functional connectivity with the seed predicted behavioural performance in the lab; in a separate dataset, we also described the intrinsic functional connectivity of the regions that were identified in these analyses. Finally, we decoded the resting state functional connectivity group maps using Neurosynth, an automated meta-analysis tool (Yarkoni et al., 2011), to obtain psychological terms associated with the patterns of activation in our results.

4.3.2.1. Experiment 1: Task-based fMRI results

A comparison of the Semantic No-Go > Go and Perceptual No-Go > Go contrasts revealed overlapping networks that were lateralised to the right hemisphere. We compared the formal conjunction of semantic and perceptual inhibition contrasts with the multiple-demand network (map taken from Fedorenko et al., 2013) and a term-based, automated meta-analysis of inhibition from Neurosynth (Yarkoni et al., 2011). This is shown in Figure 4.2. Both semantic and perceptual inhibition overlapped with the multiple-demand network in right intraparietal sulcus, right inferior frontal sulcus, and bilateral lateral occipital cortex. Both of these No-Go > Go contrasts also overlapped with the automated meta-analysis for inhibition in the right frontal pole and supramarginal gyrus. The interaction between semantic and perceptual inhibition (i.e. Semantic No-Go > Go > Perceptual No-Go > Go) yielded no significant clusters. Together these analyses show that semantic and perceptual inhibition recruit broadly the same right-lateralised regions of the multiple-demand network, and regions commonly engaged in general inhibition.

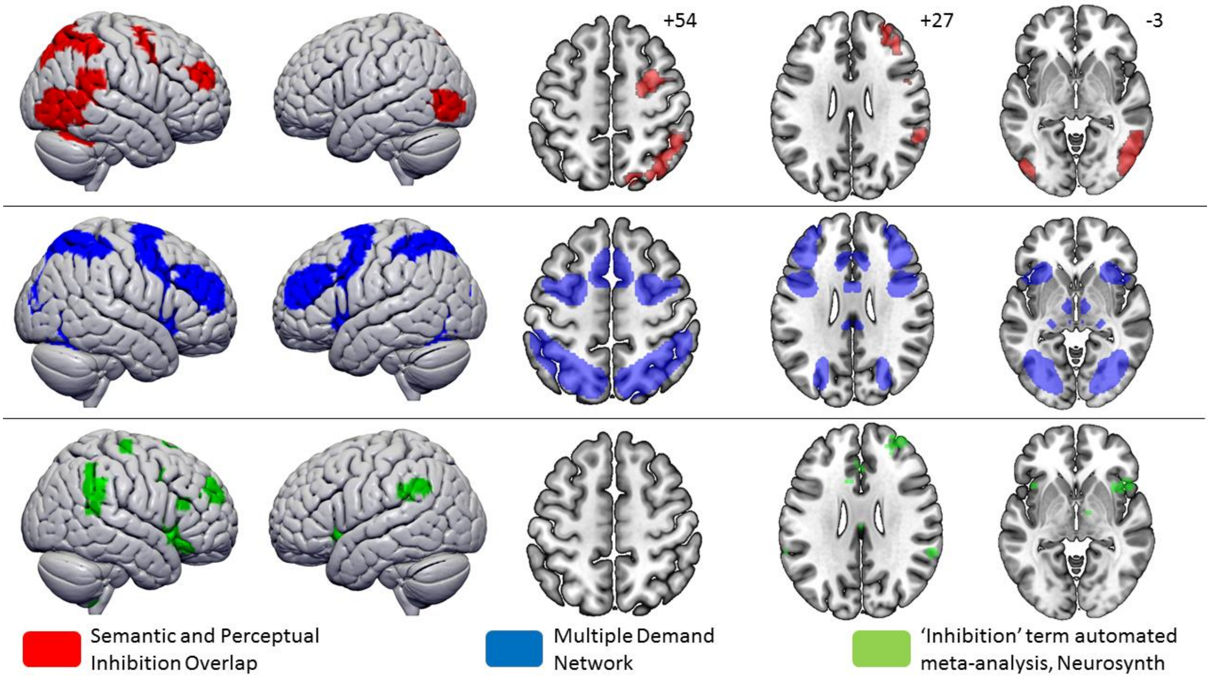


Figure 4.2. Comparison of the neural activation from a formal conjunction of Semantic and Perceptual response inhibition (i.e., No-Go > Go trials; shown in red) with the multiple-demand network (shown in blue) and an automated meta-analysis of inhibition studies (shown in green). The semantic and perceptual inhibition maps were cluster-corrected with a voxel inclusion threshold of $z > 3.1$ and family wise error rate using random field theory set at $p < .05$. Their conjunction was identified using FSL's 'easythresh_conj' tool.

Having identified regions that show common neural activity for semantic and perceptual inhibition, we next examined whether the modality and/or meaningful content of the stimulus is important in determining the neural activity during response inhibition. Although the interaction between semantic and perceptual inputs and inhibitory demands (No-Go vs. Go) yielded no significant clusters, we did find significant differences in the areas that responded to semantic stimuli (regardless of whether they were Go or No-Go trials) compared to the perceptual baseline and vice versa (Figure 4.3). Right-sided inferior and middle frontal gyri, superior lateral occipital cortex and posterior middle temporal gyrus, as well as bilateral intraparietal sulcus, were more active for perceptual than semantic trials.

Conversely, regions of bilateral fusiform cortex, extending into left anterior temporal lobe, were more active for semantic than perceptual trials.

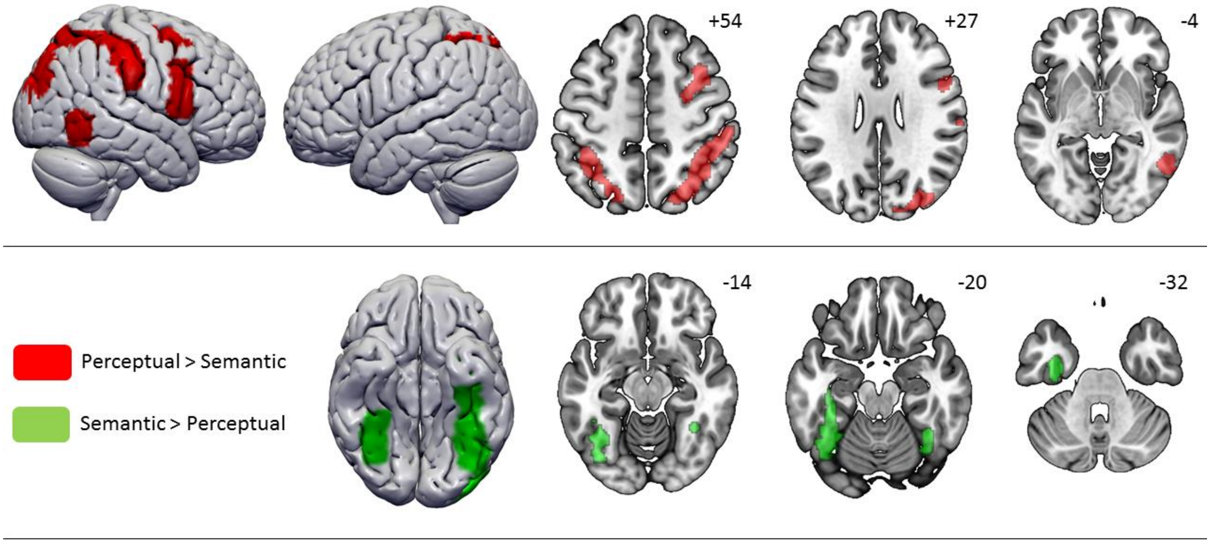


Figure 4.3. Comparison between semantic and perceptual stimuli processing. Parietal, frontal and occipital regions involved in processing perceptual more than semantic stimuli, and temporal regions processing semantic more than perceptual stimuli. Both the semantic > perceptual and the perceptual > semantic result maps were cluster-corrected with a voxel inclusion threshold of $z > 3.1$ and family wise error rate using random field theory set at $p < .05$.

We next focused on the semantic stimuli and considered whether there were differences in activation that reflected the modality of presentation. Contrasts of each modality against the perceptual baseline (Word > Perceptual, Picture > Perceptual) revealed two significant results: left IFG and bilateral anterior cingulate cortex showed increased activation when stimuli were presented as words compared to the perceptual baseline, while bilateral fusiform gyri and left intracalcarine cortex/lingual gyrus were more active in response to pictures than perceptual trials (Figure 4.4). In addition, the contrast of Picture > Word revealed bilateral fusiform cortex (Figure 4.6). These clusters overlapped with the bilateral fusiform regions revealed by the contrast of Picture > Perceptual. The direct contrast of Word > Picture revealed no significant clusters.

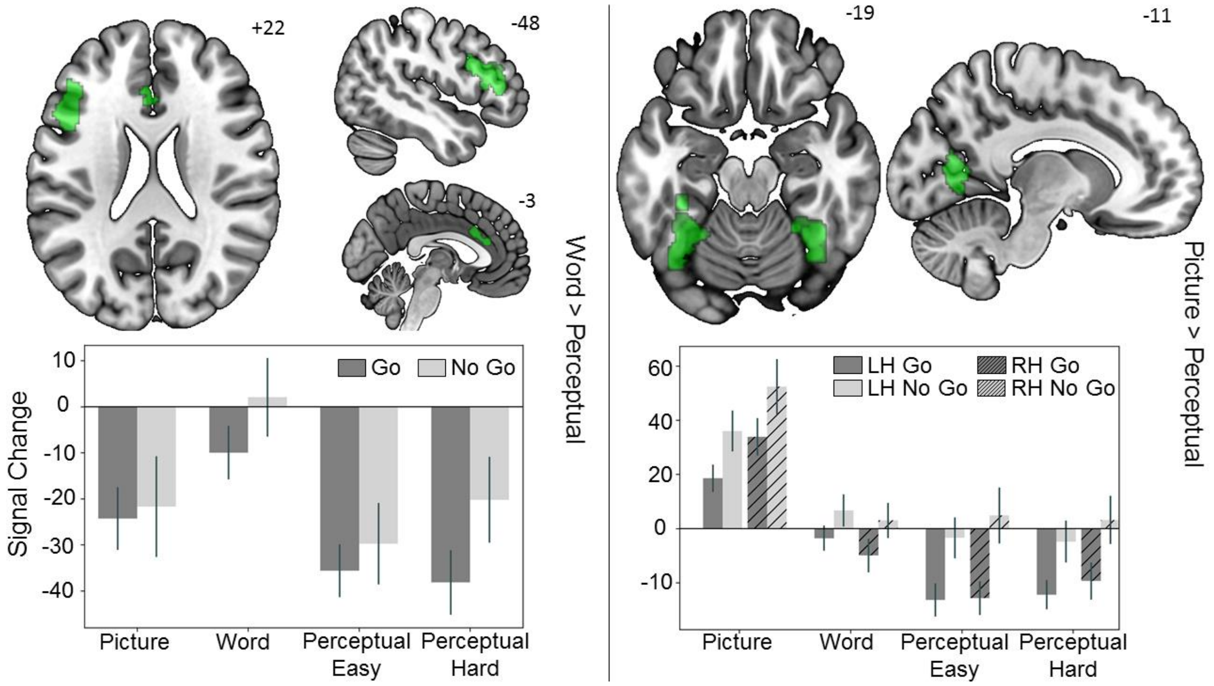


Figure 4.4. Activation associated with word and picture trials. There was activation in left inferior frontal gyrus / anterior cingulate cortex for words (two clusters), and in bilateral fusiform for pictures, relative to non-semantic trials; z > 3.1, p < .05. The bar charts plot signal change for the specified contrast as a function of condition, with the error bars depicting the standard error of the mean.

To identify any regions that showed a differential response to inhibitory demands for either words or pictures, we considered the interaction of modality and inhibition. This analysis identified a region in right occipital cortex that was more active when inhibition was driven by pictures compared with words (Figure 4.5). An examination of the parameter estimates suggested that the neural activity was highest in the picture condition and lowest in the word condition. Figure 4.6 shows a comparison of this cluster with the main effects of input modality (Pictures > Words) and inhibition (No-Go > Go conjunction across conditions). Much of the interaction cluster fell within the region showing a main effect of modality (Pictures > Words). The interaction cluster also overlapped with regions implicated in inhibition across conditions.

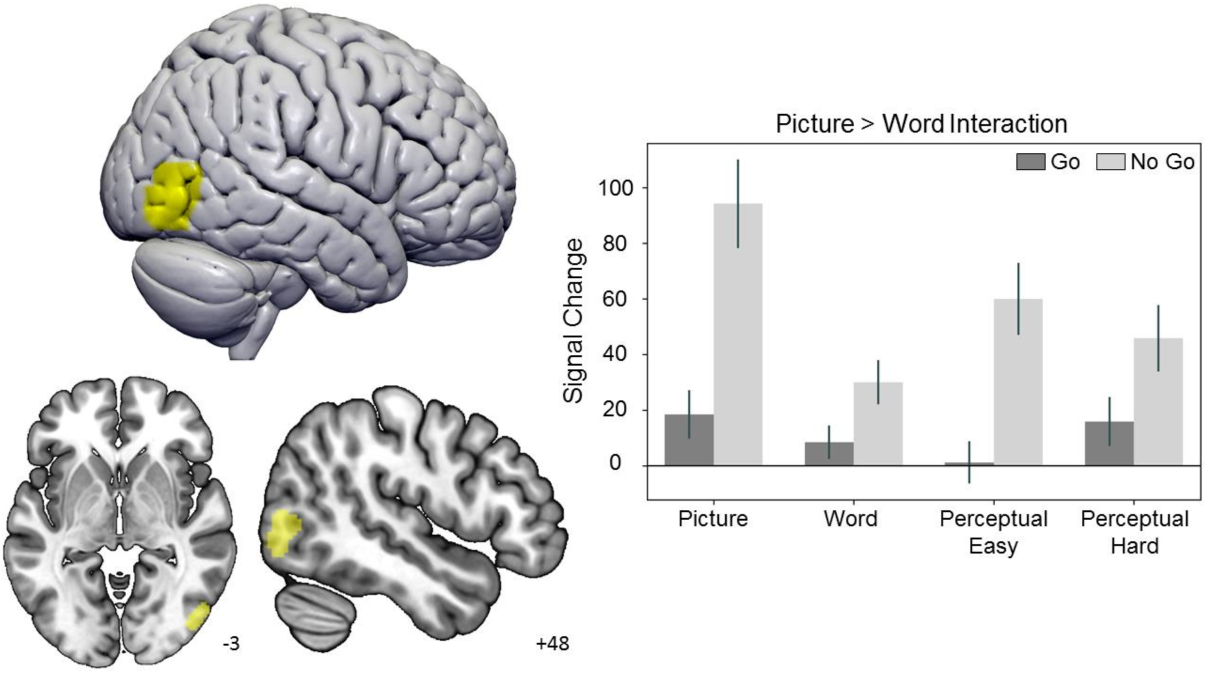


Figure 4.5. Regions showing a stronger response to inhibition events that were picture-based rather than verbal. All maps were cluster-corrected with a voxel inclusion threshold of z > 3.1 and family wise error rate using random field theory set at p < .05. The bar charts plot signal change for the specified contrast as a function of condition, with the error bars depicting the standard error of the mean.

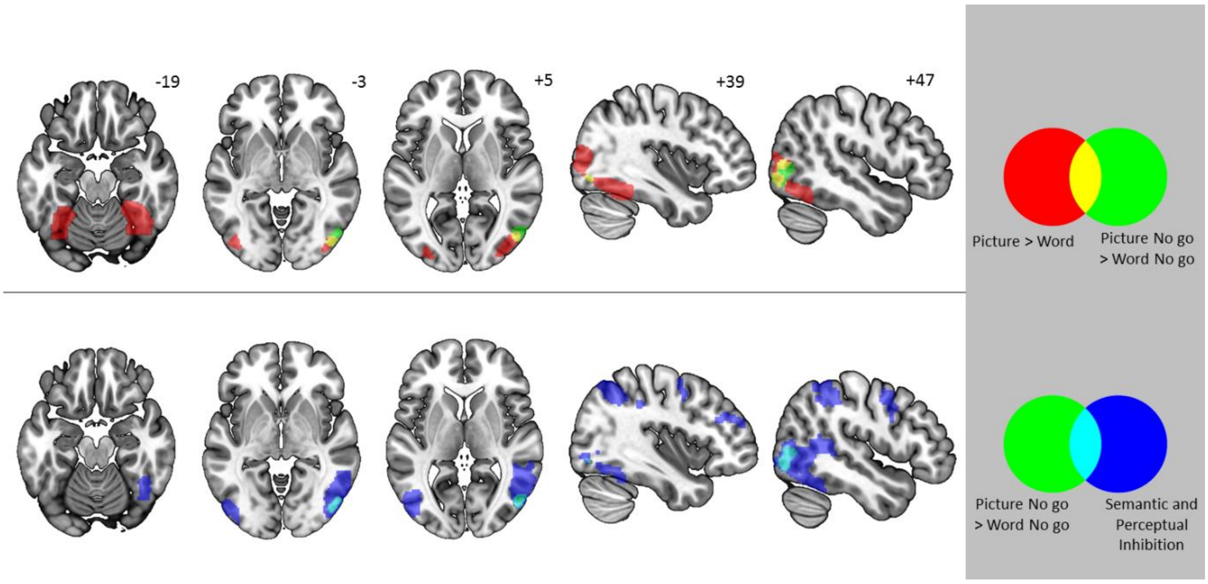


Figure 4.6. A comparison of the interaction cluster for picture-based inhibition with (i) the main effect for Pictures > Words (top row) and (ii) the inhibition conjunction (No-Go > Go across semantic and perceptual conditions; bottom row). All maps were cluster-corrected with a voxel inclusion threshold of z > 3.1 and family wise error rate using random field theory set at p < .05.

Finally, since the analysis above failed to identify a role for left-lateralised semantic control regions (e.g., left inferior frontal cortex) in semantically-guided inhibition, we performed the same contrasts within a mask encompassing areas important for semantic control from a meta-analysis (Noonan et al., 2013), to reduce the probability of a Type II error. This analysis yielded clusters in left inferior frontal gyrus, similar to the one shown in Figure 4.4, for the main effects of words vs. perceptual decisions, pictures vs. perceptual decisions and semantic vs. perceptual decisions (see Supplementary Analysis 4.1 and Supplementary Figure S4.1). These effects overlapped in mid-IFG, consistent with a role for this region in semantic processing across modalities. However, there were no interactions between inhibitory demands and modality or task.

4.3.2.2. Experiment 2: Resting-state functional connectivity analysis

Experiment 1 demonstrated patterns of common and distinct neural activity supporting the different types of response inhibition measured by our paradigm. We found that across conditions, response inhibition is guided by right-lateralised areas that overlap with the multiple-demand network. In addition, we found a region of right lateral occipital cortex that was especially important when response inhibition was driven by the semantic properties of pictures as opposed to words. In Experiment 2 we sought to investigate whether the intrinsic connectivity of these regions at rest was predictive of performance on response inhibition at a later time-point. We would expect the connectivity between general inhibition regions and modality- or task-specific regions to relate to the efficiency of inhibitory control for specific kinds of input. To test this hypothesis, we first performed a whole brain functional connectivity analysis using these regions as seeds, and then used efficiency scores for the different inhibition conditions as regressors in a group level regression.

First, we took general inhibition regions that responded to No-Go more than Go events in Experiment 1 as a seed region. The seed was defined by the conjunction of semantic and perceptual inhibition and included clusters in prefrontal cortex, intraparietal cortex and bilateral lateral occipital cortex. These regions showed stronger intrinsic connectivity to clusters in medial temporal and sub-callosal cortex related to better inhibition on semantic relative to perceptual trials (Figure 4.7).

