Uncovering Dynamic Semantic Networks in the Brain Using Novel Approaches for EEG/MEG Connectome Reconstruction

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Uncovering Dynamic Semantic Networks in the Brain Using Novel Approaches for EEG/MEG Connectome Reconstruction

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The current thesis addresses some of the unresolved predictions of recent models of the semantic brain system, such as the hub-and-spokes model. In particular, we tackle different aspects of the hypothesis that a widespread network of interacting heteromodal (hub(s)) and unimodal (spokes) cortices underlie semantic cognition. For this purpose, we use connectivity analyses, measures of graph theory and permutation-based statistics with source reconstructed Electro/MagnetoEncephaloGraphy (EEG/MEG) data in order to track dynamic modulations of activity and connectivity within the semantic networks while a concept unfolds in the brain. Moreover, in order to obtain more accurate connectivity estimates of the semantic networks, we propose novel methods for some of the challenges associated with EEG/MEG connectivity analysis in source space.

We utilised data-driven analyses of EEG/MEG recordings of visual word recognition paradigms and found that: 1) Bilateral Anterior Temporal Lobes (ATLs) acted as potential processor hubs for higher-level abstract representation of concepts. This was reflected in modulations of activity by multiple contrasts of semantic variables; 2) ATL and Angular Gyrus (AG) acted as potential integrator hubs for integration of information produced in distributed semantic areas. This was observed using Dynamic Causal Modelling of connectivity among the main left-hemispheric candidate hubs and modulations of functional connectivity of ATL and AG to semantic spokes by word concreteness. Furthermore, examining whole-brain connectomes using measures of graph theory revealed modules in the right ATL and parietal cortex as global hubs; 3) Brain oscillations associated with perception and action in low-level cortices, in particular Alpha and Gamma rhythms, were modulated in response to words with those sensory-motor attributes in the corresponding spokes, shedding light on the mechanism of semantic representations in spokes; 4) Three types of hub-hub, hub-spoke and spoke-spoke connectivity were found to underlie dynamic semantic graphs.

Importantly, these results were obtained using novel approaches proposed to address two challenges associated with EEG/MEG connectivity. Firstly, in order to find the most suitable of several connectivity metrics, we utilised principal component analysis (PCA) to find commonalities and differences of those methods when applied to a dataset and identified the most suitable metric based on the maximum explained variance. Secondly, reconstruction of EEG/MEG connectomes using anatomical or fMRI-based parcellations can be significantly contaminated by spurious leakage-induced connections in source space. We, therefore, utilised cross-talk functions in order to optimise the number, size and locations of cortical parcels, obtaining EEG/MEG-adaptive parcellations.

In summary, this thesis proposes approaches for optimising EEG/MEG connectivity analyses and applies them to provide the first empirical evidence regarding some of the core predictions of the hub-and-spokes model. The key findings support the general framework of the hub(s)-and-spokes, but also suggest modifications to the model, particularly regarding the definition of semantic hub(s).
To mum and dad...
PREFACE

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the Preface and specified in the text. The work was carried out between October 2014 and February 2018 at the Medical Research Council Cognition and Brain Sciences Unit (MRC CBU), University of Cambridge, Cambridge, UK and under supervision of Dr. Olaf Hauk and advice of Professor Richard Henson.

No part of this thesis is substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution. I further state that no substantial part of my dissertation has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution.

Collaborations:

- In Chapters 3 and 4, I have utilised a pre-existing dataset to address new questions. The experiment was designed and collected by Olaf Hauk, Anna Woollams, Karalyn Patterson, Elisa Cooper, Gemma Evans and Yuanyuan Chen at the MRC CBU.
- In Chapter 3, Dynamic Causal Modelling was conducted mostly under supervision of Richard Henson and some of the utilised code was kindly provided by him.
- Chapters 3 and 4 have been carried out in collaboration with Karalyn Patterson and Anna Woollams.

Journal publications:

- Chapters 3, 4, 5 and 7 are also in preparation and are expected to be submitted for publications without substantial modifications to the content.

Conferences presentations:

- Chapters 3 and 4 have been presented as posters at: 22nd and 23rd Annual Meeting of the Organization for the Human Brain Mapping, (OHBM) Geneva, Switzerland, 2016 and Vancouver, Canada, 2017, 8th Annual Meeting of the Society for Neurobiology of Language (SNL), London, UK, 2016 as well as local meetings in Cambridge. These chapters will be
presented as a talk (merit abstract award, honourable mention) at the 10th annual meeting of SNL, Quebec City, Canada.

- Chapter 6 has been presented at: 22nd (poster) and 23rd (poster and oral presentation, winner of a merit abstract award) Annual Meeting of the OHBM (Geneva, Switzerland, 2016 and Vancouver, Canada, 2017) as well as MEG UK Meeting (oral presentation), Oxford, UK, 2017. Some parts of this chapter together with some parts of chapter 7 will be presented as a symposium talk at the 21st international conference on Biomagnetism, Philadelphia, USA.

- Chapters 5 and 7 were accepted for poster presentations at the 24th Annual Meeting of the OHBM (Singapore, 2018). Chapter 7 will be presented as a poster at the 10th annual meeting of SNL, Quebec City, Canada.

In all the aforementioned collaborations, journal publication and conference presentations, I have been the first author, preparing the manuscripts, abstracts, posters and talks and revising them in collaboration with the co-authors. Additionally, all the data analysis codes, unless stated otherwise, have been written by myself.

This thesis does not exceed 60,000 words (excluding figure, tables, appendices and bibliography), and contains less than 150 figures as prescribed by the Degree Committee at the School of Clinical Medicine.
SUMMARY

The current thesis addresses some of the unresolved predictions of recent models of the semantic brain system, such as the hub-and-spokes model. In particular, we tackle different aspects of the hypothesis that a widespread network of interacting heteromodal (hub(s)) and unimodal (spokes) cortices underlie semantic cognition. For this purpose, we use connectivity analyses, measures of graph theory and permutation-based statistics with source reconstructed Electro-MagnetoEncephaloGraphy (EEG/MEG) data in order to track dynamic modulations of activity and connectivity within the semantic networks while a concept unfolds in the brain. Moreover, in order to obtain more accurate connectivity estimates of the semantic networks, we propose novel methods for some of the challenges associated with EEG/MEG connectivity analysis in source space.

We utilised data-driven analyses of EEG/MEG recordings of visual word recognition paradigms and found that: 1) Bilateral Anterior Temporal Lobes (ATLs) acted as potential processor hubs for higher-level abstract representation of concepts. This was reflected in modulations of activity by multiple contrasts of semantic variables; 2) ATL and Angular Gyrus (AG) acted as potential integrator hubs for integration of information produced in distributed semantic areas. This was observed using Dynamic Causal Modelling of connectivity among the main left-hemispheric candidate hubs and modulations of functional connectivity of ATL and AG to semantic spokes by word concreteness. Furthermore, examining whole-brain connectomes using measures of graph theory revealed modules in the right ATL and parietal cortex as global hubs; 3) Brain oscillations associated with perception and action in low-level cortices, in particular Alpha and Gamma rhythms, were modulated in response to words with those sensory-motor attributes in the corresponding spokes, shedding light on the mechanism of semantic representations in spokes; 4) Three types of hub-hub, hub-spoke and spoke-spoke connectivity were found to underlie dynamic semantic graphs.

Importantly, these results were obtained using novel approaches proposed to address two challenges associated with EEG/MEG connectivity. Firstly, in order to find the most suitable of several connectivity metrics, we utilised principal component analysis (PCA) to find commonalities and differences of those methods when applied to a dataset and identified the most suitable metric based on the maximum explained variance. Secondly, reconstruction of EEG/MEG connectomes using anatomical or fMRI-based parcellations can be significantly contaminated by spurious leakage-induced connections in source space. We, therefore, utilised cross-talk functions in order to optimise the number, size and locations of cortical parcels, obtaining EEG/MEG-adaptive parcellations.

In summary, this thesis proposes approaches for optimising EEG/MEG connectivity analyses and applies them to provide the first empirical evidence regarding some of the core predictions of the hub-and-spokes model. The key findings support the general framework of the hub(s)-and-spokes, but also suggest modifications to the model, particularly regarding the definition of semantic hub(s).
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First and foremost, I would like to thank my supervisor, Dr. Olaf Hauk, who has been very generous with his advice and time throughout these years, for our weekly in-depth discussions that helped me see different topics from several angles and acquire a more profound idea of the bigger pictures. For patiently guiding me through different steps but also giving me freedom to explore exciting new ideas, sometimes make mistakes, and eventually stand on my feet.

I am also very grateful to my advisor Prof. Rik Henson, whose key advice at tipping points influenced the direction of the thesis, for good. Rik is very generous with his neat codes and fitting you in his busy schedule, but most importantly, sometimes he helped me see rooms for major improvements in the work with only a one-line comment.

The next thank you goes to the CBU, for being a unique research environment, combining brilliant neuroscientific research with a friendly atmosphere with coffee breaks, cakes, and Christmas parties. I cannot possibly thank everyone, but I would like to thank the graduate tutors and pastors for providing support and helpful feedback, the admin team for making sure that participant recruitment goes smoothly and the IT team, for keeping the computing systems up and running. Thanks also to the MRI/EEG/MEG teams and the operators, in particular, Clare, Lucy, Tina, Darren and Amy for operating most of our MEG slots.

During these years, I have had the opportunity to learn very much as a student representative in the CBU’s E&D committee, a group of dedicated individuals who care about increasing equality and diversity in academic environments and go out of their ways to make a difference, where possible. Additionally, through these past years, I have been fortunate to share offices and PhD chats (and of course chocolates) with many lovely CBUers who made this journey more pleasant.

I would also like to thank Cambridge Trust for funding my studies through Cambridge International Scholarship Scheme, and my examiners, Dr. Matt Davis and Prof. Gareth Barnes for making constructive comments on the thesis, and for a profound and enjoyable discussion on my viva day. Thanks also to Selwyn College, in particular my graduate tutors Dr. Anita Faul and Prof. Nicholas Butterfield, and Samantha Carr from the tutorial office who is always there to help with admin matters, and always with a smile.

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<tr>
<td>ATL</td>
<td>Anterior Temporal Lobe</td>
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<tr>
<td>BMA</td>
<td>Bayesian Model Averaging</td>
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<td>BOLD</td>
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<td>CC</td>
<td>Correlation coefficient</td>
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1 Introduction

Conceptual knowledge of objects, people, and facts, independent of the individual episodes of one’s life is referred to as Semantics (Patterson et. al, 2007). Neural mechanisms that underpin semantic cognition, as one of the key higher-level cognitive functions of the human brain, have been a topic of great interest in cognitive neuroscience for decades (Binder & Desai 2011; Lambon Ralph et al. 2016; Pulvermüller 2013). Neuroimaging research in recent years has shed light on some aspects of the semantic system in the brain, revealing in particular, that numerous heteromodal and unimodal brain areas are involved in meaning comprehension (Binder & Desai 2011; Huth et al. 2016). However, in spite of the localisation of semantic areas, it remains unclear as to how these areas are connected, what are the mechanisms of involvement of each area and what are the temporal and oscillatory underpinnings of semantic networks while a concept unfolds in the brain. Importantly, the most prominent theories of semantic cognition (e.g. the hub-and-spokes model) propose a “network” of interacting cortices to underlie semantics. Nonetheless, due to the lack of empirical evidence or inconsistent findings, some of the key predictions of these models have remained controversial. For example, there has been no consensus to date about the roles of different heteromodal semantic areas and more specifically as to whether or not distributed semantic networks are bound by a central heteromodal semantic hub (Binder 2016; Lambon Ralph et al. 2016). Furthermore, the degree to which meaning comprehension is grounded in one’s sensory-motor-limbic experiences of the world and subsequently the specific role of lower-level unimodal cortices in semantics has remained largely unknown (Hauk & Tschentscher 2013).
The main goal of the current thesis is to address some of these questions through investigation of dynamic variations in activity and connectivity of semantic areas throughout different stages of word meaning comprehension in the brain. For this purpose, we will use advanced connectivity analysis techniques, measures of graph theory and permutation-based statistics together with the high spatio-temporal resolution of source reconstructed Electro-/Magneto-Encephalography (EEG/MEG). Additionally, we will propose methodological developments for a more accurate reconstruction of the dynamic brain networks from EEG/MEG in source space and recruit them to study the aforementioned cognitive questions of interest. In this chapter, I will first summarise the prominent theories for the organisation of semantic networks in the brain, emphasising, in particular, the hub-and-spokes model (Patterson et al. 2007; Rogers et al. 2004). Thereafter, I will provide a brief review of the spatial, temporal and spectral properties of semantic networks that have been revealed in the previous literature. Next, I will discuss some of the key outstanding questions and our approach to tackling those questions in the current thesis (cognitive scope of the thesis). In the next chapter, I will focus on the novel methods that we will propose in order to enhance EEG/MEG network reconstructions (method development scope of the thesis). The latter, even though applied to the semantic networks here, is anticipated to be applicable to EEG/MEG studies in general.

1.1 Theories of the brain semantic system

One of the key questions regarding semantic representation in the brain has been whether or not a simulation of the referent of a word in the brain is necessary for meaning retrieval. In other words, is conceptual processing in the brain grounded in our sensory-motor-limbic experiences of the world (see Figure 1.1 for an overview of different theories)? Some early theories of semantic processing in the brain proposed that concepts are represented in a symbolic manner in the brain, hypothesising that after the learning phase of a concept is completed, it will be abstracted away from the associated sensory-motor-limbic experiences and stored in/retrieved from a core amodal semantic subsystem within the language system in the brain (Collins & Loftus 1975). In this view, also known as disembodied semantics, an arbitrary relationship between a word and what it represents in real world is assumed. Instead, a word might be retrieved through superposition of symbolic lexical items (Levelt 1989) or alternatively, through its statistical co-occurrence with other words in the language (Landauer & Dumais 1997).

On the contrary, some later theories of semantics proposed that perceptual attributes that are associated with each concept are reactivated during concept retrieval in the brain. Some of these theories, referred to as strong embodiment and opposing the disembodied view, proposed that sensory-motor neurons in the brain contain built-in mechanisms that are sufficient for semantic
representation (Glenberg & Kaschak 2003). For this purpose, concepts were suggested to be constructed through weighted activation of low-level sensory areas and direct connections between these cortices without a need for a mediating subsystem for symbolic representation (Glenberg & Kaschak 2003; Zwaan 2003). Various modifications of this model with different degrees of embodiment have been proposed in the literature (Barsalou 1999; Pulvermüller 1999) with one of the key assumptions of all these models being that the brain reactivates sensory-motor-limbic signals involved in perception, action, and emotion as a part of concept retrieval.

Neuroimaging in recent years, as will be elaborated below in 1.2, has provided evidence for an intermediate position between the aforementioned disembodiment and strong embodiment views. Contemporary theories that hold an intermediate position typically postulate a widespread network of interacting heteromodal language areas and modality-specific sensory-motor-limbic cortices to underlie semantic retrieval (Meteyard et al. 2012). One of the influential models under this intermediate view has been the hub-and-spokes model (Patterson et al. 2007).

**1.1.1 Hub-and-Spokes model**

The hub-and-spokes model (Figure 1.2) proposes that sensory-motor cortices provide *ingredients* that are required to build up concepts in the brain. However, this information is proposed to be mediated and integrated by a single supramodal semantic hub (Patterson et al. 2007; Rogers et al. 2004). Therefore, a key implication of the model is that a concept is partly encoded in connectivity between the supramodal hub and unimodal sensory-motor-limbic spokes and partly in the activations of these cortices. Supported by evidence from computational connectionist modelling, Rogers et al. (2004) proposed that a single hub is necessary and sufficient to accomplish the purpose of integration
and mediation of the information provided by distributed semantic networks. According to this model, the hub area is the first to receive input from sensory cortices which will then establish functional connections to the distributed semantic cortices, sending and receiving information from those areas, accumulating and integrating this information until a meaning is retrieved.

Informed by research on semantic dementia (SD) patients, Patterson and colleagues (Patterson et al. 2007; Rogers et al. 2004) placed the semantic hub in the bilateral Anterior Temporal Lobes (ATLs). SD, a variant of fronto-temporal dementia is marked by a progressive deterioration of semantic memory, including verbal and functional knowledge of the words and their referents, while other aspects of memory and cognition are fairly preserved (Snowden et al. 1989; Warrington 1975). Neuroimaging studies have abundantly characterised this disorder with focal atrophies to the bilateral ATLs, often more emphasised in the left hemisphere (Snowden et al. 1989, 2017). Therefore, considering the crucial role of the hub in the hub-and-spokes model and the behavioural symptoms induced by ATLs atrophy in SD, Patterson et al. (2007) propose that ATLs can be considered as the semantic hub. It has been suggested that bilateral ATLs act together as a single system to fulfil the hub role (Hoffman & Lambon Ralph 2018). Additionally, introducing lesions in the hub area in the aforementioned computational model, Rogers et al. (2004) found the model to produce similar symptoms as those reported in the SD patients.

Therefore, the hub-and-spokes model provides a well-defined theoretical framework to study semantic networks in the brain. However, several of the fundamental predictions of the model are yet to be supported by empirical evidence and/or have been subject to controversy in recent years. In particular:
1. There has been a substantial controversy regarding the hub candidate (i.e. ATLs) proposed in the model (Binder 2016; Martin et al. 2014; Pulvermüller 2013). More specifically, fMRI research on modality-general semantic cognition in healthy participants has frequently reported the involvement of a group of predominantly left-hemispheric areas in temporal, parietal and frontal cortices in semantic processing (Binder et al. 2009; Price 2010; Binder & Desai 2011). Therefore, it remains unclear as to whether ATLs alone are sufficient to act as a semantic hub or a heteromodal subnetwork of fronto-temporo-parietal hubs, also referred to as convergence zones, are required to fulfil this purpose (Binder 2016; Lambon Ralph et al. 2016). The evidence for the role of the key candidate hub areas will be reviewed briefly later in 1.2.1.

2. The model predicts that sensory-motor cortices provide ingredients for building up concepts in the brain. However, the more specific role of these areas, in particular, the content of these ingredients and how they are encoded in the unimodal cortices are unknown. In other words, does the brain re-activate sensory-motor-limbic systems similar to their recruitment during perception, action and emotion? If so, what experimental manipulations and/or imaging modalities can be used to pinpoint this property? Previous evidence for modulations of spokes in semantics will be reviewed in 1.2.2.

3. Crucially, the model proposes neural activity in heteromodal and unimodal semantic cortices as well as functional connections between these areas as the two key mechanisms recruited for the encoding of semantic information in the brain. Connectivity analysis of semantic networks is a new yet emerging field and hence many aspects of the network organisation remain unknown. Some of the findings to date will be reviewed in 1.2.3.

4. Hub areas are supposedly involved in the integration of low-level unimodal information that is provided by the spokes (integration hubness) as well as a higher level abstract representation of the concepts (processing hubness). Therefore, the hub can be predicted to be involved in multiple stages of concept retrieval. Additionally, the ingredients provided by the spokes are supposedly an essential aspect of semantic retrieval in the brain, leading to the prediction that the spokes as well should get involved as of the earliest stages of semantic processing. Hence, the timing of involvement of these areas will be important in the validation of these predications. Previous findings on the temporo-spectral properties of word semantic representation in the brain will be discussed in 1.3.
Based on this reviewed evidence, I will then highlight some of the key outstanding questions and our approach to tackle them in this thesis in 1.4 (cognitive scope of the thesis).

1.2 Spatial properties of the semantic system

1.2.1 Evidence for semantic representation in heteromodal cortices

Several heteromodal brain areas have been shown to play role in semantic processing. A meta-analysis of 120 functional Magnetic Resonance Imaging (fMRI) studies over two decades (Binder et al. 2009) revealed a set of cortices in the anterior and posterior middle temporal gyri (MTG), posterior inferior parietal lobe (including but not restricted to the angular gyrus (AG)), inferior frontal gyrus (IFG), dorso-/ventro-medial prefrontal cortices as well as fusiform and para-hippocampal gyri to subserve modality-general semantic cognition (Figure 1.3). Among these areas, ATL, pMTG, IFG and AG have been more often reported in the literature (Binder 2016; Hauk & Tschentscher 2013; Lambon Ralph et al. 2016; Pulvermüller 2013). However, it remains unclear as to whether one of them plays the role of a central hub semantic hub or whether they act simultaneously or in a consecutive manner as convergence zones. The evidence for the more specific role of each of these candidate hubs will be briefly summarised here.

![Figure 1.3 Modality-general semantic cortices from meta-analysis of fMRI literature. Adapted from Binder et al. 2009.](image)

Firstly, as mentioned above, the role of ATL as a potential semantic hub was initially raised based on the studies on SD patients. Positron Emission Tomography (PET) imaging and recent fMRI studies with novel distortion correction pulse sequences (to compensate fMRI signal dropout at a proximity of air pockets) (Binney et al. 2012; Patterson et al. 2007) have also reported modulations of ATL activity by semantic variables (Binney et al. 2016; Jackson et al. 2016; Rice et al. 2015b; Visser et al. 2012) in non-clinical populations. These results are backed up by Transcranial Magnetic Stimulation (TMS) (Jackson et al. 2015; Pobric et al. 2007) and EEG/MEG (Dhond et al. 2007; Lau et al. 2013; Westerlund & Pylkkänen 2014) evidence. Importantly, some recent fMRI evidence have led to
suggesting a so-called graded functionality within the ATLs and between bilateral ATLs (Rice et al. 2015a) where the central ventrolateral subregion of the ATL might play the role of a modality-independent amodal hub while the surrounding subregions show a more specialised functionality for category-specific concepts (Lambon Ralph et al. 2016). This property is especially useful for a semantic hub since with such structure, the core amodal area can accomplish processing tasks of the hub while the neighbouring multimodal sub-regions can establish connections to the distributed semantic cortices.

Secondly, a meta-analytic investigation of fMRI literature reported the AG and posterior parts of the Supramarginal Gyrus, in the posterior inferior parietal lobe as the most consistently reported areas in contrasts of different semantic variables (Binder et al. 2009). In particular, its involvement in differentiation of words against pseudowords has been reported frequently in the literature (Lambon Ralph et al. 2016). Importantly, as a key node of the default mode network, it has been associated with different functions of this network in health and diseases such as Alzheimer’s (Seghier 2012). Furthermore, lesions of AG have been shown to introduce a variety of disorders that affect complex information processing, including but not restricted to semantic processing (Binder et al. 2009). Therefore, particularly considering its location at the intersection of visual, auditory, motion and somatosensory cortices, AG provides a perfect candidate for convergence of multimodal semantic integration of several unimodal attributes of concrete words such as colour, shape, sound, motion and action (Bonnici et al. 2016; Fernandino et al. 2016b; Handjaras et al. 2017; Lin et al. 2017). Based on this evidence, some studies have proposed a division of labour between ATL and AG as the two key candidate hub areas to underlie semantics. However, further specification of the role each area has remained highly ambiguous (Binder 2016; Lambon Ralph et al. 2016).

Thirdly, posterior parts of the superior temporal sulcus and middle temporal gyrus (STS/MTG), including but not restricted to the well-known Wernicke’s area for language comprehension (Binder 2015), have often been revealed in different semantic tasks using different imaging modalities as well as studies of semantic aphasic (SA) patients (Binder et al. 2009; Price 2012). Being located at the intersection of several sensory areas, particularly visual and auditory processing streams in the brain, STS/pMTG provides an ideal location for a convergence zone to integrate the category-specific information produced in these unimodal cortices (Beauchamp et al. 2004b; Martin 2007). Additionally, the role of MTG for pre-semantic lexical representations of the words have been reported in the literature (Taylor et al. 2009, 2011), and thus it has been suggested to play a more important role for verbal than non-verbal semantics (Patterson et al. 2007). Moreover, studies of SA patients have often highlighted a crucial role for this area. One of the key differences between SA and SD patients is that the former group often disclose an impairment in semantic control and executive demands of
semantic tasks, while in the latter the executive functions are typically intact. Thus, another key function proposed for the pMTG, not mutually exclusive from the other functions, is for the region to play role in semantic control (Jefferies 2013).

Fourthly, IFG, including the well-known Broca’s area (i.e. pars-triangularis and pars-opercularis) for language production in the posterior IFG as well as the anterior pars orbitalis cortex was shown to be involved in semantic processing in early neuroimaging research on healthy volunteers (Frith et al. 1991; Petersen et al. 1988). Subsequent studies frequently reported its role in working memory, syntactic and phonological processes as well (Binder et al. 2009). Additionally, a series of studies have shown a modulation of IFG activity by task difficulty (Lambon Ralph et al. 2016). Moreover, IFG lesions have often been associated with impairment of syntactic and phonological processes and TMS stimulation of this region has been shown to induce longer reaction times but not impairment of semantic judgement (Binder et al. 2009; Jefferies 2013; Pobric et al. 2010a). Therefore, it has been proposed that IFG might play a more important role in the efficiency of semantic retrieval rather than semantic representation per se (Lambon Ralph et al. 2016).

Based on these most recent findings for the role of ATL, AG, pMTG, and IFG in semantics, a recent theory suggests distinct yet interacting sub-systems for semantic representation and semantic control, where IFG and MTG might be best placed to play role in the latter while ATL and AG are more crucial for the former (Jefferies 2013; Lambon Ralph et al. 2016).

1.2.2 Evidence for semantic representation in sensory-motor-limbic cortices

In addition to the aforementioned supramodal semantic areas, modulation of unimodal cortices by category-specific semantics have also been studied extensively using neuroimaging techniques. One of the first studies to report distinct brain cortices responding to different word categories was (Martin et al. 1995) where the authors used PET imaging and reported more involvement of the occipito-temporal and parieto-temporal regions for words with strong colour and action attributes, respectively. The subsequent studies fine-tuned the localisation of the involved sensory cortices for semantic knowledge of objects using fMRI and reported ventral and lateral parts of the temporal cortex to be modulated by form and motion attributes of word meaning, respectively (Chao et al. 1999). The first study to localise fine-grained subdivisions of the motor cortex that were modulated by action semantics was (Hauk et al. 2004) where the authors showed that superior, middle and inferior parts of the motor cortex respond to words with strong leg, arm and face action attributes, respectively, mimicking somatotopic representations in these areas during action performance. These findings were later replicated and expanded on to the action-related sentence processing (Tettamanti et al. 2005). Furthermore, stimulation of motor cortex using TMS was reported
to affect action-related word (Pulvermüller et al. 2005a) and sentence processing (Buccino et al. 2005). Subsequently, numerous fMRI studies reported modulations of activity in sensory-motor cortices during category-specific semantic retrieval (see Meteyard et al. 2012 for a review). More recently, a few studies showed the role of the limbic and orbitofrontal cortices for representation of words with strong emotional valence, a property that has been argued to be particularly important for an embodied representation of abstract words (Kousta et al. 2011; Vigliocco et al. 2014). Therefore, this body of neuroimaging evidence on healthy participants supports the involvement of sensory-motor-limbic systems in category-specific semantic cognition.

In spite of this multitude of evidence from non-clinical populations, patient studies on the role of unimodal cortices in semantics have been less consistent (Pulvermüller 2013). While some studies have reported category-specific semantic deficits in patients with lesions in sensory-motor areas (Capitani et al. 2009; Dreyer et al. 2015; Gainotti 2010; Warrington & Shallice 1984), other studies have not found such effects (Papeo et al. 2010). Notably, this area of research is likely to have some publication bias with null results not having been reported as often.