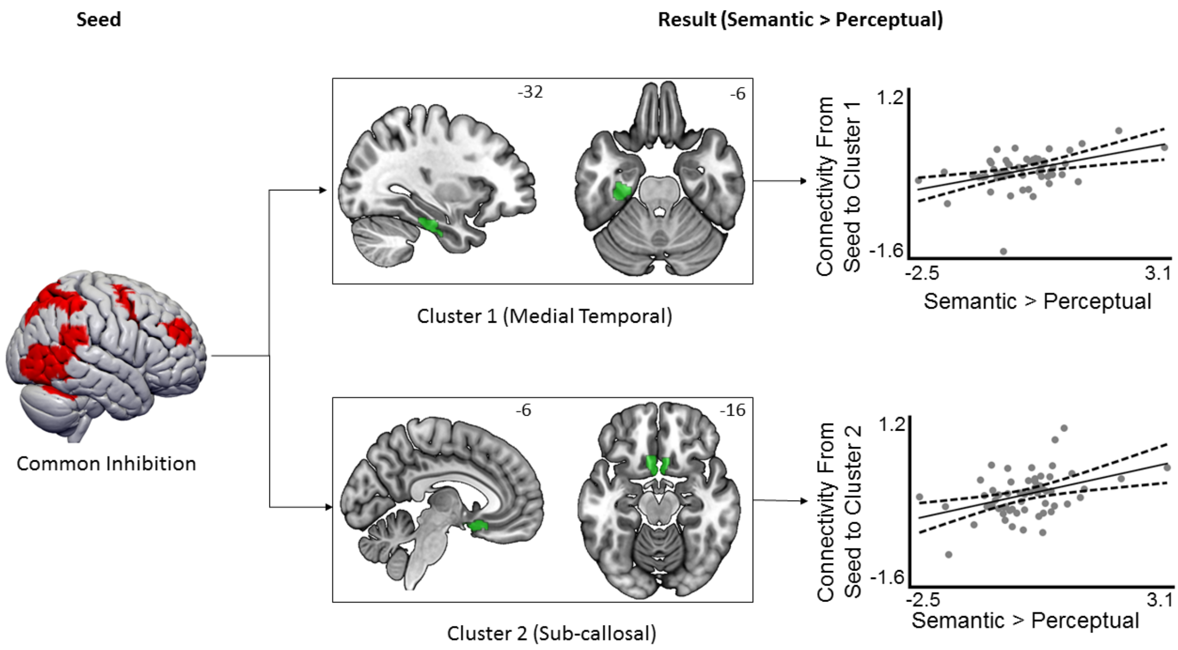


Figure 4.7. Results of a whole brain functional connectivity analysis indicating regions of heightened connectivity associated with differential performance on semantic and perceptual inhibition tasks. This identified two clusters, in medial temporal and sub-callosal cortex, which showed stronger functional connectivity for people who were better at semantic than perceptual inhibition. All maps were thresholded at $z > 3.1$ ($p<0.05$).

A second seed region in right lateral occipital cortex was defined by the interaction between modality and inhibition demands in Experiment 1. A whole-brain behavioural regression analysis for this seed revealed no clusters. However, the same analysis within a small volume defined by the multiple-demand network revealed stronger intrinsic connectivity to a cluster in thalamus / caudate for participants who were more efficient at inhibiting responses to pictures compared with both words and the matched perceptual condition. The clusters for these two effects showed a high degree of overlap (Figure 4.8).

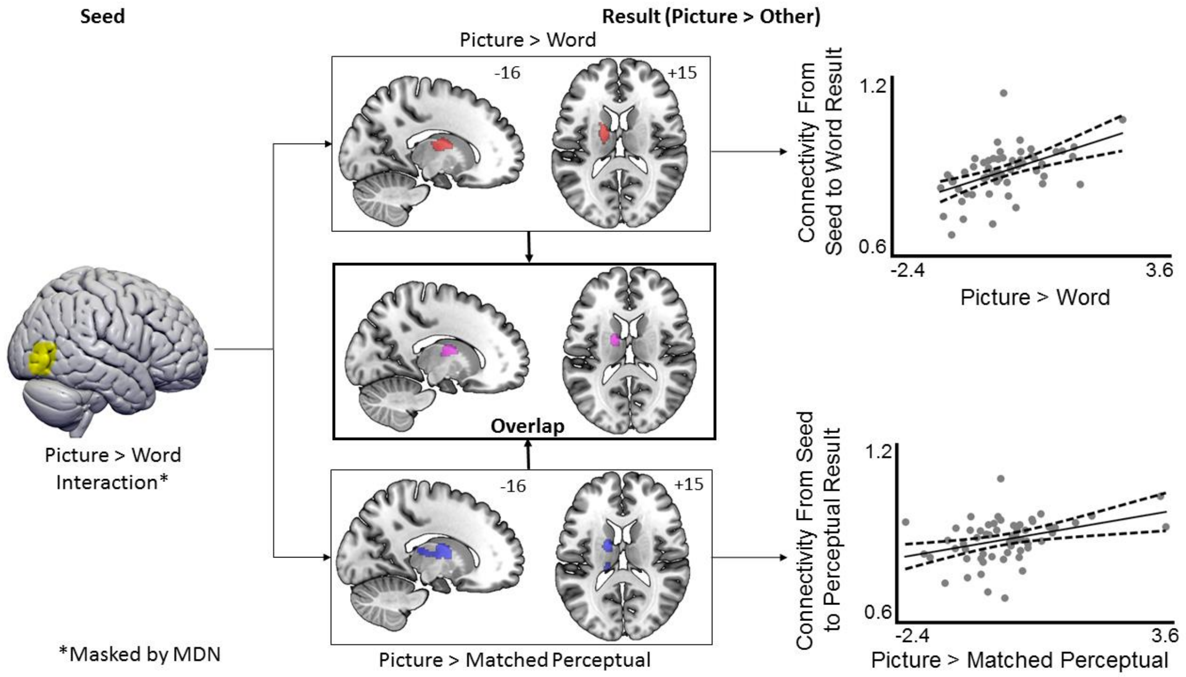


Figure 4.8. Functional connectivity analysis indicating regions of heightened connectivity associated with more efficient inhibition for pictures vs. words and for pictures vs. matched perceptual stimuli. These two clusters were highly overlapping. All maps were thresholded at z > 3.1 (p<0.05). MDN = Multiple-demand network.

In a final step, we performed resting-state functional connectivity analysis in a separate sample of 145 healthy undergraduate participants available at the University of York and decoded the resulting maps using Neurosynth (Yarkoni et al., 2011). We first examined the intrinsic connectivity of the inhibition overlap from Experiment 1. Decoding this connectivity map yielded terms associated with cognitive control (Figure 4.9, Step 1). Next we characterised the intrinsic connectivity of the behavioural regression result obtained from this seed in Experiment 2; i.e., regions that showed greater connectivity in participants with better semantic than perceptual inhibition (Figure 4.9, Step 2). Decoding this connectivity map yielded terms associated with memory. This connectivity pattern also substantially overlapped with the meta-analytic map for the term “semantic” from Neurosynth (Figure 4.9, Step 3). These results suggest that good semantically-guided inhibition is associated with greater coupling between domain-general inhibition regions and sites implicated in memory and meaning.

The lateral occipital cortex interaction cluster from Experiment 1 showed a pattern of connectivity associated with visual processing (Figure 4.10, Step 1). The pattern of intrinsic connectivity from the behavioural regression cluster in Experiment 2, which was associated with relatively good picture-based inhibition, showed substantial overlap with the multiple-demand network (Figure 4.10, Steps 2 and 3). Neurosynth's decoding tool revealed terms associated with motivation (Figure 4.10, Step 2). Therefore, good picture-based inhibition was associated with greater coupling between visual cortex and regions implicated in the control of behaviour.

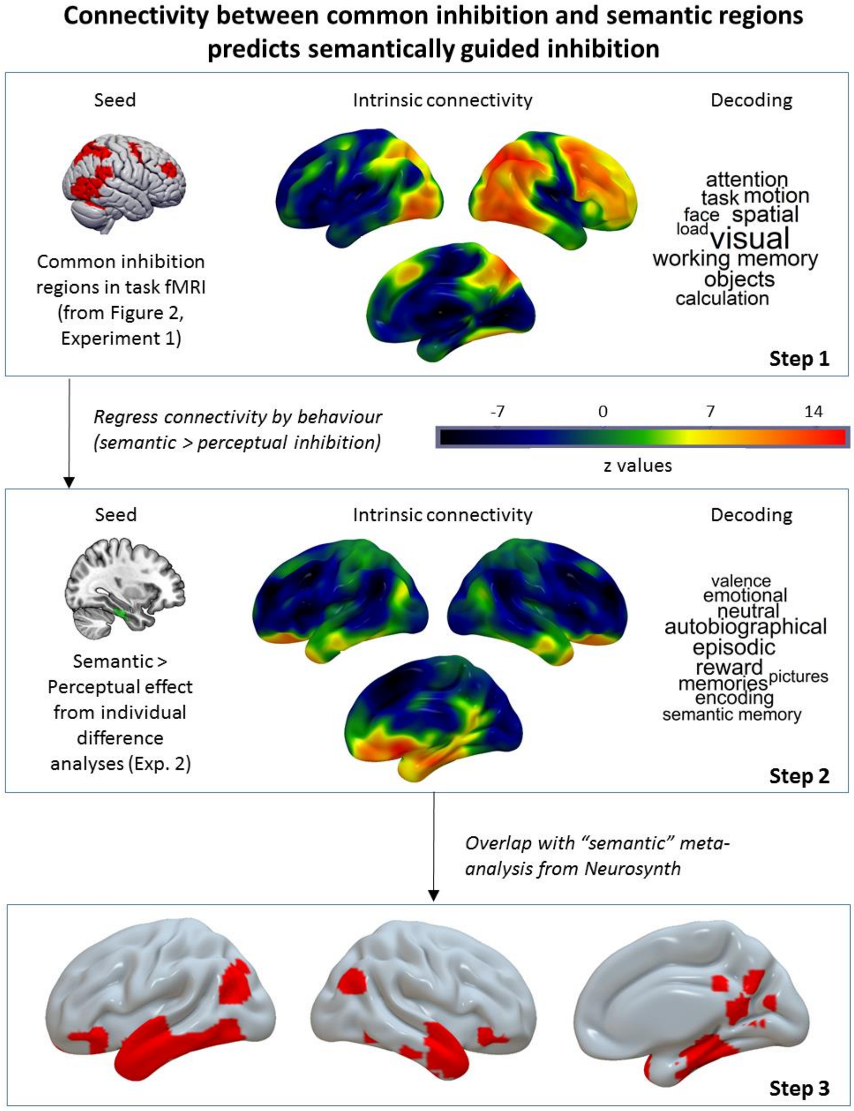


Figure 4.9. Summary of the pattern of connectivity linked to good semantic inhibition. The top row (Step 1) shows the unthresholded z-statistic intrinsic connectivity map for the common inhibition regions identified using task-based fMRI in Experiment 1, which were used as a seed in Experiment 2. Decoding of this spatial map using Neurosynth revealed terms linked to visual attention. The middle row (Step 2) shows the unthresholded z-statistic intrinsic connectivity map for significant clusters obtained from resting-state behavioural regressions in Experiment 2. Decoding of this spatial map using Neurosynth revealed terms linked to memory. The bottom row (Step 3) shows an overlap of the resting-state group maps

from Step 2 with a meta-analytic map for the term ‘Semantic’ from Neurosynth. Better semantic inhibition was linked to increased connectivity between domain-general inhibition regions and memory regions in medial temporal/ventral prefrontal regions. For further details about Neurosynth decoding and meta-analysis, see Methods and Yarkoni et al. (2011).

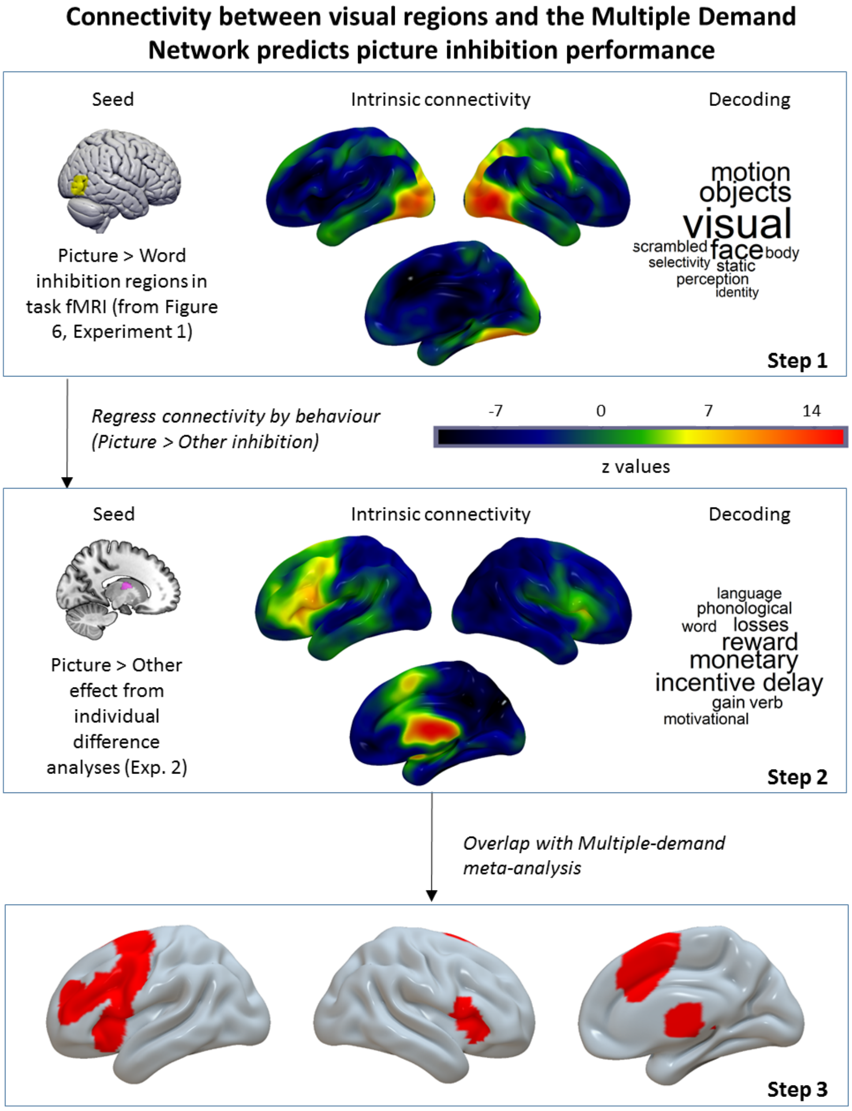


Figure 4.10. Summary of the pattern of connectivity linked to good picture-based inhibition. The top row (Step 1) shows the unthresholded z-statistic intrinsic connectivity map for the task-based fMRI cluster in lateral occipital cortex revealed by the interaction of modality and inhibition from Experiment 1, used as seed in Experiment 2. Decoding of this spatial map using Neurosynth revealed terms linked to visual processing. The middle row (Step 2) shows the unthresholded z-statistic intrinsic connectivity map for significant clusters obtained from resting-state behavioural regressions in Experiment 2. Decoding of this spatial map using Neurosynth revealed terms linked to motivation. The bottom row (Step 3) shows an overlap of the resting-state group maps from Step 2 with a meta-analytic map for the multiple-demand network from Fedorenko et al. (2013). Better picture-based inhibition was linked to increased connectivity between lateral occipital cortex and regions in thalamus / caudate. For

further details about Neurosynth decoding and meta-analysis, see Methods and Yarkoni et al. (2011).

4.4. Discussion

Inhibition activates regions implicated in cognitive control across domains (Criaud and Boulinguez, 2013; Duncan, 2010; O'Connell et al., 2007; Simmonds et al., 2008). However, inhibitory control can be guided by different types of inputs and representations. In two experiments, we used task and resting-state fMRI to examine whether the inhibitory control of behaviour recruits different neural networks depending on (i) the nature of the task (e.g., whether semantic or perceptual features determine the response) and (ii) the modality of the stimulus (e.g., whether items are presented as written words or pictures). We considered three alternative hypotheses. (i) There may be little or no difference in the No-Go > Go response across conditions: all tasks might activate right-lateralised regions in the multiple-demand network, irrespective of stimulus meaning and modality, reflecting shared cognitive control processes. (ii) There could be a shift towards left-lateralised regions implicated in semantic control when item meaning determines when a response must be withheld. By this view, although response inhibition paradigms commonly activate a right-lateralised executive network, this lateralisation might be reduced or reversed in the semantic conditions. (iii) Given Go/No-Go tasks are thought to involve attentional processes and working memory, we might expect modulation of activation in regions associated with input processing or the representation of features relevant for determining the appropriate response: for example, visual regions implicated in object recognition might show a stronger response when the features of visually-presented objects determine when to respond.

In our task-based study, we found support for the first and last of these hypotheses. First, we found that inhibition based on either semantic or perceptual features engaged a common right-lateralised network that overlapped with aspects of the multiple-demand system (Duncan, 2010). Our successful manipulation of neural activity in regions of cortex with a well-established role in accessing meaning (ventral visual stream) through the contrast of semantic and perceptual trials indicates that this common pattern cannot be attributed to a failure of the task manipulation. Instead, our data are consistent with the view that the nature of the stimulus that guides response inhibition does not markedly change activation within the multiple-demand network (Camilleri et al., 2018; Crittenden et al., 2016; Duncan, 2010, 2001; Fedorenko et al., 2013). As well as response inhibition per se, processes such as goal maintenance and attentional regulation (to promote unusual or unexpected inputs) are thought to increase on No-Go trials; the multiple-demand network is likely to underpin these various aspects of cognitive control whatever the task or stimulus (Hampshire et al., 2010; Sharp et al., 2010). A similar network is activated when a specific response, as opposed to response inhibition, is required on oddball trials – the critical factor therefore appears to be detecting a change in the relevant domain and rapidly switching from a prepotent response to an alternative behaviour (Bledowski et al., 2004; Hampshire et al., 2010). In our study, participants had to dissociate no-go targets based on either perceptual templates (How slanted was the box?) or semantic templates (Does the input represent an animal?), indicating that this process of regulation can utilise different forms of information. In general, inhibition based on meaning was guided by the same right-lateralised network that has been consistently identified in previous literature in situations with minimal semantic content (Criaud and Boulinguez, 2013; Simmonds et al., 2008). We found little evidence for engagement of the left-lateralised semantic control network (Noonan et al., 2013), even when semantic information determined when a prepotent response should be withheld.

Our results are broadly consistent with the model of Aron et al. (2004; 2014), who proposed an inhibition circuit reliant on right lateral prefrontal cortex (particularly pars opercularis within inferior frontal gyrus) and anterior insula, alongside subcortical projections to the basal ganglia. The effect of inhibition across all tasks was strongly *right-lateralised*, particularly in inferior frontal cortex, in line with this standpoint. Right inferior frontal cortex showed a strong effect of inhibition irrespective of task. In contrast, left inferior frontal cortex showed a preference for verbal and semantic tasks over perceptual tasks. Moreover, the peak response for common inhibition in our study fell within right dorsolateral prefrontal cortex (associated in this framework with representing task rules and conditional stopping), as opposed to right inferior frontal gyrus (associated with stopping per se). This pattern fits well with our data, given our paradigm required participants to use different rules to determine when to withhold a response on each block. However, right lateral prefrontal cortex was not unique in showing this response profile: left IPS also showed no differences between tasks and a strong response to inhibition, while right IPS showed a stronger response in non-meaningful tasks.

We also found important effects of modality on brain activation. Consistent with previous studies, there was a main effect of modality in Experiment 1: left IFG showed a stronger response to words than to perceptual targets (cf. Poldrack et al., 1999; Price, 2012), and regions of fusiform cortex responded more when stimuli were pictures than perceptual stimuli (cf. Carlson et al., 2013; Visser et al., 2012). Most importantly, a ventral cluster in lateral occipital/fusiform cortex showed an interaction between inhibitory demands and modality: this site responded more strongly when response inhibition was guided by images rather than words that described the same information. The interaction cluster in lateral occipital/fusiform cortex overlapped with the main effect of modality, and did not fall within common inhibition regions activated across tasks in our study (Figure 4.6). This observation is also consistent with the strong intrinsic connectivity of this cluster to visual cortex (Figure 4.9). Consequently, the interaction effect reflected visually responsive cortex showing an elevated response during picture inhibition, as opposed to domain-general control cortex showing a stronger inhibition effect for one modality than another. Lateral occipital cortex might participate in cognitive control because visual codes are often critical in controlling behaviour. This is not without precedent in the literature: (i) Lateral occipital cortex shows functional connectivity to regions in the multiple-demand network (Crittenden and Duncan, 2014; Stiers et al., 2010), (ii) it is implicated in visual working memory (Ferber et al., 2003) and (iii) it does not respond to stimuli beyond conscious awareness, consistent with a role in attention (Carlson et al., 2007).

Individuals who were better at regulating behaviour from picture inputs showed greater intrinsic connectivity between this lateral occipital region and sub-cortical regions within thalamus / caudate nucleus, which showed a pattern of intrinsic connectivity associated with the multiple-demand network. The caudate nucleus within the dorsal striatum is implicated in the ‘indirect’ inhibitory pathway: when a sensory cue indicates the need to suppress a prepotent response, projections from cortex to dorsal striatum are thought to control behaviour via the thalamus (e.g., Hikosaka and Isoda, 2010). Individual differences in the strength of connections between cortex and caudate have been previously linked to behavioural differences in inhibition tasks (Jahfari et al., 2011). Our findings are consistent with these theories and findings although our cluster did not fall solely in the caudate.

Our study also provides important constraints on our more general understanding of how we exploit meaning from the environment to regulate behaviour. Although meaningful words and pictures recruited left inferior frontal gyrus more than a perceptual task, we found little evidence that when the No-Go target was defined by semantic features, the regulation of behaviour depended on the left lateralized semantic control network (see Supplementary Analysis 4.1). This suggests an important difference between semantic control and the regulation of simple behaviour by meaning. Activation of the semantic control network occurs when conceptual retrieval must be shaped to suit task demands – i.e., when unusual aspects of knowledge must be brought to the fore (Davey et al., 2016; Jefferies, 2013). Our Go/No-Go task, however, did not involve control over semantic retrieval itself – rather, semantic categorisation was used to control a simple motor response (i.e., press a button or withhold press). Based on our data, the semantic control network is not required for *all* situations in which semantic representations guide behaviour in a controlled manner. However, interaction between multiple-demand cortex activated by inhibitory demands across tasks and regions linked to memory might be critical when semantic information is used to determine when to act. In Experiment 2, we found that individuals who were better at regulating behaviour from meaning showed stronger connectivity between common inhibition regions, activated across all No-Go conditions, and clusters in medial temporal lobe and sub-genual anterior cingulate cortex. These limbic regions are linked to conceptual, episodic and emotional memory (Dolcos et al., 2004; Euston et al., 2012; Simons and Spiers, 2003; Wang et al., 2010). We speculate that connectivity between domain-general response inhibition regions and areas implicated in memory representation is critical to the regulation of behaviour that is afforded by meaning.

4.4.1. Conclusion

Behavioural inhibition, regardless of whether it is guided by semantic or perceptual content, depends on right-lateralised regions of the multiple-demand network. However, our data show that these domain-general control regions work in concert with specialised regions of cortex, depending on the nature of the task or the input modality. When behavioural inhibition is guided by the semantic category of pictures as opposed to words, there is increased activation within a region of visual cortex associated with processing complex features (lateral occipital cortex); moreover, people who are good at this task show stronger connectivity between this region thought to represent task-relevant features and aspects of the thalamus / caudate implicated in behavioural control. Interestingly, the classic left-lateralised semantic control network (Davey et al., 2016; Noonan et al., 2013) did not appear to be critical to behavioural inhibition, even when responses were guided by meaning. Instead, we found that strong semantically-guided inhibition was associated with greater intrinsic connectivity between limbic regions implicated in memory and multiple-demand regions.

Chapter 5. Discussion

5.1. Introduction

The aim of this PhD was to investigate hemispheric differences in the components of semantic cognition, and describe their functional consequences using multiple methods – including analyses of intrinsic connectivity and behaviour, large-scale network interactions, and employing automated meta-analytic techniques and cognitive decoding. Although much research has been carried out on the topic of language lateralisation, significantly less has been devoted to understanding hemispheric differences in semantics (and no previous studies, to our knowledge, have specifically focussed on the interacting components of semantic cognition anticipated in the Controlled Semantic Cognition account).

The last decade of neuroscientific research has shed light upon several organisational principles of lateralisation and differences in hemispheric functioning. Functional homotopy –the synchrony of spontaneous activity in resting-state functional connectivity between homotopic regions in each hemisphere— has been documented as a fundamental characteristic of the functional architecture of the human brain (Jo et al., 2012; Mancuso et al., 2019; Raemaekers et al., 2018; Salvador et al., 2005). Furthermore, it is now understood that lateralisation (i.e. less functional homotopy) manifests more in primary cortices and less in higher-order heteromodal cortices (Stark et al., 2008). Evidence for two distinct modes of functional specialisation in the human brain across hemispheres has been described, with LH showing a preference for segregation and RH for integration (Gotts et al., 2013). These modes of hemispheric specialisation might relate to coupling with different large-scale networks, with the FPN showing the most striking interhemispheric differences, coupling more to DMN in LH and spatial attention networks in RH (Wang et al., 2014).

In spite of this mounting understanding, our knowledge of the lateralisation of components of semantic cognition remains poor. Is the connectivity of this network homogeneous across its proposed components, or does it vary as a function of the component examined and hemisphere? Since some domain-general executive functions, particularly inhibition, are thought to be right-lateralised, and yet semantic cognition is strongly left-lateralised, it becomes important to understand whether semantic control is functionally dissociable from multiple demand effects, with a distinctive pattern of lateralisation. Moreover, the graded hub account of semantic representation is compatible with graded differences in function between left and right ATL but little is known about how individual differences in intrinsic connectivity affect performance on different kinds of semantic tasks – for example, tasks employing places and people, or words and pictures. In general, we might expect individual differences in connectivity between the hemispheres to correlate with the efficiency of semantic retrieval.

This chapter discusses the findings of the PhD according to four themes. First, it discusses differences in patterns of intrinsic connectivity for left-lateralised semantic sites (ATL, AG, IFG and pMTG) and their right-hemisphere homotopes, and considers the way these regions couple with large-scale cortical networks in the left and right hemispheres. We found that left-hemisphere semantic sites show relatively strong connectivity with both default mode regions implicated in automatic semantic cognition and multiple demand sites. In contrast, in the right hemisphere, these sites show greater connectivity with visuospatial and attentional networks.

Second, the thesis findings show these hemispheric differences relate to the distinction between the components of semantic cognition anticipated by the Controlled Semantic Cognition account – namely bilateral conceptual representation in ATL, and a highly-left-lateralised specialised semantic control system. The semantic control network, through the integration of DMN and MDN, is thought to shape the activation of semantic representations in a context-appropriate manner (Davey et al., 2016; Lambon Ralph et al., 2017; Noonan et al., 2013). Critically, this network is functionally dissociated from both the DMN and MDN, although partially overlapping, and is specific to semantic control. We also found subtle differences between left and right ATL in the type of semantic tasks their intrinsic connectivity was linked to, in spite of the evidence of symmetrical and bilateral semantic representations (Rice et al., 2015b).

Third, the thesis provides evidence that semantic control is functionally dissociable from domain-general cognitive control, supporting the view that semantic control specifically shapes the activation of semantic information to fit the current context (including goals). The thesis findings are consistent with the view that key sites within the semantic control network - LIFG and pMTG - respond to controlled retrieval demands, and not to domain-general difficulty. The thesis therefore suggests that semantic control does not only reflect the application of domain-general control processes to semantic content.

The final theme discusses individual differences in the strength of intrinsic connectivity across participants, describing how connectivity relates to the efficiency of semantic processing. Participants with stronger left-to-right connectivity for semantic control seeds were found to be less efficient in tasks tapping semantic control than participants with more lateralised connectivity. Likewise, participants who show more integration between heteromodal hub sites (e.g., in ATL~~)~~ and modality-specific spokes might show better processing of stimuli supported by those particular hub-and-spoke interactions: within the thesis work, some effects of modality and category might be explained in this way. As a more general point examined in little previous research, all three chapters show that individual differences in intrinsic connectivity can be used to predict semantic performance (with one chapter comparing offline and online connectivity measures – i.e. when semantic tasks are performed during or separately from scanning).

The thesis work informs several theoretical debates. (i) These findings are relevant for understanding the network interactions that support semantic cognition. There is debate about whether the semantic system shows a component-based architecture, whose neural components sustain separable cognitive components, or whether its organisation can be explained by some other overarching principle. There is also disagreement about the number, location and function of semantic components. Finding different lateralisation patterns of engagement with cortical networks, or similar intrinsic connectivity across components can shed light on the architecture of this system. (ii) The results help to inform theories of lateralisation, within and beyond semantic cognition. Understanding how lateralisation varies across semantic nodes provides additional constraints on accounts of why lateralisation emerges, the kinds of tasks that are left-lateralised, and processes the left-lateralised networks may support. (iii) The work also has significance for the field of cognitive control. Recent research within the CSC framework has yielded evidence that the semantic control network overlaps with, but is functionally distinct from the MDN, and that this network integrates MDN with the usually anti-correlated DMN (Davey et al., 2016; X. Wang et al., 2018). The PhD provides new evidence consistent with this idea. (iv) Finally, the thesis work contributes to our understanding of how we compute concepts across hub and spoke regions. Semantic representations may be distributed across the cortex in a mosaic-like fashion (Huth et al., 2016), in areas evolutionarily shaped to sustain these representations (Caramazza and Mahon, 2003; Caramazza and Shelton, 1998; Mahon and Caramazza, 2009) or in local hubs that dynamically mediate the flexible interplay of multimodal and sensorimotor representations

(Reilly et al., 2016). The graded hub hypothesis extends the hub-and-spokes model stating that graded differences in connectivity to spoke regions across left and right ATL, and within the ATLs, underlie the organisation of semantic representations (Lambon Ralph et al., 2017; Rice et al., 2015a). Below, we discuss the implications of the findings relating to the four research themes outlined above, to describe how the results concur across chapters, and how they fit with published literature.

5.2. Patterns of intrinsic connectivity vary across hemispheres

5.2.1. Key findings across chapters

Across the studies in this thesis, the key nodes of the semantic system in IFG, pMTG, AG and ATL, showed different patterns of connectivity compared to their homotopic sites in the RH. In Chapter 2, seeding left and right hemisphere ROIs generated largely symmetrical and overlapping maps (Figure 2.3). Since the connectivity of LH seeds and their RH homotopes was so similar, a more nuanced analysis was necessary to reveal the differences in topography of intrinsic connectivity across sites that comprise the semantic cognition network. We projected the RH connectivity maps to LH (i.e. flipping along the x axis so that our LH maps are in neurological convention, while our RH homotope maps are in radiological convention; for details of the method, see Baciu et al., 2005, *'flip method'*) and computed a contrast subtracting the RH group mean connectivity maps from their LH counterparts for each seed. This revealed areas where LH seeds are more connected than expected from their RH counterparts and vice versa. We then compared these lateralised connectivity patterns with large-scale cortical networks (Yeo et al., 2011) to characterise the interaction of each seed with these networks across the hemispheres. This analysis yielded complex and interesting results (Figure 2.5) summarised in the following points:

- Left ATL showed selective connectivity to just a few networks, preferring only lateral DMN and limbic regions, and exhibiting the greatest separation from perceptual networks across all seeds examined. On the other hand, right ATL showed a more diffuse pattern, exhibiting substantially more overlap with control, DAN and salience networks (and to a lesser extent, visual regions and core DMN). The pattern observed is in accordance with the ATL acting as a heteromodal hub with graded differences across the hemispheres (Bajada et al., 2019; Rice et al., 2015a).

- Left AG showed a similar pattern, with a clear preference for lateral DMN and VAN regions (with minimal overlap with visual and somatomotor networks), while right AG predominantly engaged visual regions, followed by control and core DMN. This pattern of coupling for left AG is expected following the predictions of attentional accounts of parietal functions (Cabeza et al., 2012, 2008).
- Left IFG showed the greatest engagement with control/FPN (across all seeds), followed by VAN, visual and somatomotor regions; it also showed the least overlap with DMN regions across all four seeds. On the other hand, right IFG showed stronger connectivity with visual regions, followed by core DMN.
- Lastly, left pMTG showed a similar pattern to IFG with one major difference: where IFG overlapped primarily with control networks, pMTG did so with lateral DMN, followed by visual and somatomotor networks. To a lesser extent, left pMTG also overlapped with different control networks than IFG: whilst IFG overlapped more with posterior FPN, pMTG did so with anterior FPN. Anterior FPN regions show higher functional connectivity with the DMN, while posterior regions are more coupled with the DAN/MDN (Dixon et al., 2018). Together, the IFG and pMTG differential results highlight the integration of MDN (through IFG) and DMN (through pMTG) in LH in accordance with the idea of a left-lateralised semantic control network that shapes the activation of semantic representations to fit the current goals through the integration of these anticorrelated networks (Davey et al., 2016; Noonan et al., 2013). Right pMTG preferred the DAN, visual and a different control sub-network. This sub-network is comprised only of two regions: the posterior cingulate and precuneus; it does not rigorously constitute part of the FPN, as it lacks a frontal component, and has been excluded of FPN parcellation studies like Dixon et al. (2018).

Semantic cognition regions showed clear hemispheric differences in intrinsic connectivity. These patterns of lateralisation also differed across seeds, consistent with a component architecture split in control and representation components. This organisation will be discussed in more depth in the following research theme. We applied automated meta-analytic techniques and cognitive decoding to interpret the connectivity difference maps and link them to a broader, more robust and reproducible literature according to best practices (Gorgolewski et al., 2015; Poldrack et al., 2016; Yarkoni et al., 2011). This revealed that topographical differences in the intrinsic connectivity of left-lateralised sites correlate with terms that classically show left-lateralisation, including language and terms related to hand dominance. Conversely, right-lateralised homotopes of the left semantic sites were associated with classically right-lateralised functions in the neuropsychological literature, like "visuospatial", "social" and "face" (in spite of having flipped the x axis of the map, reducing the chance that this is simply due to a larger amount of activation in the right hemisphere) (Bourne, 2008; Duecker et al., 2013; Hellige, 1996; Önal-Hartmann et al., 2012; Thoma et al., 2014).

These findings suggest that regions of the semantic system could be engaging parts of cortex that are highly left lateralised, in line with the fact that the most heteromodal and associative cortices, like those examined as seeds in this chapter, usually show the smallest degree of functional homotopy (Mancuso et al., 2019; Stark et al., 2008). We clearly did not select RH regions to be nodes of right-lateralised visuospatial, social or face-processing networks, but they are homotopes of LH regions that meta-analytic evidence shows are key heteromodal nodes of the semantic cognition network (Humphreys and Lambon Ralph, 2015; Noonan et al., 2013; Rice et al., 2018c). In spite of this, all four RH homotopes' cognitive decoding converged in the same right-lateralised terms (regardless of these maps being flipped along the x-axis, which would minimise the chances of observing these terms' correlations just due to activity that falls mostly within RH). This might indicate that all four semantic ROIs connect differentially to cortex that lends itself particularly well to host lateralised functions.

The results of the cognitive decoding performed on our difference maps also concur with the morphospace described in a recent study that focussed on the architecture of functional lateralisation in the human brain (Karolis et al., 2019). The authors discovered that the different cognitive functions show patterns of lateralisation in the brain that vary in similarity across four axes, organised in a pyramidal morphospace with archetype maps at their vertices reflecting each domain. Two of these axes corresponded to terms captured by the cognitive decoding of the connectivity difference maps: symbolic communication (LH: "semantic", "words", "language", RH: "calculation") and perception/action (LH: "hand", "sensorimotor", RH: "visuospatial", "eye"). The decoding results only contained a couple of terms from the other axes ("face", "navigation"). It is possible that our difference maps captured two different modes of lateralisation: one associated with the predominantly left-lateralised language and semantics networks (expressed in the symbolic communication archetype) and the other related to the predominantly right-lateralised visuospatial and attentional network (part of the perception/action archetype). Our findings constitute further evidence of the structure of the morphospace described by Karolis et al. (2019), showing a left-right divide in lateralisation that seems to reflect a continuum between opposite symbolic communication and perception/action archetypes of lateralisation, associated with our LH seeds and RH homotopes respectively. The results of our difference analysis also seem to confirm their finding of the "attention" maps showing a negative loading in their language component. In our study, the cognitive decoding revealed "attention" terms related to our RH flipped maps, that is, the regions that were less connected to LH seeds than would be expected from RH connectivity showed a positive meta-analytic association with the term "attention", revealing that the regions *less* preferred by semantics are *more* associated with attention.

The opposing lateralisation of symbolic communication and visuospatial function has been documented in previous research, and although it has not been fully explained, it has been linked to several putative mechanisms. Some explanations invoke causal complementarity, assuming that the lateralisation of one function will cause the opposite lateralisation of other functions (Bryden, 1990). These include, for example, the "snowball" mechanism, where a small number of innate asymmetric 'seed' sub-systems facilitate other sub-systems similar in function to 'settle' in the same hemisphere (since within-hemisphere interactions are more efficient than cross-hemisphere, cfr. Hellige, 1993), or homotopic callosal inhibition (Cook, 1984). Other models assume mechanisms with statistical complementarity, where the lateralisation of one function is relatively independent from other functions, with each of them exhibiting an independent statistical probability of lateralisation to either side (Bryden, 1990). Regardless of the underlying mechanism, lateralisation of these two functions manifests at the population level through different phenotypes besides the 'normal', like functional crowding, when usually contralateral functions 'crowd' in the same hemisphere, or functional reversal, when functions lateralise to the opposite hemisphere from where they are usually instantiated (Vingerhoets, 2019a). The results of our difference analysis are in line with the observation of the contra-lateralisation of these functions, at least at the population level (due to the study design, inferences could not be drawn at the individual phenotype level).

Chapter 3 examined ATL in particular, contrasting a functionally-defined left hemisphere peak (through a meta-analysis of distortion-corrected studies in Rice et al., 2018c) and its right hemisphere homotope, as well as comparing the same left-lateralised peak with a right hemisphere peak functionally defined in the same meta-analysis. The results replicated the patterns observed in Chapter 2 described above, and reflected the complex architecture of ATL demonstrating that a minimal displacement between homotopic and functional peaks in RH engages different large-scale cortical networks. Chapter 4 also yielded results that show that patterns of intrinsic connectivity vary across hemispheres with functional consequences. These findings are discussed in greater detail below.

In sum, the results across studies confirm the first hypothesis. There were differences in intrinsic connectivity between left and right ATL, AG, IFG and pMTG. These differences revealed a distinct interplay between large-scale cortical networks and these regions in each hemisphere. They displayed a trend of systematic variation in the networks engaged across these regions: AG and ATL both showed a clear preference in LH for DMN and a separation from control networks (and in ATL, also from perceptual and motor networks), while left IFG and pMTG taken together showed a preference for MDN (the former) and DMN (the latter). Such a pattern is compatible with our hypothesis of left hemisphere semantic sites integrating control networks with regions implicated in automatic semantic cognition. The ATL showed the most bilateral and symmetrical pattern of intrinsic connectivity, and a rich functional architecture, with multiple networks engaging cortical regions separated by only a few millimetres, concordant with a representational hub that needs to access diverse regions across the brain to link together multimodal representations.

5.2.2. Novelty of these findings and their relationship to the broader literature

Few if any studies have previously investigated patterns of lateralisation for the distinct components of semantic cognition. These novel results, taken together, constitute further evidence for component accounts of semantic cognition, and fit especially well with the CSC framework (Lambon Ralph et al., 2017), since we found systematic variation of the four regions studied across the two components proposed by this model.

Our results are also in line with previous research that suggests that lateralisation in whole-brain intrinsic connectivity is common in language regions (Jo et al., 2012; Raemaekers et al., 2018); however, we add to this work by examining *heteromodal* semantic sites – associated with both the representation of concepts which can be accessed via different modalities (Rice et al., 2015b, 2015a), and control processes which extend across verbal and non-verbal semantic tasks (Noonan et al., 2013). We found stronger lateralisation in two of our four semantic seeds, and overlap across all four of them to a greater extent than their RH homotopes. We also refine the results of this previous body of research by specifically being able to pinpoint two of our four semantic seeds as the strongest contributors to this left-lateralisation, namely pMTG and IFG, which overlap significantly more in LH than RH, suggesting that left-lateralisation is not equal across all components of the language network. The similarity between the connectivity of these seeds, and their common overlap with DMN and MDN regions suggest their organisation in a left-lateralised control network specifically devoted to semantics, as has been suggested by previous research (Davey et al., 2016; Noonan et al., 2013).

We also replicated previous research that shows a gradient of lateralisation across the human cerebral cortex, with functional homotopy (the tendency that brain regions in one hemisphere have to exhibit strong functional connectivity to their equivalent regions in the contralateral hemisphere) being the norm especially in primary cortices, whilst associative and heteromodal cortices usually show functional lateralisation (Jo et al., 2012; Mancuso et al., 2019; Stark et al., 2008; Wang et al., 2014). The intrinsic connectivity of three of our four seeds, selected from meta-analyses that probed heteromodal semantics, showed strong associations predominantly with classically lateralised terms, hinting at the preference of these associative cortices for differential intrinsic connectivity with other lateralised associative cortices.

Regarding a possible mechanism for the left-lateralisation of the semantic control network, we obtained a pattern of results that is compatible with Wang et al.'s (2014) observation that the FPN fractionates into LH and RH subnetworks, interacting with the DMN on the left and attentional networks on the right. In Chapter 2, the conjunction analyses showed that pMTG and IFG – key regions involved in semantic control – had a pattern of common connectivity that overlapped largely with both control and DMN on the left, but with control and attentional networks on the right, consistent with a differentiated role for the control networks in left and right hemisphere. A speculative, finer-grained mechanism for the integration of MDN and DMN in the semantic control network can be derived from the patterns of overlap of our difference maps with Yeo networks in the same chapter (Figure 2.5): while IFG shows stronger connectivity with control/MDN regions in LH, pMTG prefers DMN. The single seed connectivity and correlations in the same study confirm that both regions strongly overlap, and in doing so, IFG's preference for control networks and pMTG's coupling with the DMN could integrate to flexibly shape semantic representations, in alignment with the conclusions from the research of Davey et al. (2016).

The discussion so far shows evidence for semantic control regions organised in a left-lateralised network, but leaves open the question of why. However, previous literature has speculated that processing in LH is optimised for sequential, time-constrained computations, while RH is better suited to process a holistic, bilateral representation of space (Gotts et al., 2013). The kinds of representations and mental processes required for these aspects of cognition could be distinct, giving rise to functional advantages of lateralisation. Retrieving context or goal-appropriate aspects of semantic representations in a controlled fashion is likely to involve sequential and time-limited computations since the environment around us and our goals both change over time – i.e. what we retrieve about a concept at one time should be distinct from what we retrieve at a different time. Gotts et al. (2013) argued that LH shows a high degree of segregation (or separation from RH regions – in line with our findings for semantic control sites) as sequential computations can be faster and more efficient without hemispheric transfer. Supporting evidence for this mode of segregated operation of the left hemisphere has been revealed by a recent study, where the architecture of lateralisation and its relationship to callosal connectivity were analysed (Karolis et al., 2019). This study found that, in Human Connectome Project data, LH regions displayed a slightly lower axonal water fraction in comparison with RH, suggesting weaker cross-hemisphere connections across the corpus callosum for LH than RH regions, which is concordant with a more segregated mode of operation for LH and integrated for RH.