In summary, in the past two decades, a substantial literature has focused on the localisation of semantic areas through investigation of modulation of cortical activity by semantic variables and revealed numerous cortical areas to play important roles (Figure 1.4). Most recently, Huth et al. (2016) provided the potentially most comprehensive atlas of the semantic areas to date. To this aim, the authors mapped the brain responses while the participants listened to natural stories in the fMRI scanner. Consistent with the previous meta-analytic observations in the literature (Binder et al. 2009; Binder & Desai 2011; Pulvermüller 2013), the acquired map in this study covered a majority of cortical areas, with different cortices responding to different words/categories.

**Figure 1.4** Modality-general and modality-specific semantic cortices identified from fMRI. Adapted from Binder and Desai 2011. Note that temporal pole in this figure is labeled as an emotion-specific cortex. However, as discussed in detail in the text, the contemporary models of semantic networks consider this area as a part of the ATL, one of the key candidate supramodal semantic hubs.
1.2.3 Static connectivity in semantic networks

In spite of having acquired a fine localisation of semantic cortices in the past decades, connectivity among these areas is much less explored/known. This is in spite of the fact that the most prominent theories of semantic cognition (e.g. hub-and-spokes model) propose a network of interacting cortices. Hence, a growing field of research is currently focused on providing empirical evidence for the characterisation of connectivity in semantic networks. This field of research to date has been predominantly focused on the the potential hub(s) and by means of structural/functional MRI connectivity and through observation of *static* connectivity (Binder *et al.* 2009; Meteyard *et al.* 2012). Among the aforementioned candidate hub areas, connectivity patterns of the ATL, AG, and MTG have been revealed more frequently.

The first group of these studies have focused on the connectivity patterns of the ATLs. For example, recent fMRI (Jackson *et al.* 2016) and DTI (Papinutto *et al.* 2016) studies have provided evidence that different parts of the ATL are structurally and functionally connected to heteromodal and modality-specific parts of the semantic network. Furthermore, fMRI connectivity studies on patients have reported reduced ATL functional connectivity to sensory and association cortices in semantic dementia (Guo *et al.* 2013) as well as positive correlations between average ATL node degree and overall performance on semantic tasks in healthy and patient cohorts (Zhao *et al.* 2016). The second group of studies, focused on the connectivity patterns of the Angular Gyrus (AG), have similarly reported structural and functional subdivisions within AG (Seghier *et al.* 2010). Structural/functional MRI and DTI research have identified this region as a core hub showing rich connectivity to sensory and language cortices involved in semantics (Hagmann *et al.* 2008; Tomasi & Volkow 2011) and this line of evidence has resulted in proposing AG as the cross-modal hub (potentially together with ATL) for integration of various sensory-motor-limbic aspects of concepts (Seghier 2012). The third group of these studies have focused on the pMTG and identification of the fibre tracts that connect this region to other heteromodal semantic areas such as ATL, AG and IFG (Binney *et al.* 2012; Catani *et al.* 2005; Fang *et al.* 2015). Based on this body of evidence and location of this area, some studies have proposed this region as a bridge that links the two key subsystems of semantic networks; i.e. ATL and AG. Putting all these three key regions together, a recent study suggested that the cluster of fronto-temporo-parietal areas might form a major interconnected hub that plays a crucial role in semantics (Jouen *et al.* 2015).

In spite of this growing evidence for connectivity patterns of the hubs, modulation of connections between hub(s) and spokes by different semantic conditions has been rarely studied. To
the best of our knowledge, the only study addressing this question explicitly is (Chow et al. 2014) where the authors had the participants in the fMRI scanner listen to stories with various sensory-motor attributes and found the connections between MTG and IFG and sensory-motor areas to be modulated by the sensory-motor attributes of the stories.

1.3 Temporo-spectral properties of the semantic system

Most of the previous neuroimaging evidence on semantic networks have been based on fMRI that measures slow-varying haemodynamic brain responses and provides a fine millimetre spatial resolution (Dale et al. 2000). However, its accuracy for tracing neural processes is limited considering that firstly, BOLD fMRI is a measure of the blood flow in the brain which provides an indirect measure of neuronal dynamics and thus the relationship between the two signals is not well understood (Brookes et al. 2011a). Secondly, standard fMRI imaging techniques typically yield one image of the brain function per second and additionally the nature of the slow-varying hemodynamic response function is such that it provides a limited capacity to track the brain processes that are faster than one second (Hämäläinen et al. 1993). This is particularly important for identification of the neural substrates of concept retrieval considering that word recognition in the brain unfolds in a fraction of a second (Hauk 2016). Therefore, in order to be able to keep track of the potentially time-varying activity and connectivity of the heteromodal and sensory-motor-limbic cortices in semantic representation, it is essential to have access to a higher temporal resolution.

EEG/MEG, in contrast, provide fine temporal resolution in the order of millisecond that is suitable for studying dynamic semantic networks. Additionally, the temporal resolution makes it possible to observe neural oscillations in different frequency bands including Theta (4-7Hz), Alpha (8-12Hz), Beta (13-30Hz) and Gamma (30Hz+). EEG/MEG are measured using sensors placed outside the head, and thus state-of-the-art forward and inverse modelling techniques are often utilised to localise the sources of activity with a reasonable spatial resolution i.e. a few centimetres (detailed description in Chapter 2). In this subsection, I briefly summarise the main temporal and spectral properties of semantic processing for written words that have been reported to date.

1.3.1 The timing of semantic processing of written words

The timing of semantic word processing has been largely studied using EEG/MEG. Semantics in EEG/MEG literature has traditionally been associated with the N400 component of the event-related potentials (ERPs), a slow-varying negative-going ERP response occurring around 400ms. Several studies have attempted at localising the sources of the N400 in the brain and, in line with the fMRI literature reviewed earlier, have identified ATL, MTG, AG, and IFG as the key regions involved in the production of N400 (Grainger & Holcomb 2009; Lau et al. 2008). Based on this evidence, Lau et al.
(2008) proposed a cortical model of the network structure among these areas to underlie N400, where MTG was deemed responsible for lexical representation, anterior and posterior IFGs were proposed to control the retrieval of lexical and semantic representations, respectively, and ATL/AG to underlie semantic representations in different contexts and tasks.

However, some studies have argued for an earlier modulation of cortical areas by semantics at around 200ms or earlier (Hauk et al. 2012; Pulvermüller et al. 2009; Sereno & Rayner 2003). For example, Hauk et al. (2012) investigated lexical and semantic effects in a Go/NoGo visual word recognition paradigm and reported a modulation of the left anterior MTG at around 200ms. In another study, Westerlund & Pylkkänen (2014) showed a modulation of the ATL at around 200ms for semantic specificity (e.g. fish versus trout) and semantic composition. Overall, recent findings suggest a flexible timing for semantic processing depending on the task and stimuli (Chen et al. 2015).

1.3.2 Role of oscillations in semantics

Neural oscillations, the periodic firings of neurons in different frequency bands, are assumed to provide a mechanistic system for neural communications that subserves cognition through orchestrating multiple neuronal populations (Siegel et al. 2012). More specifically, excitatory, inhibitory and interneurons in the brain form feedback loops that can produce oscillatory activity (i.e. repetitive activations or chains of spikes/bursts rather than single action potentials). The role of oscillations in lower-level cognition such as vision and audition has been more established based on studies of human as well as non-human primates (Engel & Fries 2010; Fries 2009). However, the oscillatory underpinnings of the higher-level cognition are less known.

The role of oscillations in semantic cognition is not established yet and different frequency bands have been reported in the literature (Bastiaansen et al. 2008; Lewis et al. 2015; van Ackeren et al. 2014). On the one hand, several EEG/MEG investigations have implicated the role of low frequencies (e.g. Theta) in semantic retrieval (Bastiaansen et al. 2005, 2008; Hald et al. 2006). For example, Bastiaansen et al. (2008) reported topography of Theta band activity to differentiate auditory- and vision-related semantic categories; i.e. higher amplitudes of temporal electrodes for auditory versus occipital for visual attributes of words. Other studies (van Ackeren et al. 2014; van Ackeren & Rueschemeyer 2014) have reported that Theta band power in ATL, as well as Theta band connectivity of ATL to several distributed semantic networks underlie feature integration from multiple modalities (e.g. integrating colour and taste to construct the concept of lemon). On the other hand, higher frequencies have been implicated in modality-specific semantic representations. For example, van Ackeren et al. (2014) showed that Gamma band power in the left ATL might underlie integration of features within a single modality (e.g. red and large under visual modality in order to
retrieve the concept of bus). Additionally, a few studies have reported a modulation of Mu band (in Alpha range) in the motor cortex and in response to action semantics, mimicking Mu band motor activity during movement (Moreno et al. 2013; van Elk et al. 2010; Vukovic & Shtyrov 2014). Therefore, while lower frequencies such as Delta and Theta might play role in modality-general memory retrieval aspects of semantic cognition, higher frequencies such as Alpha, Beta and Gamma might subserve modality-specific recruitment of sensory-motor-limbic spokes. This notion is plausible particularly considering the more established role of Theta in long-term memory retrieval (Klimesch 1999) and Alpha, Beta and Gamma in perception and action (Engel & Fries 2010; Siegel et al. 2012).

1.3.3 Spatio-temporo-spectral semantic networks

The time-varying semantic networks meanwhile a concept unfolds in the brain are largely unknown. In particular, to the best of our knowledge, no study to date has investigated dynamic connectivity between/within hub(s) and spokes. Therefore, this will be the main cognitive goal of the current thesis.

1.4 Outstanding questions: untangling semantic networks in this thesis

From the evidence reviewed so far, the hub-and-spokes model (Patterson et al. 2007; Rogers et al. 2004) can be considered a powerful theoretical framework to study semantic networks in the brain. More specifically, based on the reviewed evidence, it appears likely that semantic system comprises a network of heteromodal and unimodal brain areas where word meaning is partly encoded in the activation patterns of these areas and partly in connectivity among them. Therefore, throughout this thesis, we will use “hub” and “spoke” terminology in order to refer to the general framework. However, considering the multitude of evidence for the key role of several heteromodal areas in semantics (as reviewed above in 1.2.1), hub(s) do not necessarily refer to the ATLs, in fact, it is one of the research questions that we are aiming to address.

1.4.1 Investigating semantic hub(s)

As mentioned earlier, the hub-and-spokes model predicts that sensory-motor cortices provide ingredients for building up concepts in the brain which are then mediated and integrated by a central cross-modal semantic hub (hereafter referred to as integration hubness). In addition to the integration task, the hub is proposed to be responsible for a higher level abstract representation of the concepts (hereafter referred to as processing hubness). In order to study semantic hub(s), we draw a clear distinction between integration hubness and processor hubness roles and seek to investigate them using two separate strategies as will be outlined in the following subsections. Thus
far, semantic literature has identified ATL, IFG, MTG, and AG as the main candidate hubs. However, the specific role of each of these areas has remained ambiguous. Arguably, this is partly due to the fact that the spatio-temporal overlaps and dissimilarities between integrator and processor hubness are unknown. Therefore, we will use the spatio-temporal resolution of source-estimated EEG/MEG in order to unwrap these two aspects of the semantic hub(s).

1.4.1.1 Strategies for unravelling processor hubs

We hypothesise that the key property of a processor hub is to show differential activations in response to different semantic variables. This property is predicted to be reflected in the modulation of the processor hub(s) amplitude by different semantic contrasts, regardless of their association to the sensory-motor-limbic attributes. This role implies that activity in a semantic area can encode information that underlies higher-level category-independent semantic representation. In order to identify processor hub(s), in this thesis we will examine time-resolved modulation of cortical activity in response to a range of semantic variables with different degrees of specificity; i.e. contrasting words against meaningless pseudowords (Chapter 5), concrete versus abstract words (Chapter 3) and fine-grained categories of concrete words with differences in visual, hand-action and auditory attributes (Chapter 5).

It is worth noting that previous studies that have focused on differential activations of different brain areas in response to semantic conditions have often tested specific hypotheses using region-of-interest (ROI) analyses (Hauk et al. 2012; Moseley et al. 2013). However, this approach has two main limitations: firstly, it can arguably bias the conclusions in favour of the tested brain areas and/or time windows, increase the risk of type I error if those areas were not highlighted in the grand scheme of whole-brain responses and potentially neglect interesting effects in the unexplored regions and times. Secondly, ROI time courses will have to be computed using a summary measure such as averaging across vertices or extracting vertex with maximum power as the representative of an ROI. Therefore, if multiple distinct patterns of activations are produced in a single ROI, some potentially interesting effects will be averaged out or only one of them will be taken into account. Therefore, throughout this thesis, we seek to identify the processor hubs at different stages of semantic word processing using fully data-driven vertex-wise analyses. For this purpose, we will utilise spatio-temporal permutations for statistical analysis and correction for multiple comparisons. This approach will hopefully take a step forward in improving reproducibility and generalisability of the obtained results.
1.4.1.2 Strategies for unravelling integrator hubs

Based on the predictions of the hub-and-spokes model, we hypothesise that conceptual knowledge is partly encoded in connectivity between integrator hub(s) and other heteromodal and/or unimodal semantic cortices. For this purpose, the integrator hub(s) are hypothesised to show modulation of connectivity to distributed semantic cortices during one or multiple stages of semantic word retrieval. As elaborated earlier in 1.2 and 1.3, this characteristic has been much less tackled than processor hubness in the previous literature (and exclusively using DTI, structural and functional MRI). Importantly, the time-varying connectivity of the hubs remains largely unknown. In order to identify integrator hub(s) at different stages of semantic retrieval, in Chapter 3, we will examine connectivity among the heteromodal subnetwork of left-hemispheric semantic areas and in Chapter 4 we will investigate connectivity between the nodes of this subnetwork and all the brain vertices in order to identify their long-range connections to the more distributed semantic areas.

1.4.2 Investigating semantic spokes

One of the long-lasting debates regarding the role of unimodal spokes in semantics is whether or not their activation is an essential part of semantic retrieval. In other words, whether or not the brain should simulate the referent of a concept as a sub-process of semantic retrieval or the activation reported in the previous studies might be attributed to the epiphenomenal spread of activity (aka. activation through association) (Mahon & Caramazza 2008) or post-semantic neural processes such as mental imagery (Hauk & Tschentscher 2013). This scepticism was initially raised considering that a majority of the studies that had reported an involvement of spokes had utilised fMRI where earlier and later stages or semantic and post-semantic processes cannot be distinguished. Since then, some EEG/MEG studies (Hauk & Pulvermüller 2004; Kiefer et al. 2008; Moseley et al. 2013) have focused on the timing of spoke modulations, arguing that “early” modulations of spokes activity (at around 200ms; i.e. before the word meaning is fully unwrapped) can be regarded as an evidence for the primary role of these areas in semantics. More directly, TMS (Vukovic et al. 2017) findings of early involvement of these areas have been regarded as an evidence for a causal role of these cortices in semantic retrieval. However, it has been argued that early modulation of these areas does not reveal the content of information produced in these cortices, nor does it unravel the mechanisms of semantic access in these areas (Papeo & Caramazza 2014).

In order to further specify the content of information encoded (i.e. addressing what are the ingredients?) in semantic spokes, it is important to take note that embodied semantics and the hub-and-spokes model essentially predict a re-activation of sensory-motor-limbic cortices in the same manner as when the referent of a concept is encountered/experienced in real world (Barsalou 2010).
In recent years, it has been suggested that if unimodal cortices are to be re-activated, it is reasonable to assume that similar oscillatory dynamics as those in perception and action should get modulated (van Elk et al. 2010). Neural oscillations have been shown to provide signatures for local sensory-motor information processing in unimodal regions (Engel & Fries 2010). In particular, Alpha and Gamma bands have been shown to play important roles for encoding motor, auditory and visual stimuli (more details in Chapter 5). To date, modulations of sensory-motor oscillations in spokes during semantic retrieval have been tested in a few studies on action semantics against different baselines. These studies have reported a modulation of Mu band (in Alpha/low Beta range) in the motor cortex, a frequency band that is established for movement encoding, by motor attributes of words (Moreno et al. 2013; van Elk et al. 2010; Vukovic & Shtyrov 2014). Nevertheless, the fact that Alpha band activity is modulated by action semantics in the motor cortex is arguably insufficient to conclude that a similar Mu band as in actual movement is invoked. More specifically, these findings do not rule out the possibility that Alpha band might as well be modulated for other word categories in their corresponding spokes. We propose that such conclusion would require contrasting two or more word categories with different characteristic frequencies for their corresponding spokes (e.g. visual Gamma versus action Mu) and testing the interaction effects of semantic condition by frequency (more details in Chapter 5).

In Chapter 5, we will take into account early timing and sensory-motor oscillations as two key aspects of the involvement of spokes, in an effort to shed more light on the content of information represented in the spokes during semantic retrieval. For this purpose, we will take into account two caveats of the previous research. Firstly, as elaborated above, we will study multiple word categories with distinct corresponding spokes and characteristic frequency bands for perception and action. Secondly, most of the aforementioned studies have focused on specific hypothesised ROIs investigated at specific time windows. We propose that a data-driven whole-brain investigation of temporo-spectral modulation of these cortices can provide a stronger evidence and reveal further details about temporal and oscillatory underpinnings of their involvement in semantic representation. This approach might prove particularly useful considering that patient studies on the role of unimodal cortices in semantics have been inconsistent, leaving their involvement a matter of high controversy to date.

1.4.3 Investigating whole-brain semantic connectome

The aforementioned steps 1.4.1 and 1.4.2 focus on either hubs or spokes. Nonetheless, in order to obtain a more comprehensive picture of the semantic networks, dynamic connectivity between and within these areas is crucial. Considering the widespread activation of the brain areas in
response to semantics, a whole-brain connectomic approach is desirable. However, to the best of our knowledge, no study to date has addressed this issue. For this purpose, we will examine parcellated whole-cortex networks together with measures of graph theory that provide powerful tools to summarise connectivity results. Thereafter, we will contrast graphs that are extracted from brain responses to word categories with different sensory-motor attributes in order to: a) identify network communities that appear as hubs; b) network communities that appear as spokes and c) modulations of hub-hub, hub-spoke and spoke-spoke connections by different semantic variables.

Graphs model each region of the brain as a node and connections between these areas as edges between the nodes. Applications of graph theory to the neuroimaging data in recent years has revealed several local and global properties of the human brain networks in health and disease (Bassett & Bullmore 2009; Bullmore et al. 2009; Bullmore & Bassett 2011). In particular, at a global level, the brain networks have been shown to depict characteristics of small-worldness and scale-freeness that enable fast and efficient flow of information through high clustering, short path lengths and highly connected central hubs (Bullmore & Sporns 2012).

The brain graphs have additionally been shown to be highly modular, with denser intra-modal connections and sparser inter-modal connections (Sporns & Betzel 2016). For example, it has been shown that multiple anatomically distinct brain regions in the occipital cortex are functionally clustered as a module in the visual cortex, several pre-/post-motor areas are functionally connected as a central module and similarly for other functionally-united cortices (Cole et al. 2014; Geerligs et al. 2015). This approach has resulted in summarising a network of over 200 nodes in less than 20 functionally distinct modules where connectivity among them can have clearer cognitive interpretations. For example, more recent studies have shown that intra-/inter-modal connections can be used to identify similarities and differences between different brain states and tasks, and utilise these characteristics to study age-related changes of the brain (Geerligs et al. 2015).

We consider this approach to be suitable for unravelling semantic hub(s) and spokes noting that candidate hub and spokes identified in the past literature are in fact groups of anatomical nodes rather than individual anatomical parcels (see Figure 1.4). Additionally, due to the spatial resolution of the EEG/MEG (that will be discussed in detail in Chapter 2), we consider modules of functional nodes to be more interpretable compared to single nodes. In order to identify semantic hubs and spokes modules, in Chapter 7 we contrast concrete words with fine-grained boundaries of sensory-motor attributes. We will parcellate the cortex and use functional connectivity to quantify connectivity among the brain areas in different time windows and frequency bands. Thereafter, we will find modules on the cortex and find differences between module-module connectivity matrices for
contrasts of semantic variables in order to identify integrator hub(s) and spokes modules as well as types of connections among semantic modules (e.g. hub-hub, spoke-spoke and hub-spoke connections). It is worth noting that numerous connectivity metrics are available for EEG/MEG that can be used to reconstruct the semantic connectome. We will overview these metrics in Chapter 2 in order to identify the most suitable methods for the type of data in this thesis.

1.5 Interim summary (cognitive scope of the thesis)

Therefore, some of the key outstanding questions regarding the organisation of semantic networks that underlie semantic processing concern temporal and oscillatory dynamics and time-varying connectivity of hub(s) and spokes. As elaborated above, we will utilise source estimated EEG/MEG to address some of these questions. However, in order to obtain interpretable connectivity estimates, in the next chapter, we will take note of two methodological challenges that are associated with EEG/MEG connectivity and might affect our results. We will, therefore, propose methodological developments for addressing these two challenges (method development scope of the thesis). The general outline of the thesis will also be presented at the end of Chapter 2.
2 EEG/MEG Source Estimation and Two Challenges for Connectivity Analysis

Based on the main cognitive scope of this thesis described in Chapter 1, time-varying connectivity, temporal and oscillatory dynamics are required to address the unresolved characteristics of the semantic networks that were outlined earlier. We identified EEG/MEG with source localisation as suitable means to tackle these questions. However, dynamic connectivity analysis of source estimated EEG/MEG in general and higher level cognitive functions in particular (given the lower signal to noise ratios (SNRs) and higher variability across subjects, tasks, etc.) is methodologically challenging and might affect the cognitive interpretability of the results (Bastos & Schoffelen 2016; Schoffelen & Gross 2009). In this chapter, we introduce the method development objective of the current thesis where we propose methods to increase the accuracy of reconstruction of dynamic networks based on EEG/MEG data and their application to semantic networks.

EEG/MEG signals are measured non-invasively from sensors placed outside the head. Hence, sensor-space data can reveal the topography of the sensors that are involved in semantic processing. Nonetheless, they are not sufficient to pinpoint the cortical regions that underlie the observed effects (Hämäläinen et al. 1993). Mathematical models known as inverse solutions have therefore been proposed and widely applied to EEG/MEG data in order to localise the sources of activity in the brain (Barnes et al. 2006; Hämäläinen & Ilmoniemi. 1994). Among numerous methods that are available for
source estimation, we will focus on the so-called distributed source models where no constraints on
the locations of the sources are assumed and therefore, time courses of all the brain vertices/voxels
are estimated (Dale & Sereno 1993; Hauk 2004). The procedure of source estimation using linear
distributed source models consists of the following steps: firstly, a head model is constructed (e.g.
based on the individual MRI scans or a template) for a subject; secondly, based on this head model, a
so-called forward model is constructed to map the brain sources (i.e. vertices or voxels) to the
EEG/MEG sensors. Thirdly, through inversion of this forward model, an inverse operator is created to
map the signals measured at sensors to the source activities (details of this procedure are presented
below in 2.1.1). By applying the inverse operator to the sensor data, time courses of the brain sources
(i.e. vertices or voxels) is reconstructed. Thereafter, through observation of source-estimated time
courses, temporal and spectral fluctuations of different voxels can be compared between different
semantic conditions using statistical methods in order to identify the locations, times and frequencies
at which those conditions are significantly different.

Additionally, once source activities are reconstructed, connectivity among them can be
calculated and compared between different conditions. Connectivity estimation is a multi-stage
process. The first step is to draw boundaries between sources of interest in the brain and define
vertices/ROIs/subnetworks among which connectivity is to be computed (Schoffelen & Gross 2009).
There are two main approaches that have been used for this purpose (Joel et al. 2011). In the first
approach, also known as seed-based connectivity, sources are defined manually or based on
anatomical or functional atlases of the brain. Thereafter, connectivity among each source of interest
(aka. seed) and all other sources in the brain is calculated. The most general version of seed-based
connectivity consists of selecting brain vertices as seeds and computing connectivity between the seed
and all the vertices in the brain. The second method utilises data-driven approaches to delineate
separate subnetworks in the brain (Brookes et al. 2011b). Throughout this thesis, we will utilise the
former approach. After defining the seeds, one metric among numerous methods that are available
for connectivity estimation from EEG/MEG data can be chosen to quantify connectivity between
semantic areas. Some of the most common connectivity methods for EEG/MEG will be overviewed in
2.2 and are summarised in Figure 2.1. After connectivity estimations, in some applications (e.g. whole-
brain semantic connectome in section 1.4.3), it might be of interest to compute measures of graph
theory in order to summarise the connectivity results.

Therefore, source reconstructed EEG/MEG with excellent temporal and good spatial
resolution provides a suitable mean to study temporal, spectral and connectivity fluctuations of
semantic networks meanwhile a word meaning is retrieved in the brain. However, two key challenges
associated with connectivity analysis of EEG/MEG in source space might impose serious limitations on the interpretability of our results:

1. In EEG/MEG source estimation using distributed source models, time courses of several thousands of vertices/voxels are typically estimated from a much lower number of sensors (typically < 400). Therefore, finding an inverse solution is a mathematically underdetermined problem with no unique solution and thus the neural activity of cortical vertices can only be estimated with a limited accuracy (Hämäläinen et al. 1993). As will be elaborated below in 2.1.1 and 2.1.2, this introduces a so-called leakage problem for connectivity analysis which results in finding spurious connections that can significantly reduce the reliability of connectivity estimations, particularly for the whole-brain connectomes (Colclough et al. 2015). In the first half of this chapter (subsection 2.1), we will first describe EEG/MEG source localisation and mathematical approaches for quantification of the leakage problem (aka cross-talk functions or CTFs). Thereafter, we will briefly summarise the solutions previously proposed in the literature to alleviate leakage problem, highlighting that utilisation of anatomical ROIs for EEG/MEG connectivity estimation can exacerbate the effects of leakage. Finally, we will motivate the concept of CTF-informed ROIs and introduce EEG/MEG-adaptive cortical parcellations as a novel solution for alleviation of the leakage problem for whole-brain EEG/MEG connectomes. These adaptive parcellations will then be introduced in detail in Chapter 6.

2. Considering the multifaceted nature of the neuronal dynamics measured by EEG/MEG, numerous methods have been introduced to quantify connectivity between neuronal populations, each of which focusing on one or a few key properties of the signals (see (Bastos & Schoffelen 2016; Greenblatt et al. 2012) for reviews). Therefore, an arbitrary choice of some connectivity measure among a range of methods is not ideal. In recent years, a few studies have proposed the so-called ensemble connectivity approaches in order to obtain a more generalisable connectivity estimation from a given dataset. In the second half of this chapter (subsection 2.2), we will first overview the most prominent connectivity analyses approaches for EEG/MEG. Thereafter, we will briefly summarise a few ensemble connectivity approaches from the previous literature (mostly introduced for fMRI/DTI), motivating a novel ensemble connectivity approach based on Principal Component Analysis (PCA) that can be used for dimensionality reduction of multiple connectivity metrics for a given dataset and identification of the most suitable connectivity method based on the maximum explained variance. Details of this approach will be elaborated in Chapter 4 where it will also be applied
2.1 Spatial resolution of EEG/MEG source estimation and adaptive parcellations

2.1.1 EEG/MEG forward and inverse solution

In forward modelling of EEG/MEG data, assuming a linear relationship between data and sources, the so-called leadfield matrix \( G \) is defined to map the sources of activity on the cortex to the electric and magnetic signals measured using EEG and MEG sensors (Hämäläinen & Ilmoniemi. 1994). Therefore, the signal at each sensor is modelled as a weighted sum of the activities of all the sources in the brain:

\[
Y = GS
\]  

(2.1)

where \( Y \) is an \( N_{ch} \times N_t \) matrix of the measured signal at the sensor locations, the time-invariant matrix \( G \) denotes the leadfield of size \( N_{ch} \times N_s \) and \( S \) denotes the source activity matrix which is of size \( N_s \times N_t \) (\( N_{ch}: \) Number of recording channels, \( N_t: \) number of time points, \( N_s: \) number of sources).