If controlled retrieval involves a sequential manipulation of information, a bilateral system would slow down computations through interhemispheric transfer, with no clear advantage. From an optimisation perspective, it makes computational sense to lateralise this process to a hemisphere that preferentially segregates like LH. The RH, on the other hand, may be better equipped to deal with processes that need symmetry, like navigating and perceiving space. Heteromodal semantic representations in ATL, due to their diversity of features, necessitate involvement of both hemispheres: input from spatial, somatosensory or visual processes, which are bilateral in nature, may be better represented in the integrative RH. This suggests the need for the semantic system to be organised in two distinct components with separate patterns of lateralisation: (1) a bilateral semantic representation system that profits from the distinct specialisations of left and right hemisphere to maximise the range of concepts it can store (showing subtle hemispheric differences as a function of graded differences in connectivity), and (2) a semantic control system that integrates DMN and control networks to retrieve aspects of these representations that are appropriate to the current context or goals, left-lateralised in order to capitalise on the rapid computations afforded by LH thanks to the sequential nature of this process. Next, we will consider the evidence from this PhD that supports this component-process account of semantic cognition.

5.3. The two components of the semantic system – supporting control and representation – show different lateralisation patterns

5.3.1. Key findings across chapters

The evidence reviewed so far establishes there are hemispheric differences in the patterns of intrinsic connectivity across all four ROIs examined in this PhD project. The connectivity of these four seeds interacted differently with large-scale cortical networks across the hemispheres, revealing principles of brain organisation. There was also systematic variation across our seeds, in accordance with a component-process architecture of semantic cognition (Lambon Ralph et al., 2017), which suggests that the semantic network includes at least two highly interactive components, supporting heteromodal representation and control over semantic retrieval. The thesis work found that these putative components showed different lateralisation. There was evidence for (i) a left-lateralised semantic control network, supporting the controlled retrieval of semantic content, and not difficult perceptual tasks or situations in which behaviour has to be controlled on the basis of semantic information, even when control demands are high (such as semantically-guided response inhibition). (ii) In contrast, the heteromodal representational hub centred on vATL was bilateral, with largely symmetrical connectivity: graded differences in connectivity across hemispheres were found to relate to the efficiency with which participants processed stimuli that relied on different modalities for their representation. To the best of our knowledge, no other study has characterised the distinct lateralisation patterns of the components of semantic cognition.

5.3.1.1. IFG and pMTG form a left-lateralised network specific for semantic control

An analysis in Chapter 2 examined the conjunction of intrinsic connectivity of left IFG and pMTG, which a previous meta-analysis revealed as key LH regions for semantic control (Noonan et al., 2013), as well as that of their RH homotopes. The common connectivity of these sites overlapped equally with both DMN and control networks in the LH (Figure 2.4), while in RH it overlapped equally with control networks and DAN. This is in line with previous research that suggests a separation of FPN function in the left and right hemispheres, with control networks integrating with DMN in LH, and with attentional networks in RH (Wang et al., 2014). This also confirms that the flexible response properties of the FPN other studies have found (Parlatini et al., 2017, for example) are present in the intrinsic connectivity of IFG, pMTG and their interaction across the hemispheres.

In the same study, the similarity of the intrinsic connectivity patterns across pairs of seeds was measured in LH and, separately, in their RH homotopes. IFG and pMTG showed significantly greater similarity in LH than RH, consistent with their coupling in a left-lateralised control network, with no other pair of regions exhibiting this property in either hemisphere. Previous research supports the view that left IFG and pMTG are two nodes of a distributed network – for example, perturbing the recruitment of left IFG through the application of inhibitory TMS increases the effect of semantic control demands in left pMTG (Hallam et al., 2016), and damage to left IFG leads to increased recruitment of left pMTG suggesting functional compensation (Hallam et al., 2018). This thesis' current findings strengthen the evidence that these regions form a network, given their extensive overlap and high similarity in intrinsic connectivity.

The behavioural regression results in the same chapter showed that the strength of intrinsic connectivity from pMTG to either left or right perisylvan regions related to the efficiency with which participants performed an offline semantic task in which control demands were manipulated. Participants with stronger within-hemisphere connectivity in LH showed increased efficiency for strong association judgements (thought to reflect more automatic semantic processing), whilst those who showed strong interhemispheric connectivity from LH to RH showed poorer performance for weak associations, which require semantic control to be exerted to find the weak link between probe and target. This fits the idea that the left-lateralisation of this semantic control network is important for its functioning and will be discussed in more depth over the following research themes.

5.3.1.2. vATL is a bilateral, symmetrical, graded hub supporting semantic representations through interactions with lower-level spokes

In contrast to the lateralised connectivity of the semantic control regions, the thesis work found evidence of bilateral engagement for the putative semantic 'hubs'. In the conjunction analysis in Chapter 2, regions identified as representational hubs like ATL and AG (Humphreys and Lambon Ralph, 2015; Rice et al., 2015b) showed a more bilateral and symmetrical pattern of shared connectivity, with subtle hemispheric differences. These included coupling to different aspects of the DMN, with the left hubs preferring lateral DMN, whilst the right favoured core DMN, consistent with a potential role in semantic representations and automatic semantics, but hinting at hemispheric differences in the type of content represented. In Chapter 2, ATL showed the greatest interhemispheric similarity of all pairs of seeds (i.e. the intrinsic connectivity of left ATL was more similar to its right hemisphere homotope than for any other seed region).

This bilateral and symmetrical pattern was confirmed by both the intrinsic connectivity of left and right ATL separately examined, as well as their flipped and direct difference analyses in Chapters 2 and 3 respectively. The seed-based connectivity analysis in Chapter 2 revealed highly similar patterns of intrinsic connectivity for left and right ATL (see Figure 2.3, and the correlations between left and right ATL in the same chapter). In both, the direct LH vs. RH comparisons, and analyses examining differences between LH and RH-flipped into LH space, ATL showed the least amount of difference across all ROIs (see Figures 2.5, S2.3, and 3.3), confirming that the connectivity of this region is not only the most similar across hemispheres, but also the most symmetrical of all the semantic ROIs we explored.

In Chapter 3 we focused specifically on ATL, examining the difference between a functionally-defined LH peak and its RH sign-flipped homotope, as well as the comparison between the same left-lateralised peak and a functionally defined RH peak. Our results largely replicated what we observed in Chapter 2: the connectivity maps of left and right homotopic ATL showed minimal differences upon visual inspection. In this dataset, left ATL showed engagement with the central sulcus and paracingulate cortex that was not observed in right ATL, while the right showed anti-correlations with visual cortex and significant connectivity with subgenual regions and basal ganglia that was not observed in left ATL. However, a formal difference analysis revealed minimal differences, localised to ventral ATL as would be expected from a bilateral, symmetrical system (Rice et al., 2015a). A conjunction analysis confirmed predominantly shared connectivity of left and right ATL, showing remarkable similarity to both single seed maps (see Figure 3.3 for these maps).

A comparison of the connectivity of the functional peaks in the two hemispheres, as opposed to the homotopic seeds, yielded different results. The difference analysis revealed greater involvement of left than right ATL in left superior temporal and bilateral central sulci. Conversely, the right functional ATL peak showed greater connectivity than the left peak with left superior frontal, fronto-orbital and right ventral ATL regions. A direct comparison of the RH homotope's connectivity with the functional peak in right ATL showed that the homotope had greater connectivity with left TPJ, right prefrontal and bilateral ventral ATL regions, while the functional peak was more connected to bilateral posterior parietal / dorsal lateral occipital, fusiform and hippocampal cortex, as well as parieto-occipital sulcus (see Figure 3.4 for these maps; see also the supplementary analyses of chapter 2). The fact that a displacement of less than four millimetres from the homotopic to the functional peak was enough to yield significant differences in temporal, parietal and frontal connectivity to ATL is a demonstration of the complex organisation of this region. Previous studies have showed functional divisions in multimodal and modality-specific regions spanning language, semantics, auditory and visual areas, as well as multiple large-scale cortical networks depending on the exact ATL location queried and task performed (Bajada et al., 2019; Binney et al., 2012; Jackson et al., 2019, 2017, 2016; Murphy et al., 2018; Papinutto et al., 2016). The homotopic seed, being more posterior than the functional peak, may have more strongly engaged the ventral visual stream, as it showed stronger intrinsic connectivity with ventral temporal regions reaching occipital cortex. A stronger pattern of connectivity to visual regions from this homotopic seed is important for understanding the functional consequences of individual differences in connectivity, since ATL to occipital lobe connectivity was associated in this thesis with performance on visually-presented semantic tasks, in accordance with the graded hub hypothesis (Rice et al., 2015a). Besides contributing evidence to the complexity of ATL architecture, this fact points to the importance of a careful selection of homotopic regions for comparison in fMRI studies of interhemispheric differences, preferably through the use of specialised atlases or more sophisticated methods (Baciu et al., 2005; Joliot et al., 2015; Karolis et al., 2019; Mancuso et al., 2019).

The results did not show any evidence of individual differences in intrinsic connectivity from ATL associated with efficient performance on semantic tasks in Chapter 2.

However, the tasks in this study were not designed to assess specific-level concepts (e.g., particular people and places) across categories and they may not have been sensitive to differences in semantic processing within left and right ATL. Previous studies have shown that deficits in semantic processing caused by unilateral damage to ATL necessitate sensitive instruments to be detected (Lambon Ralph et al., 2012). Evidence of ATL being particularly implicated in specific, as opposed to general, concepts has been reported in SD (Hodges et al., 1995; Rogers and Patterson, 2007) and task-based neuroimaging studies (Rogers et al., 2006; Tranel, 2009); furthermore, previous studies have found differences in left vs. right ATL for representing names versus faces (Gainotti, 2007b; Snowden et al., 2012, 2004). We conducted the study reported in Chapter 3 to test hemispheric differences in the graded hub hypothesis using more sensitive tasks. To this end, we employed a paradigm that was specifically designed to compare category-selective and modality-selective responses within and across the ATLs, and has been successfully employed in a recent study (Rice et al., 2018c). Using this paradigm, the study found regions of ATL that display a transmodal response across all categories examined, with partial specialisation in adjacent regions (responding selectively for people, or abstract social words) in accordance with the graded hub hypothesis.

The results in Chapter 3 showed that individual differences in patterns of lateralisation assessed through intrinsic connectivity had an impact on the efficiency of semantic categorisation in this task outside the scanner. Participants that showed greater integration between left and right ATL (i.e. a strongly bilateral system) were more efficient in processing visual landmarks. In addition, participants that had stronger right relative to left ATL connectivity to ventral medial occipital regions showed increased efficiency in semantic processing in all tasks probed, but especially in retrieving the names of people; conversely, stronger left relative to right connectivity to a more dorsal region of medial occipital cortex was associated with worse performance in all tasks. Integration between left and right ATL might give rise to more efficient conceptual retrieval about landmarks from the visual system since left ATL has stronger connectivity to semantic retrieval sites (e.g. in left pMTG, IFG and AG – see Chapter 2), yet right ATL might receive stronger visuospatial inputs, especially about landmarks which are thought to be right-lateralised (H. Liu et al., 2009; Stevens et al., 2012). Moreover, the general semantic retrieval advantage exhibited by participants with stronger differential right ATL connectivity to visual cortex can be explained in terms of the graded hub hypothesis (Rice et al., 2015a). All the conditions of the task were visually presented (written words or pictures), and some aspects of visual-spatial processing have been shown to be right-lateralised (Durnford and Kimura, 1971; Gonzalez Alam et al., 2019; Hougaard et al., 2015; Thiebaut De Schotten et al., 2011). Chapter 2 found that, on average, right ATL is more strongly linked to visual cortex than left ATL (Figure 2.5). In Chapter 3, participants who showed an exaggeration of this normal pattern of functional lateralisation had more efficient semantic retrieval, in line with the view that lateralised function is beneficial to cognition.

Another region posited as a potential representational hub together with ATL is AG. Some studies have suggested involvement in combinatorial (Price et al., 2015) or event/thematic semantics (Binder and Desai, 2011; Boylan et al., 2015), but this role is debated, with some studies suggesting it is more involved in processing context (Hoffman et al., 2018), or even just de-activates less for semantic than non-semantic tasks (Humphreys et al., 2015). Even though its role remains unclear, a large-scale meta-analysis confirmed the involvement of left AG in semantics, with a laterality effect: executive semantics displayed a left only distribution, while automatic semantic retrieval showed a more graded left > right pattern in AG (Humphreys and Lambon Ralph, 2015). The role of AG might therefore not be specific to semantics and, indeed, transcend it. In Chapter 2, the results of individual differences analyses in intrinsic connectivity showed that when participants had stronger connectivity from the left AG peak to occipital visual regions, performance in a perceptual task was poor. This peak was reported as the highest point of meta-analytic activation for contrasts involving semantics and, since most of the semantic cognition system is left-lateralised, there may be functional benefits of segregating the left AG semantic peak from regions of cortex involved in right-lateralised functions such as vision.

A conjunction analysis of intrinsic connectivity of ATL and AG in Chapter 2 confirmed interhemispheric differences consistent with the involvement of both regions in left-lateralised heteromodal semantic processing. In the left hemisphere, these regions showed common connectivity to lateral aspects of the DMN, which are implicated in semantic processing, while in the RH there was common connectivity with the DAN and different aspects of the DMN. As mentioned above, the AG is a region that shows abundant functional complexity, being involved in a multitude of tasks not limited to semantics (Humphreys and Lambon Ralph, 2015). Different parts of AG are implicated in automatic and controlled retrieval, and it is not clear how this region fits into the CSC framework. In this thesis, ATL and AG share DMN connectivity but do not share patterns of lateralisation.

This is consistent with AG having an important role in integrating bilateral representations with lateralised retrieval mechanisms.

5.3.2. Novelty of these findings and their relationship to the broader literature

These results support the hypothesis that the two components of the semantic cognition system – heteromodal representations and control – show different patterns of lateralisation. The nodes of the semantic control network showed left-lateralisation and overlap with both DMN and MDN, with the strength of left-lateralisation associated with efficient performance on tasks that required semantic control as will be discussed in the next research theme. On the other hand, vATL showed a bilateral and largely symmetrical pattern of intrinsic connectivity, where graded differences across the hemispheres in connectivity were associated with the efficiency of semantic categorisation in accordance to the graded hub hypothesis. This difference in lateralisation across components is consistent with the neuropsychological literature: the semantic store can be affected by damage to either left or right vATL regions (but impairment is more severe following bilateral atrophy, in SD). In contrast, controlled retrieval is usually impaired after left-sided lesions, as in post-stroke semantic aphasia (Jefferies and Lambon Ralph, 2006).

Although severe impairment of heteromodal semantic knowledge results from bilateral damage to vATL in SD (Bozeat et al., 2000; Jefferies and Lambon Ralph, 2006), left and right-sided atrophy are associated with subtle differences. In some studies, left-sided damage results in greater difficulties in tasks that require verbal processing – particularly picture naming, whilst right-sided atrophy is more strongly associated with deficits in visual matching tasks and assessments of social knowledge, such as face recognition (Lambon Ralph et al., 2001; Mion et al., 2010; Snowden et al., 2004; Thompson et al., 2003). Our results are partially consistent with these differences: people with stronger right relative to left ATL connectivity to visual regions were better at categorising visually presented words and pictures (although the task did not compare these visual inputs with another modality, such as spoken words). The functional advantage of stronger connectivity from right ATL to visual cortex was clearest for categorising famous people from their written names. This result is consistent with the view that right ATL plays an important role in social knowledge but why would this effect be stronger for names than for faces? There are three possible contributory factors: (i) Even if the mode of presentation was verbal, the knowledge retrieved was social in nature, and the verbal task was more sensitive to individual differences in social knowledge (perhaps because faces are a stronger cue); (ii) it is possible that in normal cognition, visual imagery mediated by a right ATL-occipital interaction is an integral part of retrieving information of people from their names; (iii) since all the conditions in our task were visually presented, we cannot be confident that presenting people's names as spoken words would engage the RH to the same extent.

In contrast to patients with SD that are impaired in all aspects of heteromodal semantic representations, patients with SA, usually as a consequence of a LH stroke, show deficits in the controlled retrieval of aspects of these representations that are necessary for the current goal or context (Jefferies and Lambon Ralph, 2006). Some studies have found right IFG involvement in the application of control to semantic stimuli presented visually (Krieger-Redwood et al., 2015), and some aspects of it are consistently activated across studies, as shown in meta-analytic evidence (Noonan et al., 2013). In line with this, our difference analysis showed that both, right IFG and pMTG showed increased connectivity to visual regions than would be expected from the LH seeds. Regardless, this thesis did not find any evidence of the right homotopes of this regions organising into a network or being involved in semantic control. On the other hand, the thesis results were compatible with a left-lateralised semantic control network in the following ways:

1. It has been proposed that the semantic control network would need to integrate two usually anti-correlated networks: aspects of the DMN that sustain automatic semantics and regions of MDN/FPN that represent current goals (Davey et al., 2016). Previous studies have shown that pMTG and anterior IFG, within this network, communicate with both DMN and MDN regions in line with this hypothesis (Davey et al., 2016). Consistent with this account, pMTG and IFG's intrinsic connectivity were more similar in LH than RH: a formal conjunction of their shared connectivity in Chapter 2 revealed that these regions engage both control and DMN in LH, but not in RH. Chapter 2 also found greater connectivity from both these regions separately to lateral DMN and control networks than would be expected compared to their RH homotopes. This difference analysis revealed that pMTG and IFG engage different parts of the FPN. A recent study using hierarchical clustering on Yeo networks showed that the FPN is fractionated into a system that is in charge of internally-directed control, and another that mediates externally-directed control, which couple more to the DMN and DAN respectively (Dixon et al., 2018). The results of this thesis showed that while

IFG coupled more to the external FPN (allied to DAN), pMTG preferred the internal FPN (DMN) in LH than would be expected from their RH counterparts. This could constitute a clue about how the semantic control network integrates these anti-correlated networks, which we will discuss in the following section.

2. The integrity of this left-lateralised network is associated with good performance on tasks that require controlled semantic retrieval, both in tasks employing explicit cues (like in feature matching tasks) and in the absence of a goal (in global association judgements). Previous studies have shown that brain damage or TMS to either of these regions cause impairments in tasks with demanding conditions that require greater control, e.g., when there are fewer shared features or weak associations (Davey et al., 2016; Wagner et al., 2001; Whitney et al., 2011b). In Chapter 2, individual differences in the lateralisation of left pMTG were associated with the efficiency of global associations: participants with stronger left-lateralisation showed good performance, whilst those with weaker lateralisation or right-lateralised patterns performed worse. This result shows that the integrity of left-lateralisation of this network has important functional consequences when performing tasks that require semantic control, in line with the patient literature.
3. Finally, such a network should be *specific* to controlling semantic retrieval, and not support domain-general control. Chapter 4 provides evidence to support this view (discussed in detail in the next research theme). We manipulated a challenging inhibition paradigm such that participants had to use semantic information to guide their decision to inhibit a pre-potent response. We failed to observe involvement of the left-lateralised semantic control network, even in a lenient region-of-interest analysis. Instead, the same right-lateralised, domain-general inhibition network was engaged whether inhibition was guided by perceptual or semantic information. This constitutes evidence for the specificity of left pMTG/IFG for semantic control: this network is not engaged by difficult tasks that include semantic content, but instead by tasks in which semantic retrieval itself has to be controlled.

Taken together, these findings are consistent with the CSC framework, with separate networks supporting conceptual representation in a long-term store and semantic control processes (Lambon Ralph et al., 2017). In line with the two largest meta-analyses of fMRI evidence to date, this thesis found evidence for a bilateral, symmetrical hub-and-spoke system centred on vATL, where graded differences in connectivity relate to the efficient storage of semantic representations (Rice et al., 2015b, 2015a), and a left-lateralised network in charge of retrieving aspects of these representations that are appropriate for the current goals or context (Noonan et al., 2013). This PhD project provides the first set of studies that dissociate these components in terms of their patterns of lateralisation and the consequences of this lateralisation.

5.4. The Semantic Control Network is overlapping with, yet functionally dissociable from the default mode and multiple demand networks

5.4.1. Key findings across chapters

The previous two research themes documented hemispheric differences in intrinsic connectivity between key regions of the semantic cognition network in LH and their RH homotopes, explored their functional significance and described how they give rise to two distinct lateralisation patterns for the representation and control components. The studies provide evidence for a set of regions involved in semantic control, lateralised to the left hemisphere, which could potentially integrate semantically-relevant aspects of DMN and MDN. This might allow semantic retrieval to be flexibly shaped to fit the current goals, environmental demands or context. An important question arising from this work concerns whether these semantic control regions constitute a dedicated network that is specifically involved in the shaping of semantic representations to meet current demands, or whether semantic control recruits a subset of MDN regions that support executive control across tasks.

The tasks that have been used in determining this network (like the ones explored in Noonan et al., 2013) are, by definition, more demanding than their ‘baseline’ contrasts. Semantic control is usually gauged by comparing a task thought to involve largely automatic semantic retrieval (i.e. dominant semantic associations, no distracters), with a similar task with higher control demands (i.e. weak sematic associations, strong distractors, interfering context such as a miscue). All of these contrasts can be argued to include difficulty as a confound, as the need for semantic control is, by definition, more effortful than automatic semantic retrieval. The meta-analysis used to determine the semantic control seeds in this PhD project addressed this issue by contrasting high-control semantic tasks with high-control phonological tasks, thereby controlling for difficulty, and providing a first piece of evidence of the specificity of the semantic control network (Noonan et al., 2013). This view – that the semantic control network does not support the control of cognition more widely – is supported by several thesis findings, as outlined below.

Chapters 2 and 4 provided evidence in favour of a left-lateralised semantic control network that partially overlaps with, yet is functionally dissociable from the DMN and MDN. Chapter 2 shows that left IFG and pMTG seeds have highly similar patterns of intrinsic connectivity (Figure 2.3). The similarity of intrinsic connectivity maps across all semantic seed regions was quantified, and left IFG and pMTG showed the highest similarity across all within-hemisphere pairs of seeds, which was significantly higher in the LH than in RH. This evidence is compatible with the view that the semantic control network is strongly left-lateralised, unlike domain-general control regions within the MDN.

The same chapter yielded evidence of this network's privileged position to integrate MDN regions that show adaptive coding (and can thus represent current context, goals or task demands) with semantic DMN regions (which are anti-correlated with, and hence not easily accessible to, MDN). In this chapter, a formal conjunction analysis was conducted on the intrinsic connectivity of IFG and pMTG in LH and RH separately, quantifying their differential engagement of large-scale functional networks, counting the proportion of voxels that were significantly activated in the intrinsic connectivity of both networks for each hemisphere that overlapped with each large-scale network. The results show that these regions' shared intrinsic connectivity in LH fell primarily in control regions thought to reflect MDN functioning, and in lateral DMN regions to the same extent (Figure 2.4). On the other hand, in RH these regions' shared connectivity overlapped primarily with the two main FPN divisions (as per Dixon et al., 2018), followed by the DAN. This pattern aligns with an FPN division of labour across the hemispheres, characterised by stronger integration with DMN in LH and with DAN in RH (Wang et al., 2014).

In a more fine-grained analysis, we examined the differential connectivity of each of these seeds separately, contrasting their intrinsic connectivity in LH with that of RH flipped into LH space as described in the previous research theme. The results of this difference analysis (Figure 2.5) showed that IFG and pMTG separately engaged control (FPN/MDN) and DMN regions. Left IFG showed greater connectivity to FPN_A regions associated with the MDN (as per Dixon et al., 2018) than would be expected from its RH counterpart, as well as weaker connectivity with core DMN regions . Left pMTG showed a complementary pattern: greater connectivity with lateral DMN, followed by FPN_B , which is itself associated with the

DMN. The connectivity of left pMTG and IFG was distinct from both MDN and DMN (and in fact only approximately 30% of their common connectivity overlaps with MDN and DMN, with the remaining 70% distributed across other networks).

Chapter 4 builds on this evidence for a left-lateralised semantic control network using task-based fMRI. We used a Go/No-Go task known to activate reliably right-lateralised MDN regions linked to domain-general control, specifically the inhibition of pre-potent behaviour (Criaud and Boulinguez, 2013; Simmonds et al., 2008). We manipulated the task structure so that in half the trials the signal that drives inhibition was perceptual in nature, while in the other half it was semantic. We ensured the task was fast-paced, with inhibition trials representing only 20% of the total trials, to establish a pre-potent button press response, such that the inhibition of this behaviour was demanding.

If the activation tied to the semantic control network was just a manifestation of MDN regions showing greater engagement in challenging tasks/conditions, left-lateralised due to their semantic nature, then by performing a domain-general inhibition task (that engages MDN regions) and contrasting semantic versus perceptual content, one should observe left-lateralised activation of these MDN/semantic control regions. This was not the case. Instead, we found that inhibition, regardless of whether it was driven by perceptual or semantic content, engaged the same set of MDN regions in the RH. This directly dispels one of the major objections against the specificity of the semantic control network.

After failing to observe left-lateralised activation related to the inhibition trials in semantic control regions, we conducted a conservative check using a semantic control network mask as ROI (from Noonan et al., 2013). The results showed that left IFG responded to all semantic trials, but this response was not specific to the inhibition trials, with higher control demands. This, together with the fact that both, perceptual and semantic inhibition engaged a right-lateralised set of areas commonly associated with domain-general inhibition, increases our confidence in the view that the semantic control network can be functionally dissociated from the MDN.

5.4.2. Novelty of these findings and their relationship to the broader literature

The results summarised above constitute some of the strongest evidence for the specificity of semantic control regions, showing they do not respond simply to challenging tasks or conditions with semantic content and are thus functionally dissociable from the MDN. They also constitute confirmation that the intrinsic connectivity patterns of the semantic control seeds examined are compatible with a left-lateralised network that integrates DMN and MDN to shape semantic representations to fit current task demands, contexts or goals (Davey et al., 2016).

Perhaps the most relevant recent evidence of a functional dissociation between these regions and the MDN comes from a study by Mineroff et al. (2018). The authors examined the response profiles of DMN, MDN and what they deem a ‘core language network’, determined in their sample by the relevant contrasts across a language and a working memory task in a separate sample. They found that the response profile of their core language network is functionally distinct to both the DMN and MDN in these contrasts. Further to this, the correlations of effect sizes to these contrasts across participants for the nodes of each network were significantly greater within than across networks, providing further evidence of a functional dissociation between language, MDN and DMN regions. This tripartite functional division was confirmed by data-driven hierarchical clustering of their correlation matrix. Interestingly, the methods above converged in a laterality effect only for the language network: the correlations of effect sizes and hierarchical clustering yielded evidence of separate response profiles for LH and RH language regions.

Due to the way the ROIs were defined, this investigation cannot make claims about the specificity of semantic control regions. The authors defined their ‘core language network’ as the result of a functional localiser task involving passive sentence reading (the contrast was sentences > nonwords) in a separate sample, and then examining the 10% top responding voxels with cross-validation across two runs in the sample to be investigated (Julian et al., 2012). If we, however, limit our examination to their left IFG and posterior temporal ROIs (see Figure 1 of the work cited), which are the closest to the left IFG and pMTG regions examined in this PhD, we can observe that the evidence aligns with the findings in this thesis. These regions responded to language tasks, but not difficult WM tasks. This thesis’ findings extend this study results showing that, even when semantic content is introduced to challenging tasks that engage the MDN, the left-lateralised semantic control regions are still not engaged. Furthermore, it is worth noting that IFG and pMTG, considered in this study as language regions, respond to non-verbal as well as verbal semantic tasks (Corbett et al., 2009; Jefferies and Lambon Ralph, 2006; Noonan et al., 2013, 2010), which clarifies their involvement as semantic regions, transcending a strict role as part of a ‘core language network’.

Similar evidence comes from recent work from Diachek et al. (2019). They examined the response profiles of MDN and language regions across a very large number of scans completed for various experiments conducted over the course of 10 years in order to explore MDN involvement in language processing. They measured the activation of both networks separately in each hemisphere to language and spatial working memory tasks. The MDN was active during various language tasks, and this response was indeed stronger in LH MDN regions. However, as a critical dissociation, the authors report a task-independent response profile in the language network across linguistic tasks, whilst the MDN was not activated by passive comprehension tasks. Furthermore, opposite to the language network, the MDN showed a stronger response to unconnected lists of words than to sentences. As expected, the main effect that predicted MDN engagement in language paradigms was whether the experiment involved an explicit task and not just passive comprehension. The authors conclude the MDN does not support core aspects of language comprehension, like inhibiting irrelevant meanings, since in that case it should show a task-independent response profile for language tasks. Although the authors did not specifically examined semantic control (and in fact, their critical contrast of sentences > non-words in a large number of experiments actually contrasts an easier task with a harder one), their results are consistent with those reported in this thesis, showing that even though language tasks elicit a left-lateralised activation of MDN regions under certain conditions, this is related to general task demands more than core linguistic operations, showing a functional distinction between MDN and language networks.

The results above suggest that semantic control might depend on both, domain-general control processes implemented in the MDN, and domain-specific components that are particularly suited for the processing challenges posed by semantic tasks. Further evidence of this functional dissociation comes from Whitney et al. (2011), who applied TMS to left IFG and pMTG while participants performed a Navon task involving congruent and incongruent global and local features (probing domain-general control) and a semantic association task, with strong associations (retrieved relatively automatically) and weak associations (with increased control demands). TMS to both semantic control sites disturbed participants’ performance in the weak association condition, but spared both strong associates and the Navon task, showing that the semantic control network is causally involved in tasks that require semantic control, but not necessary for domain-general control or more automatic aspects of semantic processing that might be mediated by the DMN (Simmons et al., 2008).

These results are reflected by more structural measures of this network's functionality. A recent study by Wang et al. (2018) examined cortical thickness covariance networks of regions involved in semantic control. Left pMTG's structural covariance with left aMFG was associated with participants' ability to perform a weak associates task offline, even after controlling for performance in the strong associates condition. In contrast, the ability to perform a hard perceptual task relative to the strong associates condition was not associated with the covariance of these two regions, suggesting that this pattern was specific to semantic control. It is thought that structural thickness covariance across brain regions reflects their organisation in a network (Alexander-Bloch et al., 2013; Evans, 2013), and further evidence of this was that the intrinsic connectivity of both these regions was highly similar, and overlapping with the left-lateralised semantic control network identified in previous meta-analyses (Noonan et al., 2013). In conclusion, this study yields structural evidence of the organisation of left pMTG and frontal regions in a semantic control network functionally dissociable of domain-general control regions like the MDN. This pattern of structural results resembles that of recent studies using a combination of task-based and resting-state fMRI (Humphreys and Lambon Ralph, 2017), which find that IFG and pMTG in LH show a response profile sensitive to semantic difficulty (weak > strong associations) but not to non-semantic, domain-general difficulty. Both the functional and structural studies described above point to the same conclusion as the evidence in Chapter 4: the left-lateralised semantic control network is specific to shaping semantic representations to fit current demands, and does not respond to challenging tasks with semantic content, thus being functionally dissociable from the MDN.

5.5. Individual differences in intrinsic connectivity are associated with behavioural performance

5.5.1. Key findings across chapters

The last theme that extends across multiple chapters concerns associations between individual differences in intrinsic connectivity and task performance outside the scanner. Our knowledge of neurocognitive function is mostly based on a model of the average brain, which, although important to establish generalisable findings, neglects individual variability and diverse phenotypes. The body of work presented in this thesis contributes evidence regarding to what degree individual variability in connectivity is associated with functional consequences in cognition, which is relevant to refine our theories of brain organisation.

Chapter 2 revealed that the strength of intrinsic connectivity of the two most lateralised sites of the semantic cognition network according to previous evidence — left AG and pMTG — was associated with the efficiency with which participants performed semantic and perceptual relatedness judgements. The meta-analyses we used to define the ROIs in this PhD project did not identify right-lateralised AG or pMTG regions associated with semantics, in contrast with ATL and frontal activation in Rice et al. (2018c) and Noonan et al. (2013), respectively, and these were precisely the seeds whose intrinsic connectivity was associated with functional consequences. This is further evidence that the left-lateralisation of these regions has functional consequences.

Participants with stronger cross-hemispheric connectivity from left pMTG, a key control site, to a cluster spanning right Anterior Insula/Frontal Operculum (AI/FO), IFG, anterior Superior Temporal Gyrus (aSTG), planum polare and temporal pole showed poor performance on weak semantic association judgements, which maximise control demands. Conversely, participants that showed greater within-hemisphere intrinsic connectivity from pMTG to left perisylvan regions associated with language, showed increased efficiency in strong semantic association judgements, which reflect a more automatic mode of semantic retrieval. In other words, the strength of left lateralisation of the intrinsic connectivity of left pMTG was positively associated with relatively automatic semantic retrieval, and right lateralisation was negatively associated with semantic control.

The other seed that showed behavioural associations in this study was AG. The strength of intrinsic connectivity from left AG to a region in medial occipital cortex was associated with the efficiency with which participants performed a perceptual matching task. Participants with stronger connectivity from this heteromodal semantic region to visual regions showed poorer performance in matching a scrambled figure to its rotated perceptual target.

Chapter 3 examined the relationship between the intrinsic connectivity of ATL, a key region of the semantic representation system and participants' ability to categorise different types of stimuli (landmarks vs faces) presented through different modalities. There were two main findings pertaining to individual differences in intrinsic connectivity of ATL. First, the strength of cross-hemispheric integration within this bilateral system was related to participants' efficiency in semantic categorisation judgements of landmarks, especially when these were presented as pictures. Participants that showed stronger integration (i.e. more intrinsic connectivity) between left and right ATL showed increased efficiency in categorising landmarks as European or non-European when these were presented as pictures; interestingly, when the names of landmarks were presented as written words, this increased integration was actually associated with worse performance in landmark categorisation.

Second, individual differences in strength of intrinsic connectivity from left versus right ATL to medial occipital visual regions were associated with efficiency in performing all conditions of the semantic categorisation task in the same study. Participants with stronger intrinsic connectivity from right relative to left ATL to ventral occipital regions encompassing lingual gyrus showed increased efficiency in all conditions of the task, regardless of stimuli or modality of presentation. Conversely, participants that exhibited greater left relative to right intrinsic connectivity from ATL to a more dorsal occipital region, including the cuneus, showed decreased efficiency in performing all the conditions of the task, regardless of stimuli or modality of presentation. Within this general occipital effect, there were two clusters associated with performance in two particular conditions: (1) a large bilateral occipital cluster associated with categorising famous people by written name, and (2) a polar occipital cluster was associated with performance in landmark judgements, regardless of modality.

The interaction between ATL and the visual system is particularly important for human conceptual knowledge (Clarke et al., 2013; Clarke and Tyler, 2015), with this pattern of connectivity being normally stronger in RH (Gonzalez Alam et al., 2019; cf. Fig 2.5 and S2.2). This interaction is important for categorisation of images/pictures presented through the visual modality, as well as for accessing conceptual information about people or places from their names using visual imagery, thought to be supported by medial aspects of visual cortex (Kosslyn et al., 1999, 1995).

Lastly, in Chapter 4 we determined that the strength of intrinsic connectivity from the regions found in our task-based Go/no-go experiment was associated with participants' ability to perform the Go/no-go task outside the scanner. Participants with stronger connectivity from the right-lateralised inhibition regions (that responded both to semantic and perceptual inhibition) to a medial temporal and a subgenual region, both of which are implicated in memory and semantics, showed increased efficiency in the inhibition of semantic relative to perceptual trials. Likewise, stronger intrinsic connectivity from the modality-sensitive left LOC cluster to regions in basal ganglia/thalamus (whose connectivity, in turn, overlapped with the MDN) was associated with more efficient inhibition when stimuli were presented as pictures. This is probably the most striking demonstration of the potential of individual differences in intrinsic connectivity as an informative marker of brain organisation across our studies. We were able to demonstrate, using the same task in and outside the scanner, that the regions discovered in task-based fMRI associated with general inhibition, and modality specific effects, are themselves associated with participants' ability to perform semantic inhibition when they connect more to semantic regions, and picture-based inhibition when visual regions connect to MDN-associated regions respectively

5.5.2. Implications of the findings and their relationship to broader literature

These results across all three chapters, taken together, suggest a flexible, highly interactive organisation of large-scale brain networks potentially giving rise to different phenotypes. This highlights the importance of the examination of individual differences in connectivity to inform our views on brain organisation. Although neuroscience models based on the average brain make statistical sense, they discard a potentially informative, valuable source of data that would allow description not only of the average brain, but also of its variability, possible configurations and boundaries.

Our results yielded evidence that individual differences in intrinsic connectivity from heteromodal semantic cognition sites predict the efficiency with which participants implement semantic behaviour outside the scanner. This relationship between connectivity and behaviour can have a positive impact, like in the case of left pMTG's connectivity to other LH perisylvan areas implicated in language, predicting good performance in strong associations, or right ATL's connectivity to left ATL, associated with good performance on visual landmarks, and to visual occipital regions, associated with heightened efficiency in all tasks. Connectivity from regions not originally defined as heteromodal semantic seeds was also associated with improved performance. In Chapter 4, connectivity from inhibition regions (common to semantic and perceptual trials) to areas implicated in memory predicted increased efficiency in semantic trials, and the connectivity of a modality-sensitive LOC cluster to basal ganglia regions connected to the MDN was associated with more efficient picture-based inhibition. However, in other results, there was a negative association between connectivity and semantic performance. In Chapter 2, the intrinsic connectivity of left pMTG to right AI/FO and aSTS regions showed a negative relationship with participants' efficiency in retrieving weak associations requiring semantic control. In the same study, intrinsic connectivity from left AG to medial occipital regions showed a negative effect on a perceptual matching task. Lastly, connectivity from left ATL to right ATL was associated with poor performance on categorisation of landmarks from their written name, and connectivity from left ATL to medial occipital regions was associated with poor performance on all conditions of the categorisation task.

This pattern of results shows that for some regions, straying from their average pattern of connectivity might have a detrimental effect. We selected our left AG seed from a meta-analysis that determined it was the peak of a heteromodal semantic contrast (Humphreys and Lambon Ralph, 2015). In participants where this heteromodal semantic region showed higher coupling to a lower-level visual perceptual region, performance in a perceptual task suffered. Previous research implicates ventral parietal regions (including AG) in regulating internally-directed attention (Cabeza et al., 2008). It is possible that cognition is less efficient when this region, which is optimised for regulating internally-directed attentional processes, shows more coupling to regions involved with perceiving the external world. This is consistent with a neural architecture in which cognitive processes reflect a trade-off between different patterns of connectivity within hub regions.

We observed results compatible with this claim for ATL: when left ATL exhibited stronger intrinsic connectivity to visual occipital regions than right, performance suffered in all conditions, regardless of modality or type, in our categorisation task. Conversely, when right ATL exhibited stronger intrinsic connectivity to adjacent occipital regions than left (a pattern shown in the difference analysis in Chapter 2), participants showed an advantage in all conditions of the same task. If, on average, right ATL exhibits higher connectivity to visual regions in accordance with this hemisphere's specialisation for visuospatial processes (Durnford and Kimura, 1971; Gonzalez Alam et al., 2019; Hougaard et al., 2015; Thiebaut De Schotten et al., 2011), it is possible that participants with a phenotype showing a more extreme version of this normal pattern might be specially good at visually-guided semantic behaviour. If, on the other hand, left ATL is more strongly connected to these regions, this behaviour suffers, since the LH is less specialised for handling visuospatial processing than RH. In a similar fashion, when right ATL was more integrated with left ATL, people were better at categorising stimuli that were visually rich, potentially as a result of a right-lateralised advantage for processing visual stimuli integrating into the left-lateralised semantic system. However, they were also worse at categorising those same stimuli by name. It is possible that when the ATLs are integrated as a more bilateral system, participants' left-lateralised semantic system can better exploit the advantages of RH specialisation for visual processing, which allows them to categorise landmarks from pictures. However, at the same time, this comes at the cost of having a less segregated left-lateralised ATL, which potentially could provide optimal computations when stimuli must be categorised from their written names.

These findings (and other individual differences results in this body of work) are reminiscent of the Pareto-optimal distributions that have been described by recent studies of delayed gratification and lateralised functions (Cona et al., 2019; Karolis et al., 2019), suggesting this might be a useful framework for studying individual differences in intrinsic connectivity, possibly capturing a principle of brain organisation. This application of pareto-optimality starts from defining a *morphospace* of traits (like visual versus verbal categorisation abilities, for example). The theory states that if these traits indeed show trade-offs, then exemplars, or phenotypes, will fall within a defined geometric domain of this morphospace called a *polytope* (e.g. a triangle, pentagon, et cetera, depending on the number of traits and relationship amongst them), which will include the phenotypes that have found the best possible trade-offs solutions amongst traits for a given environment. Phenotypes can then vary between *generalists* in the middle of the morphospace (e.g. somebody that is moderately good at both, visual and verbal categorisation of people, but excels at neither) and *specialists* at the extremes (someone that excels at visual categorisation at the expense of poor verbal categorisation). The particular distribution of phenotypes will depend on the traits or functions being traded off and the environment for which they are tuned to (Cona et al., 2019).

The results reviewed in this section also reveal that lateralisation has a functional impact on the implementation of cognitive processes. The pMTG results, taken together, indicate there is a behavioural advantage to having a more left-lateralised semantic control network, and that performance suffers when parts of it show greater right-lateralised connectivity to perisylvan regions.