However, with EEG/MEG data we do not have access to the source time courses, reversely, measured sensor data should be used to estimate source activities. Thus, linear source estimation methods are often employed in order to obtain a solution for \( S \) in Equation 2.1. If \( D = Y + \epsilon \) is the matrix of the measured data of size \( N_{ch} \times N_t \) (which contains activity from brain sources in Equation 2.1 plus noise), the source activity is estimated as:

\[
\hat{S} = WD = W(Y + \epsilon) = WGS + W\epsilon = RS + W\epsilon
\]  

(2.2)

where \( W \) is the inverse operator of size \( N_s \times N_{ch} \) that maps measurements to the sources, \( \hat{S} \) is the matrix of estimated sources of size \( N_s \times N_t \), \( \epsilon \) denotes the measurement noise matrix of size \( N_{ch} \times N_t \) and \( R = WG \) is the resolution matrix (Grave De Peralta Menendez et al. 1997).

2.1.2 Leakage problem: resolution matrix and CTFs

In Equation 2.2, the resolution matrix \( R \) can be used to quantify the relationship between true and estimated sources. The diagonal elements of \( R \) indicate the sensitivity of each estimated source to itself, and off-diagonal elements quantify the degree to which estimated sources are affected by the signal from all other sources in the brain (Grave De Peralta Menendez et al. 1997; Liu et al. 1998). A precise and unique estimation of source activity in the brain would be possible if \( G \) was a full-ranked square matrix (i.e. equal number of sensors and sources) and in the absence of measurement noise. In such an ideal scenario \( W \) would be the inverse of \( G \), \( R = G^{-1}G = I \) would be an identity matrix and the
estimated sources would precisely match the true sources. However, the EEG/MEG inverse problem is a highly underdetermined problem; i.e. the resolution matrix has non-zero off-diagonal elements and is highly rank-deficient. These off-diagonal elements introduce the leakage or cross-talk in the EEG/MEG inverse solutions. One of the simplest methods of estimating the inverse operator is L2 minimum norm estimates (MNE) which we consider suitable for this thesis considering that it imposes minimal assumptions about the source configurations (Hämäläinen & Ilmoniemi. 1994; Hauk 2004). The method defines an inverse operator as:

$$ W = G^T (GG^T + \lambda^2 C)^{-1} \quad (2.3) $$

where $\lambda$ is the regularisation parameter and $C$ is the noise covariance of the data. According to Backus and Gilbert (Backus & Gilbert 1970), $\lambda$ provides a trade-off between spatial resolution and stability for the source estimate. Consequently, the resolution matrix for the L2 MNE will be obtained as:

$$ R = WG = G^T (GG^T + \lambda^2 C)^{-1} G \quad (2.4) $$

It is worth noting that the $i^{th}$ row of $R$ describes the cross-talk from all sources in the brain into the estimate for activity of the $i^{th}$ source. These rows have therefore been called cross-talk functions (CTFs) (Hauk et al. 2011; Liu et al. 1998). Thus, the cross-talk from the $j^{th}$ to the $i^{th}$ source is defined as:

$$ CTF_{ij} = R_{ij} = \sum_{c=1}^{n} W_{ic} G_{cj} \quad (2.5) $$

where $n$ is the number of sensors in the brain. As explained above, ideally $R_{ij}$ should be 0 for any $i \neq j$ and 1 for $i = j$. If an element $R_{ij}$ is zero, there is no cross-talk from the $j^{th}$ source into the estimate for the $i^{th}$ source. If two CTFs are largely non-overlapping, this means they are sensitive to different areas of the brain. If $R_{ij}$ is much larger than the value of $R_{ik}$ ($k$ being a third source in the brain), this means that the estimator is more prone to receive cross-talk from the $j^{th}$ source than from the $k^{th}$ source. Therefore, CTFs offer a direct way of quantifying the cross-talk problem for linear estimators of a given measurement configuration.

### 2.1.3 Leakage problem and whole-brain EEG/MEG connectomes

Due to the aforementioned cross-talk problem (often referred to as leakage), activity estimated in one ROI can be affected by leakage from locations outside this ROI, possibly including locations at large distances (Hauk et al. 2011; Lachaux et al. 1999; Schoffelen & Gross 2009). This poses serious challenges for the interpretation of connectivity results, since increased connectivity between two ROIs may not only be caused by true connections between the time courses of these ROIs, but also by signals leaked into these ROIs from other brain locations, leading to spurious connectivity findings (Colclough et al. 2015). This is particularly important for the estimation of whole-brain connectivity and applications of graph theoretical measures. For example, one ROI in a network may
be identified as a hub (i.e. showing strong connections to several other ROIs) if it receives strong leakage from multiple other ROIs. In spite of this caveat, when conducting whole-brain connectivity analysis, most previous EEG/MEG studies have adopted parcellations from anatomical or fMRI research (Brookes et al. 2016; Colclough et al. 2016; Tewarie et al. 2016). More recently, two solutions have been proposed to alleviate this problem. Firstly, some studies have orthogonalised source-reconstructed time series across parcels, in order to remove any zero-lag correlation, such as that induced by leakage (Brookes et al. 2012; Colclough et al. 2015; Hipp et al. 2012). This method has often been used with connectivity estimation from more slowly-varying amplitude envelopes of ongoing oscillatory activity. However, it also potentially removes true zero-lag connectivity that is not an artefact of cross-talk. Secondly, considering the spatial resolution of EEG/MEG, anatomical parcellations may not be optimal and hence recent studies have suggested that parcellations that are designed specifically for EEG/MEG can yield more informative connectomes (Brookes et al. 2016). An optimal parcellation should be sensitive to as much of the cortex as possible, with each parcel having high sensitivity to activity arising from itself, and low leakage from other parcels. A few previous studies elaborated below have embarked on the notion of EEG/MEG-informed parcellations.

2.1.3.1 EEG/MEG-informed parcellations in the previous literature

To the best of our knowledge, Palva et al. (2010) presented the first study that has used an EEG/MEG-informed parcellation at single subject level. They utilised the forward and inverse modelling of simulated noise in source space and by means of k-means clustering identified 365 patches on the cortex that showed high within-patch phase synchrony. This method has several advantages including: a) yielding parcellations based on EEG/MEG data; b) yielding individualised parcellations that are suitable for single subject connectivity analysis and c) it is not restricted to the linear/linearly constrained distributed source models. However, there are a few caveats to the method, namely: 1) in Palva et al.’s study, the parcellation was done at the single-subject level and therefore the locations of different parcels can vary significantly across the subjects. This makes the method unsuitable for group analysis; 2) number of parcels in the brain were fixed at the same number as the utilised sensors. This is arguably an arbitrary choice for the number of spatially independent parcels and thus might yield some highly dependent parcels on the cortex (the parcel sensitivity and specificity was not reported). In particular, the spatial resolution of EEG/MEG is confined by the measurement configurations, head models, and inverse operators. Ideally, a method should be able to quantify these spatial limitations in order to determine the number, location, and sizes of independent parcels; 3) parcels were determined based on forward and inverse modelling of random noise. Therefore, the identified patches can be good representatives of independent patches for the real datasets only if the simulated noise properties provide a good model of the real data; 4) parcels
were determined based on a specific connectivity metric (e.g. phase-locking values). The choice of connectivity metric can change and the algorithms will adapt to a different choice of connectivity metrics and yield connectivity-dependent parcellations. However, if a comparison of the results of network reconstructions using several connectivity metrics is of interest in one study or comparison between different studies, the algorithm will yield different parcellations for different metrics which makes such comparison difficult.

In a more recent study, Korhonen et al. (2014) introduced sparse weights to collapse the source space, based on the forward and inverse modelling of simulated noise in source space, so that vertex selection is optimised for a fixed set of pre-defined anatomical parcels. Their method, likewise Palva et al.’s, has the advantage of being generalisable to the source models that are not distributed and linear/linearly-constrained. Furthermore, their method is suitable for group-level analysis while it takes the individual differences into account. This is achieved by fixing the number and locations of parcels based on the anatomical atlases while selecting representative vertices for each parcel based on the forward and inverse models of each individual. However, the aforementioned disadvantages 2-4 for Palva et al.’s study are also applicable to the sparse weights approach. Therefore, obtaining a parcellation that can overcome these problems and at the same time optimise both parcellation resolution (i.e. the number of parcels in a parcellation) and vertex selection with respect to EEG/MEG spatial limitations, have remained a challenge (Korhonen et al. 2014).

2.1.4 EEG/MEG-adaptive parcellations proposed in this thesis

An ideal parcellation should be sensitive to as much of the cortex as possible, with each parcel having high sensitivity to activity arising from itself, and low leakage from other parcels. CTFs described in 2.1.2 can be used to characterise leakage among different brain areas (Hauk et al. 2011; Liu et al. 1998). As will be elaborated in Chapter 6, we propose that CTFs can be used to define cortical parcellations that are adaptive to the spatial resolution of source estimated EEG/MEG in order to optimise number, size, and locations of parcels for the spatial resolution of EEG/MEG source estimation and thus obtain more accurate connectome reconstructions.

2.2 EEG/MEG connectivity and most suitable connectivity method

After ROIs/parcels are defined in the brain, their time courses will be extracted and connectivity among the sources of interest will be computed.

2.2.1 An overview of connectivity metrics for EEG/MEG

Numerous methods have been introduced to quantify connectivity based on the EEG/MEG data. In this section, we will summarise the core ideas that have often been utilised in the previous literature. The overviewed measures are also categorised in Figure 2.1.
2.2.1.1 Functional Connectivity

Functional connectivity refers to the estimation of statistical dependencies between two brain signals, or the probability of co-activation of two brain sources (Friston 2011). Three principal categories under this group are: temporal correlation, spectral dependencies, and information-theoretic measures.

2.2.1.1.1 Temporal Correlation

Temporal correlation calculates the probability of the co-activation of two brain areas and is one of the most frequently used connectivity metrics for EEG/MEG data (Shaw 1984). By assuming each signal mean as its baseline (i.e. no activation), cross-correlation measures the probability of two signals deviating from their average simultaneously, normalised by the probability of the two being activated independently (Lee & Nicewander 2016):

$$\rho_{X,Y}(\tau) = \frac{\text{cov}_{X,Y}(\tau)}{\sigma_X \sigma_Y} = \frac{\mathbb{E}[(X-\mu_X)(Y(\tau)-\mu_Y)]}{\sigma_X \sigma_Y} \quad (2.6)$$

where $\rho$ denotes correlation, $E$ is the expected value or average, $\mu$ is the signal mean, $\sigma$ is the standard deviation and $\tau$ is the lag. For $\tau = 0$ the Equation 2.6 will yield zero-lag correlation which is also known as Pearson Product Correlation Coefficient that is more commonly used in EEG/MEG studies (Greenblatt et al. 2012). Additionally, if normalisation by the variances of the two signals is not included in the equation, it will yield the cross-covariance between the two signals. Advantages, limitations and assumptions of the correlation coefficient method are summarised in Table 2.1.

Table 2.1 Advantages, assumptions and limitations of CC and some of the modified versions.

<table>
<thead>
<tr>
<th>Correlation Coefficient (CC)</th>
<th>Advantages:</th>
<th>Assumptions &amp; limitations:</th>
<th>Modified versions (alleviated limitations)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fast algorithms available</td>
<td>1. Linearity</td>
<td>Nonlinear CC (1, 2, 4)</td>
</tr>
<tr>
<td></td>
<td>Robust to deviations from linearity assumption</td>
<td>2. Stationarity</td>
<td>Non-parametric CC (1, 2, 3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Parametric</td>
<td>Time-lagged CC (6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Long data required</td>
<td>Partial/conditional/multivariate CC (5, 6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Bivariate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6. Susceptible to leakage</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7. Contamination by similar biological noise results in high connectivity</td>
<td></td>
</tr>
</tbody>
</table>
Figure 2.1 In this chart, red layer represents methods to define sources of interest in the brain (e.g. parcels or subnetworks), blue layer represents the definitions of different types of connectivity, purple boxes are the main ideas to represent each type of connectivity quantitatively, yellow boxes are detailed algorithms to quantify each idea and orange boxes represent modifications to the original algorithms in order to overcome some of the limitations.
Non-Parametric or Rank Correlation

Non-parametric correlation measures, such as Spearman and Kendall tau rank CC (Croux & Dehon 2010), compute the associations between ordinal representations of the signals. Therefore, instead of linear relationships between two signals, monotonic relationships between the signals are of interest. In other words, if each pair of data points in a signal, regardless of the occurrence time, have the same ranks in the pooled data points, the rank correlation between the two signals will be high. Therefore, these methods relax the constraints of linearity, stationarity, and parametric estimation. However, considering that time points are pooled, the temporal order does not matter and thus the methods might lack specificity.

Nonlinear CC

This measure is based on the assumption that non-linear correlations can be calculated by piecewise linear approximations. In order to compute nonlinear CC, a scatter diagram of the time courses of two sources \( x(t) \) and \( y(t) \) will be plotted against one another subdivided into small bins. For each bin, a linear function (f) is fitted so that \( y(t) = f(x(t)) \) and compared to the measured \( y(t) \) value at each time. The less the average of these residuals for different time bins, the more the overall correlation. This procedure is formulated as:

\[
C = \frac{\sum_{k=1}^{N} y(k)^2 - \sum_{k=1}^{N} (y(k) - f(x(k)))^2}{\sum_{k=1}^{N} y(k)^2}
\]

where \( N \) is the number of bins. The non-zero-lag extension of this approach can be calculated by replacing \( k \) (time points) with \( k-\tau \).

Partial/conditional/multivariate CC

Multivariate CC (Ellett & Ericson 1986; Marrelec et al. 2006) computes correlations between each pair of signals, after removing the linear projections of all other signals/sources in the network on the pair of interest. Considering \( x(t) \) and \( y(t) \) as two signals of interest and \( z(t) \) being a third source to which both \( x(t) \) and \( y(t) \) are connected, the correlation between \( x(t) \) and \( y(t) \) conditional on \( z(t) \) is calculated as:

\[
\rho_{xy|z} = \frac{\rho_{xy} - \rho_{xz}\rho_{yz}}{\sqrt{(1-\rho_{xz}^2)(1-\rho_{yz}^2)}}
\]

Hilbert Amplitude CC

Hilbert amplitude CC (Brookes et al. 2011a) starts by applying Hilbert transform to obtain instantaneous frequency and phase of a signal. Thereafter, CC between the low-frequency power...
envelope variations of a pair of signals is computed over time. The method has been often used for resting state EEG/MEG connectivity.

2.2.1.1.2 Spectral connectivity

Spectral measures find associations between two signals in frequency/time-frequency domain, assuming that each brain signal can be decomposed into a linear sum of sinusoidals/wavelet basis functions with different frequencies and amplitudes (Schoffelen & Gross 2009). For this purpose, Fourier or Wavelet transforms are usually applied to the data.

2.2.1.1.2.1 Coherency

Coherency between two signals is the probability of two sources co-activating at the same frequency normalised by the probability of their independent activation (Nunez et al. 1997). It is formulated as:

\[ S_{XY}(f) = \langle x_i(f)x_j^*(f) \rangle \]
\[ C_{XY}(f) = \frac{S_{XY}(f)}{\sqrt{S_{XX}(f)S_{YY}(f)}} \]  \hspace{1cm} (2.9)

Where \( S \) is the cross-spectrum, \( X(f) \) and \( Y(f) \) are Fourier transforms of the brain signals, \( f \) denotes frequency and * is conjugate transpose. It is worth noting that \( S \) is Fourier transform of the cross-covariance in Equation 2.6 and hence coherency can be thought of as the analogue of cross correlation in the frequency domain. \( C_{ij}(f) \) is complex with real and imaginary parts which could also be expressed in terms of amplitude and phase. As will be elaborated below, different aspects of \( C_{ij}(f) \) have been used to calculate connectivity between two signals. Advantages, assumptions and limitations of coherency as well as modified versions to alleviate the limitations are presented in Table 2.2. In theory, an infinite length of the data is required, hence the given quantity is always an estimation. In practice, EEG/MEG signals are usually subdivided into M epochs of equal length, and the spectra are estimated by averaging the periodogram over these epochs (Welch’s method).

Table 2.2 Advantages, assumptions and limitations of spectral coherency and some of the modified versions.

<table>
<thead>
<tr>
<th>Spectral Coherency</th>
<th>Advantages:</th>
<th>Assumptions &amp; limitations:</th>
<th>Modified versions (alleviated limitations)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Fast algorithms available</td>
<td>1. Linearity</td>
<td>Imaginary Coherency (5)</td>
</tr>
<tr>
<td></td>
<td>• Robust to deviations from linearity assumption</td>
<td>2. Stationarity</td>
<td>Partial Coherence (4, 5)</td>
</tr>
<tr>
<td></td>
<td>• Yields direct information for each frequency band of interest</td>
<td>3. Signal length is important</td>
<td>Partial directed coherence (4, 5)</td>
</tr>
<tr>
<td></td>
<td>• Separation of different frequency bands allows to isolate some noise patterns from the data</td>
<td>4. Bivariate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Susceptible to leakage</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6. Relative importance of amplitude and phase covariance unclear</td>
<td></td>
</tr>
</tbody>
</table>
Imaginary Coherence

Imaginary part of coherency (Nolte et al. 2004) measures associations between a pair of signals after omitting the real part of $C_{ij}(f)$. It is, therefore, less affected by the leakage problem in source reconstructed EEG/MEG and volume conduction problem in EEG sensor space. However, as will be elaborated in Chapter 6, the method is still susceptible to leakage and additionally, it neglects potential true zero-lag connections in the data. See Chapter 6 for a detailed theoretical discussion and results of reconstructions of simulated networks.

Magnitude Squared Coherence

Magnitude squared Coherence between two signals is measured as the absolute value of $C_{ij}(f)$ in Equation 2.9. Partial/multivariate coherence, an extension to this method, finds coherence between two signals after removing the linear effects of other possibly interfering sources on each pair of interest, in an approach similar to partial correlation explained above (Equation 2.8).

Partial Directed Coherence

This method falls into the category of directed (i.e. causal) measures of connectivity and is similar to the Multivariate Spectral Granger Causality which will be elaborated in 2.2.1.2.1.

2.2.1.2.2 Phase Synchronisation and Phase Locking Value

Two signals are considered phase synchronised at a particular frequency if the phase difference (i.e. relative delay) remains stable over time (e.g. over trials), which is:

$$|\phi_x(t) - \phi_y(t)|_{f=f_0} = \text{Constant} \quad (2.10)$$

where $\phi$ denotes phase, $t$ is time and $f$ is frequency. The traditional method to quantify phase synchronisation is phase locking value (PLV) (Lachaux et al. 1999). In order to compute PLV, likewise for coherency, signals are decomposed in the time-frequency domain using Wavelet or Fourier transform and signal amplitude and phases are extracted. Phase synchrony is then defined as:

$$PLV(t, f) = \frac{1}{N} \left| \sum_{n=1}^{N} e^{-i\Delta\phi(t, f, n)} \right| \quad (2.11)$$

where $\Delta\phi$ stands for the phase difference, $n$ stands for EEG/MEG trial number, $t$ for time and $f$ for frequency. Hence, if two brain signals have random delays relative to each other over trials, the phase difference will cancel out in averaging over trials, resulting in low PLV while if the phase difference is consistent across trials, PLV will be high (Figure 2.2).
Table 2.3 Advantages, assumptions and limitations of PLV and some of the modified versions.

<table>
<thead>
<tr>
<th>Phase Locking Value (PLV)</th>
<th>Advantages:</th>
<th>Assumptions &amp; limitations:</th>
<th>Modified versions (alleviated limitations)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Nonlinear</td>
<td>1. Large number of trials/data points required</td>
<td>Pairwise Phase Consistency (1)</td>
</tr>
<tr>
<td></td>
<td>- Fast algorithms available</td>
<td>2. Phase delay caused by signal propagation is assumed negligible compared to the original signal phase</td>
<td>(Weighted) Phase Lag Index (3)</td>
</tr>
<tr>
<td></td>
<td>- Robust to deviations from linearity assumption</td>
<td>3. Sensitive to leakage</td>
<td>De-biased squared phase lag index (1, 3)</td>
</tr>
<tr>
<td></td>
<td>- Yields direct information for each frequency band of interest</td>
<td>4. Insensitive to the shape of response</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Separation of different frequency bands allows isolating some noise patterns from the data</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pairwise Phase Consistency (PPC)

One limitation of PLV is that if phase differences between two signals are random across trials, the number of trials should be high enough for these random phases to cover the whole unit circle in Figure 2.2 in order to obtain an accurate estimation of PLV and therefore this measure is dependent on the number of trials. Pairwise Phase Consistency (PPC) (Vinck et al. 2010) has been proposed to overcome this problem by:

- Taking the absolute value of $\Delta \phi$ so that all the vectors in Figure 2.2 lie in the upper half of the unit circle and computing $\Delta \Delta \phi$, that is the difference of phase differences across trials;
- Consistent $\Delta \phi$ across trials results in a $\Delta \Delta \phi$ that is close to zero and thus a cosine of $\Delta \Delta \phi$ that is close to one.
- PPC is thus computed by taking the average of $\cos(\Delta \Delta \phi)$ for all the pairwise comparisons of the trials. Therefore, the accuracy of estimation of phase synchrony will not rely on the number of trials.
Phase Lag Index (PLI)

Phase lag index (PLI) is designed to remove the spurious zero-lag connections. It is defined as the mean of the sign of the phase difference between two signals across trials/times windows. Therefore, it is insensitive to the amount of phase differences between two signals. Considering that the sign of the phase difference is the only important parameter, if there is zero-lag connectivity between two signals (Stam et al. 2007), there will be zero phase difference between them and hence PLI will be zero. Modified versions of PLI such as weighted PLI and debiased PLI have been introduced to overcome the limitations of insensitivity to the value of phase difference and dependence on the number of trials, respectively (Wang et al. 2014b).

2.2.1.1.3 Information Theoretic Measures

This family of methods perform in the time domain and are inherently non-linear (Greenblatt et al. 2012). That is, they do not assume that brain signals are linear, nor do they assume that connectivity between them is linear. Thus they have been proposed as more suitable measures of connectivity for stimulus-response data where the linearity and stationarity assumptions can be significantly violated. They have also been used frequently for studying neuronal firing rates, synaptic connections and neuronal encoding signals.

2.2.1.1.3.1 General Synchronisation

The key idea of general synchronisation (Stam & Van Dijk 2002) is that time points in the brain signals are not independent but rather that time points with specific lags amid (referred to as signal “memory”) form coordinates of a single data point in a high dimensional space. This method therefore requires calculation of the so called “embedding dimension” (d) and lag (τ) of a signal. Details of how to calculate these parameters can be found elsewhere (Stam 2005). However, an embedding dimension of d and a lag of τ would mean that a signal should be investigated in a d-dimensional space where coordinates of the d-dimensional representation of each time point of the signal \( x(t) \) are defined as

\[
X_i = x_i, x_{i+\tau}, x_{i+2\tau}, x_{i+3\tau}, x_{i+4\tau}, x_{i+5\tau}, x_{i+6\tau}.
\]

General Synchronisation then defines connectivity between brain signals \( x(t) \) and \( y(t) \) as: if \( X_1 \) and \( X_2 \) are within a spatial neighbourhood in the d-dimensional embedding space, then corresponding \( Y_1 \) and \( Y_2 \) should be within a spatial neighbourhood too. Different algorithms have been proposed to quantify this criterion, among which synchronisation likelihood (SL) (Stam & Van Dijk 2002) has been more often used in the previous studies. The key advantage of this method is being inherently nonlinear, non-stationary and non-parametric. However, the accuracy of final results is strongly dependent on the accuracy of estimating embedding dimension \( d \) and time lag \( \tau \). Additionally,
current algorithms for estimating these two parameters are typically slow and thus applications to large data (such as source reconstructed EEG/MEG) has been limited.

2.2.1.1.3.2 Mutual Information

The idea of mutual information is based on the Shannon definition of entropy (Shannon 1948): If a sequence of bits is to be encoded using a subset of bits within the sequence, the more uncertainty in the sequence, the larger the subset required to encode the entire sequence, and hence the higher the entropy of the sequence. Now considering two sequences of \( x(t) \) and \( y(t) \), if \( y(t) \) is to be encoded given that \( x(t) \) is known, conditional entropy of \( y(t) \) given \( x(t) \) is defined as the number of EXTRA time points that are required to be added to the information from sequence \( x(t) \) in order to fully encode \( y(t) \). Mutual information (MI) (Greenblatt et al. 2012) utilises a similar concept and calculates the degree to which the uncertainty (entropy) about \( y(t) \) will be reduced if \( x(t) \) is known. Since this measure calculates the amount of information that the two signals share, it is named mutual information and is formulated as:

\[
I(x(t), y(t)) = H(y(t)) - H(y(t)|x(t)) = H(x(t)) - H(x(t)|y(t)) = H(x(t)) + H(y(t)) - H(x(t), y(t)) \tag{2.12}
\]

where \( I \) denotes mutual information, \( H \) is entropy and \( x(t) \) and \( y(t) \) are two brain signals that are assumed as random procedures. Therefore, MI is inherently nonlinear and model free (i.e. non-parametric). Conditional/multivariate extensions of mutual information have been introduced to account for spurious connectivity through a shared third source. Details of advantages, assumptions and limitations of MI and some of the modified versions are presented in Table 2.4.

Table 2.4 Advantages, assumptions and limitations of Mutual Information and some of the modified versions.

<table>
<thead>
<tr>
<th>Mutual Information (MI)</th>
<th>Advantages:</th>
<th>Assumptions &amp; limitations:</th>
<th>Modified versions (alleviated limitations)</th>
</tr>
</thead>
</table>
|                        | • Inherently Nonlinear  
                        | • Non-parametric  
                        | • Suitable for non-stationary data  
                        | • Fast algorithms available  
                        | 1. Sensitive to the signal length  
                        | 2. Sensitive to noise  
                        | 3. Exact analytical value of probabilities and hence MI cannot be calculated, instead, binning of the histogram or nearest neighbour estimation must be used.  
                        | 4. No temporal information is provided  
                        | 5. Sensitive to Leakage  
                        | Multivariate MI (5) |
2.2.1.3.3 Transfer Entropy

With analogy to the description provided for entropy and MI in the previous subsection (2.2.1.3.2), transfer entropy is defined as: The degree to which uncertainty about the current value of \( y(t) \) is reduced, given the past values of itself and the past values of \( x(t) \). It is formulated as:

\[
H_{x(t) \rightarrow y(t)} = H(y_1|y_{t-1:t-L}, x_{t-1:t-L}) - H(y_1|y_{t-1:t-L}, x_{t-1:t-L}, x_{t-1:t-L}) 
\]

where \( H \) is entropy (uncertainty), \( t \) is time and \( L \) is the length of the previous time points of interests. This measure is also referred to as non-parametric Granger Causality.