Lateralisation of function and its advantages (and sometimes, disadvantages) has been shown in fish, reptiles, amphibians, birds, some invertebrates and primates (Halpern et al., 2005; Rogers et al., 2004; Vallortigara and Rogers, 2005), but it has been mostly discussed in terms of a evolutionarily stable strategy at the population, and not individual, level, with relatively few studies (cf. Rogers et al., 2004) describing specific advantages at an individual level, for example, in multitasking in strongly lateralised chicks. Regardless, the available evidence suggests that lateralisation of functions may have been finely tuned through the evolution of the species (Thiebaut de Schotten et al., 2019), and alterations in its balance might have negative consequences, as has been shown in psychiatric disorders, attention and language (Bishop, 2013; Knaus et al., 2010; Oertel et al., 2010; Sanefuji et al., 2017; Wexler, 1980).

Studies in humans, however, have yielded mixed results. A study that examined the impact of strength of lateralisation in dual-task processing in humans using functional transcranial Doppler sonography (Lust et al., 2011) found that having a typical lateralisation pattern (but not the strength of lateralisation per se) conferred an advantage in dual-task performance. Atypical lateralisation patterns, however, did invoke a relationship between strength of lateralisation and negative task performance. A study by Mellet et al. (2014) found a different pattern; when participants showed strong lateralisation, they performed better in a language production task than when they showed little lateralisation. Even a right-lateralised pattern was associated with better performance than no lateralisation at all. This, however, could be a result of the language production task not detecting the most lateralised components of the language network; this study did not use a contrast that was sensitive to semantic control (contrasting producing sentences > list of months in a year), and as this thesis stated in Research Theme 2, it is now clear not all aspects of semantic cognition are lateralised.

The results of our individual difference analysis in Chapter 2 do not support the view that lateralisation does not confer cognitive advantages, being more in line with Lust et al.'s (2011) results of typical lateralisation patterns conferring advantages in performance and extending them to semantics. We found that in a typical lateralisation pattern – when left-lateralised semantic control regions connect to left perisylvan regions associated with language – the strength of intrinsic connectivity is positively associated to performance in a task that requires semantic control. When the lateralisation pattern is atypical, like when normally left-lateralised pMTG connects to right-lateralised perisylvan regions, performance suffers. Similarly, Chapter 3 yielded results that follow this pattern. Participants who exhibited the expected lateralisation pattern of right ATL coupling more into visual regions than left showed a performance advantage over participants with atypical lateralisation patterns in all conditions of a visually presented semantic categorisation task. Interestingly, both the pMTG results of the study we report in Chapter 2 and Lust's results suggest that the typical lateralisation of control processes in particular is associated with advantages in cognitive performance, which is compatible with an account of hemispheric specialisation driven by FPN fractionation into LH and RH sub-systems (cf. Wang et al., 2014). In the final section, we will propose a framework for future research to pursue this hypothesis. These findings are in line with hypotheses that suggest that lateralisation of functions enhances cognitive ability, likely through minimising redundancy and functional overlap (Vingerhoets, 2019).

In sum, our findings across all chapters reviewed in this research theme show that individual differences in the strength of intrinsic connectivity are associated with the efficiency with which participants perform behavioural tasks outside the scanner. This association can have positive or negative consequences on behaviour, sometimes reflecting the maximisation of an average pattern, trade-offs between two apparently opposite cognitive archetypes (i.e. better picture-based categorisation of landmarks at the cost of written names, or vice versa), or deviations from the usual connectivity targets of a seed (i.e. the semantic part of left AG straying into visual cortex). In addition, typical lateralisation patterns are associated with more efficient behaviour, and deviations from this typical laterality relate to poor behavioural performance, implying that lateralisation as assessed through intrinsic connectivity has functional consequences. This evidence is compatible with average patterns of intrinsic connectivity (and its lateralisation) being optimised as a function of a population-level evolutionary stable strategy, with phenotypical variation across a pareto-optimal morphospace as suggested by recent research (Cona et al., 2019; Karolis et al., 2019).

5.6. Limitations and Directions for Future Research

In this final section, we consider the limitations of the body of work undertaken during this PhD together with suggestions of potentially fruitful avenues for future research.

First, across two out of our three studies we conducted seed-based analyses in opposition to full correlation matrix analysis or other data-driven techniques such as ICA. This approach has the advantage of providing a detailed analysis for particular critical sites but the disadvantage that the patterns described are selective. Even though we determined the functional peaks for our ROIs from the largest, most recent and more relevant high-quality meta-analyses we could find, we are aware that we did not look at all the regions identified. For example, we excluded midline structures like anterior medial prefrontal cortex, which by virtue of its location would introduce confounds when trying to separately examine the left and right aspects (since any spherical ROI centred in a midline structure is likely to capture both left and right hemisphere time-series). We also excluded right-lateralised peaks like in the case of IFG for semantic control in Noonan et al. (2013), since we opted to produce RH homotopes from the LH peaks. The inclusion of all possible ROIs would have risked Type II errors given the severe nature of the Bonferroni correction which would be needed. However, we are confident to have captured key regions involved in semantic cognition in the CSC framework, as a relatively hypothesis-free, large-scale automated meta-analysis performed through Neurosynth shows high convergence with the peaks where we placed our spherical ROIs (cf. Figure 2.3). Moreover, ROI selection could not be avoided, given that we were looking to conduct hypothesis-driven research, in the context of a widely accepted framework that has formed coherent theories sustained in a robust body of evidence (see, for recent examples, Hoffman et al., 2018; Lambon Ralph et al., 2017). Future research might benefit of confirming our results utilising data-driven methods like ICA or full-correlation matrix analysis.

Secondly, in Chapter 2, we determined homotopy by the rather crude method of flipping the sign from negative to positive in MNI coordinates. Functional and structural homotopies are hard problems in neuroscience that, in themselves, merit further research that eludes the scope of this PhD project. Since the conception of this project, new methodologies have been derived and popularised that show promise to increase the accuracy of future research, like using correlations of the geodesic distance of centroids to gyral and sulcal landmarks to determine structural homotopy, or using atlases and techniques derived from the functional homotopy effect observed in whole-brain correlation matrix analysis, like the AICHA atlas, or voxel-mirrored homotopic connectivity, and even meta-analytic methods focused in homotopy (for a non-comprehensive list of examples, see Jo et al., 2012; Joliot et al., 2015; Mancuso et al., 2019; Zuo et al., 2010). However, due to the confluence of time and resources constraints together with the lack of these methodological tools when this PhD project was first conceived, we used sign-flipping for sites that did not have a homotopic RH functional peak in Chapter 2. The approach used in Chapter 3, where we contrasted both a sign-flipped homotope and a functionally defined (from a meta-analysis) homotope to left ATL confirms the importance of accurate determination of homotopic locations, since we found different networks were engaged after a minimal displacement of the homotopic seeds (also see Figure 2 of Cole et al., 2010 for an illustration of the importance of seed selection). Future research should aim to use more sophisticated methods to determine homotopes, and compare patterns of intrinsic connectivity between the left and right hemispheres for semantic sites to confirm the findings described in this thesis.

All three studies in this PhD were based to varying degrees in Resting State fMRI (RS-fMRI), a method that has several advantages but also inherent limitations. This technique measures low frequency, spontaneous fluctuations in the BOLD signal, allowing investigation of the functional architecture of the brain (Lee et al., 2013). It encompasses a family of methods, of which we used concretely seed-based correlations. Some general advantages of RS-fMRI include a good signal-to-noise ratio compared to task-based fMRI (Fox et al., 2007, 2006), moderate to high reliability (Chou et al., 2012; Shehzad et al., 2009), economy, ease of use and robustness (i.e. in RS-fMRI it is possible to study several networks or test various hypothesis with one scan, as well as integrate across samples, while in task-based fMRI this would require separate scans/experiments; besides, since it is task-free, there is no room for measurement error introduced in the tasks used, cfr. Cole et al., 2010; Daliri and Behroozi, 2014). RS-fMRI also has some general disadvantages, with the most critical being that data analysis choices might bias results: whether to perform global signal regression (which might introduce spurious, anti-correlated networks), head motion correction (when inadequate, introduces spurious correlations), and amount of smoothing to cite a few (Lee et al., 2013; Margulies et al., 2010; Murphy et al., 2009). Additionally, sometimes multiple networks can have spatial overlap in a location, but underlie different aspects of cognition, and non-ICA approaches may not be able to separate them (Braga et al., 2013; Braga and Leech, 2015; Leech et al., 2012). Lastly, it is worth remembering that RS-fMRI is a correlational approach, and as a consequence not suitable for causal inference, for which it must be complemented with other approaches like neuropsychology or TMS (Cole et al., 2010).

Specific advantages to the seed-based correlation method we used include straightforward statistics and comprehensible results that are highly interpretable, providing a direct answer to a question, relatively established validity and allowing detection of functional subdivisions in regions with relatively few participants compared to meta-analyses (Cole et al., 2010; Margulies et al., 2010). The specific disadvantages of seed-based correlation include, critically, that this is the most model-based method in RS-fMRI, and the a priori selection of seed region and seed size can heavily bias results (Margulies et al., 2010). This method is subject to the influence of structured spatial confounds; physiological noise or other RS networks residual in the seed time-series can generate correlation maps that include voxels that reflect the artefact. It is also worth noting that univariate approaches disregard the richness of information available in the statistical relationships between multiple data points; the choice of seed may bias connectivity towards specific, smaller, or overlapping sub-systems, rather than larger, distinct networks. Besides, the results are contingent on investigator (seed size, location) and subject-specific (spatial normalisation, functional localisation) choices potentially resulting from the method of a priori selection used, which can result in a large variability in the results and interpretation (see, for example, Figure 2 on Cole et al., 2010). On a related note, prior selection of one sub-region to correlate with and inform the activity of the network as a whole imposes anatomical restrictions on measures of network connectivity, and limits interpretation at systems level (Cole et al., 2010; Margulies et al., 2010). Considering all these limitations, an important future direction might be continuing the study of hemispheric differences in semantic cognition using model-free RS-fMRI methods, as well as complementing them with methods that allow to establish causal relations, like TMS or neuropsychology.

Lastly, whenever we conducted GLM analyses using individual differences in semantic performance as explanatory variables, we relied mainly on threshold-based statistics. These methods suffer of the inherent flaw of having to determine a relatively arbitrary cut-off point to highlight significant results, and this cut-off point is liable to change with the advancement of the field (cfr. Eklund et al., 2016, for an example of a critical study published during the course of this PhD that modified the standard of the field for cluster-based statistics). To address this issue, wherever possible we conducted permutation testing or other forms of cluster-free analyses to supplement the confidence in that our results were not dependant on an arbitrary choice of threshold. Furthermore, our use of automated meta-analytic tools and cognitive decoding helped us strengthen our confidence in our interpretation.

Neurosynth and Neurovault, in combination, allow for uploading the results obtained in any study and perform cognitive decoding, comparing the spatial maps of activation obtained with a very large database of studies that have been text-mined to establish brain-behaviour associations (Gorgolewski et al., 2015; Yarkoni et al., 2011). This approach offers multiple advantages, like pooling together very large datasets for increased statistical power and decreased false positive rates, and especially associating spatial maps with cognitive terms on the basis of peer-reviewed research. This allows an evidence-based approach to the problem of reverse inference based on very big data. The cognitive decoding performed using these methods has reasonable accuracy when tested with naïve Bayes classifiers; and the results converge with conventional meta-analyses, suggesting good validity and reliability. Additionally, being fully automated and extremely easy to use, it minimises the possibility of human error in comparison with manual methods. This approach is not without limitations, however. For instance, text extraction may raise concerns about data quality (i.e. if an article's focus is on 'lack of pain' and the term 'pain' gets mentioned repeatedly, the automated extraction will associate the maps with pain; it could also incorrectly classify numbers in a table as an activation focus and generate a false positive; the software does not detect different coordinate systems, or positive vs negative activations; but see Yarkoni et al., 2011, for evidence of good sensitivity and specificity). This method rests on the assumption that that word count is a good proxy for the content of the article or processed studied, which might not always be the case (but see supplementary note to Yarkoni et al., 2011). Besides, the lexical coding approach (1) imposes psychological terms to neural processes (that do not necessarily represent the ground truth); (2) does not capture term redundancy; and (3) does not allow closely related concepts to be distinguished. Lastly, the coordinate extraction method lacks granularity, which limits the usefulness to broad domains, and not fine-grained processes (for example, 'emotion' vs different negative or positive emotions) and, despite the tests reported, the specificity and accuracy of the results could be improved (Gorgolewski et al., 2015; Yarkoni et al., 2011). However, this approach allows, for the first time in the history of neuroscience, to compare automatically, and at no cost (time or resources) the activation maps derived from one study with a very large (more than 14k studies at the time of writing) database to contextualise them in the updated neuroscientific landscape.

An unanswered question remaining in this PhD concerns the relationship between heteromodal association cortices and lateralisation. When we performed difference analyses of the intrinsic connectivity of four ROIs derived from peak coordinates reported in heteromodal semantic meta-analyses in LH, contrasting them with their RH homotopes flipped to LH, we discovered patterns of intrinsic connectivity engaging preferentially other heteromodal cortices associated with lateralised functions. The cognitive decoding of these maps revealed terms associated with hand dominance and language frequently as the most correlated terms in differential LH, and terms related to visual perception or spatial processing for RH. This reveals that LH heteromodal semantic peaks prefer other cortices associated with left-lateralised functions when compared to their RH homotopes, but surprisingly, this was also true for RH homotopes compared to the LH semantic peaks. Even though we did not select these RH homotopes as peaks of right-lateralised networks (and in fact, we inverted these maps flipping them into LH), we still observed a similar pattern of results with LH, in that their spatial maps yielded cognitive decoding associated with right-lateralised functions. Previous research has shown reduced homotopic intrinsic connectivity in heteromodal areas compared to primary regions (Mancuso et al., 2019; Stark et al., 2008), but the observation of their differential intrinsic connectivity engaging other lateralised cortices is novel. Future research should investigate whether this was an accidental finding for the LH heteromodal semantic peaks investigated during this PhD, or a property of lateralised nodes. One possible avenue for this would be to perform a similar set of analyses to those in Chapter 2, but taking as ROIs the peaks of a right-lateralised network, like spatial attention, and investigating whether their homotopes differentially engage left-lateralised functions.

A second unanswered question pertains to the ATL results obtained in Chapter 3. We reported that when participants connect more strongly to ventral occipital visual regions from right relative to left ATL, their general performance is better. Participants with stronger left relative to right ATL to occipital regions showed the reverse pattern, with poorer performance in all conditions of the task. Visual input is particularly important for human semantic knowledge (Clarke et al., 2013; Clarke and Tyler, 2015), yet our task design presented both pictures and verbal stimuli visually (i.e. written words). Further research should help clarify if the ATL-occipital interaction we observed in this study is a consequence of the hub-spoke organisation of the ATL representation system, that prioritises the visual system due to its privileged position in knowledge acquisition in humans, or a consequence of task design. This could be tested adding auditory conditions to the categorisation task. It would also be interesting to research semantic categorisation via other senses that have been underrepresented in neuroscientific research of semantics, to map the different interactions in the hub-and-spokes model. Studying categorisation based on taste, olfaction and touch has been challenging due to the limitations of on-task fMRI, but resting-state studies of individual differences in performance outside the scanner could prove fruitful.

Finally, during the course of the research reported here, we documented hemispheric differences in the semantic cognition system, but could not advance a complete explanation of their origin. Different lines of evidence potentially converge to support a putative mechanism explaining the relative specialisation of LH for language/semantics and RH for visual and spatial processes. Recent research suggests the fronto-parietal network, which is implicated in domain-general control, is divided both in terms of intrinsic connectivity and meta-analytic activation into FPN_A and FPN_B sub-systems: the former more allied with the DMN, and the latter with the DAN (Dixon et al., 2018). These two sub-systems that apply cognitive control to introspective (internal) versus perceptual (external) modes of processing might be mediated by different branches of the Superior Longitudinal Fasciculus (SLF), given that the SLF I branch connects a dorsal FPN sub-system in charge of spatial/motor control, whilst the SLF III connects a ventral non-spatial/motor sub-system (Parlatini et al., 2017). Given the involvement of DMN in semantics/language and of the DAN in regulating spatial attention, it is plausible that a differential specialisation of FPN that emphasises its DMN sub-network in LH, and its DAN subnetwork in RH could sustain hemispheric specialisation for these processes, which correspond to two of the major axes of hemispheric specialisation (Karolis et al., 2019). Evidence of this differential specialisation of FPN has been documented using hemispheric autonomy indices in previous research (Wang et al., 2014), showing that the two most specialised networks in LH are FPN and DMN, whilst in RH they are FPN and attentional networks (including DAN). This is compatible with a potential dominance of FPN_A / SLF-III mediated regions in LH, and FPN_B / SLF-I in RH, when considered in the context of the previous two studies cited. This research, however, did not focus on the sub-components of FPN/SLF, and how they might differentially support interactions with DMN and DAN in both cerebral hemispheres in the human brain. This should be a focus for future investigations.

5.7. Conclusion

Over the course of this PhD we examined hemispheric differences in intrinsic connectivity of key semantic regions and their contribution to behaviour. We utilised as our main tools resting-state and task-based fMRI, as well as behavioural tasks especially tailored to probe lateralised cognitive processes. We applied these methods to four meta-analytically derived seeds of the semantic cognition network, within the CSC framework (Lambon Ralph et al., 2017). We discovered systematic hemispheric differences in intrinsic connectivity across these four semantic seeds, reflecting their organisation in two separate components: a bilateral and symmetrical system in charge of storing semantic representations, and a left-lateralised semantic control system, tasked with retrieving aspects of those representations that are pertinent to the current context.

These lateralisation patterns have functional consequences, reflected in the individual differences in intrinsic connectivity having an impact in the efficiency with which participants performed our behavioural tasks outside the scanner. Stronger left-lateralisation of intrinsic connectivity of semantic control regions predicted good performance, whilst right-lateralisation was associated with poor performance. In the semantic representation system, a stronger pattern of typical lateralisation, showing increased coupling between right ATL and visual regions predicted good performance in all condition of our semantic categorisation task, while stronger left ATL connectivity related to poor performance in the same task.

These patterns of distinct lateralisation of the two components of semantic cognition and their functional consequences might arise from a different interplay of large-scale networks in the two cerebral hemispheres. While in the LH regions implicated in semantic control span both MDN and DMN, these networks are kept separate in RH, which is further evidence to the hypothesis that semantic control implies an integration of these two anti-correlated networks. Furthermore, we demonstrated the specificity of this semantic control component by showing it does not respond to challenging tasks where semantic content has been introduced. In the representation system, each ATL shows different patterns of connectivity, engaging other language/semantic regions in LH and more visual regions in RH in accordance with each hemisphere’s putative specialisation. This might help the semantic hubs store different types of representations according to their preferred content in accordance with the graded hub hypothesis.

Given the scope and methods of this PhD thesis, we could not offer evidence regarding causal mechanisms or specific implementations underlying the LH specialisation for semantic control. In its stead, we proposed a framework suggesting future research should investigate a potential hemispheric specialisation of the FPN, showing left-lateralised dominance of one of its sub-divisions (of which previous structural and functional evidence exists), leading it to integrate better with DMN, whilst in RH the other sub-division could be dominant, facilitating integration with DAN. This would potentially give rise to two of the most archetypically lateralised cognitive functions: language and spatial attention.

Accompanying Materials (Appendices)

Accompanying Materials, General.

The NIFTI files corresponding to the results of the studies reported in this PhD thesis are publicly available in Neurosynth, at the URLs listed below:

Chapter 2.

https://neurovault.org/collections/4683/

Chapter 3.

https://neurovault.org/collections/5687/

Chapter 4.

https://neurovault.org/collections/3158/

Accompanying Materials, Chapter 2.

Supplementary Analysis S2.1. ATL analyses based on coordinates from Rice et al., 2018c.

We used spatially identical LH and RH seeds in our main analysis, derived by flipping left-lateralised semantic sites into the RH. This method allowed for consistency across sites, since not all RH regions show a semantic response. However, a RH region important for semantic processing has been identified for the ATL (Rice et al., 2018c), consistent with the putative bilateral nature of this semantic component (Rice et al., 2015a, 2015b, Lambon Ralph et al., 2017), and this RH ATL (MNI: 44, -11, -36) peak is in a slightly different location from the one in our main analysis (MNI coordinates: 41, -15, -31). We therefore replicated our analysis using the task-based right ATL co-ordinates reported by Rice et al. Figure S2.1 below shows a comparison of the connectivity patterns for these two right ATL sites.

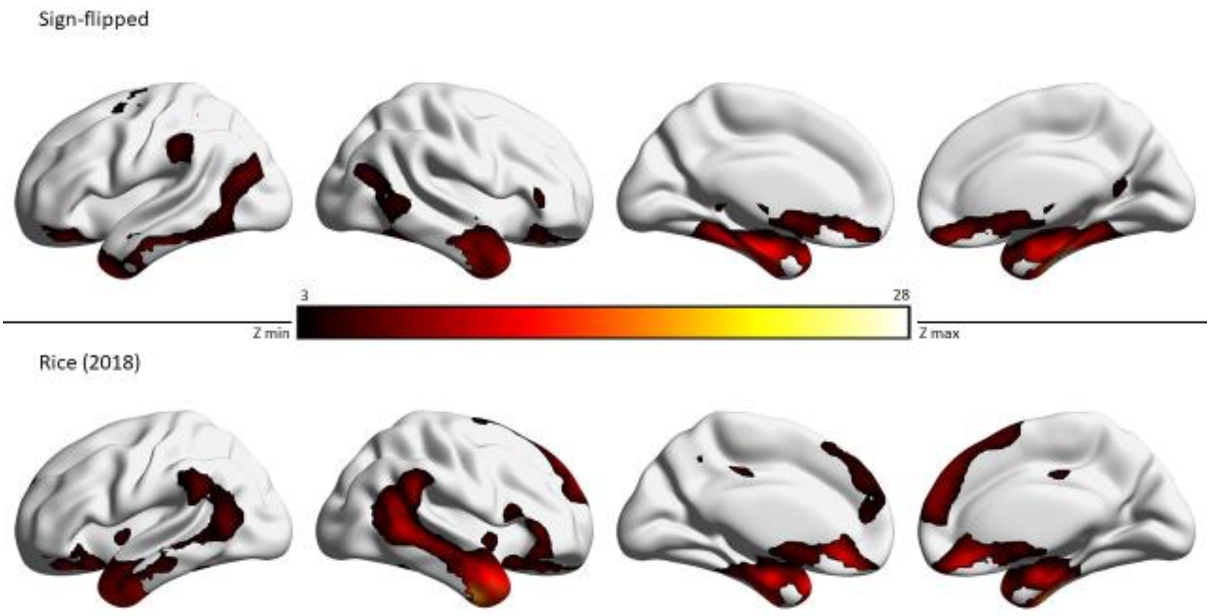


Figure S2.1. Connectivity for right ATL comparing two seed locations. Top row: data from our main analysis, using a seed derived by sign-flipping the ventral ATL peak in LH to RH. Bottom row: alternative RH site localising the semantic peak in right ATL using task activation data reported by Rice et al. (2018c).

A comparison of the connectivity of our sign-flipped homotope with Rice et al.'s alternative site reveals a high similarity. The maps are highly correlated (r = .7). Both seeds show intrinsic connectivity with bilateral ATL, inferior parietal, bilateral medial temporal and ventromedial prefrontal cortex. The seed functionally localised by Rice et al. (2018c), unlike our sign-flipped homotope, also shows connectivity with dorsomedial prefrontal cortex, in line with the results reported by Jackson et al. (2016).

Next, we examined the effects of seed selection on the difference analysis comparing the connectivity of left and right ATL presented in Figure 5 (Supplementary Figure S2.2 below). There were more extensive differences in connectivity when left ATL was compared with the functional peak for right ATL (taken from Rice et al., 2018c), than when it was compared with the sign-flipped homotope used in the main analysis. However, this may have reflected differences in the spatial localisation of these seeds, since the connectivity of ATL changes from medial to lateral and from anterior to posterior regions. For our RH (flipped) > LH contrast, we observe greater involvement of the contralateral hemisphere (where RH>LH connectivity differences were absent for our sign-flipped homotope), as well as more anterior frontal and medial connectivity differences across hemispheres.

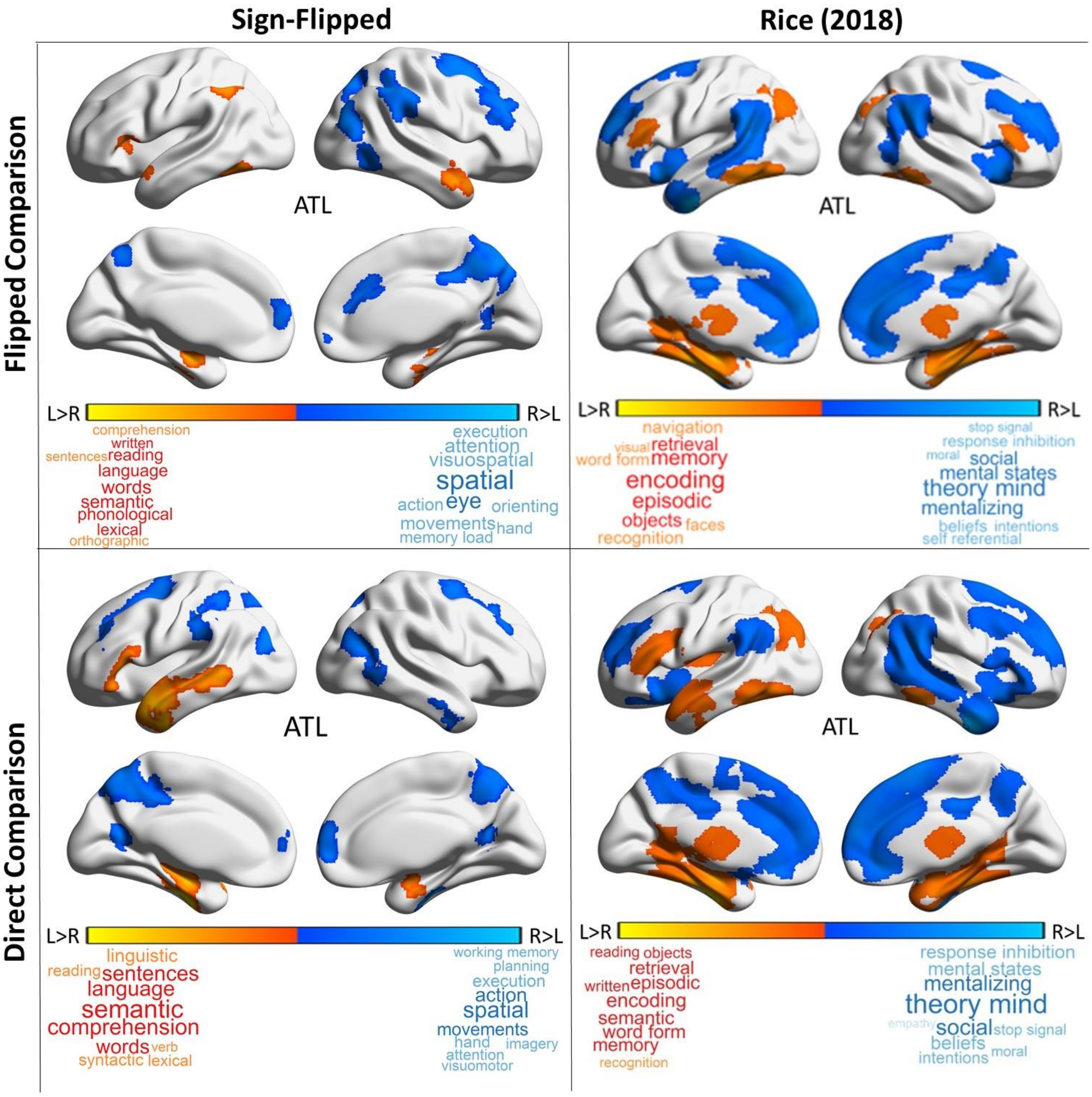


Figure S2.2. Comparison of intrinsic connectivity difference maps for our sign-flipped homotope and Rice's (2018c) right ATL coordinate.

We examined the effect that our selection of the ATL seed had on the correlations and equivalence testing reported in Table 2.2 (main analysis). We recomputed the relevant correlations and equivalence tests for the pairs involving the ATL seed (namely, IFG, pMTG and AG to ATL, as well as L-ATL to R-ATL). The results, shown in Table S2.1 reveal greater similarity between IFG and ATL for Rice's RH ATL seed, and greater differences between ATL and AG, and ATL and pMTG. A new finding was that connectivity between left pMTG and left ATL was significantly higher than between right pMTG and right ATL using the seed from Rice et al. (2018c) – this finding was not observed with the RH homotope seed. Unsurprisingly, there was stronger similarity between the connectivity patterns of left and right ATL using the sign-flipped homotope (Pearson's r = 0.85) than for Rice's alternative ROI (r = 0.61).

	LH	RH	LH vs. RH: Fisher r to z	Equivalence test for difference in r (TOST)
IFG to ATL	.129	.107	z=0.22, p>.1	r(194)=0.02, p=.004
pMTG to ATL	.298	.092	**z=2.11, p<.05**	**r(194)=0.21, p=.491**
ATL to AG	.141	.055	z=0.85, p>.1	r(194)=0.09, p=.042

Table S2.1. Within-hemisphere correlations for the new ATL group mean connectivity maps derived from Rice et al. (2018c) compared to our three other seeds. All correlations are significant at p < .001. Correlations that are different between LH and RH, and those that are not statistically equivalent across hemispheres, are highlighted in bold.

Finally, we examined the relationship between individual differences in connectivity from the alternative right ATL seed provided by Rice et al. (2018c) and behavioural performance but there were no significant results.

Supplementary Analysis S2.2. Direct comparison of differential connectivity

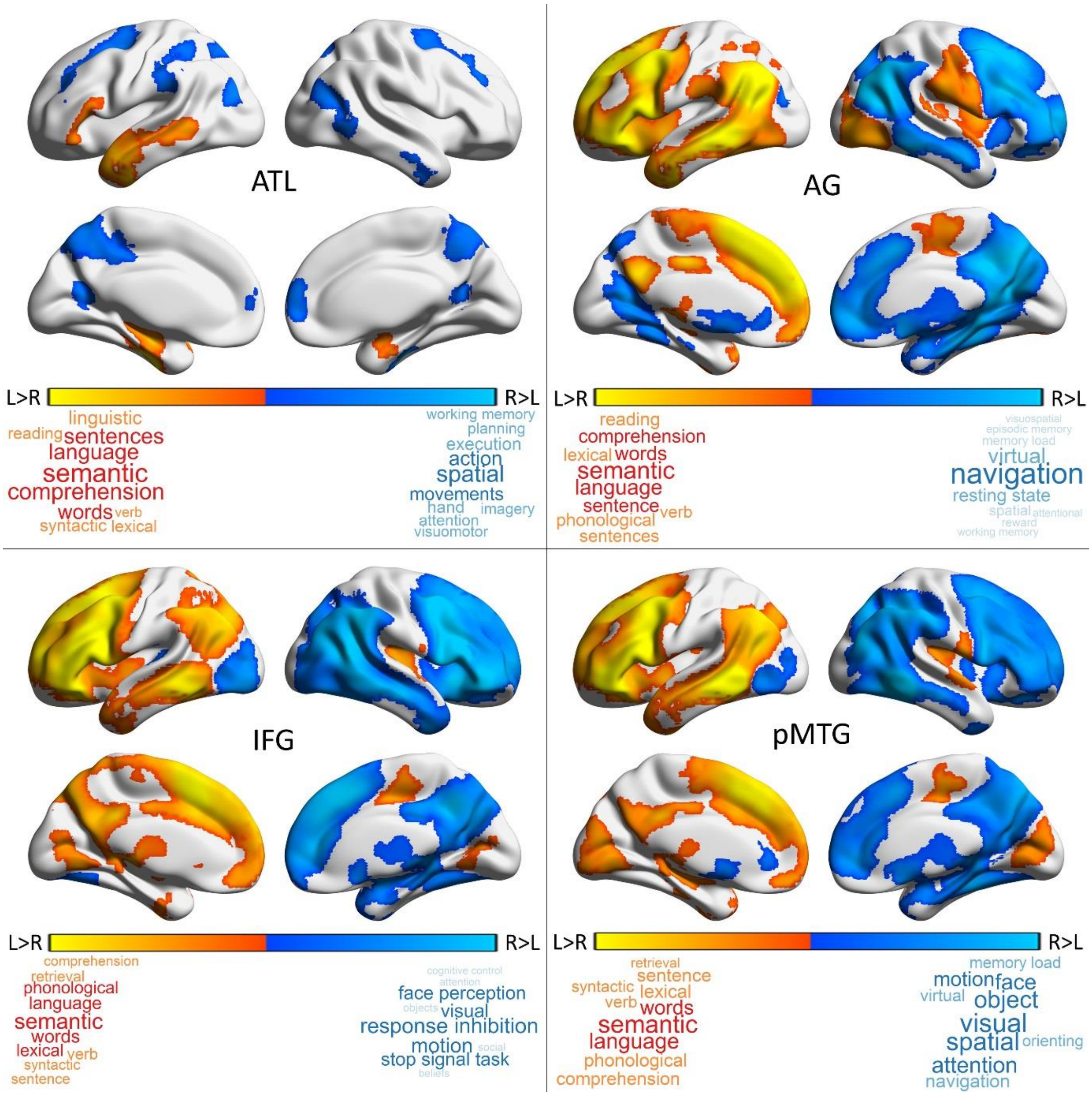


Figure S2.3. Intrinsic connectivity group maps showing the difference in connectivity between our semantic seeds of interest (left hemisphere) and their homotopes (right hemisphere). Each panel shows a direct comparison of left and right hemisphere seeds for a specific brain region (z = 3.1, p < .05). The results of cognitive decoding using Neurosynth (Yarkoni et al., 2011) are shown in the word clouds.

Supplementary Analysis S2.3. Conjunctions of homotopes

In this supplementary analysis, we repeated our conjunction analysis (see Methods for details: we used easythresh_conj.sh with p = .05 and a cluster-forming threshold of Z=3.1) but focussing on the common connectivity shared by each LH seed and its RH homotope this time.

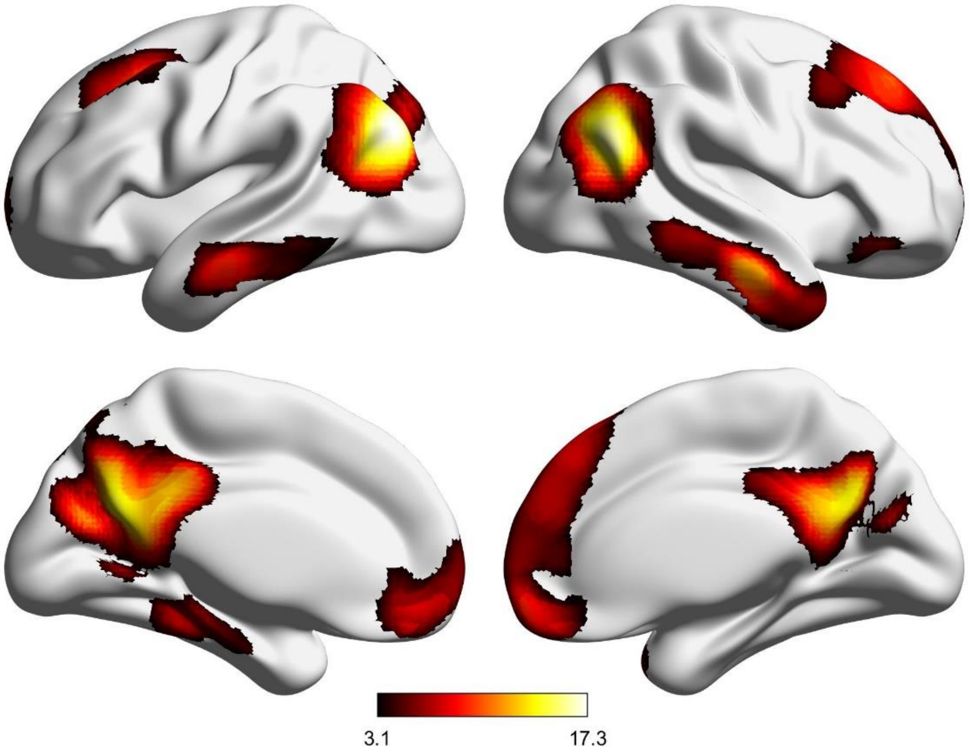


Figure S2.4. Common connectivity for left and right Angular Gyrus.

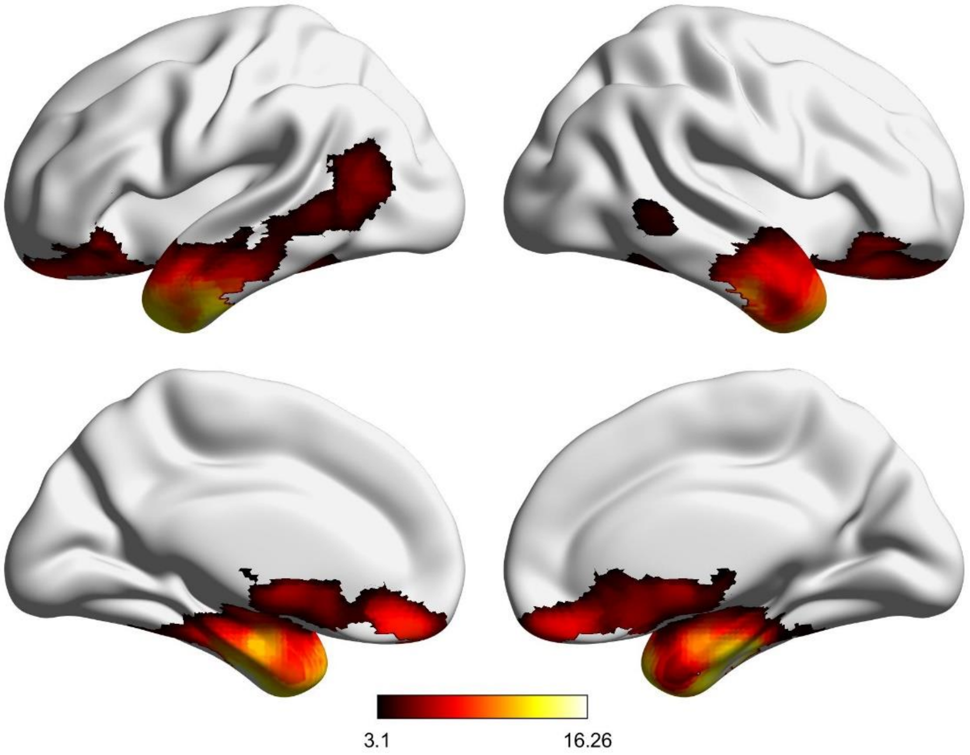


Figure S2.5. Common connectivity for left and right Anterior Temporal Lobe.

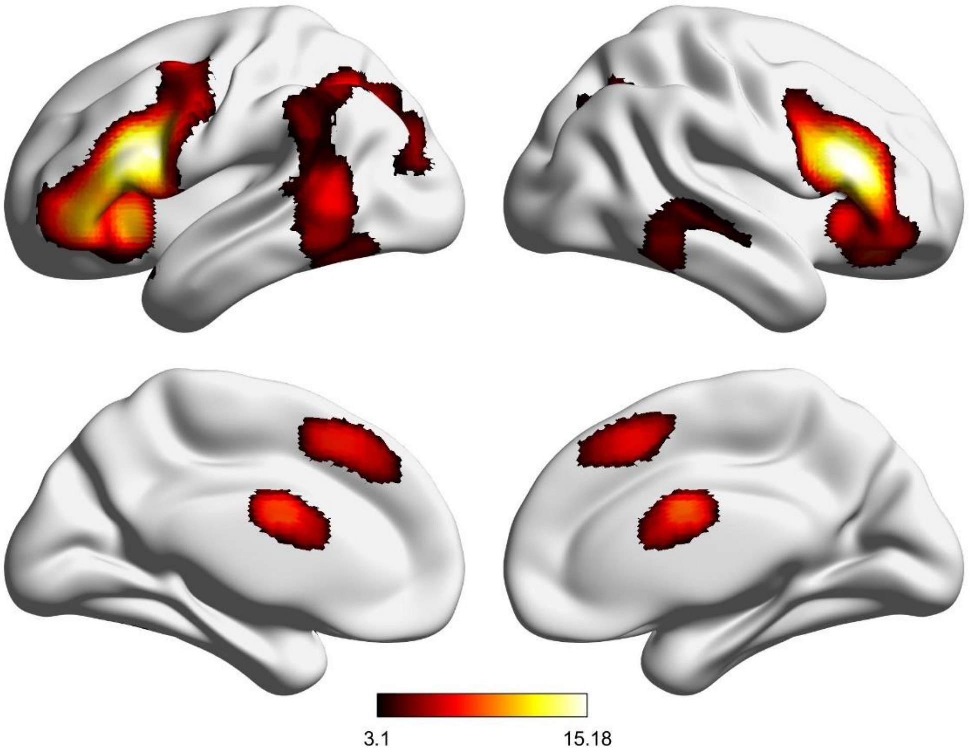


Figure S2.6. Common connectivity for left and right Inferior Frontal Gyrus

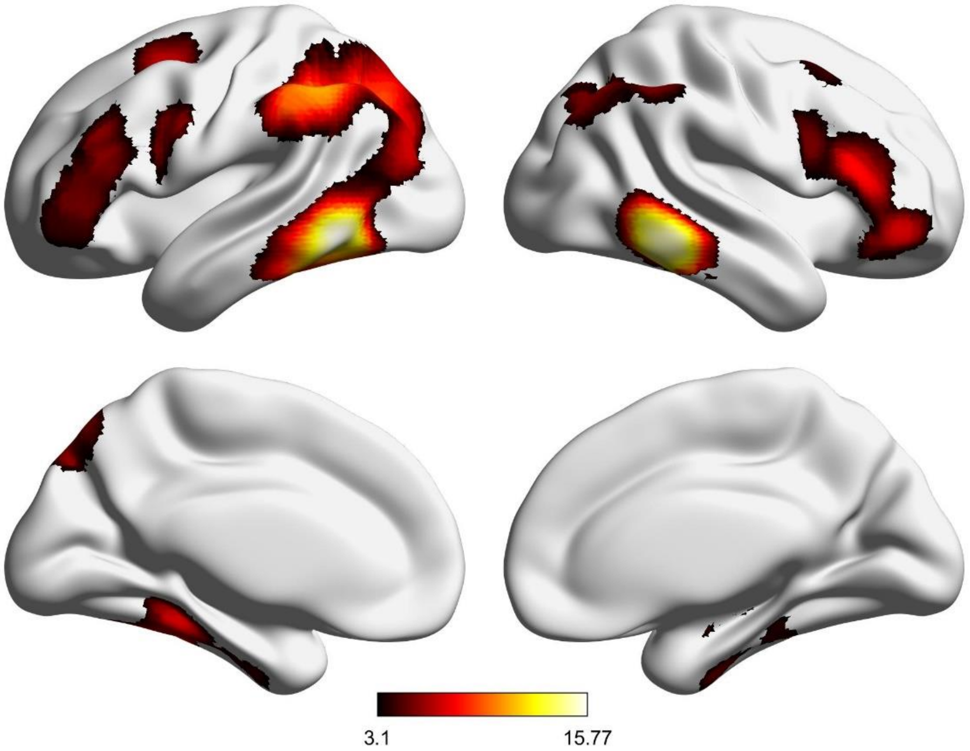


Figure S2.7. Common connectivity for left and right posterior Middle Temporal Gyrus

The results show that both left AG and its homotope show a pattern of common connectivity with regions in the DMN, including bilateral AG, lateral temporal cortex, anterior and posterior cingulate, and dorsolateral prefrontal cortex (Fig S2.4). The common connectivity for both ATLs covers lateral and medial aspects of the temporal lobe, more extended in the left than right hemisphere, as well as bilateral medial orbitofrontal cortex (Fig S2.5). Common connectivity for left and right IFG includes inferior and middle frontal gyri, pre-supplementary motor area/paracingulate cortex, pMTG and parietal regions that are close to AG, more extended in the left than right hemisphere (Fig S2.6). Lastly, pMTG's common connectivity included bilateral pMTG, IFG and superior frontal sulcus, and intraparietal sulcus, more extended in left than right hemisphere (Fig S2.7).