2.2.1.2 Causal Connectivity

Causal connectivity metrics measure the direction of information flow in the brain. Two main definitions of causal connectivity have been used in the past literature: temporal precedence (e.g. Granger Causality measures (Ding et al. 2000)) and effective connectivity (e.g. Dynamic Causal Modelling (DCM) (Kiebel et al. 2008)). While the former is based on the statistical dependencies and in some literature has been categorised along with measures of functional connectivity metrics (Faes et al. 2017), the latter is inherently causal in nature. More specifically, effective connectivity is aimed at modelling changes in the output of neuronal populations and connectivity among the neuronal populations as a consequence of (i.e. caused by) experimental manipulations. Therefore, while granger causality measures focus on predicting future signal values using past values as evidence of one brain source causing activity in the other, DCM measures model changes in uni-/bidirectional connections among the brain sources that are caused by the variations in the brain inputs.

2.2.1.2.1 Granger Causality (GC)

According to the Granger Causality (Granger 1969), if current activation of signal \( x(t) \) (i.e. \( x_t \)) can be estimated with more accuracy based on the past values of \( x(t-\tau) \) \( (x_1, x_2, ..., x_{i-1}) \) plus past values of \( y(t-\tau) \) compared to when based on the past values of \( x(t-\tau) \) only, then \( y(t) \) is thought to granger cause \( x(t) \). In other words, by adding past values of \( y(t-\tau) \) to the past values of \( x(t-\tau) \) in order to predict the current \( x(t) \), the variance of the prediction error should be reduced. Thus:

\[
x(t) = \sum_{\tau=1}^{\infty} A_1 x_{t-\tau} + \varepsilon_1 \quad \text{then} \quad \hat{x}(t) = \sum_{\tau=1}^{\infty} A_2 x_{t-\tau} - \sum_{i=1}^{\infty} B y_{t-\tau} + \varepsilon_2 
\]

Where \( A_1, A_2 \) and \( B \) are vectors of coefficients which are estimated using a least mean square fitting approach and \( \varepsilon_1 \) and \( \varepsilon_2 \) are vectors of prediction errors throughout time that are modelled as zero-mean Gaussian variables. The variances of the prediction errors (\( \Sigma_1, \Sigma_2 \)) are calculated and granger causality of \( y(t) \) on \( x(t) \) is thus defined as:

\[
G_{y(t) \rightarrow x(t)} = \frac{\Sigma_1}{\Sigma_2} 
\]
Based on this linear bivariate implementation of GC the magnitude of GC is computed and subsequently can be put through statistical testing. Properties of this method as well as modified versions are elaborated in Table 2.5.

| Table 2.5 Advantages, assumptions and limitations of granger causality and some of the modified versions. |
|---------------------------------|-----------------|-----------------|
| **Granger Causality (GC)** | **Assumptions & limitations:** | **Modified versions (alleviated limitations)** |
| Advantages: | 1. Linearity | 3. Multivariate GC (2) |
| Causal | Linear | Linear |
| Less sensitive to zero-lag connections | Bivariate | Spectral GC (7) |
| Fast and easy to compute | Stationarity | Non-parametric GC (1, 3) |

Multivariate/conditional/partial GC

Similar to the other multivariate connectivity metrics explained above, multivariate GC (Bressler & Seth 2011) aims at reducing the spurious connectivity between two sources that is caused by shared a third source. For this purpose, multivariate GC takes into account the past information from all the sources of interest to model the current values of the sources, all inverted in a single scheme. It is formulated as:

\[ M(t) = \sum_{\tau=1}^{L} A_{\tau} M(t - \tau) + \epsilon(t) \quad (2.16) \]

where \( M \) is a matrix of concatenated time series for all the brain sources of interest and \( A \) is the coefficient matrix. Non-zero values in \( A \) indicate granger causality between the corresponding time series at time point \( \tau \). Therefore multivariate GC is both multivariate and time-varying (\( A \) elements are time dependent). It is worth noting that \( A \) is asymmetric, i.e. if signal \( y(t) \) is granger causing \( x(t) \) at time \( t \), \( x(t) \) does not necessarily cause \( y(t) \) too. In the special case of three sources the multivariate CG (mGC) can be calculated as:

\[ mG_{y\rightarrow x|x} = \frac{\ln \left( \sum_{x, y, z} \right)}{\ln \left( \sum_{x, y, z} \right)} \quad (2.17) \]

It is worth noting that spectral GC can be obtained by investigating \( M \), \( A \) and \( \epsilon \) in the frequency domain (e.g. by applying Fourier transform to these matrices).
Spectral GC

Fourier transformation of Equation 2.14 will result in obtaining Spectral GC (Faes et al. 2017; Seth 2010) (note that convolution in time domain turns into multiplication in frequency domain):

\[ A(f)X(f) = E(f) \quad \text{OR} \quad X(f) = H(f)E(f) \quad \text{where} \quad H(f) = A^{-1}(f) \quad (2.18) \]

\( H \) is called transfer function, which is asymmetric and complex. Multivariate Spectral Granger Causality (aka. Partial Directed Coherence (Baccalá & Sameshima 2001)) is defined based on \( A \) and Directed Transfer Function, another measure of GC is defined based on \( H \).

2.2.1.2.2 Bayesian Modelling

2.2.1.2.2.1 Dynamic Causal Modelling (DCM)

The main idea of the DCM is to consider the brain as a deterministic nonlinear dynamic system that in response to inputs activates unobserved neuronal populations (hidden states) and modulates connections among these hidden states. These changes produce a primary (hidden) output that is then transferred to the surface of the scalp (EEG/MEG forward modelling to map sources to sensors) and measured using EEG/MEG sensors (Kiebel et al. 2008). Thus DCM aims at modelling:

- The effect of input (e.g. perceptual stimuli or a cognitive task) on changes in the activity of a brain source;
- The effect of other brain sources on changes in the activity of a specific brain source;
- The effect of input on the directed connection between two brain sources.

The model is formulated as:

\[ \dot{x} = f(x, u, \theta) + \omega \quad y = g(x, u, \theta) + \nu \quad (2.19) \]

where \( u \) is the input, \( x \) is the hidden state and \( y \) is the measured output. \( f, g \) are functions to map inputs to hidden states and input/hidden states to output respectively. \( \omega \) and \( \nu \) are noise vectors, respectively. Three key aspects of DCM analysis are (Stephan et al. 2010):

1. Defining input, hidden state and output in DCM for EEG/MEG:
   - Input to the brain (e.g. experimental manipulations) affects spiny stellate cells (SSC) as receiver cells, these input neurons communicate with excitatory/inhibitory interneurons through internal connections and produce a preliminary output at pyramidal cells. This stage is modelled using Neural Mass Models (David & Friston 2003) in DCM.
   - Output from pyramidal cells (i.e. electro-magnetic brain activity) is transmitted through different brain and head layers to reach the scalp and measured by EEG/MEG channels. This stage is modelled using EEG/MEG forward modelling that maps brain sources (i.e.
output of pyramidal cells) to the EEG/MEG sensors though linear application of the leadfield.

2. **DCM model selection:**
   - In order to apply DCM to a dataset, a hypothesis about the regions involved in a particular task is required. Entering all the brain regions in an analysis is computationally and theoretically implausible.
   - Moreover, it is also required to have hypotheses about the number and direction of connections between the regions of interest in the model. For example, in a model that includes three ROIs only, 64 different scenarios can be drawn as possible connections among these ROIs. Therefore, psychophysiological restrictions are usually applied to keep the model space within a manageable size.
   - Finally, Bayesian Model Selection (BMS) is used to identify the model with the highest evidence for the data:
     i. If the optimal model is thought to be the same across subjects, the model with the highest average evidence across subjects is selected as the winner (fixed effect inference, aka. FFX). This approach is often used with homogeneous subject populations (e.g. control young adults performing a cognitive task).
     ii. If the optimal model is thought to differ between subjects, random effect analysis (RFX) is used to find the most consistent model across subjects. This approach is more common when studying inhomogeneous populations (e.g. controls vs. patients).

3. **DCM parameter estimation:**
   After identifying the winner model, DCM can be used to estimate the model parameters ($\theta$) using a Bayesian approach. For this purpose:
   - Based on the physiology and mathematical constraints, prior probabilities (Gaussian) are assigned to each parameter $p(\theta)$;
   - Under the Gaussian assumption, the likelihood of the data given the parameters is computed ($p(y|\theta)$). This likelihood is often referred to as model evidence;
   - Posterior probability of the parameters are computed based on the model evidence and parameter priors: $p(\theta|y)=p(y|\theta)p(\theta)/p(y)$.
   - Finally, fixed effect or random effects can be used to evaluate the estimated parameters at population level, e.g. to test whether each parameter is significantly different between different conditions in an experiment.
Table 2.6 Advantages, assumptions and limitations of DCM and some technical improvements to date.

<table>
<thead>
<tr>
<th>Dynamic Causal Modelling (DCM)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages:</strong></td>
</tr>
<tr>
<td>• Is a direct/effective connectivity which takes into account inputs, outputs and hidden states that are not observed, hence there is no break in the chain of causalities;</td>
</tr>
<tr>
<td>• Provides models of how the underlying mechanisms change the observed outputs;</td>
</tr>
<tr>
<td>• Bilinear</td>
</tr>
<tr>
<td>• Non-stationary</td>
</tr>
<tr>
<td>• Minimal sensitivity to leakage</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

2.2.1.2.2.2 Structural Equation Modelling (SEM)

Structural Equation Modelling (SEM) (Astolfi et al. 2004) can be considered as a limited version of DCM where directed connections (referred to as path coefficients) between two areas are time-constant and must be set between each pair of sources. Considering the static nature of the method, its applications to EEG/MEG data, where dynamicity is one of the key advantages, has been limited.

2.2.2 Which connectivity method to select?

Thus, among this multitude of methods devised to quantify connectivity between the brain sources, each focuses on different definitions and aspects of connectivity. Therefore, selecting one connectivity measure among a range of methods is challenging and ideally requires a profound knowledge of the mechanisms that underlie orchestrating the neuronal populations. However, such mechanisms, particularly for higher level cognitive functions, are typically not known to date. Thus, an insightful selection of the most suitable connectivity metrics remains a challenge.

This issue has been acknowledged recently (Bastos & Schoffelen 2016; Wang et al. 2014a) and tackled in a few studies using different approaches such as test-retest reliability (Pestilli 2015), optimisation of connectivity metrics/parameters using realistic simulations (Wang et al. 2014a). Most recently, the so-called ensemble methods have been proposed that combine information from multiple connectivity methods/parameters in order to obtain a more generalisable connectivity estimation (Takemura et al. 2016). The ensemble connectivity approaches to date have been mostly focused on optimisation of connectivity parameters for DTI and fMRI (Pestilli et al. 2014; Takemura et al. 2016).
al. 2016). To the best of our knowledge, only one study has focused on intracranial EEG (with generalisability to EEG/MEG) and fMRI: Wang et al. (2018) utilised a method that started by identification of a few optimal connectivity metrics/parameters (referred to as input basic metrics or BMs) based on simulated data (Wang et al. 2014a). Data were simulated using neural mass models and in an ideal scenario in the absence of leakage. Thence, the method utilised the optimal BMs to quantify connectivity of a real dataset, obtaining multi-vector connectivity of BM results. Next, by applying a fuzzy algorithm to the results of these sub-selected BMs, the most probable estimate of connectivity for the data was extracted (Wang et al. 2018). Importantly, however, the initial sub-selection of the BMs and consequently the accuracy of the final results is dependent on the degree to which simulations are representative of a real dataset. Considering the breadth of leakage problem for connectivity analysis of source-estimated EEG/MEG, it is desirable to either find a mechanism to incorporate leakage in the original simulations or proposing a different method that relies on the real data only. This issue has not been addressed in any previous studies.

2.2.3 PCA-based selection of the most suitable connectivity

Principal component analysis is a multivariate statistical method that has been used abundantly for dimensionality reduction, feature selection and artefact rejection of EEG/MEG data (Jung et al. 2000; Lagerlund et al. 1997). The core idea of PCA is to project several possibly correlated variables on a set of orthogonal axes referred to as Principal Components (Abdi & Williams 2010; Wold et al. 1987). By doing so, the method finds similarities and differences between the original variables, where similar aspects can be projected on a single PC while unique aspects might be reflected on distinct PCs. Importantly, by measuring the amount of variance across the original variables that is explained by each PC, it is possible to tease apart the key features (i.e. those with maximum explained variance) from the noisy aspects of data (i.e. typically those with minimum explained variance). Considering that different connectivity methods might measure similar and/or different aspects of an EEG/MEG dataset, we propose that PCA can be applied to:

1) Find similarities between different methods;
2) Find unique aspects of each method;
3) Identify the method that with highest correlation with the first PC (i.e. maximum explained variance) as the most suitable connectivity (MSC) metric for a dataset;
4) Provide the first PC as an ensemble connectivity estimate that can be analysed instead of the original metrics.
It is worth noting that depending on the purposes of a study, one of the options 3 and 4 might prove more useful. Considering that PCA method will only rely on the real datasets (i.e. no simulations), the leakage patterns are automatically included in the computations.

2.3 An outline of this thesis

The current thesis aims at addressing some of the unresolved or controversial predictions of recent models of the semantic brain system, such as the hub-and-spokes model. In particular, we tackle different aspects of the hypothesis that a widespread network of interacting heteromodal (hub(s)) and unimodal (spokes) cortices underlie semantic cognition. For this purpose, we use connectivity analyses, measures of graph theory and permutation-based statistics based on source reconstructed EEG/MEG data in order to track dynamic modulations of activity and connectivity within semantic networks while a concept unfolds in the brain. Moreover, in order to obtain more accurate connectivity estimates of semantic networks, we propose novel methods for some of the challenges associated with EEG/MEG connectivity analysis in source space.

In Chapter 3, we will utilise EEG/MEG recordings from a concreteness decision task (a pre-existing dataset) in a visual word recognition paradigm in order to examine the heteromodal part of the semantic network in the brain. We will test the hypothesis of a single hub against several convergence zones. For this purpose, we seek to identify processor hubs by examining modulations of whole-brain evoked responses by the contrast of concrete and abstract words and integrator hubs by investigation of effective connectivity (DCM for evoked responses) among the main candidate hubs in the left hemisphere.

In Chapter 4, we aim to extend the findings of Chapter 3 for identification of the integrator hubs. For this purpose, we will test for modulation of dynamic whole-brain seed-based connectivity of the candidate hubs by concreteness effect (using the same dataset as Chapter 3) in an effort to unravel hub-spoke connectivity. However, considering that an arbitrary choice of one connectivity metric among dozens is sub-optimal, we will take note of the properties of the prominent connectivity methods overviewed in 2.2.1 and propose a novel PCA-based approach to identify the most suitable connectivity method for the dataset.

In Chapter 5, we will design and analyse a new EEG/MEG dataset with fine-grained word categories where the role of sensory-motor cortices can be untangled with more accuracy. We will combine some of the predictions of the hub-and-spokes model with ideas of embodied semantics in order to further specify the mechanism of semantic representation in spokes through observation of their timings and oscillations. Furthermore, we will expand on the explorations of Chapter 3 regarding
the processor hub area(s) by examining more general (words versus pseudowords) and more specific (fine-grained categories of concrete words) semantic contrasts.

The final aim of the current thesis is to observe dynamic semantic graphs using a whole-brain data-driven approach. However, considering the limitations of the spatial resolution of EEG/MEG for whole-brain connectome reconstruction, in Chapter 6 we will propose adaptive cortical parcellations for source-reconstructed EEG/MEG data. We will further validate the suitability of the proposed methods on realistically simulated data. This chapter has been published (Farahibozorg et al. 2017).

In Chapter 7, we will use the same dataset as Chapter 5 in order to examine the time-varying semantic networks using a whole-brain connectomic approach. We will utilise the adaptive parcellations introduced in Chapter 6 for network reconstruction and apply measures of graph theory to identify semantic modules in the cortex. Thereafter, we will examine differences of inta-/inter-modular connectivity matrices between different semantic word categories in order to identify global integrator hubs, spokes and types of connectivity in the semantic networks.

Finally, in Chapter 8 the key findings about the organisation of semantic networks and methodological developments proposed in this thesis will be summarised and discussed, and future directions will be proposed.
3 Processor Hub versus Integrator Hubs: Distinct Roles for Anterior Temporal Lobe and Angular Gyrus in Semantic Retrieval

Brain imaging research to date has not reached a consensus as to whether distributed semantic networks are organised encompassing one central hub, or a sub-network consisting of several heteromodal convergence zones. In this Chapter, we seek to address this question by drawing a distinction between two roles of a semantic hub, namely higher-level abstract processing and modality-specific cross-modal integration, at different stages of word processing. We hypothesised these two properties to be reflected in the modulation of amplitude and connectivity of a hub by semantic variables, respectively. We utilised the spatio-temporal resolution of source-estimated concurrent EEG/MEG in a concreteness decision task to address this question by: (i) observing time-resolved whole-brain evoked responses in different time windows; (ii) explicitly testing the single hub model versus multiple convergence zones using Dynamic Causal Modelling (DCM) of evoked responses within the heteromodal part of the semantic network in the left hemisphere comprising Anterior Temporal Lobe (ATL), Supramarginal/Angular Gyrus (SMG/AG), Middle Temporal Gyrus (MTG), Inferior Frontal Gyrus (IFG) and Word Form Area (WFA). Our results suggest distinct roles for the ATL and AG: ATL appeared as the processor hub as early as 100ms post-stimulus, persisting into later stages of semantic word processing at ~400ms, while both ATL and AG subserved integration hubness during earlier (0-250ms) and later (0-450ms) time windows of DCM investigations, respectively. Therefore, our results suggest that distinct yet overlapping brain areas might underlie processing and integration hubness in dynamic semantic networks.
3.1 Introduction

One of the key ongoing debates regarding the neural mechanisms that underpin semantic cognition has been as to whether there exists one central heteromodal semantic hub in the bilateral anterior temporal lobes (ATLs), as proposed by the hub-and-spokes model (Lambon Ralph et al. 2016; Patterson et al. 2007; Rogers et al. 2004), or several predominantly left hemispheric hubs in the temporal, parietal and frontal cortices (often referred to as convergence zones) as has been proposed based on meta-analytic evidence from fMRI literature (Binder 2016; Martin et al. 2014; Pulvermüller 2013; Taylor et al. 2011). These theories, in spite of proposing different number and locations for the hub(s), have implicated a two-fold role for the heteromodal semantics hub(s) (Binder 2016; Lambon Ralph et al. 2016; Woollams & Patterson 2017), which we will refer to as integration hubness and processor hubness, as elaborated below.

Firstly, integration hubness involves mediation and integration of sensory-motor-limbic attributes of a concept that are supposedly provided by the distributed lower-level unimodal cortices. In order to fulfil this task, the candidate hub area(s) should show rich structural and functional connections to the distributed semantic areas, so that it will be able to send/receive information to/from those unimodal regions. An emerging field is currently focused on providing empirical evidence in support of this property, predominantly using structural or functional MRI connectivity and DTI fibre tracts (see 1.2.3 in Chapter 1 for more details). Among the main heteromodal semantic cortices, it has been shown that different subdivisions of ATL (Jackson et al. 2016; Papinutto et al. 2016), MTG (Binney et al. 2012; Catani et al. 2005; Fang et al. 2015) and AG (Hagmann et al. 2008; Seghier 2012; Tomasi & Volkow 2011) show rich connectivity patterns to multiple heteromodal and modality-specific parts of the semantic network, depicting that in principle, these areas are suitable candidates for integrator hubs.

Secondly, processor hubness involves representation of concepts at a supramodal level; i.e. a higher-level abstract/symbolic representation of concepts in addition to the mediation of the modality-specific information from unimodal areas (Binder 2016; Lambon Ralph et al. 2016). This property has been explored extensively by measuring regional modulations of activity in response to modality-general semantic variables and ATL, AG, MTG and IFG have been identified as the main candidate hubs using fMRI (Binder & Desai 2011; Jefferies 2013; Pulvermüller 2013). Further investigation of the timings of these modulations using EEG/MEG (Hauk et al. 2012; Moseley et al. 2013; Westerlund & Pylkkänen 2014) and Transcranial Magnetic Stimulation (TMS) (Jackson et al. 2015) have also confirmed the importance of these four areas as the main processor hub candidates. In particular, ATL has been implicated as a potential source of N400 ERP component for semantics and
has additionally been shown to be modulated during earlier stages of semantic word processing (e.g. around 200ms post-stimulus).

Therefore, an important difference between a processor and an integrator hub is that while the former is expected to show modulations of activation in response to the contrasts of different semantic variables, the latter is involved through modulations of its connections to the distributed semantic areas. Thus, activations of an integrator hub may or may not be modulated by semantic contrasts. In this chapter, we propose that an important next step towards addressing a single hub versus several convergence zones debate is to explicitly evaluate these two-fold properties for the main candidate hub regions during multiple stages of semantic word processing.

For this purpose, we utilise source-estimated EEG/MEG recordings of a concreteness decision task in a visual word recognition paradigm. Firstly, we will test the processor hubness role by examining time-resolved whole-brain evoked responses from 50-550ms post-stimulus in order to detect areas that underlie differentiation of concrete/abstract words at different stages of word recognition. We predict that the single hub view will be reflected in early modulation of one processor hub that remains modulated throughout the course of semantic processing while several convergence zones might be reflected in modulations of several areas, in parallel or serially, during the course of semantic cognition. Secondly, we will test the role of integration hubness within a left hemispheric subnetwork of heteromodal semantic areas by comparing Dynamic Causal Models (DCM) of evoked responses (David et al. 2006a). For this purpose, we apply DCM to a network consisting of the left ATL, IFG, MTG, AG/SMG and visual Word From Area (vWFA as input region for visual stimuli) in order to unravel the most likely organisation of this network within 250ms and 450ms post-stimulus. More specifically, we will construct a hierarchy of model comparisons comprising two levels, focused on addressing: a) is the single hub structure suitable for modelling the heteromodal subnetwork of the semantic areas in the brain? b) If so, which area(s) among the ATL, IFG, MTG and AG plays the role of a hub within 250ms and 450ms post-stimulus? If not, what is a more suitable alternative model?

3.2 Materials and methods

3.2.1 Data acquisition and pre-processing

3.2.1.1 Participants

20 healthy native English speakers participated in the study, but 3 subjects were removed due to excessive movement artefacts or measurement error. Hence, 17 participants (age 27±6 years, 12 female) entered the final analysis. A handedness laterality quotient of 82±23 was obtained from a reduced version of the Oldfield handedness inventory (Oldfield 1971). All participants had normal or
corrected-to-normal vision with no reported history of neurological disorders or dyslexia. The experiment was approved by the Cambridge Psychology Research Ethics Committee and volunteers were paid for their time and effort.

3.2.1.2 Stimuli

Participants were presented with 184 monomorphemic abstract and concrete words (92 each), matched for a number of psycholinguistic variables including Kucera-Francis (KF) and CELEX frequencies, familiarity, concreteness and imageability ratings as well as the number of letters/phonemes/syllables (see Table 3.1 for details). KF Frequency, Familiarity, Concreteness and Imageability values were taken from the MRC Psycholinguistic Database (Coltheart 1981) and CELEX Frequency taken from the MCWord Database (Binder & Medler, 2005). The two categories differed significantly on concreteness and imageability (t_s>19.3575, p_s<.0005) as indicated by unpaired t-tests, but not with respect to the other aforementioned variables.

3.2.1.3 Procedure

Single-word stimuli appeared as 28-point Arial font in white on a black screen within a visual angle of 4 degrees in a slightly dimmed and acoustically shielded MEG chamber. Duration of stimulus presentation was 150 ms, with an average SOA of 2400 ms (uniformly jittered between 2150 and 2650 ms). Participants responded by making button presses with their right hand, using index and middle finger to distinguish between conditions. Short breaks were included after about every 50 trial. Participants were given a few minutes of practise time prior to the experiment and using different stimuli until they felt comfortable with the task. The first two trials (filler items) after each break and at the beginning of each block were not included in the analysis.

<table>
<thead>
<tr>
<th></th>
<th>Concrete mean ± std</th>
<th>Abstract mean ± std</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Letters</td>
<td>5.9 ± 0.8</td>
<td>6.0 ± 0.8</td>
</tr>
<tr>
<td>Number of Phonemes</td>
<td>5.0 ± 1.2</td>
<td>5.2 ± 1.2</td>
</tr>
<tr>
<td>Number of Syllables</td>
<td>2.0 ± 0.6</td>
<td>2.1 ± 0.8</td>
</tr>
<tr>
<td>KF Frequency</td>
<td>15.0 ± 18.0</td>
<td>15.0 ± 15.0</td>
</tr>
<tr>
<td>CELEX Frequency</td>
<td>12.0 ± 15.0</td>
<td>15.0 ± 14.0</td>
</tr>
<tr>
<td>Familiarity Rating</td>
<td>462.0 ± 59.0</td>
<td>447.0 ± 98.0</td>
</tr>
<tr>
<td>Concreteness Rating</td>
<td>590.0 ± 26.0</td>
<td>303.0 ± 39.0</td>
</tr>
<tr>
<td>Imageability Rating</td>
<td>566.0 ± 41.0</td>
<td>388.0 ± 78.0</td>
</tr>
</tbody>
</table>

KF: Kucera-Francis; std: standard deviation.
3.2.1.4 EEG/MEG data acquisition and pre-processing

MEG data were acquired in a magnetically shielded room using a Neuromag Vectorview system (Elekta AB, Stockholm, Sweden), with 204 planar gradiometers and 102 magnetometers (i.e. 306 channels overall). EEG data were collected concurrently using a 70-electrode EEG cap (EasyCap GmbH, Herrsching, Germany). EEG reference and ground electrodes were attached to the nose and left cheek, respectively. The Electro-Oculo-Gram (EOG) was recorded by placing electrodes above and below the left eye (vertical EOG) and at the outer canthi (horizontal EOG). Data were acquired with a sampling rate of 1000Hz and a band pass filter of 0.03 to 330 Hz. Prior to the MEG recording, the positions of 5 Head Position Indicator (HPI) coils attached to the EEG cap, 3 anatomical landmark points (two ears and nose) as well as approximately 50-100 additional points covering the whole EEG cap were digitised using a 3Space Isotrak II System (Polhemus, Colchester, Vermont, USA) for later co-registration with MRI data. Data were acquired using imaging facilities at the MRC Cognition and Brain Sciences Unit, University of Cambridge, UK. Note that this dataset was acquired prior to the start of this PhD and details of contributions from collaborators are presented in the Preface.

Our analysis pipeline for the data is illustrated in Figure 3.1. The First step of data pre-processing included applying a signal-space separation (SSS) method implemented in the Maxfilter software (Version 2.0) of Elekta Neuromag to the raw MEG data in order to remove noise that were generated from sources distant to the sensor array (Samu Taulu and Matti Kajola 2005). The Maxfilter software involved movement compensation and bad channel interpolation. All the next steps of analysis were performed in the MNE-Python software package (http://martinos.org/mne/stable/index.html) (Gramfort et al. 2013, 2014). Raw data were visually inspected for each subject, and consistently bad EEG channels were marked and interpolated. Data were then FIR band-pass filtered between 1 and 48 Hz with a window length of 40 s and using forward backward technique to achieve zero phase delay. Independent Component Analysis (ICA) was applied to the filtered data in order to remove eye movement and heart artefacts. We used FastICA algorithm (Hyvärinen et al. 2000) as included in scikit-learn python package (Pedregosa et al. 2011) and implemented in MNE-Python meeg-preprocessing package (with minor manual changes to achieve a better artefact rejection for some subjects) for artefact rejection. After ICA, data were divided into epochs from -500ms to 700ms around the word onsets. Epochs were rejected if peak-to-peak amplitudes were higher than the following thresholds: 120 µV in the EEG (except for 2 cases where we increased the threshold to 150 µV, because high rejection rates could be identified as due to excessive Alpha activity at good behavioural performance), 2500 fT in magnetometers, 1000 fT/cm for gradiometers. Trials with incorrect responses were also excluded from further analysis.
3.2.1.5 Forward model and inverse solution

We used MNE-python software to compute forward and inverse models. The forward model was computed based on a Boundary Element head Model (BEM) of the head derived from structural MR images for each subject. EEG/MEG sensor configurations and MRI images were co-registered based on the aforementioned digitisation points. Structural MRI images were processed using the automated segmentation algorithms in FreeSurfer software (Version 5.3; http://surfer.nmr.mgh.harvard.edu/) in order to obtain the reconstructed scalp surface (Dale et al. 1999; Fischl et al. 1999). The result of the FreeSurfer segmentation was processed further using MNE software package (Version 2.7.3) and the original triangulated cortical surface which included more than 160,000 vertices per hemisphere was down-sampled to a tessellated grid where the average edge of each triangle was approximately 2.5mm (Segonne et al. 2004). A three-layer BEM consisting of 5120 triangles per layer was created for EEG and MEG from scalp, outer skull surface and inner skull.
surface, respectively. The noise covariance matrices for each dataset were computed and regularised in a single framework which computes the covariance using the diagonal technique with regularisation factor of 0.1 for all the channel types. Baseline intervals of 500ms duration pre-stimulus were used for noise covariance estimation. The resulting regularised noise covariance matrix was used to assemble the inverse operator for each subject using L2 minimum-norm estimation (L2 MNE) with a loose orientation constraint 0.2 and no depth weighting.

### 3.2.2 Whole-brain evoked analysis

After removing bad trials according to aforementioned criteria, the number of epochs was equalised between concrete and abstract words. The equalisation of the number of trials was performed so as to remove any potential biases due to the differences in signal to noise ratios (SNR). In particular, considering that error rates were significantly higher for the abstract words (section 3.3.1), equalisation procedure can compensate for SNR inequalities. Trials for each condition were averaged in sensor space in order to yield an evoked response per subject and condition, which were then projected onto the source space using L2 MNE. We used MNE-Python’s default SNR = 3.0 for evoked responses in order to regularise the inverse operator. Afterwards, the individual subject results were morphed to the standard average brain (fsaverage5) in Freesurfer software, yielding the time courses of activity for 20484 vertices for each subject and condition. Source-estimated time courses were then averaged in five time windows from 50ms to 550ms with 100ms increments for further analysis.

### 3.2.3 Statistical analysis: cluster-based permutation

We used a cluster-based permutation test (Maris & Oostenveld 2007) for statistical analysis of the whole-brain evoked and seed-based functional connectivity results. For this purpose, we computed univariate vertex-wise t-tests and thresholded them at a t-value corresponding to an initial p-value of p0 (two-tailed). Cluster-based permutation was applied to these thresholded t-maps and randomisation was replicated 5000 times in order to obtain the largest random clusters. The cluster-level significance for the original clusters was then calculated as the percentile of the cluster size compared to the largest random clusters across the 5000 permutations. We used spatio-temporal clustering (accounting for multiple comparisons across vertices and time windows) and, considering that cluster-based permutation results can be sensitive to the choice of p0 (Smith & Nichols 2009), we tested five thresholds (0.05, 0.045, 0.04, 0.025 and 0.01) and only robust clusters that appeared based on more than one p0 will be reported. Considering the low spatial resolution of EEG/MEG and our source localisation method for deeper brain areas (see Chapter 6 for more details), before conducting cluster-based permutation, the green bilateral areas shown in Figure 3.2 were excluded.
3.2.4 Dynamic Causal Modelling (DCM)

The DCM analysis was focused on the aforementioned candidate hubs: left ATL, IFG, MTG and AG as well as the visual word form area (vWFA) in the posterior fusiform gyrus of the left hemisphere as the input region. As the first step, we computed evoked source estimates in the same manner as outlined in 3.2.2 with two exceptions. Firstly, since DCM for ERP requires signed evoked responses, here we computed source reconstructed ERPs by taking dipole components perpendicular to the cortical surface. Secondly, in order to obtain more compatibility with the previous DCM ERP literature (Chennu et al. 2016; Garrido et al. 2008; Phillips et al. 2015), we used an extra band-pass filter between 1-35 Hz. Next, in order to compute the ROI time courses, we used cross-talk functions (CTFs) to identify one representative vertex inside each ROI, the time course of which was extracted and utilised in the subsequent analyses. The representative vertex for each ROI was the vertex with the highest sensitivity to that particular ROI which was defined as receiving the highest CTF value from the ROI. More details of the computation of the ROI CTFs are presented in Chapter 6.

After extraction of the ROI time courses, we used SPM12 (version r6909) for DCM analysis. The model space, as displayed in Figure 3.3, comprised 28 models. We defined a hierarchical organisation of DCM families in two levels in order to address the following two questions. In the first level of hierarchical comparison, aimed at identification of the winner grand-family, all the 28 models were categorised into three families of hub models, no-hub models and no-modulations. The hub family consisted of models 1-16 where either of ATL, IFG, MTG and AG areas played the role of a hub that received input from the vWFA and was connected to the other semantic areas in the model space. The no-hub family consisted of models 17-26. In models 17-18, all the candidate areas where included as multiple convergence zones and received input directly from the vWFA. In models 20-26, connections of the vWFA to only one of the semantic areas, but no further connections to the rest of the semantic network, were modulated by the semantic contrast. No-modulation family comprised models 27-28.

Thereafter, in the second level of hierarchical comparison, fine-grained families within the winner grand-family were compared. More specifically, depending on the winner grand-family, a group of the following 10 families were compared in the second hierarchical comparison: 1) ATL hub...
Each model included evoked responses of both concrete and abstract words and was inverted for each subject. Therefore, intrinsic connections were assumed to be common between the conditions while extrinsic connections were used to model condition-induced modulations of a preselected set of connections. Each model was inverted in two time windows of 0-250ms and 0-450ms, and data were reduced to 8 spatial modes. No down sampling, detrending or hanning windows were used. Furthermore, we used the traditional ERP model for DCM inversion (David et al. 2006a) instead of the more recently introduced canonical microcircuits (CMC) (Bastos et al. 2012) since the former showed higher model evidence for all the models in the model space (see Appendix 3.A for results).

Furthermore, considering the lengths of the time windows of the DCM analysis (i.e. 250ms and 450ms), we included modulations of both forward and backward connections in the model. This choice was made heuristically and informed by the previous literature where semantic effects have been reported as early as 150ms (Moseley et al. 2013) and thus it was considered reasonable to include bidirectional connections within 250ms and 450ms post-stimulus. Furthermore, models within each fine-grained family spanned different scenarios of self-modulation of the candidate hub areas while self-modulation of vWFA was included in all the models.

Finally, we used family-level Bayesian Model Selection (BMS) with Fixed Effect Inference (FFX) on the free-energy approximation to the model evidence, in order to identify the winning families in each hierarchy of DCM evaluations (Stephan et al. 2007). FFX was considered as more suitable for the current study given that we are studying a homogenous group of healthy young adults and the purpose is to obtain a generalisable model of semantic representation across subjects. This requirement is fulfilled by the FFX where the winning model is assumed invariant across subjects. Furthermore, we verified that winning models were not driven by outliers in the free-energy. In addition to the BMS, we utilised Bayesian Model Averaging (BMA) (Penny et al. 2010), in order to estimate mean (mEP) and standard deviation (sEP) of the posterior probabilities of the parameters within the winner fine-grained family. These parameters were estimated for each subject and statistical significance of mEP across subjects was tested using paired t-tests.
3.3 Results

3.3.1 Behavioural results

We conducted paired t-tests in order to compare reaction times (RT) and error rates (ER) for abstract and concrete words and found that the former showed significantly higher RTs and ERs (RTs for abstract/concrete: 879.76±118.85 vs 778.67±111.42ms, ERs: 8.06±5.01 vs 4.48±4.29%).
3.3.2 Whole-brain evoked analysis

Whole-brain evoked analysis was aimed at identifying the potential processor hubs and their timings using a data-driven approach. More specifically, we hypothesised that while single processor hub view can be reflected in the early modulation of a single heteromodal semantic cortex that remains modulated into later time windows, the multiple convergence zone view might be reflected in parallel activation of several heteromodal cortices and/or modulation of different areas at different times. We defined five time windows of interest covering the key stages of written word comprehension and excluding the later stages when response coding or mental imagery might interfere with the semantic effects of interest: 50-150ms, 150-250ms, 250-350ms, 350-450ms, 450-550ms. In the following subsections, they will be referred to by their central time point, e.g. 100ms for 50-150ms.

After source estimation, we examined the grand average brain responses to visual word stimuli across subjects, and observed that both conditions showed a posterior-to-anterior flow of current along the ventral occipito-temporal pathway which is a typical pattern for visual word recognition (Chen et al. 2015; Marinković 2004). Thereafter, using spatio-temporal cluster-based permutations to compare responses between concrete and abstract words, we found two significant clusters, both including bilateral ATLs and IFGs. The effect started as early as 100ms in the left ATL and was extended to the left IFG as well as right ATL/IFG at 300ms, lasting until 450ms. The largest cluster appeared in the time window of 350-450ms. All bilateral clusters showed higher amplitudes for the abstract word processing. Results of cluster-based permutation and univariate paired t-test are shown in Figure 3.4.
Figure 3.4 Whole brain evoked responses for concrete minus abstract words, averaged within five time windows of 100ms duration spanned between 50 and 550ms. Left: uncorrected univariate t-tests. Right: significant clusters of spatio-temporal cluster-based permutation test. Warm colours indicate higher values for concrete words, and cool colours for the abstract words.

3.3.3 Dynamic Causal Modelling

We conducted Dynamic Causal Modelling (DCM) of evoked responses between vWFA, ATL, IFG, MTG and AG in order to test the hypothesis of a single hub against multiple convergence zones within 250ms and 450ms post-stimulus. For this purpose, we built up a two-level hierarchy of model comparisons to address: a) whether or not a single hub structure is suitable for modelling connectivity among these areas. This was addressed by comparing grand-families shown in Figure 3.3; b) If a single hub model is suitable, which of the four semantic areas plays the role of a hub within 250ms and 450ms post-stimulus? Otherwise, what is a more suitable substitute model? This question was addressed by comparing fine-grained families within the winning grand-family from step (a).
3.3.3.1 ROIs and time courses

ROIs included in the DCM models and their average signed ERP responses across subjects are shown in Figure 3.5. We used paired t-test to find significant differences between absolute ERP responses to concrete and abstract words in the averaged time windows of exploration (i.e. 0-250ms and 0-450ms) and found that only ATL showed a significant difference between the two conditions ($p = 0.016$ and $p = 0.031$ for earlier and later time windows respectively).

![Figure 3.5](image)

Figure 3.5 Left: ROIs included in the DCM models including ATL, IFG, MTG, AG and vWFA; right: signed ERP time courses of the ROIs from -50ms to 450ms.

3.3.3.2 First hierarchy: which grand-family?

In this step of analysis, we compared three grand-families of hub models, versus no-hub models versus no-modulation (see Figure 3.3) using FFX BMS and found that the first family showed the highest posterior probability (Figure 3.6), within both 250ms and 450ms post-stimulus windows. This grand-family consisted of four fine-grained families including ATL hub, IFG hub, MTG hub and AG hub. Each of these families consisted of four models where the hub received input from the vWFA and established connections to the other nodes of the heteromodal subnetwork. BMS results and predicted ERPs for the five ROIs averaged across hub models and subjects are shown in Figure 3.6.
In the next step, we compared the fine-grained families within the grand-family of hub models, and found that ATL and AG families showed the highest posterior probabilities within 250ms and 450ms, respectively (Figure 3.7). In the former family, ATL received input from the vWFA (via

**3.3.3.3 Second hierarchy: which hub family?**

In the next step, we compared the fine-grained families within the grand-family of hub models, and found that ATL and AG families showed the highest posterior probabilities within 250ms and 450ms, respectively (Figure 3.7). In the former family, ATL received input from the vWFA (via Figure 3.7).
bidirectional connections) and was connected to the IFG, MTG and AG, while in the latter, AG received input from vWFA and was connected to ATL, IFG and MTG. Each family comprised four models where inter-areal connections were bidirectional and self-modulations of the vWFA were switched on. However, self-modulation of ATL/AG hubs in their corresponding family, as well as self-modulations of other heteromodal nodes were varied (refer to section 3.2.4 for more details).

Figure 3.7 Results of FFX BMS for comparing four fine-grained families within the grand-family of hubs: a) ATL hub plus multiple convergence zones in IFG, MTG and AG showed the highest posterior probability within 250ms; b) AG hub plus multiple convergence zones in IFG, MTG and AG showed the highest posterior probability within 450ms. The right column shows predicted ERPs for ATL, IFG, MTG, AG and vWFA on average across models within ATL hub family (top) within 250ms and AG hub family within 450ms (bottom).
3.3.3.3.1 Single models within ATL and AG hub families

After identifying ATL and AG hubs within 250ms and 450ms post-stimulus as the winner fine-grained families, we also compared the single models within each family and conducted a Bayesian Model Averaging for parameter estimation of the winner models. The significance of the mean of the posterior probability of each parameter across subjects was tested using paired t-test. Results are shown in Figure 3.8. Within ATL hub family in the 0-250ms time window, model 3 was identified as the conclusive winner (ΔF>1000) where self-connections of vWFA and convergence zones as well as forward-backward connections of ATL to all the nodes of the network but not self-connections of ATL were modulated. Among these connections, only backward connection from MTG to ATL was found to be significant (p = 0.03) across subjects. Within AG hub family in 0-450ms time window, model 16 was identified as the conclusive winner (ΔF>2500). In this model, self-connections of vWFA and forward-backward connections of AG to all the nodes of the network but not self-connections of AG or convergence zones were modulated. Mean posterior probability of none of the parameters reached significance level when tested across subjects.

Figure 3.8 Comparisons of single models within ATL (top) and AG (bottom) hub families within 0-250ms and 0-450ms, respectively. Within ATL family, model 3 of the model space (Figure 3.3) was identified as the winner and within AG family, model 16 showed the highest model evidence. Both models are conclusive winners according to the FFX framework. *significant parameter with p < 0.05.
3.4 Discussion

This chapter provides novel evidence for distinct roles of the Anterior Temporal Lobe (ATL) and Angular Gyrus (AG) in semantic brain networks with the former appearing as a processor hub while both regions underpinning integration hubness. More specifically, firstly, using a data-driven whole-brain evoked analysis with spatio-temporal cluster-based permutations, we found that the left ATL was the first area modulated by concreteness within 150ms post-stimulus. This modulation persisted into the later time windows (i.e. 400ms) and was spread to the bilateral ATLs and inferior frontal gyri (IFGs). We found no other brain areas to be significantly modulated by concreteness in this analysis. Secondly, effective connectivity computed by Dynamic Causal Modelling (DCM) among the key heteromodal semantic cortices (i.e. ATL, IFG, Middle Temporal Gyrus (MTG) and AG) revealed a grand-family comprising single hub models to provide the best fit to the data in both time windows of exploration (i.e. 0-250ms and 0-450ms). Furthermore, our investigations of the fine-grained families within the grand-family of hub models opted for the left ATL hub and left AG hub models for the earlier and later time windows, respectively. Therefore, our results suggest that while left ATL might act as both processor and earlier integrator hub within the heteromodal part of the semantic networks, AG might perform as a later integrator semantic hub.

3.4.1 ATL as processor hub: data-driven evidence

The hub-and-spokes model of semantic networks postulates the hub region as a link between sensory input areas and distributed heteromodal and uni-modal semantic cortices (Lambon Ralph et al. 2016; Patterson et al. 2007) and thus predicts an early modulation of the semantic hub (i.e. before other semantic regions). Whole-brain evoked responses in this study provide the first data-driven evidence for modulation of the left ATL within 150ms post-stimulus. This finding is in line with a pre-existing idea in the literature that meaning comprehension starts well before 400ms (i.e. around 200ms or earlier) (Hauk et al. 2012; Sereno & Rayner 2003). Such early modulations have been previously reported for modality-general semantic access between 180-260ms in the left ATL and MTG (Hauk et al. 2012; Westerlund & Pylkkänen 2014) and modality-specific semantic access between 140-160ms in the sensory-motor cortices (Moseley et al. 2013).

However, previous studies have often tested specific hypotheses using ROI-based approaches. This approach has two main limitations: firstly, it might neglect interesting effects in the unexplored regions. Secondly, ROI time courses will have to be computed using a summary measure which is not sensitive to the variability of activations inside an ROI. The data-driven vertex-wise approach with spatio-temporal permutations utilised in this study eliminates these two limitations. Moreover, even
though this more strict criterion might increase the probability of type II error in statistical testing, it can be expected to improve the reproducibility and generalisability of the results.

In addition to the earliest modulations of the left ATL, we found the largest cluster differentiating concrete and abstract words in the N400 time window (350-450ms) in the bilateral ATLs and anterior IFGs. This is in line with recent EEG/MEG and TMS findings that have proposed ATL as one of the potential sources for the N400 semantic component of ERP. In a concreteness judgement paradigm similar to the current study, Dhond et al. (2007) reported a maximal recruitment of the left frontotemporal cortices between 330-465ms as well as later modulation of similar regions in the right hemisphere. In another study, Lau et al. (2013) found effects of semantic facilitation by comparing word-evoked responses after related and unrelated masked priming, and reported a modulation of the left superior ATL between 300-500ms. In a recent TMS study, Jackson et al. (2015) confirmed the involvement of the left ATL in semantic representations, particularly in the time window of N400. Therefore, our results corroborate the role of ATL as a potential source of N400 semantic ERP component.

Furthermore, consistent with meta-analytic evidence from fMRI research on concrete and abstract concepts (Binder et al. 2005), we found higher absolute activations for the abstract words in both bilateral fronto-temporal clusters. Considering that abstract words are typically more difficult to process (both in terms of response accuracy and reaction times), and are less dependent on the distributed sensory-motor networks, they can be expected to pose higher processing demand on the processor hub. This interpretation is additionally in line with a previous TMS study where abstract words were found to be slowed down more compared to concrete words in response to repetitive stimulations to the ATLs, mimicking a behavioural symptom that has also been reported in semantic dementia (Pobric et al. 2009).

In addition to the ATLs’ activation, we found modulations of the bilateral anterior IFGs, in particular between 350-450ms. This finding might be attributed to three underlying mechanisms. First, it is possible that anterior IFGs also contribute to the production of the N400 component. This interpretation is in agreement with some studies that have suggested the role of the anterior IFG in semantic processing as one of the several areas that underlie the N400 component (Binder et al. 2009; Hagoort 2004; Lau et al. 2008). Second, IFG modulation might be attributed to differences in stimulus difficulty (and efficiency of performance) rather than semantic representation per se (Binder et al. 2009; Lau et al. 2008). This explanation is also likely, considering that bilateral clusters showed higher amplitudes for the abstract words which also invoked slower reaction times and lower response accuracies. Third, considering the source leakage problem in the EEG/MEG source localisation (Liu et
al. 1998), IFG modulations might be attributed to the spread of activity from the ATLs which become particularly evident at the peak of activity in the ATLs (i.e. 350-450ms). This explanation is plausible considering that IFG activation in Figure 3.4 occurred mostly on the ventral surface of the IFG, i.e. close to the ATL. Investigation of cross-talk functions (see Chapter 2) between the two regions might further validate the third explanations, however, we did not conduct this analysis here.

3.4.2 Dynamic Causal Modelling (DCM)

Our DCM evaluation of evoked responses provides the first evidence towards specification of effective connectivity among the left-hemispheric heteromodal hub candidates (i.e. ATL, IFG, MTG and AG) in semantic retrieval.

3.4.2.1 Grand-family of models with single hub showed the highest evidence

Our results highlighted that a grand-family consisting of DCM models with a single central hub provided the best fit to the data both in the earlier and later time windows of exploration (i.e. 0-250ms and 0-450ms). In all the models within this family, one central hub (ATL, IFG, MTG or AG) received input from the visual word form area (vWFA) and established connections to the other heteromodal semantic areas in the model. These results take a step towards addressing single hub versus multiple convergence zones debate. Looking into the previous literature, on the one hand, a group of studies that have focused on modality-general semantic cognition in healthy participants have reported an involvement of a set of areas in temporal, parietal and frontal cortices such as anterior and middle temporal gyri, angular gyrus and inferior frontal gyrus (Binder et al. 2009; Binder & Desai 2011; Price 2010). On the other hand, studies of semantic dementia (SD), a type of dementia that is characterised by a specific impairment to the conceptual knowledge, have highlighted focal atrophies in the ATLs as a characteristic of this disease (Snowden et al. 1989, 2017). Consequently, ATL atrophy, as well as alterations in the structural connectivity between ATLs and other parts of the semantic system have been reported as some of the characteristics of the SD (Agosta et al. 2010; Guo et al. 2013; Patterson et al. 2007). Therefore, even though multiple heteromodal semantic cortices have been shown to play important roles in semantics, the organisation of the network that links these areas has remained largely unknown. To the best of our knowledge, the current study is the first to provide evidence in support of a single integrator semantic hub within the subnetwork of heteromodal semantic areas using a direct investigation of effective connectivity among these heteromodal cortices.

3.4.2.2 ATL versus AG: early versus late hubness?

Our further investigation of the more fine-grained families within the grand-family of hubs revealed that on the one hand, in the earlier time window of exploration (i.e. 0-250ms), left ATL acted
as a central hub receiving input from vWFA and connecting to IFG, MTG and AG. On the other hand, in the later time window of exploration (i.e. 0-450ms), left AG played the role of a central hub that received input from vWFA and was connected to the ATL, IFG and MTG. Growing evidence in recent years suggests that among these four heteromodal cortices that are often raised as potential hubs for semantic processing, ATL and AG might play more important roles for semantic representation (Binder et al. 2009; Lambon Ralph et al. 2016) while IFG and MTG might be more crucial for semantic control (Jefferies 2013; Lambon Ralph et al. 2016). With respect to the role of the ATL, recent EEG/MEG studies have shown cross-modal feature integration in the left ATL (van Ackeren et al. 2014; van Ackeren & Rueschemeyer 2014) and TMS studies have reported that stimulation of the ATLs can mimic behavioural symptoms of SD in healthy participants for both word and picture semantic processing (Pobric et al. 2007, 2010a). Furthermore, recent fMRI evidence has suggested a graded specialisation within ATLs, with central core acting as an amodal hub and surrounding medial, ventral and dorsolateral ATLs acting as a cross-modal hub (Binney et al. 2016; Rice et al. 2015a). With respect to the role of AG, its involvement in modality-general semantic cognition, particularly for multi-sensory integration for concrete concepts has been reported in several previous studies (Fernandino et al. 2016b; Handjaras et al. 2017; Wang et al. 2010). For example, recent fMRI research suggests that brain areas responding to imageability and sociability attributes of concepts (Lin et al. 2017) overlap in AG. Furthermore, TMS evidence suggests that inferior parietal cortex (including AG) is crucial for man-made objects (Pobric et al. 2010b). However, AG activation in semantic retrieval has been less often reported in the EEG/MEG literature and thus the timing of its activation and potential underlying mechanisms for the involvement of this area in semantics remains unclear. Our DCM results suggest that while ATL might coordinate connectivity between heteromodal semantic cortices in the left hemisphere during the earliest time windows, AG might be responsible for such coordination during later time windows.

3.4.3 Processor hub versus integrator hubs

Prominent models for the brain semantic networks, regardless of single hub or multiple convergence zones view, typically propose that heteromodal semantic areas are involved in semantic representation through modulation of both activity and connectivity (Lambon Ralph et al. 2016; Patterson et al. 2007; Pulvermüller 2013; Woollams & Patterson 2017). Here for the first time, we find a clear distinction between processor hubness and integration hubness by disentangling different stages of semantic processing and teasing them apart from the later post-semantic processes such as mental imagery. Our whole-brain evoked results suggest that ATL acts as the processor hub during multiple stages of word semantic retrieval, while DCM results suggest that both ATL and AG are involved as integrator semantic hubs. This result can be interpreted in the light of two key findings in
the past literature. Firstly, both ATL and AG have been shown to have extensive structural and functional connections to numerous unimodal and cross-modal brain cortices (Jackson et al. 2016; Seghier 2012) and hence, in principle, are suitable for the integration of information provided by the distributed semantic areas. Secondly, while fMRI research has found a set of heteromodal cortices including ATL and AG to be involved in supramodal semantic representation (Binder et al. 2009; Lambon Ralph et al. 2016; Pulvermüller 2013), EEG/MEG research in recent years has provided growing evidence for early modulations of the ATL activation but less so for the AG and other heteromodal semantic areas (Hauk et al. 2012; Lau et al. 2013; van Ackeren & Rueschemeyer 2014; Westerlund & Pylkkänen 2014). Arguably, using fMRI, different stages of word processing including semantic and post-semantic processes are pooled together. Therefore, some of the heteromodal cortices identified using fMRI might in fact play role in non-semantic stages of visual word recognition. Thus, we propose that distinct yet overlapping heteromodal cortices in the left hemisphere underlie semantic processing and integration within 500ms after word presentation.

3.4.4 Limitations and next steps

Results of this chapter provide the first evidence towards the identification of distinct processor and integrator hubs during early stages of semantic word processing. However, further specification of this proposal is required. Firstly, as explained earlier in the Introduction, an integrator hub is defined through its connectivity not only to the heteromodal and multimodal semantic cortices but also to the sensory-motor-limbic areas. In this chapter, we focused on connectivity within the heteromodal subnetwork of semantics in the left hemisphere. Chapter 4 will focus on extending these results by examining seed-based connectivity of the candidate hub areas to all the brain vertices in order to identify more distributed networks. Secondly, we have only focused on the left hemispheric candidate hubs. Even though semantic areas are thought to be predominantly left-hemispheric, a body of evidence suggests that interplays between the left and right hemispheres might play a crucial role in semantic cognition and explaining deficits of the SD (Gainotti & Gainotti 2015; Snowden et al. 2017). However, such connections, as well as the mechanisms that underlie the role of each hemisphere, remains largely unknown. This issue will be addressed in Chapter 7 using whole-brain graph theoretical analysis of the semantic networks.
Appendix 3.A  Comparing ERP and CMC models for DCM

In this analysis, we aimed to find which of the neurophysiological models that are available for inversion of the DCMs is better for our data: classic DCM for ERP (David et al. 2006a) or canonical microcircuit models (CMC) (Bastos et al. 2012). For this purpose, we inverted all the 28 models in Figure 3.3 and compared the model evidence for ERP and CMC in 0-250ms and 0-450ms time windows. Results are shown in Figure A 3.1. We found that classic ERP model shows notably higher log model evidence than CMC for this dataset and therefore the former was used for the rest of the analyses.