The findings reported here are consistent with the connectivity of the seeds reported in the literature and in the main body of our manuscript: both AG seeds are allied to all core regions of the DMN (Bellana et al., 2016) while both ATLs show common connectivity to DMN and memory regions, as would be expected for the storage of semantic representations (Rice et al., 2015a, 2015b). IFG and pMTG showed similar common connectivity across LH and RH, including to each other and other control regions, adding further evidence that both these seeds form part of a network supporting controlled aspects of semantic cognition (Davey et al., 2016; Hallam et al., 2016).

Accompanying Materials, Chapter 4

Supplementary Analysis S4.1. Analysis within a semantic control mask

This analysis was performed as a conservative check to verify whether brain regions within the semantic control network support inhibition for meaningful stimuli, even though this effect was not found within the whole-brain analysis. We performed the same contrasts as for the whole-brain analysis within a semantic control mask, defined by the meta-analysis of Noonan et al. (2013). The results are shown in Figure S4.1. There were no significant interactions between inhibition and modality or task, confirming that inhibition, regardless of meaning and presentation modality, was largely mediated by the right-lateralised network depicted in Figure 4.2. There was also no conjunction between inhibition across tasks and modalities within the semantic control network. This analysis did reveal clusters in left inferior frontal gyrus for the main effect of meaningful stimuli (both pictures and words) over meaningless perceptual stimuli, in line with the role of left inferior frontal gyrus in semantic processing. The analysis also reproduced effects for inhibition (No-Go > Go for Perceptual trials) in intraparietal sulcus, where the semantic control network overlaps with multiple-demand regions (peaks at 4, 22, 42; -38, 16, -8; -50, -64, -4; 40, 20, -14; 50, 30, 26 and -38, -44, 50). This activation is shown in Figure 4.2 and not reproduced in Figure S4.1.

Overall, these findings suggest that demanding semantic tasks do not necessarily activate the left-lateralised semantic control network. Our semantic inhibition tasks required meaning to be used to withhold a prepotent button press, but the task did not require an unusual or challenging pattern of semantic retrieval to be established per se. In contrast, tasks that activate the left-lateralised semantic control network involve retrieving weak associations or non-dominant features, and directing retrieval away from distractors or dominant but currently-irrelevant aspects of knowledge.

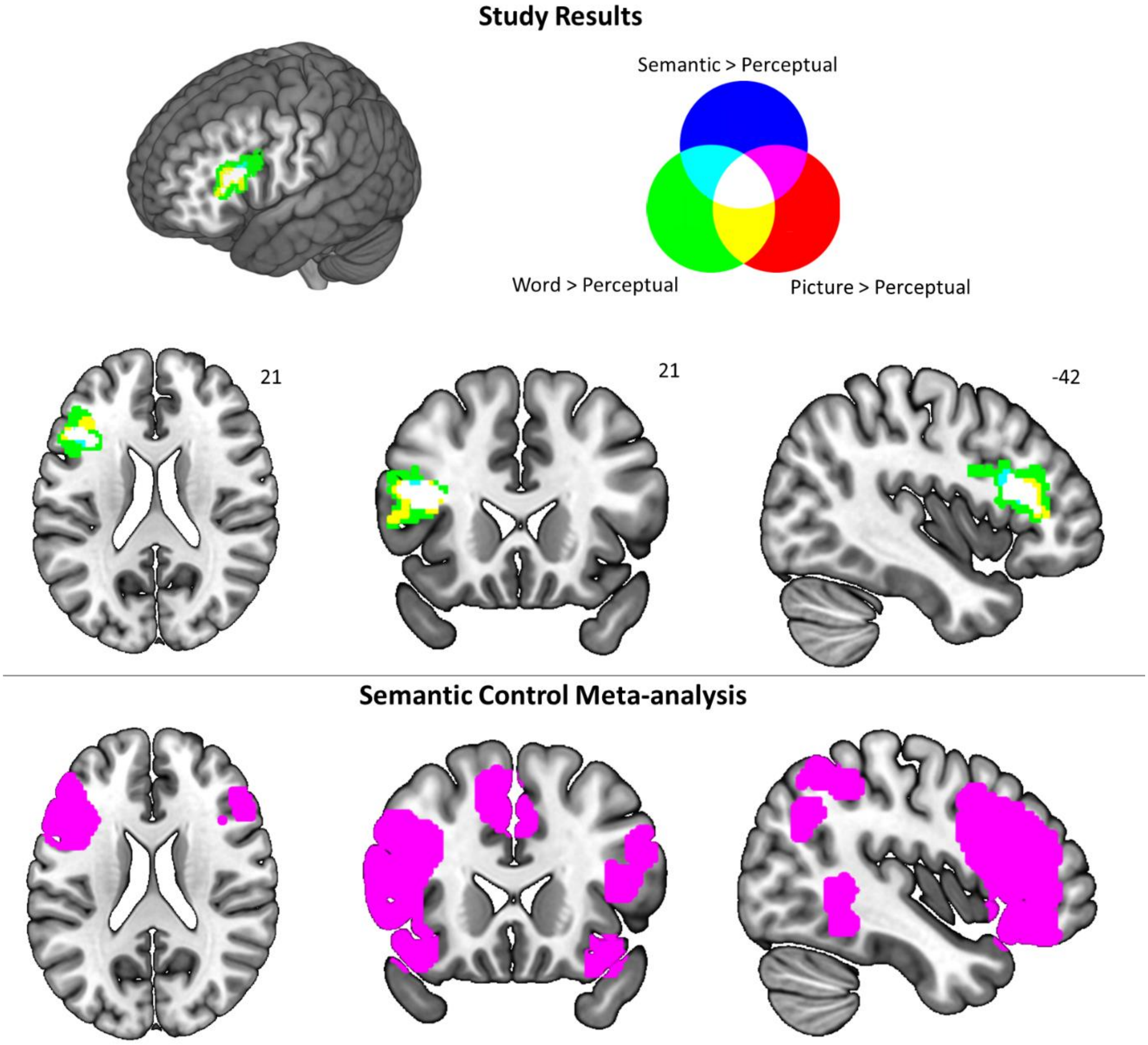


Figure S4.1. Task contrasts from Experiment 1 masked by the semantic control meta-analysis of Noonan and colleagues (2013).

Supplementary Analysis S4.2. Regions-of-interest analysis of activation in multiple-demand system

We extracted the signal per condition for 8 ROIs within MD cortex, defined by Duncan (2010), using 3mm radius spheres. The sites were right and left inferior frontal sulcus (IFS), intraparietal sulcus (IPS), frontal operculum/anterior insula (FO/AI), and two medial sites, pre-supplementary motor area (pre-SMA) and anterior cingulate cortex (ACC). Activation within each MD region is shown in Figure S4.2. Supplementary Table 4.1 shows the results of repeated-measures ANOVAs for each site, including two factors: inhibition (with 2 levels: go and no-go) and task (with 4 levels: word, picture, easy perceptual and hard perceptual). Supplementary Table 4.2 shows additional t-tests for those sites showing a main effect of task. The t-tests assessed differences between words and pictures, easy and hard perceptual decisions, and semantic and perceptual trials (combining words and pictures, as well as easy and hard perceptual trials). There was some effect of inhibition (i.e. no-go > go events) in all of these MD sites, although this was only approaching significance in left IFS, preSMA and ACC. Four of the sites also showed a main effect of task. Left IFS showed greater activation for words than pictures, and a main effect of semantic > perceptual which was approaching significance. This pattern was similar to our semantic control ROI (Supplementary Analysis 4.1), which bordered left IFS. Left AI/FO showed greater activation for the hardest task conditions (word and hard perceptual trials). Both right hemisphere sites (right AI/FO and IPS) showed a perceptual > semantic effect, even though the difficulty of those decisions was broadly matched. Critically, none of the sites showed an interaction between inhibition and task, suggesting the magnitude of the inhibition effect was similar across semantic and perceptual trials.

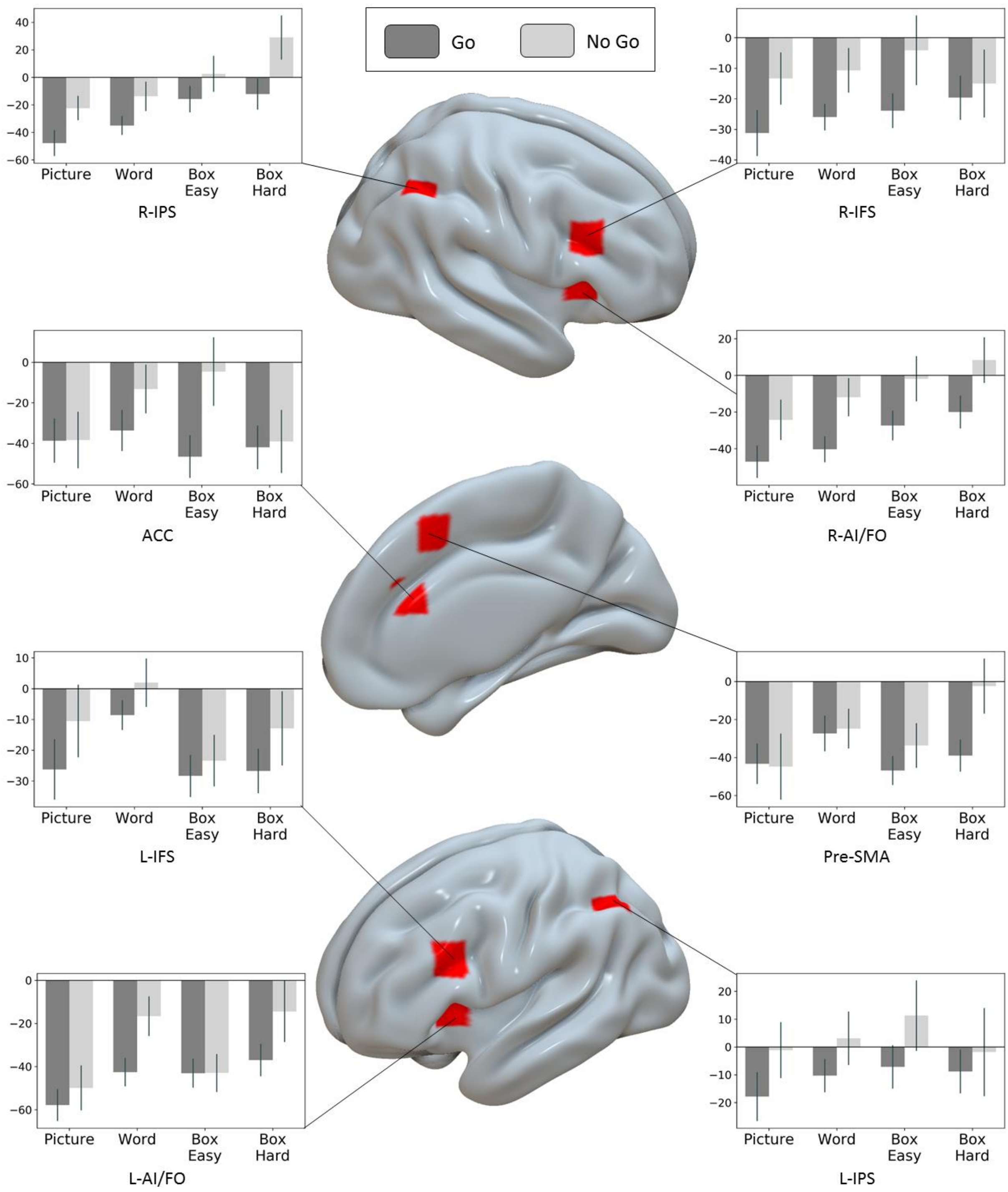


Figure S4.2. Results of a ROI analysis examining multiple-demand peak regions taken from Duncan (2010). The error bars depict the standard error of the mean and the fMRI signal units are arbitrary. ACC: Anterior Cingulate Cortex, AI/FO: Anterior Insula / Frontal Operculum, IFS: Inferior Frontal Sulcus, IPS: Intra-Parietal Sulcus, pre-SMA: Pre-Supplementary Motor Area

Sphere	Contrast	F	p
Left Anterior Insula / Frontal Operculum	Condition	5.03	.003
	Inhibition	5.34	.029
	Condition*Inhibition	1.34	.257
Right Anterior Insula / Frontal Operculum	Condition	4.26	.008
	Inhibition	24.09	< .001
	Condition*Inhibition	0.08	.973
Left Inferior Frontal Sulcus	Condition	2.8	.046
	Inhibition	4	.056
	Condition*Inhibition	0.22	.882
Right Inferior Frontal Sulcus	Condition	0.3	.828
	Inhibition	8.05	.009
	Condition*Inhibition	0.49	.692
Left Intraparietal Sulcus	Condition	0.44	.723
	Inhibition	5.64	.025
	Condition*Inhibition	0.19	.902
Right Intraparietal Sulcus	Condition	4.83	.014
	Inhibition	24.4	< .001
	Condition*Inhibition	1.04	.381
Pre Supplementary Motor Area	Condition	2.38	.076
	Inhibition	3.78	.063
	Condition*Inhibition	1.93	.132
Anterior Cingulate Cortex	Condition	0.92	.434
	Inhibition	4	.056
	Condition*Inhibition	1.38	.254

Table S4.1. Results of 4 x 2 repeated-measures ANOVAs examining activation in multiple-demand peaks from Duncan (2010). The ANOVA examined the effects of inhibition (Go vs. No Go events) and task (Word, Picture, Perceptual Easy and Perceptual Hard trials).

Sphere	Contrast	t	p
Left Anterior Insula / Frontal Operculum	Word > Picture	2.82	.009
	Hard > Easy	2.33	.028
	Perceptual > Semantic	1.26	.22
Right Anterior Insula / Frontal Operculum	Word > Picture	1.19	.246
	Hard > Easy	1.48	.151
	Perceptual > Semantic	2.47	.02
Left Inferior Frontal Sulcus	Word > Picture	2.05	.051
	Hard > Easy	0.77	.446
	Semantic > Perceptual	1.87	.072
Right Intraparietal Sulcus	Word > Picture	1.22	.233
	Hard > Easy	1.69	.103
	Perceptual > Semantic	2.49	.02

Table S4.2. Results of t-tests comparing activation in different tasks within multiple-demand peaks from Duncan (2010). Hard vs. Easy compared perceptual decisions of different difficulty. The Semantic score was an average of Words and Pictures. The Perceptual score was an average of Hard and Easy.

Discussion: An important research question within the literature on cognitive control concerns whether there are functional divisions within MD cortex. By definition, these sites show stronger responses to difficult trials across a range of tasks. However, Hampshire et al. (2007) found a clear fractionation within this system using a target detection paradigm: sites within the frontoparietal network responded to both targets and related distractors, while sites in the salience network responded more selectively to targets. In the whole-brain analysis (Figure 2 in main body), our Go/No-Go task elicited stronger activation within the frontoparietal network. This might be because participants were required to maintain an abstract category (either semantic or perceptual) and then use this to determine whether to withhold a button press. Activation in these regions is consistent with the view that this network maintains abstract goals and/or allocates attention to items with behaviourally-relevant features (Hampshire et al., 2007).

The ROI analysis above provides further evidence for MD fractionation in the left hemisphere, although this functional dissociation does not appear to characterise the whole network. Left IFS within the frontoparietal network showed a marginally-significant main effect of semantic vs. perceptual decisions, while left AI/FO within the saliency network showed a main effect of difficulty (words and hard perceptual judgements elicited more activation than easier picture and perceptual judgements). Hampshire et al. (2007) discussed alternative accounts of MD fractionation, in which the critical distinction between frontoparietal and saliency networks was thought to reflect abstract vs. concrete representations, or more general vs. specific attentional allocation. The functional specialisation we observed in left PFC is consistent with a combination of these accounts. The results for left IFS are broadly consistent with a representational account, since conceptual distinctions are more abstract than the perceptual features that defined the non-semantic decisions. The results for left AI/FO fit better with a process account, since these areas responded more strongly in conditions in which the selection of targets and non-targets was more difficult (e.g., word and hard perceptual conditions). These differences were relatively subtle and not present for all sites.

				Coordinates (in mm)			
Analysis	Hemisphere	Cluster Peak	Z	x	y	z	Cluster Volume
		Experiment 1					
Semantic and Perceptual Inhibition Common Regions	Right	Lateral Occipital Cortex	4.75	50	-74	-4	1768
	Right	Intraparietal Sulcus	4.34	44	-38	48	1222
	Right	Precentral Gyrus	4.2	46	0	46	538
	Left	Lateral Occipital Cortex	4.32	-46	-80	2	351
	Right	Frontal Pole	3.88	32	52	26	211
Perceptual > Semantic	Right	Intraparietal Sulcus	5.04	42	-40	50	1504
	Left	Intraparietal Sulcus	5.1	-36	-56	56	430
	Right	Precentral Gyrus	4.85	54	10	18	411
	Right	Middle Frontal Gyrus	4.29	38	2	56	183
	Right	Posterior Middle Temporal Gyrus	4.15	52	-56	-2	181
Semantic > Perceptual	Left	Fusiform Gyrus	5.43	-38	-46	-24	1082
	Right	Fusiform Gyrus	4.78	38	-54	-24	289
Word > Perceptual	Left	Inferior Frontal Gyrus	4.79	-42	30	16	477
	Left	Anterior Cingulate Gyrus	3.84	-6	18	26	150
Picture > Perceptual	Left	Fusiform Gyrus	5.12	-36	-44	-24	753
	Left	Intracalcarine Cortex	4.76	-10	-64	6	398
	Right	Fusiform Gyrus	5.03	36	-54	-24	376
Picture > Word Inhibition Interaction	Right	Lateral Occipital Cortex	4.65	52	-74	0	191
Picture > Word	Right	Occipital Pole	6	32	-90	6	1649
	Left	Fusiform Gyrus	5.94	-34	-74	-14	915
		Experiment 2					
Semantic & Perceptual Inhibition Common Regions - Semantic > Perceptual Result	Left	Subcallosal Cortex	5.23	-6	16	-16	176
	Left	Parahippocampal Gyrus	4.64	-28	-24	-26	163
Picture > Word Inhibition Interaction - Picture > Word	Left	Thalamus	4.42	-16	-6	14	98
Picture > Word Inhibition Interaction - Picture > Perceptual	Left	Thalamus	4.31	-18	-28	14	203

Supplementary Figure S1

Word > Perceptual	Left	Inferior Frontal Gyrus	4.99	-36	20	16	808
Picture > Perceptual	Left	Inferior Frontal Gyrus	4.23	-36	20	16	205
Semantic > Perceptual	Left	Inferior Frontal Gyrus	4.04	-40	20	18	133

Table S4.3. Clusters of activity for Experiments 1 (task-based fMRI) and 2 (resting state fMRI), and supplementary analysis. Note. Coordinates are in MNI space.

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