![Figure A 3.1 Model evidence for ERP and CMC models for 0-250ms (left) and 0-450ms (right). Odd numbers show ERP results while even numbers show CMC results. Therefore, models inverted using the former approach show substantially higher model evidence.](image-url)
4 PCA-Based Identification of the Most Suitable EEG/MEG Connectivity Metric Reveals New Aspects of Anterior Temporal Lobe and Angular Gyrus as Integrator Semantic Hubs

One of the key predictions of the hub-and-spokes model is that concepts in the brain are partly encoded in connectivity between the heteromodal hub(s) and modality-specific spokes. However, empirical evidence for modulations of these connections for different semantic variables has been scarce. In this Chapter, we addressed this question by measuring modulations of seed-based connectivity between candidate hub areas and every vertex in the brain by concreteness of a word. We utilised source-estimated concurrent EEG/MEG and: (i) utilised a novel PCA-based approach across several connectivity methods to identify the most suitable connectivity (MSC) metric for the data; (ii) utilised spatio-temporo-spectral cluster-based permutations to compare whole-brain seed-based connectivity of the key candidate hubs (left Anterior Temporal Lobe (ATL), Inferior Frontal Gyrus (IFG), Middle Temporal Gyrus (MTG) and Angular Gyrus (AG)) for the contrast of concrete and abstract words in four frequency bands (Theta, Alpha, Beta, Gamma) and two time windows (150-350ms, 250-450ms). Coherence was identified as the MSC, explaining ~60% of the variance across connectivity methods and correlating above 0.8 with the first PC. Among the tested possible hubs, left ATL showed significantly higher Coherence to the right orbitofrontal cortex for the abstract words (more emotional) in Beta/Gamma and AG showed higher connectivity to the left somatosensory cortex for the concrete words (more tangible) in Alpha/Beta, both in both time windows. These results, expanding on the results of Chapter 3, support the role of ATL and AG as integrator hubs and provide the first evidence that dynamic connectivity between the hub(s) and spokes is modulated by semantics.
4.1 Introduction

Most recent models of the brain semantic networks such as the hub-and-spokes model (Lambon Ralph et al. 2016; Patterson et al. 2007) hypothesise a network of interacting heteromodal and unimodal cortices to underlie semantic representation in the brain (Binder 2016; Patterson et al. 2007). However, in spite of a multitude of evidence for differential activation of various brain areas in response to semantic variables (Binder & Desai 2011; Huth et al. 2016), connectivity among them has remained largely unknown (Hauk & Tschentscher 2013). More recently, a growing field of fMRI and DTI research has focused on the structural and functional connectivity patterns of the potential hub areas (i.e. heteromodal semantic cortices), details of which were elaborated in Chapter 1. However, connectivity between potential hubs and spokes and importantly the temporal and spectral trajectories of these connections have remained largely unexplored (Jackson et al. 2015). This is in spite of the fact that semantic networks have been shown to be highly dynamic and time-varying (Chen et al. 2015; Hauk et al. 2012; Moseley et al. 2013).

Source reconstructed EEG/MEG data provide a unique opportunity to study the rich patterns of neuronal connectivity and significantly expand on the connectivity estimations that have been obtained from hemodynamic responses in the past decade (Baker et al. 2014; Brookes et al. 2011b). As reviewed in Chapter 2, due to the complexity of the neuronal dynamics measured by EEG/MEG, numerous methods have been proposed to quantify connectivity between cortical sources, each designed to capture one or a few aspects of the signals. For example, functional connectivity metrics have been introduced to measure statistical dependencies between the brain signals while causal connectivity metrics have been proposed to find the direction of information flow among the brain areas (e.g. Granger Causality) (Blinowska et al. 2004; Bressler & Seth 2011) or modulation of uni-/bi-directional information flow between the brain areas as a consequence of experimental manipulations (e.g. Dynamic Causal Modelling) (David et al. 2006b).

Furthermore, among the functional connectivity measures, firstly, temporal correlations, as one of the most commonly used metrics in neuroimaging, focus on temporal co-activation of different brain areas and are sensitive to the shape and delay of the signals (Greenblatt et al. 2012; Lee & Nicewander 2016). Secondly, spectral measures that are focused on co-activations in the frequency domain and are theoretically more suitable for untangling neuronal communication through oscillations are particularly sensitive to the phase differences of two brain areas across data epochs/trials (Bastos & Schoffelen 2016; Lachaux et al. 1999; Nolte et al. 2004; Nunez et al. 1997). And thirdly, information theoretic measures, such as mutual information, that are inherently non-linear, focus on the probability distribution of the signals rather than conducting pairwise comparisons.
of individual time/frequency bins between signals of interest (Daub et al. 2004; Greenblatt et al. 2012). Additionally, bivariate versus multivariate and zero-lag versus non-zero-lag connectivity metrics have been introduced for different types of connectivity estimations (Bastos & Schoffelen 2016). Therefore, selecting one connectivity method among numerous metrics ideally requires a profound knowledge of the mechanisms that underpin orchestration of neuronal populations. However, such mechanisms for semantic networks are not known to date, making an insightful selection of the most suitable connectivity metrics a challenge.

The issue of finding the most suitable connectivity metrics/parameters has been acknowledged recently (Bastos & Schoffelen 2016; Wang et al. 2014a) and addressed in a few studies using three main approaches. The first group of these studies have focused on test-retest reliability (Pestilli 2015). For example, Colclough et al. (2016) investigated reproducibility and consistency of several EEG/MEG connectivity methods within/between subjects as an approach of evaluating the robustness of different connectivity methods. The second group of these studies have utilised simulated data in order to optimise connectivity metrics and parameters (Wang et al. 2014a). The third group of these studies (predominantly for DTI/fMRI connectivity) have proposed the so-called “ensemble methods” that combine information from multiple connectivity methods/parameters in order to obtain a more generalisable connectivity matrix for the data (Takemura et al. 2016). To the best of our knowledge, the only ensemble method for functional connectivity was introduced by Wang et al. (2018) that starts by identifying a few optimal connectivity metrics/parameters (referred to as input basic metrics or BMs) based on extensive data simulations using biologically inspired neural mass models (Wang et al. 2014a). Thereafter, the method applies a fuzzy algorithm to the results of the input BMs in order to obtain the most probable topology of connectivity for a dataset (Wang et al. 2018).

However, each of the aforementioned three approaches has a few drawbacks for source estimated EEG/MEG. Firstly, test-retest reliability and simulations are arguably essential but not sufficient for determining the optimal connectivity matrices. That is, the most reproducible methods and/or best performing on simulations are not necessarily those that can explain most of the variance of a real dataset. Secondly, ensemble methods will essentially yield a combined measure based on the original BM results. Therefore, if some of those BMs were not generating accurate results, this might affect the final ensemble connectivity estimates (Wang et al. 2018). Thirdly, to the best of our knowledge, the only method of ensemble connectivity for functional neuroimaging data has been originally proposed for intracranial EEG and fMRI while generalisability of this approach to the source estimated EEG/MEG in the presence of leakage is unknown. Therefore, no study to date has investigated ensemble methods in the presence of leakage in EEG/MEG source space.
We propose that Principal Component Analysis (PCA) can be used to address some of these drawbacks (Jung et al. 2000; Lagerlund et al. 1997). More specifically, as will be elaborated below in the Theory section (4.2), by projecting the multidimensional data on orthogonal axes (aka. PCs), PCA can find similarities and differences between the connectivity estimations yielded by different metrics and project them on a single PC and distinct PCs, respectively. Additionally, it can identify principal axes along which the maximum variance of a data is explained as well as the original connectivity metrics that are highly correlated to the most prominent (i.e. first) PC. These metrics can be regarded as the most suitable connectivity metrics (MSC) for a data.

In Chapter 3, we explored dynamic connectivity among the key left-hemispheric heteromodal semantic areas. In this Chapter we utilise the same dataset as Chapter 3, however, we focus on time-varying connectivity between the main candidate semantic hubs and all the brain vertices in a whole-brain seed-based connectivity approach, where potential hubs are used as seeds. Firstly, in order to identify the MSC method, we utilise PCA to identify: a) the connectivity method that is most highly correlated with the first PC and thus explains most of the variance of the data; b) connectivity metrics that are highly correlated with a single PC and thus measure similar aspects of the data and c) connectivity metrics that are correlated with PCs that explain less variance and thus are potentially the least reliable methods (most sensitive to noise) or alternatively measure unique aspects of the data. For this purpose, we will first select a few of the state-of-the-art EEG/MEG connectivity methods that are theoretically most suitable to address the questions of this study and apply the novel PCA approach to identify the MSC among the tested metrics. Secondly, we will examine seed-based connectivity results obtained from applying MSC to the concreteness dataset in order to find number, locations and timings of the hub(s) and their connectivity to the distributed semantic cortices. More specifically, considering that concrete words in this study are more imageable and abstract words are more emotionally valenced, we hypothesise that semantic hub(s) should show higher connectivity to the sensory-motor areas for concrete words and higher connectivity to the limbic system for the abstract words.

4.2 Theory

4.2.1 Theoretical sub-selection of connectivity metrics

Considering the properties, advantages and limitations of different connectivity metrics overviewed in Chapter 2, we aimed to identify a few connectivity metrics that were theoretically most suitable for the purposes of this study.

Firstly, considering that in this chapter we aimed to find connectivity between each seed (i.e. potential hubs) and all the cortical vertices, methods that are suitable for pairwise comparisons of
sources in a whole-cortex analysis were considered more desirable. Therefore, DCM (David et al. 2006a) that requires defining ROIs and general synchronisation (Stam & Van Dijk 2002) that computes a summary measure of connectivity between a seed and all other sources were excluded. Even though estimation of pairwise connections in the latter is theoretically plausible, it is computationally expensive.

Secondly, we focused on examining time windows that have been proposed as being critical for semantic processing in the previous literature, namely 150-350ms and 250-450ms. Considering the length of the time windows, we focused on bidirectional information flow between the brain sources and thus functional connectivity methods that are inherently bidirectional were considered sufficient for the purposes of this study. This choice was made somewhat heuristically also considering an ongoing debate regarding the application of Granger Causality metrics to neuroscientific problems (Barnett et al. 2017; Faes et al. 2017; Haufe et al. 2013; Stokes & Purdon 2017) which is likely to lead to significant methodological adaptations of GC and sub-families in a near future.

Finally, from the overview of the core ideas in Chapter 2 (see also Figure 2.1), we categorised the remaining functional connectivity methods in three families: phase plus amplitude coupling, phase coupling and information theoretic (focused on probability distributions). Next, we selected one from each family, to address the questions of this study: magnitude-squared Coherence (COH), Pairwise Phase Consistency (PPC) and mutual information (MI).

It is worth noting that two of the three selected metrics are among the spectral measures. Spectral connectivity measures have often been used in the past EEG/MEG event-related studies (Wang 2010). This is due to the fact that spectral measures are thought to be able to capture some fundamental properties of the neuronal communication through oscillations in the brain, owing to the fact that these methods are specifically designed to target different frequency bands (Siegel et al. 2012). Information in the neural signals could be coded in the amplitude and/or phase of oscillations. Signal amplitude is thought to encode information based on the local specialisation of different brain areas. Phase synchrony, on the other hand, is based on phase-locking among the brain sources and thus can be used to detect long-range connections (Rodriguez et al. 1999). Therefore, we used COH which is sensitive to both amplitude and phase couplings and PPC that is only sensitive to the phase difference. PPC, as elaborated in Chapter 2, is a modified version of PLV that is not biased by the number of trials (i.e. SNR) (Vinck et al. 2010).

In addition to these two spectral measures we computed MI. MI is a nonlinear measure of statistical similarities between two signals (Daub et al. 2004) and measures the degree to which two brain sources encode similar information throughout the exploration time windows. Considering that
connectivity among neuronal signals, particularly in task-response datasets, is non-linear, it is desirable to utilise an inherently non-linear method to quantify connectivity between the brain areas (Reshef et al. 2011). It is worth noting that while utilisation of valid and robust linear approximations can still reflect useful aspects of data connectivity, adding a non-linear approach can account for potential non-linearities in the connectivity patterns. It is also worth noting that MI is mainly sensitive to the amplitudes as it pools the time points within the time window of interest and infers connectivity solely based on histograms that are insensitive to the ongoing phases of signals.

Considering that these three metrics might measure similar and/or different aspects of the data, we utilised PCA in order to: 1) find similarities between them; 2) find unique aspects to each method; 3) identify the method with the highest correlation to the first PC as the MSC and 4) identify the first PC as an ensemble connectivity estimation.

4.2.2 Computing PCA

In this subsection, we briefly overview the mathematical basis of PCA. Let us assume that we have extracted seed-based connectivity between seed $s$ and all the brain vertices ($N_v$ vertices) using $N_c$ ($N_c = 3$ here) connectivity metrics, and obtained a matrix $M$ of size $N_v \times N_c$. PCA aims at linear transformation of this matrix and mapping it to another matrix ($P$), the columns of which (i.e. transformed variables) are orthogonal in an $N_c$-dimensional space. Thus:

$$P = MQ \quad (4.1)$$

where $Q$ (aka loading matrix) is the conversion matrix which is of size $N_c \times N_c$ and $P$ is the matrix of principal component scores. Therefore, every column of the $P$ matrix (i.e. PC scores at different vertices) is represented as a weighted sum of the original connectivity estimates at those vertices. The first column of $Q$ (i.e. PC1) is obtained as:

$$Q_{(1)} = \arg\max_{\|Q\|=1} \|MQ\|^2 \quad (4.2)$$

where $Q_{(1)}$ is the first PC. Next PCs are computed after subtraction of the successive PCs from $M$, that is:

$$\tilde{M}_k = M - \sum_{i=1}^{k-1} MQ_i Q_i^T$$

$$Q_{(k)} = \arg\max_{\|Q\|=1} \|\tilde{M}_k Q\|^2 \quad (4.3)$$

Columns of $P$ in the Equation 4.1 are aligned alongside the direction of eigenvectors of the covariance of $M$ and in descending order according to eigenvalues. Thus, the ratio of each eigenvalue to the sum of eigenvalues yields the percentage of data variance explained by each PC. In terms of geometrical interpretation, PCA rotates the matrix basis of $M$ in the $N_c$-dimensional space such that the new basis vectors are successively aligned to the directions of maximum variance of $M$. This is
illustrated in Figure 4.1. It is worth noting that the aforementioned matrix transformations of PCA ensure that the overall variance remains the same after conversion (see (Abdi & Williams 2010; Jolliffe 2002) for more details).

Figure 4.1 A schematic illustration of principal component decomposition of a 2D data. In the space of PC scores, data points are projected on PC1 and PC2 and explained based on these axes.

4.3 Materials and methods

4.3.1 Data acquisition and pre-processing

Details of participants, stimuli, procedure, EEG/MEG pre-processing, forward modelling and source localisation were described in Chapter 3. Briefly, 17 native English speakers performed a concreteness decision task (making button press responses) in a visual word recognition paradigm. A flowchart of pre- and post-processing steps is presented in Figure 4.2.
4.3.2 Seed-based connectivity analysis

We computed whole-brain seed-based connectivity with seeds in the main semantic hub candidates in the left hemisphere: ATL, MTG, AG and IFG. For this purpose, we extracted the ROI time courses and computed COH, PPC and MI between each ROI time course and every vertex in the brain. Details of connectivity methods and equations were presented in Chapter 2. In order to extract each ROI time course, we first identified a vertex within the ROI that showed the highest sensitivity to that ROI. To this aim, we computed cross-talk functions (CTFs) and identified the vertex inside that ROI that showed the largest CTF value (for details of ROI$_{CTF}$ calculations refer to Chapter 6). Thereafter, we extracted ROI time courses based on this vertex for each epoch. Next, in order to compute MI across epochs, we computed seed-based connectivity for each trial using the classic binning method (Daub et al. 2004) for MI and averaged the results across trials. For PPC and COH, the phase and amplitude/phase consistency were calculated using a multitaper algorithm using the default implementation in MNE-Python (version 0.9). All measures were computed for four different
frequency bands of Theta (4-7 Hz), Alpha (8-12 Hz), Beta (13-30 Hz) and Gamma (31-45 Hz) (Engel & Fries 2010) and in early (150-350ms) and late (250-450ms) time windows.

4.3.3 PCA across connectivity methods

As described in section 4.2, we utilised PCA in order to identify the aspects of connectivity that are common to COH, PPC and MI for seed-based connectivity of the current dataset, as well as aspects that are unique to the individual measures. For each condition, we concatenated the whole brain connectivity vectors (length \( N_{\text{vertices}} \)) from all subjects, times, seeds, frequency bands and connectivity methods in one matrix yielding grand connectivity matrices \( \text{CMc} \) and \( \text{CMa} \) of size \( N_{\text{vertex}} \times N_{\text{subjects}} \times N_{\text{seeds}} \times N_{\text{times}} \times N_{\text{bands}} \times N_{\text{conn}} \) for concrete and abstract words, respectively. We concatenated \( \text{CMc} \) and \( \text{CMa} \) alongside the first dimension and obtained a CM matrix. Thereafter, PCA was computed on 2D sub-matrices obtained from the first and last dimension of CM for each subject, time, seed and band (i.e. sub-matrix size \( 2N_{\text{vert}} \times N_{\text{conn}} \)) with dimension reduction along the second dimension (i.e. connectivity methods).

We computed variance explained by each PC as well as correlation of each PC to each connectivity method. The explained variance and correlation values were then averaged over times, seeds and subjects in order to yield one value for each connectivity method at each frequency band. In order to account for the potential non-normalities or differences in the probability distribution of different connectivity methods, Box-Cox transform (Sakia 1992) was used to obtain a Gaussian distribution for each connectivity method before conducting PCA. Furthermore, considering the fact that COH, PPC and MI have different scales, we conducted weighted PCA (i.e. normalised by variance across rows of each \( 2N_{\text{vert}} \times N_{\text{conn}} \) sub-matrix) on centred data.

4.3.4 Statistical analysis: cluster-based permutation

We conducted whole-brain spatio-temporo-spectral cluster-based permutation tests in order to find the brain vertices to which each hub candidate showed significant differences between concrete and abstract words. Details of the statistical analysis are similar to Chapter 3 except that we tested five stricter thresholds (0.025, 0.01, 0.008, 0.002 and 0.001) in order to also account for multiple comparisons across the four seeds (i.e. candidate hubs). Additionally, considering that four frequency bands were tested, we sought to identify whether spatio-temporal or spatio-temporo-spectral clustering is more suitable. For this purpose, we assigned a condition that if a PCA across frequency bands identifies that different frequency bands are projected on the same PC, spatio-temporo-spectral correction for multiple comparisons is more suitable while if different frequency bands are projected on different PCs, spatio-temporal corrections are more suitable. Details of this
analysis are elaborated in Appendix 4.A where we found spatio-temporo-spectral clustering to be more suitable.

4.4 Results

We measured seed-based connectivity with seeds in four left-hemispheric candidate hubs shown in Figure 4.3.

Figure 4.3 Seed regions for seed-based connectivity. From left to right: posterior IFG, ATL, AG/SMG and MTG.

4.4.1 PCA across connectivity methods

Results of the PCA analysis across connectivity methods (COH, PPC and MI) are elaborated in Table 4.1 and Figure 4.4. On the one hand, we found that COH and PPC are highly correlated with the first PC (correlation 0.85 or higher). This is reflected in diagrams of COH and PPC plotted against different PC scores across times and vertices (Figure 4.4), where an approximate one-to-one mapping between these metrics and PC1 (blue data points) can be noticed while for PC2, PC3 such distinction is not clear. The first PC explained more than 50% of the variance for every frequency band. On the other hand, MI was partially correlated with the spectral measures. However, it was predominately projected on the second PC that explained approximately 30% of the variance of the data. Based on these findings, COH and PPC were identified as the more suitable measures for the data. Considering that the former is sensitive to both amplitude and phase couplings while the latter is only sensitive to the phase, we selected COH as the representative connectivity metric for the rest of the study.

Table 4.1 PCA analysis of seed-based connectivity across connectivity methods

<table>
<thead>
<tr>
<th>Pooled</th>
<th>Con/Abs</th>
<th>1st PC</th>
<th>2nd PC</th>
<th>3rd PC</th>
</tr>
</thead>
<tbody>
<tr>
<td>%EV</td>
<td>MI</td>
<td>Theta</td>
<td>Alpha</td>
<td>Beta</td>
</tr>
<tr>
<td>54.7±3.8</td>
<td>0.37±0.1</td>
<td>0.86±0.03</td>
<td>0.86±0.03</td>
<td>0.86±0.03</td>
</tr>
<tr>
<td>55.9±3.7</td>
<td>0.44±0.1</td>
<td>0.86±0.03</td>
<td>0.86±0.03</td>
<td>0.86±0.03</td>
</tr>
<tr>
<td>61.1±4.5</td>
<td>0.5±0.2</td>
<td>0.86±0.03</td>
<td>0.86±0.03</td>
<td>0.86±0.03</td>
</tr>
<tr>
<td>62.1±4.6</td>
<td>0.58±0.1</td>
<td>0.87±0.03</td>
<td>0.89±0.05</td>
<td>0.82±0.2</td>
</tr>
<tr>
<td>Theta</td>
<td>Alpha</td>
<td>Beta</td>
<td>Gamma</td>
<td>Theta</td>
</tr>
<tr>
<td>31±1.5</td>
<td>30.1±1.7</td>
<td>28.2±3.4</td>
<td>26.3±3.3</td>
<td>14.2±2.9</td>
</tr>
<tr>
<td>Alpha</td>
<td>Beta</td>
<td>Gamma</td>
<td>Theta</td>
<td>Alpha</td>
</tr>
<tr>
<td>30±1.7</td>
<td>28±3.4</td>
<td>26.3±3.3</td>
<td>14.2±2.9</td>
<td>14±3</td>
</tr>
</tbody>
</table>

EV: Explained Variance; MI: Mutual Information; PPC: Pairwise Phase Consistency; COH: Coherence
Figure 4.4 Boxcox-transformed a) COH; b) PPC and c) MI plotted against distributions of the first (blue), second (red) and third (yellow) principal component scores over vertices and time windows (averaged across seeds and subjects). The first PC showed high linear correlation with COH and PPC (>0.8) while the second PC showed higher correlation with MI. More details are presented in Table 4.1. COH: Coherence, PPC: Pairwise Phase Consistency, MI: Mutual Information, PCA: Principal Component Analysis.

4.4.2 Functional connectivity results

We found seed-based COH between the time courses of four candidate semantic hubs in the left ATL, IFG, AG and MTG and every vertex in the brain. The connectivity was calculated in Theta, Alpha, Beta and Gamma bands and in two earlier and later time windows of 150-350ms and 250-450ms. Significant clusters for differentiating concrete and abstract concepts were identified using spatio-temporo-spectral cluster-based permutations. Among the tested seeds, only left ATL and AG showed significant differences in connectivity between concrete and abstract words. Left AG showed higher Alpha and Beta band COH to the left somatosensory cortex for the concrete words (Figure 4.5). Left ATL showed higher Beta and Gamma band COH to the right orbitofrontal cortex for the abstract words (Figure 4.6). Both effects started at the early time window of interest (150-350ms) persisting to the later time window (250-450ms).
Figure 4.5 Results of whole-brain seed-based connectivity with seed in the left AG. Left AG showed higher COH to the left somatosensory cortex for concrete words and in Alpha/Beta bands, in later and earlier + later time windows, respectively.

Figure 4.6 Results of whole-brain seed-based connectivity with seed in the left ATL. Left ATL showed higher COH to the right orbitofrontal cortex, in the Beta/Gamma bands in later and earlier + later time windows, respectively.
4.5 Discussion

This study provides the first evidence for connectivity among heteromodal and sensory-motor-limbic cortices during the earliest stages of semantic word processing (i.e. 150-350ms, 250-450ms). Moreover, it provides additional evidence supporting left anterior temporal lobe (ATL) and angular gyrus (AG) as integrator hubs, complementing the conclusions of Chapter 3. Using time-resolved seed-based functional connectivity with seeds in potential left-hemispheric hub regions (ATL, IFG, MTG and AG) and whole-brain spatio-temporal cluster-based permutation tests, we found higher connectivity between left ATL and right orbitofrontal cortex for the abstract words and higher connectivity between AG and left somatosensory cortex for the concrete words. Importantly, these results were obtained using a novel principal component analysis (PCA) approach across several connectivity metrics that identified magnitude squared Coherence as the most suitable measure of functional connectivity (among the tested methods) for these data.

4.5.1 The most suitable connectivity (MSC) method

Considering the complex nature of the dynamic neuronal signals measured using EEG/MEG, numerous methods have been introduced to quantify connectivity between these signals, each of which focused on some aspects of connectivity. In this study, we computed Coherence (COH), Pairwise Phase Consistency (PPC) and Mutual Information (MI) as three measures under three of the main families of functional connectivity focusing on amplitude plus phase coupling, phase coupling and shared probabilistic information, respectively. Thereafter, we utilised a PCA approach across connectivity methods that received the results of seed-based connectivity from COH, PPC and MI as input and found commonalities and differences between them. We found that the first PC explained ~60% of the variance of the data and was highly correlated (>0.8) with COH and PPC results while the second PC explained ~30% of the data and was highly correlated (>0.8) with MI. Therefore, considering that COH takes both amplitude and phase into account while PPC is only sensitive to phase, the former was selected as the representative connectivity measure. Importantly, however, results of COH and PPC where highly correlated, potentially indicating that the main information in this dataset is encoded in phase.

The issue of identifying suitable connectivity methods/parameters among a multitude of options has come to attention only recently and efforts to date to address this issue have been predominately focused on structural DTI and fMRI connectivity. For example, the so-called ensemble methods have been introduced to identify the most probable connectivity matrix for a given dataset based on the results of connectivity analyses from multiple metrics/parameters (Pestilli et al. 2014; Takemura et al. 2016; Wang et al. 2018). PCA approach utilised in this study alleviated two key issues
that have not been addressed for the application of the ensemble methods for connectivity analysis of EEG/MEG in source space. Firstly, ensemble methods often combine results of multiple connectivity metrics and thus the final accuracy depends on the accuracy of individual metrics (Wang et al. 2018). On the contrary, PCA projects different aspects of connectivity metrics on orthogonal axes and can separate the most robust from the least robust aspects in terms of the explained variance. Using this approach, PCA can be expected to disentangle signal connectivity from noise-induced connectivity, a property that has often been utilised to isolate bio-signals from noise (Castells et al. 2007; Wold et al. 1987). Secondly, to the best of our knowledge, the only previous study focusing on ensemble connectivity approaches for functional connectomes has specifically been proposed for fMRI and intracranial EEG (Wang et al. 2018) and thus, it is unclear as to how the leakage can be taken into account in order to obtain generalisability to source-estimated EEG/MEG. Importantly, as a part of that approach, a few connectivity metrics were sub-selected from numerous available methods based on their performance on the reconstruction of simulated connectomes (Wang et al. 2014a) where simulated EEG signals were obtained from neural mass models and in the absence of leakage. Nonetheless, as has been discussed in the past literature and will be elaborated in Chapter 6, source leakage contaminates connectivity analysis of EEG/MEG in source space. Considering that PCA directly receives the results of connectivity from the real data with no intermediate simulation step, the leakage-induced connections, along with the true connections, will automatically be taken into consideration for identification of the optimal connectivity matrix.

It is worth noting that even though three connectivity metrics were theoretically evaluated to be sufficient in this study, this number can be increased and the performance of the PCA approach is not expected to change significantly. This is due to the fact that the number of features (i.e. connectivity metrics) will be much less than the number of vertices in the brain and thus a robust PCA decomposition is readily possible. It is also worth noting that in this study we identified the connectivity matrix that was mostly correlated with the first PC but used the original connectivity values for the subsequent analyses. This was due to the fact that scaling and signs of PCs can change across subjects and/or frequency bands and therefore the original coherence results were considered as being more suitable for the consequent cognitive interpretation of the results. This choice was justified in this study considering the high correlation between the first PC and coherence results. In studies where the first PC is less correlated with any individual connectivity values, it might be more desirable to utilise the first PC (after appropriate re-scaling) as the ensemble connectivity method.

4.5.2 Hub(s) and Spokes connectivity

Our whole-brain functional seed-based coherence analyses with candidate hubs revealed higher connectivity between left ATL and right orbitofrontal cortex for abstract words in Beta/Gamma
bands, and between left AG and left somatosensory cortex for concrete words in Alpha/Beta bands both in earlier (150-350ms) as well as later (250-450ms) time windows. Concrete words are more tangible and thus, according to the hub-and-spokes model, higher connectivity between the hub and sensory-motor areas was predicted (Lambon Ralph et al. 2016; Patterson et al. 2007). Additionally, abstract words in this study were more emotionally biased (i.e. higher absolute valence difference to the neutral) and hence higher connections between the hub and orbitofrontal cortices were expected (Binney et al. 2016; Lambon Ralph et al. 2016). Therefore, connections of modality-specific cortices were modulated as expected (i.e. somatosensory for concrete versus orbitofrontal for abstract).

However, while concrete words were more imageable and thus were predicted to show higher connectivity between integrator hub(s) and visual spoke, we did not find modulation of any connections to the visual cortex. This was unexpected and might be attributed to the visual presentation of words in this study leading to non-semantic information processing in the visual cortex that might have overshadowed the more subtle semantic effects in this area. Alternatively, it might be due to the fact that concrete words were not explicitly selected to have strong visual attributes.

In addition to the spokes, two out of the four tested hub candidates were highlighted in functional connectivity analyses. ATL and AG have been the two most frequently discussed hub candidates in recent literature (Binder 2016; Lambon Ralph et al. 2016; Seghier et al. 2010) (see Chapters 2 and 3 for more details). Results of the current study, together with findings of Chapter 3, suggest that while ATL might play the role of a domain-general processor hub (whole-brain evoked results in Chapter 3), both ATL and AG might play the role of integrator hubs. The latter was reflected both within the modality-general heteromodal semantic subnetwork and modality-specific semantic subnetwork through connectivity to the sensory-motor-limbic areas (DCM and Coherence results of Chapter 3 and this chapter, respectively). In particular, the idea that AG might be a key integrator hub for the concrete words is in-line with recent fMRI evidence that has shown an integration of sensory-motor attributes of concrete words in AG (Bonnici et al. 2016).

We also explored the role of oscillations by examining four frequency bands of Theta, Alpha, Beta and Gamma. The role of oscillations in semantics has remained largely unknown and different frequency bands have been implicated in the previous research (Bastiaansen et al. 2008; Lewis et al. 2015; van Ackeren et al. 2014). Among the tested bands, we found the involvement of higher frequencies (i.e. Alpha, Beta and Gamma) for interactions between the heteromodal and modality specific cortices. Higher frequencies are thought to play role in local information processing in sensory-motor cortices (Siegel et al. 2012; Von Stein & Sarnthein 2000). For example, in recent years, there has been growing evidence that Gamma band activity reflects local information processing in the visual and auditory cortices (Brosch et al. 2002; Edwards et al. 2005; Muthukumaraswamy et al. 2010;
Muthukumaraswamy & Singh 2013; Pantev et al. 1991). Moreover, the role of Mu band (Alpha and lower Beta) during movement and motor imagery in the motor cortex has been a well-replicated finding in the literature (McFarland et al. 2000; Pineda 2005). Considering the fact that involvement of sensory-motor cortices in semantic representation is essentially predicted as re-activation of these areas as in sensory-motor stimulation, Alpha, Beta and Gamma band can be expected to play important roles in the modality-specific aspect of semantic cognition. However, as will be discussed below in 4.5.3, our access to specific sensory-motor cortices was limited in the current experiment and hence frequency bands are interpreted with caution.

4.5.3 Limitations and future directions

Our findings of this Chapter together with Chapter 3 suggest ATL as potential processor hub and ATL/AG as potential integrator hubs for semantic representation in the brain. However, using the current dataset we were only able to study the contrast of concrete and abstract words and thus some of these findings might be specific to this contrast. More importantly, different word categories with strong sensory-motor spokes were combined under the concrete category and hence access to specific sensory-motor cortices was limited. Subsequently, the role of different oscillations for different word categories could not be tackled optimally. Therefore, in order to better understand the role of spokes and connectivity between the hub(s) and spokes, in the next experiment (Chapters 5, 7), we will examine differences between fine-grained sensory-motor word categories.

Additionally, functional connectivity analysis in this Chapter was restricted to seed-based connectivity with left hemispheric hubs. Ideally, however, whole-brain networks should be examined to get a more complete picture of the semantic networks. This is particularly important considering the widespread activation of different brain areas in response to semantics that has been reported in the past literature (Binder et al. 2009; Huth et al. 2016). Thus, the whole-brain semantic networks will be studied in Chapter 7.
Appendix 4.A  PCA across frequency bands

Cluster-based permutations are normally applied spatio-temporally (e.g. Chapter 3). However, when multiple frequency bands of a dataset are explored, it might be more efficient to correct for multiple comparisons across vertices, time windows and frequency bands in a single spatio-temporo-spectral clustering framework. However, before assuming that clustering across frequency bands is justifiable, it is useful to investigate the degree to which connectivity estimations in different bands measure similar aspects of data connectivity. Subsequently, if high similarities were found between them, it is justifiable to assume continuity across frequencies for clustering. For this purpose, we used a PCA approach similar to 4.3.3 across frequency bands in order to check whether for each connectivity method different frequency bands reflect different aspects of seed based connectivity. We computed PCA across frequency bands (i.e. sub-matrices of size $2N_{\text{vert}} \times N_{\text{bands}}$ obtained from CM described in 4.3.3) and the explained variance and correlation values were averaged over time, seeds and subjects to yield one value for each frequency band and each connectivity method. Considering that each PC is computed on the values derived from one connectivity metric, the scales are not different and differences in the variances of different frequency bands will be informative. Therefore, unlike in 4.3.3, we used the original PCA on the centred data with no weighting. We further assumed the same distributions between frequency bands.

We found that, on the one hand, more than 95% of the variance of COH and PPC across frequency bands was explained using 2 PCs, with the first PC explaining more than 80% of the variance and showing a high correlation to COH/PPC in all the frequency bands ($R>0.8$). The second PC showed a high correlation to the Gamma band. We found a different pattern for MI where the first PC explained around 50% of the variance and was highly correlated to all the frequency bands while PCs 2-4 explained approximately 20%, 15% and 10% of the data and were highly correlated with Theta, Alpha and Beta bands respectively. Details of this analysis are presented in Table 4.A 1.

Table 4.A 1 PCA analysis of seed-based connectivity across frequency bands

<table>
<thead>
<tr>
<th>Pooled Con/Abs</th>
<th>1st PC</th>
<th>2nd PC</th>
<th>3rd PC</th>
<th>4th PC</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>PPC</td>
<td>COH</td>
<td>MI</td>
<td>PPC</td>
</tr>
<tr>
<td>%EV</td>
<td>55.1±9.6</td>
<td>89.3±3.7</td>
<td>85.5±3.7</td>
<td>21.1±6.9</td>
</tr>
<tr>
<td>Theta</td>
<td>0.54±0.11</td>
<td>0.93±0.03</td>
<td>0.94±0.03</td>
<td>0.7±0.34</td>
</tr>
<tr>
<td>Alpha</td>
<td>0.69±0.1</td>
<td>0.95±0.03</td>
<td>0.96±0.02</td>
<td>0.17±0.37</td>
</tr>
<tr>
<td>Beta</td>
<td>0.79±0.13</td>
<td>0.98±0.01</td>
<td>0.97±0.02</td>
<td>-0.11±0.1</td>
</tr>
<tr>
<td>Gamma</td>
<td>0.81±0.14</td>
<td>0.91±0.06</td>
<td>0.81±0.09</td>
<td>0.13±0.12</td>
</tr>
</tbody>
</table>

EV: Explained Variance; MI: Mutual Information; PPC: Pairwise Phase Consistency; COH: Coherence
5 Brain Oscillations Involved in Perception and Action are Modulated during Semantic Word Processing

Theories of embodied semantics and the hub-and-spokes model predict that sensory-motor brain areas, referred to as spokes, re-activate during meaning comprehension. However, empirical evidence supporting content and mechanisms of semantic representation in spokes has been scarce. We hypothesised that early activation together with modulations of similar oscillations as those identified as signatures of perception and action can further specify the mechanisms of semantic representation in spokes. For this purpose, we utilised the spatio-temporo-spectral resolution of the source-estimated EEG/MEG and a data-driven whole-brain analysis approach to examine differences between words with distinct visual (e.g. sun), auditory (e.g. whistle) and hand-action (e.g. wrench) attributes. Based on the previous literature, we considered lower Gamma (31-45Hz) for visual words and Alpha (8-12Hz) for auditory/hand words as characteristic sensory-motor frequencies invoked in occipital and superior temporal/central cortices, respectively. We tested for an interaction effect of frequency band (Gamma versus Alpha) by semantic condition (visual versus auditory/hand) throughout the cortex and in 17 consecutive time windows spanning 50-450ms post-stimulus. We found distinct and overlapping clusters for the two contrasts, all starting around 200ms or even earlier. Visual/hand-specific clusters comprised left motor cortex and medial secondary visual cortex. Visual/auditory-specific clusters comprised left auditory cortex, right medial and left lateral secondary visual cortices as well as bilateral parieto-occipital cortices. Common clusters included a set of bilateral temporal regions and right motor cortex. Furthermore, extending the results of Chapter 3 regarding processor hubs, we found different sub-regions of ATLs to be involved in differentiation of general (word categories versus pseudowords) and specific (fine-grained aforementioned categories) semantic contrasts. These results provide new evidence regarding the mechanisms of semantic representation in spokes and additionally corroborate the role of ATLs as the processor hub.
5.1 Introduction

The role of unimodal sensory-motor-limbic systems, namely spokes, in semantic retrieval has been one of the highly debated topics in the semantic literature (Binder & Desai 2011; Mahon & Caramazza 2008; Meteyard et al. 2012; Pulvermüller et al. 2005a). The hub-and-spokes model (Lambon Ralph et al. 2016; Patterson et al. 2007; Rogers et al. 2004) proposes that sensory-motor cortices provide the ingredients that are required to build up concepts in the brain. However, mechanisms of semantic representation in these areas and the content of these so-called ingredients have remained unknown (Hauk & Tschentscher 2013; Papeo et al. 2015; Pulvermüller 2013). In order to further specify their involvement, timings and oscillatory underpinnings of their modulations have been proposed to carry crucial information. More specifically:

Firstly, embodied views of semantic cognition and the hub-and-spokes model predict that a primary role of spokes should be reflected in early (i.e. pre-N400) modulations of these cortices by category-specific semantics (Hauk et al. 2008; Pulvermüller 2005) while alternative theories propose that modulations of spokes might be attributed to the epiphenomenal spread of activity from language areas (Mahon & Caramazza 2008; Toni et al. 2008) which are likely to be reflected in later post-semantic neural processes such as mental imagery (see Hauk & Tschentscher 2013 for a review). A group of EEG/MEG (Kiefer et al. 2008; Moseley et al. 2013; Pulvermüller et al. 2005b) and TMS (Vukovic et al. 2017) studies in recent years have reported the involvement of spokes within 200ms post-stimulus. Importantly, when these early modulations are invoked in tasks that do not require explicit access (e.g. imagining a visual feature) to the sensory-motor attributes of interest, then the effects are deemed stronger evidence for primary embodiment (Moseley et al. 2013).

Secondly, aforementioned theories suggest a re-activation of spokes in semantic retrieval (Barsalou 1999; Patterson et al. 2007; Pulvermüller 2005); i.e. similar to their recruitment in perception, action and emotion, implying the same mechanisms and content of information processing. Nevertheless, modulation of spokes per se, be it early or late, is silent about the content of representations (Papeo & Caramazza 2014). One step forward for further specification of such content is to investigate whether similar oscillatory dynamics as those involved in perception and action are invoked. Neural oscillations in Alpha (8-12Hz) and Gamma bands (30Hz and higher) have been shown to provide signatures for local sensory-motor information processing in unimodal regions (Engel & Fries 2010). More specifically, the role of Gamma band in local sensory-motor processing and particularly for visual perception in the occipital cortex has often been reported in the previous literature (Fries 2009; Herrmann et al. 2010) and Tau and Mu rhythms have been reported as characteristic frequencies for auditory perception in the superior temporal cortex (Lehtelä et al. 1997).
and movement encoding in the motor cortex (Pfurtscheller & Aranibar 1979), respectively. Moreover, Alpha has also been shown to respond to the visual stimuli (Palva & Palva 2007). Therefore, Alpha and Gamma are sensitive to sensory-motor stimuli and thus, if semantic memory is to be retrieved through re-activation of the sensory-motor cortices, the same oscillations can be expected to play a role for word categories with those sensory-motor attributes.

However, this idea has not been much explored previously (Meteyard et al. 2012) and band-limited responses of spokes have been almost exclusively focused on the role of Mu rhythms for action semantics where early modulations (i.e. within 200ms) of Alpha/lower Beta bands in the motor cortex have been reported (Moreno et al. 2013; van Elk et al. 2010; Vukovic & Shtyrov 2014). Nevertheless, the fact that Alpha/Beta bands are modulated by action semantics in the motor cortex does not avert the possibility of Alpha modulation for other semantic categories in different spokes. Therefore, we propose that a next step for untangling this matter could be to contrast two or more word categories with different characteristic frequencies (e.g. visual Gamma versus action Mu) and investigate the interaction effects of semantic condition by frequency in different cortical areas.

In this chapter, we take into account these two key predictions, namely early timing and sensory-motor oscillations, in an effort to shed more light on the mechanisms of semantic representations in spokes. For this purpose, we utilise source-reconstructed concurrent EEG/MEG recordings of a semantic target detection task in a visual word recognition paradigm and contrast fine-grained word categories with distinct visual (e.g. sun), auditory (e.g. whistle) and hand-action (e.g. wrench) attributes. Additionally, we compare each of the word categories against meaningless pseudowords. The paradigm employs a semantic task that focuses on smell and taste attributes of the targets in order to ensure no explicit access to the sensory-motor attributes of interest. We aim to address the following two hypotheses: firstly, we test that brain oscillations associated with specific sensory-motor information processing will also play role in semantic representation in those sensory-motor cortices. In particular, we focus on Gamma band as a characteristic frequency for visual and Alpha band for auditory and hand-action information processing. However, considering that, as explained above, both of these frequency bands have been shown to play role for all the three categories, we seek to identify the brain areas where differentiation of the conditions depends on the frequency. For this purpose, we test for an interaction effect of frequency band by condition using a whole-brain spatio-temporal cluster-based permutation and hypothesise an early interaction effect of frequency (Gamma versus Alpha) by condition (visual versus hand/auditory): a) in occipital and superior temporal cortices for visual-auditory contrast and b) in occipital and middle central cortices for visual-hand contrast. Secondly, further to the main focus on the spokes, we seek to extend the
findings of Chapter 3 for processor hub through examination of more general (i.e. words versus meaningless pseudowords) and more specific semantic contrasts (i.e. pairwise contrasts of visual, auditory and hand-action words). For both of these analyses, we compare whole-brain band-limited evoked responses for different contrasts of interest using cluster-based permutations for statistical analyses in several time windows spanning 50-450ms post-stimulus.

5.2 Materials and methods

We conducted an EEG/MEG visual word recognition experiment as well as a behavioural word rating study (with non-overlapping subjects). The latter was aimed at providing word lists required for the EEG/MEG experiment. Details of both studies are elaborated in the following sub-sections.

5.2.1 Behavioural word rating experiment

This behavioural study was conducted as a pre-EEG/MEG experiment in order to provide materials for the main EEG/MEG study. The purpose of this experiment was to provide lists of word categories (50 words per category) that are strongly associated with one of the following sensory-motor attributes of interest: visual (e.g. sun), auditory (e.g. whistle) and hand action (e.g. wrench).

5.2.1.1 Participants

41 healthy native adult English speakers (aged 18-75) participated in the study, but one subject was removed due to inaccuracies in following the instructions. Hence, 40 participants (age 38.3±17.9, 25 female) entered the final analysis. All participants had a normal or corrected-to-normal vision with no reported history of neuropsychological disorders or dyslexia. The experiment was approved by the Cambridge Psychology Research Ethics Committee and volunteers were paid for their time and effort.

5.2.1.2 Stimuli

A set of 586 words was collected for rating and subjects were asked to make judgements about concreteness, visual, auditory and hand-action attributes of each word (details below in 5.2.1.3). We initially selected the words subjectively (checked by two authors) such that they were associated with at least one of the attributes of interest in order to ensure a suitable preliminary list. However, the final evaluations were solely based on the rating study. In order to maintain subjects’ efficiency and avoid a prolonged experiment, participants were divided into two groups of 20 and each group performed the rating for half of the word list.
5.2.1.3 Procedure

Word rating experiment consisted of four blocks with an overall duration of approximately 90 minutes including three short breaks between the blocks. In each block, subjects rated 293 words in response to the following four questions focused on concreteness, visual-relatedness, auditory-relatedness and hand-action relatedness of the concepts. Participants were given a maximum of 8 seconds to rate each word and were asked to rate on a scale of 1 to 7 with 1 indicating a low rating and 7 corresponding to a high rating. The experiment was implemented in PsychoPy (version 1.82.01) (Peirce 2007) and details of the questions were:

1- How concrete is the following word?

Concrete words refer to persons, places and things that can be seen, heard, touched, smelled, tasted or acted upon, and abstract words refer to the concepts that cannot be experienced by your senses. Concrete words should receive high ratings and abstract words should receive low ratings. Please rate on the scale of 1 to 7 with 1 indicating highly abstract and 7 indicating highly concrete.

2- Does the following word immediately and vividly remind you of something you can hear?

If a word meaning is strongly associated with auditory properties, including but not restricted to sounds, music and voices, you should rate it highly. Otherwise, it should be given a low rating. Please rate on the scale of 1 to 7 with 1 indicating not at all and 7 indicating extremely.

3- Does the following word immediately and vividly remind you of an action that you can perform with your hands?

Only if a word is strongly associated with hand actions, you should rate it highly. If it is associated with actions of other body parts or not associated with actions at all, it should be given a low rating. Please rate on the scale of 1 to 7 with 1 indicating not at all and 7 indicating extremely.

4- Does the following word immediately and vividly remind you of features that you can visually perceive?

If a word meaning is strongly associated with visual properties, including but not restricted to shape, form and colour, you should rate it highly. If you do not think that the word is associated with visual features at all, it should be given a low rating. Please rate on the scale of 1 to 7 with 1 indicating not at all and 7 indicating extremely.

The response times to questions 1-4 were 1.99±0.41, 1.67±0.26, 1.54±0.24 and 1.63±0.25 seconds, respectively.
5.2.1.4 Word categorisation

As the first step, we made a preliminary list of auditory, hand and visual words by selecting words that were rated at least one standard deviation above average in response to questions 2, 3 and 4, respectively. Thereafter, we removed list overlaps and limited each list to the concrete words (i.e. rated one standard deviation above average on concreteness rating). Additionally, considering that a majority of the hand words were found to be highly visual as well, we restricted the visual word list to the words that were distinctly visual. That is, at least one rating point difference between the ratings of questions 3 and 4. These preliminary selection criteria resulted in 94 visual, 87 auditory and 69 hand-action words. Thereafter, we used Match software (Van Casteren & Davis 2007) in order to find 50 words per category that were matched with respect to a group of psycholinguistic variables elaborated in section 5.3.1. Additionally, we selected 50 pseudowords matched to the categories of words. It is worth noting that in addition to these categories of interest, two categories of emotional and neutral abstract words (50 per category) and additional filler pseudowords (to keep response balance in lexical decision task- details below) were also included in the EEG/MEG experiment but will not be analysed in this study.

5.2.2 EEG/MEG experiment data acquisition

5.2.2.1 Participants

27 healthy native adult English speakers (age 18-40) participated in the study (with no overlap with the word rating study), among which 2 were removed due to problems with structural MRI scans, 3 were removed due to inadequate behavioural response accuracies and 3 were removed due to excessive movement artefacts. Hence, 19 participants (mean age 27.00±5.13, 12 female) entered the final analysis. A handedness laterality quotient of 89.84 ± 0.2 was obtained from a reduced version of the Oldfield handedness inventory (Oldfield 1971). All participants had a normal or corrected-to-normal vision with no reported history of neurological disorders or dyslexia. The experiment was approved by the Cambridge Psychology Research Ethics Committee and volunteers were paid for their time and effort.

5.2.2.2 Stimuli

Participants were presented with 150 mono-morphemic concrete words categorised into three categories of visual, auditory and hand-action words (50 words per category) as well as 50 matched pseudowords yielding 300 stimuli overall. Additional abstract words and filler pseudowords were also included in the experiment, which are not of interest in this study. Details of stimuli are
elaborated in section 5.2.1. Word categories were matched for a number of psycholinguistic variables, details of which are presented in the Results section (Table 5.1, section 5.3.1).

5.2.2.3 Procedure

The EEG/MEG experiment consisted of four randomised blocks and a brief localiser task towards the end and lasted approximately 90 minutes. We included short breaks every three minutes and longer breaks between the blocks. Duration of stimulus presentation was 150ms, with an average SOA of 2400ms (uniformly jittered between 2150 and 2650ms). Stimuli appeared as 30-point Arial font in black on a grey screen within a visual angle of 4 degrees in a slightly dimmed and acoustically shielded MEG chamber. Three blocks of the experiment consisted of semantic target detection tasks and the fourth block was a lexical decision task where half of the subjects performed the lexical decision block before semantic blocks and half of them afterwards. Details of these blocks were as follows:

1- Semantic target detection blocks

In each block, participants were presented with 330 words and pseudowords including 300 stimuli (3 subcategories of concrete, 2 subcategories of abstract and 1 group of pseudowords, with 50 items per group) and 30 targets. They were asked to quietly read the strings of letters as they appeared on the screen and make button press responses with the middle finger of their left hand whenever a target appeared on the screen. Each block had different targets which were selected from three groups of “non-citrus fruits”, “something edible with distinctive odour” and “food that contains milk, flour or egg”. These semantic questions, all focused on olfactory and gustatory attributes of concepts, were designed so as to ensure full access to the semantic retrieval while not explicitly requiring access to the visual, auditory and hand-action attributes of interest. Blocks were presented in a random order and data obtained from the three blocks were combined in the later EEG/MEG analyses so as to obviate possible question-specific effects.

2- Lexical decision task

In addition to the main semantic target detection task, subjects were also asked to perform a lexical decision task with all the words and pseudowords (and additional 150 filler pseudowords in order to match the overall number of words to acquire response balance). Subjects were asked to make button press responses with the index and ring fingers of their left hand indicating whether or not “the following string of letters refers to a meaningful word”. EEG/MEG data from this block or comparison between the two presented tasks were
not of interest for this study. However, we used behavioural responses from this block as a measure of subjects’ performances.

5.2.3 EEG/MEG pre-processing

MEG and EEG data were acquired simultaneously using a Neuromag Vectorview system (Elekta AB, Stockholm, Sweden) and MEG-compatible EEG cap (EasyCap GmbH, Herrsching, Germany) installed at the MRC Cognition and Brain Sciences Unit, University of Cambridge, UK. MEG was recorded using a 306-channel system that comprised 204 planar gradiometers and 102 magnetometers. EEG was acquired using a 70-electrode system with an extended 10-10% electrode layout. EEG reference and ground electrodes were attached to the left side of the nose and the left cheek, respectively. ElectroOculoGram (EOG) was recorded by placing electrodes below and above the left eye (vertical EOG) and at the outer canthi (horizontal EOG). Electrocardiogram (ECG) was recorded by placing one electrode on the lower left rib and another electrode on the right wrist. Data were acquired with a sampling rate of 1000Hz and an online band-pass filter of 0.03 to 330Hz. During pre-acquisition preparations, positions of 5 Head Position Indicator (HPI) coils attached to the EEG cap, 3 anatomical landmark points (two ears and the nose) as well as approximately 50-100 additional points that covered the whole scalp were digitised using a 3Space Isotrak II System (Polhemus, Colchester, Vermont, USA) and later used for co-registration of EEG/MEG recordings with MRI data.

Our analysis pipeline is illustrated in Figure 5.1. The First step of data pre-processing included applying a signal-space separation (SSS) method implemented in the Max-filter software (Version 2.0) of Elekta Neuromag to the raw MEG data in order to remove noise that was generated from sources distant to the sensor array (Samu Taulu and Matti Kajola 2005). The Max-filter software involved movement compensation and bad channel interpolation. All the next steps of analysis were performed in the MNE-Python software package (http://martinos.org/mne/stable/index.html) (Gramfort et al. 2013, 2014). Raw data were visually inspected for each subject, and consistently bad EEG channels were marked and interpolated. Data were then FIR band-pass filtered. Noting that two main analyses will be conducted in order to investigate the role of processor hubs and band-limited oscillations in spokes, two different filters were used. More specifically, in the first analysis, broad-band evoked responses were of interest and thus for the sake of compatibility with the previous research, data were filtered between 0.1 and 30Hz (Chen et al. 2015; Hauk et al. 2012; Moseley et al. 2013). However, in the second analysis, it was particularly of interest to have access to Gamma band and thus a passband of 0.1-45Hz was used. We used forward-backward filtering technique in order to achieve zero phase delay. Independent Component Analysis (ICA) was applied to the filtered data in order to remove eye movement and heartbeat artefacts. We used FastICA algorithm (Hyvärinen et al. 2000) as
implemented in Scikit-learn python package (Pedregosa et al. 2011) and included in the MNE-Python meeg-preprocessing package for artefact rejection (with occasional manual adaption to obtain a better artefact rejection for some subjects). After ICA, data were divided into epochs from 300ms pre-stimulus to 600ms post-stimulus. For data filtered up to 30Hz, epochs that showed peak-to-peak amplitudes higher than the following thresholds were rejected: 2500fT in magnetometers, 1000fT/cm for gradiometers, 100µV for the EEG (except for 2 cases where we increased the threshold to 120µV, because excessive amplitudes were manually assessed as being due to individual differences in brain responses rather than artefacts). For data filtered between 0.1-45Hz we used the same thresholds for MEG channels but increased the EEG thresholds to 120µV (and 150µV for the two aforementioned subjects). Trials with incorrect responses were also excluded from further analysis.

![Figure 5.1 A flowchart of different steps of data analysis. Sign × denotes interaction effect in statistical testing.](image)

5.2.4 Band-limited evoked responses for oscillations

In order to get band-limited responses, we further filtered raw data after band-pass filtering between 0.1-45Hz and ICA artefact rejection. More specifically, in order to examine Alpha and Gamma bands, data were filtered between 8-12Hz and 30-45Hz, respectively. Thereafter, band-limited trials were averaged in order to obtain band-limited evoked responses and projected onto the source space using the approach elaborated below in 5.2.6. In this way, we investigated the oscillatory responses
that were phase-locked to the stimulus. This approach has been used frequently in the EEG/MEG literature (Herrmann et al. 2010). However, in recent years, EEG/MEG studies of event-related data have often utilised time-frequency (TF) decomposition where the so-called evoked and induced powers that supposedly provide complementary yet overlapping insights into the brain function can be studied separately or in combination (David et al. 2006b; Koelewijn et al. 2011). Investigation of the induced power is particularly useful with stimuli that shows high inter-trial variability (Kalcher & Pfurtscheller 1995). However, by studying power and phase of oscillations in isolation (typically focusing on the power only), TF studies ignore the interplay between power and phase which is also likely to play an important role in the brain function. Therefore, band-limited evoked responses compromise the ability to study induced power and TF power does not allow for investigation of the combined effects of amplitude and phase. In this study, we used visual presentation of single words with stimuli that were carefully matched with respect to length, frequency, etc. and we were interested in fast transient brain states within 500ms post-stimulus that are supposedly somewhat automatic. Due to these reasons, we made an assumption that the timings of spoke activations might not jitter significantly across trials and thus induced responses were not particularly of interest. Instead, considering that both amplitude and timing of spokes were deemed informative, it was considered important to investigate both amplitude and phase of spoke modulations (ideally combined than in isolation) and thus we examined band-limited evoked responses.

5.2.5 Forward model and inverse solution

We used MNE-python software to compute the forward and inverse models. The forward model was computed based on a Boundary Element head Model (BEM) derived from structural MR images for each subject. EEG/MEG sensor configurations and MRI images were co-registered based on the aforementioned digitisation points. Structural MR images were processed using the automated segmentation algorithms in FreeSurfer software (Version 5.3; http://surfer.nmr.mgh.harvard.edu/) in order to obtain the reconstructed scalp surface (Dale et al. 1999; Fischl et al. 1999). The result of the FreeSurfer segmentation was processed further using MNE software package (Version 2.7.3) and the original triangulated cortical surface which included more than 160,000 vertices per hemisphere was down-sampled to a tessellated grid where the average edge of each triangle was approximately 2.5mm (Segonne et al. 2004). A three-layer BEM containing 5120 triangles per layer was created for EEG and MEG from the scalp, outer skull surface and inner skull surface, respectively. The noise covariance matrices for each dataset were computed and regularised in a single framework which computes the covariance using empirical, diagonal and shrinkage techniques and selects the best fitting model by log-likelihood and three-fold cross-validation on unseen data (Engemann & Gramfort 2015). Baseline intervals of 300ms duration pre-stimulus were used for noise covariance estimation.
The resulting regularised noise covariance matrix was used to assemble the inverse operator for each subject using a loose orientation constraint of 0.2 and no depth weighting.

5.2.6 Whole brain source reconstruction

The assembled inverse operator was applied to the broad-band and band-limited evoked responses in order to estimate the time courses of every cortical vertex. For this purpose, firstly, bad trials were removed according to the criteria described in 5.2.3. Thereafter, the number of epochs were equalised between the four lists (i.e. visual, auditory, and hand words as well as matched pseudowords). The equalisation of the number of trials was performed so as to remove any biases due to differences in the signal to noise ratio (SNR) that is potentially caused by a different number of epochs. Data acquired from the three blocks of semantic target detection (i.e. “fruit”, “milk”, “odour”) were combined and trials were averaged in sensor space and an evoked response was extracted. The evoked response was then projected onto the source space using L2-minimum norm estimate (L2 MNE) with default SNR of 3.0 for regularisation. Only dipole components perpendicular to the cortical surface were kept in order to obtain “signed” evoked responses. After source reconstruction, the individual subject results were morphed to the standard average brain (fsaverage5) in the Freesurfer software, yielding time courses of activity for 20484 vertices for each subject.

5.2.7 Statistical analysis

5.2.7.1 Spatiotemporal cluster-based permutation of whole-brain band-limited evoked analysis

We considered Gamma band as a characteristic frequency for visual information processing (Brunet et al. 2014; Fries 2009), Alpha band as a characteristic frequency for auditory (Tau rhythm (Lehtelä et al. 1997)) and action processing (Mu rhythm (Pfurtscheller & Aranibar 1979)) and examined condition by frequency band interaction effects throughout the cortex in different time windows. For this purpose, we used spatiotemporal cluster-based permutation analysis with 10,000 permutations (Maris & Oostenveld 2007), details of which were elaborated in Chapter 3 (section 3.2.3). In order to compute mass univariate tests that were used as input to the clustering procedure, we computed a two-way Analysis of Variance (ANOVA) with two factors and two levels per factor. Next, we computed F-values for condition × band interaction and thresholded F-values corresponding to a range of p-values. It is worth noting that a range of thresholds was tested due to the fact that cluster-based permutations have been known to be sensitive to the choice of threshold (Smith & Nichols 2009). Therefore, in order to avoid reporting threshold-specific clusters, we tested five thresholds.
corresponding to p-values of 0.05, 0.025, 0.01, 0.005, 0.001, and only clusters that survived at least three out of the five thresholds were considered robust and reported.

5.2.7.2 Spatiotemporal cluster-based permutation of whole-brain broad-band evoked analysis

Broad-band evoked responses were compared for two types of contrasts: first, to find brain areas and time windows at which each word category shows differences to the pseudowords; second, to find brain areas and time windows at which different pairs of word categories show differences against each other. For this purpose, we used spatiotemporal cluster-based permutation analysis with 10,000 permutations (Maris & Oostenveld 2007) on the source reconstructed evoked data that were filtered between 0.1-30Hz. The univariate vertex-wise paired t-tests that were used as input for clustering were computed for each pairwise contrast and thresholded at a t-value corresponding to a range of p-values/2 (i.e. two-tailed) and only robust clusters will be reported (details robustness evaluation the same as above in 5.2.7.1).

5.3 Results

5.3.1 Word rating results

We selected a final list of 50 words per category for the visual, auditory and hand-action words using the criteria described in 5.2.1.4 that were matched with respect to the psycholinguistic variables elaborated in Table 5.1. Additionally, we selected 50 pseudowords that were matched to every word category. The list of final words and pseudowords are presented in Appendix 5.A. The values for CELEX frequency, orthographic neighbourhood and unconstrained unigram/trigram frequencies were obtained from MCWord Database (Binder and Medler, 2005), valence ratings were based on (Warriner et al. 2013) and age of acquisition ratings were based on (Kuperman et al. 2012). In addition to these general variables, we attempted at matching each pair of word categories with respect to the third sensory-motor attribute of interest. As a result, hand-visual and auditory-visual pairs were matched with respect to the auditory- and hand-relatedness, respectively. However, in spite of our efforts to minimise visual attributes of hand word category, they were still significantly more visual compared to the auditory words (Figure 5.2). This was due to the fact that hand-action words were more likely to be among the action verbs or objects while many of the auditory words were sounds and therefore the former were perceived as having stronger visual attributes and hence being more concrete by the subjects. However, the visual category was still found to be significantly more visual compared to both other groups (both p-values < 0.00001, Figure 5.2).
Table 5.1 Means and standard deviations for relevant psycholinguistic variables for the stimuli utilised in semantic decision task.

<table>
<thead>
<tr>
<th></th>
<th>Visual</th>
<th>Auditory</th>
<th>Hand</th>
<th>Pseudoword</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Letters</td>
<td>5.18±1.48</td>
<td>5.16±1.22</td>
<td>5.02±1.2</td>
<td>4.82±0.75</td>
</tr>
<tr>
<td>CELEX Frequency</td>
<td>13.32±17.58</td>
<td>11.03±17.25</td>
<td>19.67±30.86</td>
<td></td>
</tr>
<tr>
<td>Orth Neighbourhood</td>
<td>4.5±5.44</td>
<td>5.28±5.24</td>
<td>5.44±5.25</td>
<td>5±4.68</td>
</tr>
<tr>
<td>Valence</td>
<td>0.68±0.51</td>
<td>0.69±0.51</td>
<td>0.68±0.47</td>
<td>N/A</td>
</tr>
<tr>
<td>Age of Acquisition</td>
<td>6.34±1.77</td>
<td>6.52±1.65</td>
<td>6.11±1.73</td>
<td>N/A</td>
</tr>
<tr>
<td>Bigram Frequency</td>
<td>20089.5±11698.6</td>
<td>17599.13±9171.36</td>
<td>17369±9580.5</td>
<td>16569.3±087.5</td>
</tr>
<tr>
<td>Trigram Frequency</td>
<td>1867.2±3314.7</td>
<td>1825.17±2526.59</td>
<td>1690.8±2505.1</td>
<td>1451.4±2244.2</td>
</tr>
<tr>
<td>Concreteness Rating</td>
<td>6.5±0.27</td>
<td>5.01±0.96</td>
<td>5.49±0.88</td>
<td>N/A</td>
</tr>
<tr>
<td>Visual-relatedness</td>
<td>6.28±0.27</td>
<td>3.69±1.61</td>
<td>4.74±0.8</td>
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</tr>
<tr>
<td>Auditory-relatedness</td>
<td>2.66±1.16</td>
<td>2.62±1.55</td>
<td>5.57±0.65</td>
<td>N/A</td>
</tr>
<tr>
<td>Hand-relatedness</td>
<td>2.18±0.96</td>
<td>6.23±0.46</td>
<td>2.88±0.97</td>
<td>N/A</td>
</tr>
</tbody>
</table>

mean±STD, STD: standard deviation, Orth: Orthographic.

Figure 5.2 Statistical comparisons of the final word lists for visual, auditory and hand-action categories with respect to concreteness, visual, auditory and hand-relatedness attributes. P-values for each pairwise comparison are presented underneath each figure. VIS: Visual, HND: Hand, AUD: Auditory
5.3.2 EEG/MEG behavioural results

Based on the lexical decision task described in 5.2.2.3, we computed response accuracies and reaction times to different word categories and matched pseudowords. Two of the auditory words and one visual word had 50% or less response accuracy across all participants in the lexical decision task. These were removed from the dataset for all the analyses.

![Figure 5.3 a) Reaction times and b) response accuracies for different word categories and matched pseudowords based on lexical decision task.](image)

We found no significant differences between reaction times of the concrete word categories, but significantly higher reaction times for the pseudowords. Additionally, response accuracies were statistically similar for pairwise comparisons, except for a significant difference between visual and auditory words where auditory words were on average less accurate by approximately two words. Details are presented in Figure 5.3 and Table 5.2.

<table>
<thead>
<tr>
<th>Word Category</th>
<th>Visual</th>
<th>Auditory</th>
<th>Hand</th>
<th>Pseudowords</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction Time (s)</td>
<td>0.66±0.07</td>
<td>0.67±0.06</td>
<td>0.67±0.07</td>
<td>0.74±0.06</td>
</tr>
<tr>
<td>Resp. Accuracy (/1)</td>
<td>0.96±0.04</td>
<td>0.94±0.05</td>
<td>0.95±0.04</td>
<td>0.93±0.07</td>
</tr>
</tbody>
</table>

Resp: Response

5.3.3 Oscillations and semantic spokes

This step of analysis was aimed at untangling temporo-spectral properties of the involvement of sensory-motor cortices in semantic representation in the brain. For this purpose, we focused on Alpha and Gamma bands for different conditions. More specifically, we tested the hypothesis that an interaction of band × condition effect can differentiate between visual and auditory/hand words in the occipital and superior temporal/middle central cortices. We used a whole-brain spatio-temporal cluster-based permutation approach for this purpose and examined 17 averaged consecutive time
windows spanning 50ms to 450ms. We found distinct as well as overlapping clusters for the two comparisons. Visual/hand-specific clusters consisted of the left motor cortex (starting 150ms) and medial secondary visual cortex (onset 175ms). Visual/auditory-specific clusters consisted of the left auditory cortex (onset 200ms), right medial secondary visual cortex (onset 50ms), left lateral secondary visual cortex (onset 50ms) as well as bilateral parieto-occipital cortices (onset 50ms). Common clusters between the two comparisons comprised bilateral Perisylvian language cortices (onset before 100ms), left anterior and posterior superior temporal lobes (onset before 100ms), right medial anterior temporal lobe (onset 225ms) as well as the right motor cortex (onset 50ms). The raw uncorrected F-test results are shown in Figure 5.B 1.
Figure 5.4 Significant clusters obtained from spatio-temporal cluster-based permutation analysis of band (Gamma vs. Alpha) × condition (visual vs. auditory/hand) interaction effect. The comparisons were conducted pairwise between different word categories, as explained in the text, and overlaid in this figure. We observed the differences in 17 averaged consecutive time windows spanning 50-450ms and found distinct as well as overlapping clusters for the two comparisons. Distinct clusters were located at the proximity of the left motor cortex and right visual cortex for visual/hand contrast and at the proximity of the left auditory cortex, bilateral visual cortices and parieto-occipital cortices for visual/auditory contrast. Common clusters included bilateral Perisylvian language areas, anterior temporal lobes and right motor cortex. VA: Visual-Auditory contrast, VH: Visual-Hand contrast, VA/VH: overlapping clusters. The key sensory-motor clusters are marked with blue arrows (note the temporal changes of these clusters).

5.3.4 Processor hub(s) differentiating general and specific semantic contrasts

We investigated whether or not the findings of Chapter 3 regarding the role of the bilateral ATLs as processor hubs for concrete/abstract contrasts can be extended to more general (words versus pseudowords) and more specific (fine-grained categories of visual, auditory and hand-action words) semantic contrasts.

5.3.4.1 Whole-brain evoked analysis of words versus pseudowords

We contrasted each word category against pseudowords. As elaborated in Chapter 3, the hub-and-spokes model predicts that a single hub should be modulated by different semantic conditions early on during the course of semantic word processing and should remain involved through later stages of semantic retrieval. Significant clusters obtained from the pairwise comparison of the signed evoked brain responses to each word categories (visual, auditory and hand action) against pseudowords are shown in Figure 5.5.

We found overlapping clusters for all the word categories against pseudowords spanning anterior and posterior superior temporal cortices as well as Perisylvian language areas and perirhinal cortex in the left hemisphere. More specifically, clusters for the visual-pseudoword comparisons were at the proximity of the left lateral and medial ATLs (250ms onwards). Clusters for hand-pseudoword comparisons were located in the left anterior and posterior parts of the superior temporal gyrus (100ms onwards), temporo-parietal junction (100ms onwards) as well as perirhinal cortex (20ms onwards) and showed notable overlaps with the cluster for the visual words. Auditory-pseudoword comparisons showed a cluster predominantly in the left posterior superior temporal gyrus (100ms onwards). It is worth noting that auditory-pseudoword contrasts resulted in smaller spatio-temporal clusters but showed very similar univariate t-test results to those of the other two contrasts (see Figure 5.B 2 in Appendix 5.B). Thus, some of the clusters started as early as 100ms while some others appeared around 250ms. We found no significant clusters in the right hemisphere.
5.3.4.2 Whole-brain evoked analysis of word category contrasts

We contrasted word categories against one another. Significant clusters obtained from pairwise comparisons of the signed evoked brain responses are shown in Figure 5.6. We found a left-lateralised anterior fronto-temporal cluster for visual-hand contrast which was found to be significant between 100-475ms, a right-lateralised anterior fronto-temporal cluster for visual-auditory contrast which was significant between 50-450ms and a left-lateralised perirhinal cluster for auditory-hand contrast which was significant between 200-400ms. In spite of differences in timings and
laterisation, all the clusters were localised to ATL/IFG cortices. The raw univariate t-test results are shown in Figure 5.B 3. It is worth noting that our whole-brain broad-band evoked results highlighted heteromodal semantic areas but not the modality-specific spokes. In Appendix 5.C, we conducted an ad-hoc test to specifically investigate a few hypothesised spokes in an effort to replicate the previous findings in the literature (e.g. (Moseley et al. 2013)).

Figure 5.6 Significant clusters obtained from spatio-temporal cluster-based permutation of pairwise comparison of different word categories (visual, auditory, hand action) overlaid. We examined different contrasts in 17 averaged consecutive time windows spanning 50-450ms and found a left-lateralised anterior fronto-temporal cluster for visual-hand contrast (starting around 100ms), a right-lateralised anterior fronto-temporal cluster for visual-auditory contrast (starting before 100ms) and a left-lateralised perirhinal cluster for auditory-hand contrast (starting around 200ms). VA: Visual-Auditory contrast, VH: Visual-Hand contrast, AH: Auditory-Hand contrast.
5.4 Discussion

In this study, we utilised the spatio-temporo-spectral resolution of source-reconstructed concurrent EEG/MEG and: a) provided novel evidence that brain oscillations associated with perception and action are modulated by similar sensory-motor attributes of words in corresponding sensory-motor cortices during semantic processing and b) replicated and expanded on some of the findings of Chapter 3 regarding the processor hubness of the ATLs. Firstly, in a whole-brain analysis of band-limited evoked responses, we found a significant interaction effect of frequency band (Gamma versus Alpha) by condition (visual versus hand/auditory) in the occipital and motor cortices for visual/hand-action contrast and in the occipital, parieto-occipital and superior temporal cortices for visual/auditory contrasts. Secondly, matching our criteria for supramodal processor hub, we found that left-lateralised fronto-temporal areas were modulated by general word/pseudoword contrasts and bilateral ATLs and surrounding frontal areas, in particular, differentiated fine-grained concrete word categories. Interestingly, in spite of differences in timings and lateralisation, the identified potential processor hubs from different contrasts included a sub-region of ATLs. Importantly, all the results were obtained from a data-driven whole-cortex analysis with spatio-temporal cluster-based permutations to ensure no prior subjective restrictions on the investigated brain areas and/or time windows.

5.4.1 Gamma/Alpha oscillations and semantic spokes

In examination of the band-limited evoked responses, we found distinct brain cortices that differentiated semantic categories based on the frequency bands of exploration which was reflected in significant band (Gamma vs. Alpha) × condition (visual vs. hand/auditory) interaction effects. Visual/hand-specific clusters comprised left middle central motor cortex and medial secondary visual cortex (overlapping with V2 and V3). Visual/auditory-specific clusters comprised left superior temporal auditory cortex, right medial/left lateral secondary visual cortices (overlapping with V2 and V3) as well as bilateral posterior parieto-occipital areas. Common clusters included a set of bilateral temporal regions and the right motor cortex. These results provide novel evidence for the involvement of occipital, middle pre-/post-central and superior temporal cortices as visual, hand-action and auditory spokes and suggest that the same oscillations involved in perception and action are evoked during semantic retrieval of the words that hold those sensory-motor attributes. The common clusters for the two contrasts included bilateral frontotemporal cortices that are highly overlapping with the identified processor hub(s) (see 5.4.2 below) and right-hemispheric central cortices that are likely to play a role in response planning and execution (considering that button press responses were made with the left hand).
The role of oscillations in semantic processing is not established to date. However, embodiment views and the hub-and-spokes model predict a re-activation of sensory-motor areas in response to the concepts that hold those sensory-motor attributes (Barsalou 1999; Pulvermüller 2005), implying an involvement of similar oscillations as those involved in perception and action. Results of the current study support this hypothesis using two key considerations that have been unprecedented in the previous literature. Firstly, using several word categories with clear sensory-motor boundaries and distinct characteristic frequencies in perception and action, we were able to show that Alpha and Gamma band oscillations that are supposedly involved in perception and action (Brunet et al. 2014; Lehtelä et al. 1997; Palva & Palva 2007; Pfurtscheller & Aranibar 1979) were invoked during semantic retrieval in the corresponding spokes and as of the early time windows of exploration (onset typically between 100-200ms). These results take a step forward from the previous research by showing that the role of oscillations in spokes is not limited to one specific frequency band (e.g. mu) and/or sensory-motor attribute (Moreno et al. 2013; van Ackeren et al. 2014; van Elk et al. 2010; Vukovic & Shtyrov 2014). Secondly, the aforementioned studies have often analysed sensor-space data and source localisation, if at all conducted, has been focused on localising the effects that were found to be significant in sensor space. Furthermore, they have predominantly focused the analyses on a few hypothesised brain areas and/or time windows (Moreno et al. 2013; van Elk et al. 2010; Vukovic & Shtyrov 2014). Here for the first time, we utilised a distributed source model together with a data-driven statistical analysis approach in source space that corrects for multiple comparisons at single vertex level and multiple time windows (i.e. 17 windows of 25ms duration from 50-450ms). This will minimise the possibility of omitting potentially interesting effects/cortices and is expected to improve the reproducibility of the results. Moreover, utilisation of multimodal MEG/EEG recordings allowed us to improve the localisation accuracy (Molins et al. 2008).

We focused our analyses on Alpha and Gamma bands considering that among the frequency bands that have often been studied using EEG/MEG (i.e. Delta, Theta, Alpha, Beta and Gamma) (Siegel et al. 2012), the role of Alpha and Gamma has been more frequently reported in sensory-motor information processing (Brunet et al. 2014; Haegens et al. 2015; Jensen et al. 2014). Firstly, event-related desynchronization of the classic somatosensory Mu rhythm in the motor cortex (Pfurtscheller & Aranibar 1979) and Tau rhythm in the auditory cortex (Tiihonen et al. 1991), both in the range of the Alpha band, have been frequently reported in the literature. Additionally, the Alpha band in the parieto-occipital cortex has been associated with the lack of visual input (i.e. increased when eyes are closed) and it has been shown to desynchronise in response to visual stimuli, particularly in the context of visual attention and awareness (Palva & Palva 2007). Secondly, Gamma band has been repeatedly found to play a role in the bottom-up sensory processing in the primary sensory areas and it has been
shown that this frequency band is most suitable for orchestrating local sensory information (Fries 2009). Importantly, however, a majority of these studies have used visual stimuli (Brunet et al. 2014) and therefore the role of Gamma band for visual information processing in the visual cortex is more established in the literature (Brunet et al. 2014; Hermes et al. 2015a, 2015b). Therefore, in this study, we considered Gamma as the characteristic frequency band for vision and Alpha for audition/hand-action.

It is worth noting that in order to test visual Gamma versus auditory/hand-action Alpha, the interaction effect of band × condition was considered sufficient and we did not explore the main effects of condition in each frequency band. The reasons for this choice included: a) as mentioned above, both Alpha and Gamma have been shown to play important roles in all the three categories of investigation. Therefore, it was generally of interest to identify the cortices at which differentiating the conditions depended on the frequency band rather than examination of each separate band; b) considering that we utilised signed evoked responses throughout this chapter, the positive/negative sign of activity can indicate either activation/deactivation at each vertex or ingoing/outgoing current depending on the curvature of the cortex at each vertex. Hence, after subtraction of two conditions for calculation of the paired main effects, the sign of differences will not be informative and different scenarios might produce similar outcomes. Therefore, we focused on the interaction effects. However, the main effect of the semantic category at each frequency is expected to further specify the role of each oscillation in sensory-motor cortices of interest. Unwrapping these underlying mechanisms remains an intriguing question for the future research. In particular, intracranial EEG recordings might shed more light on the matter.

5.4.2 Processor semantic hubs in broad-band evoked responses (0.1-30Hz)

We found a set of frontotemporal cortices that matched our criteria for processor semantic hubs. That is, considering that semantic hubs are proposed to act as a linking layer between input (visually presented words in this study) and distributed semantic networks (Rogers et al. 2004), one key prediction for hubs was that they should be the first areas to be modulated by semantic variables and remain active throughout the course of semantic processing.

Interestingly, ATLs were the only cortices highlighted in all the pairwise comparisons of the broad-band (i.e. 0.1-30Hz) evoked responses. However, the lateralisation and sub-regions differed depending on the contrasts. While pairwise contrasts of different word categories against pseudowords and pairwise contrasts of visual/auditory words against hand words were localised to the left ATL, the pairwise contrast of visual versus auditory words was localised to the right ATL. Additionally, auditory/hand contrast was constrained to the medial ATL (perirhinal cortex) while the
other effects involved both lateral and medial sub-regions. Effects typically started between 100-150ms and persisted on to later time windows. In addition to the ATLs, we also found a modulation of the broader left hemispheric fronto-temporo-parietal cortices in response to word/pseudoword contrasts. Several of the key hub candidates identified in the previous literature (e.g. ATL, MTG and AG as discussed in earlier Chapters 1 and 3) overlap with these regions.

Therefore, our findings here replicate and expand on the findings of Chapter 3 where ATLs were found to be modulated by concreteness. Crucially, the fact that ATLs have been involved for general contrasts (words vs. pseudowords) as well as the more specific contrasts (fine-grained categories of concrete words as well as concrete versus abstract words) indicates that this region is involved in multiple aspects of semantic differentiation (Lambon Ralph et al. 2016), fulfilling one of the key properties of a processor semantic hub. Moreover, the broader fronto-temporo-parietal cluster might be involved in distinguishing a meaningful word from a meaningless string of letters, potentially by incorporating lexical-semantic features, but less so for the more specific differentiation of categories of concepts.
Appendix 5.A  Lists of word stimuli utilised in EEG/MEG experiment

The final lists of concrete words and pseudowords utilised as stimuli in the EEG/MEG experiment as well as their psycholinguistic variables (based on MCWord Database (Binder and Medler, 2005)) are presented in Tables 5.A 1-4. These words were selected based on the word rating study, details of which were elaborated in 5.2.1.

Table 5.A 1  Final list of words with strong visual attributes utilised in the EEG/MEG experiment.

<table>
<thead>
<tr>
<th>Word</th>
<th>Cnct</th>
<th>VIS</th>
<th>HND</th>
<th>AUD</th>
<th>Valence</th>
<th>AoA</th>
<th>LEN</th>
<th>FREQ</th>
<th>Orth</th>
<th>UN2_F</th>
<th>UN3_F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anchor</td>
<td>6.8</td>
<td>6.5</td>
<td>2.8</td>
<td>2.45</td>
<td>0.096</td>
<td>5.72</td>
<td>6</td>
<td>6.72</td>
<td>0</td>
<td>30207.04</td>
<td>1448.51</td>
</tr>
<tr>
<td>Bottle</td>
<td>6.55</td>
<td>6.4</td>
<td>3.45</td>
<td>2.7</td>
<td>0.406</td>
<td>3.56</td>
<td>6</td>
<td>87.22</td>
<td>3</td>
<td>12148.15</td>
<td>1221.51</td>
</tr>
<tr>
<td>Candle</td>
<td>6.5</td>
<td>6.2</td>
<td>3.05</td>
<td>1.65</td>
<td>1.076</td>
<td>5.37</td>
<td>6</td>
<td>8.03</td>
<td>2</td>
<td>30857.08</td>
<td>9196.01</td>
</tr>
<tr>
<td>Canyon</td>
<td>6.3</td>
<td>5.9</td>
<td>1.2</td>
<td>2.4</td>
<td>0.436</td>
<td>8.39</td>
<td>6</td>
<td>8.86</td>
<td>2</td>
<td>28078.17</td>
<td>1839.29</td>
</tr>
<tr>
<td>Cloud</td>
<td>6.05</td>
<td>6.7</td>
<td>1.25</td>
<td>1.3</td>
<td>1.136</td>
<td>3.63</td>
<td>5</td>
<td>32.54</td>
<td>2</td>
<td>15306.54</td>
<td>629.77</td>
</tr>
<tr>
<td>Comet</td>
<td>6.55</td>
<td>5.9</td>
<td>1.45</td>
<td>2.7</td>
<td>1.836</td>
<td>8.16</td>
<td>5</td>
<td>1.55</td>
<td>3</td>
<td>20318.14</td>
<td>4757.95</td>
</tr>
<tr>
<td>Curtain</td>
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<td>6.65</td>
<td>3.6</td>
<td>2.45</td>
<td>0.296</td>
<td>4.95</td>
<td>7</td>
<td>19.99</td>
<td>2</td>
<td>23194.52</td>
<td>2062.96</td>
</tr>
<tr>
<td>Deer</td>
<td>6.7</td>
<td>6.75</td>
<td>1.75</td>
<td>3.9</td>
<td>1.826</td>
<td>5.17</td>
<td>4</td>
<td>12.37</td>
<td>12</td>
<td>33957.57</td>
<td>493.61</td>
</tr>
<tr>
<td>Desert</td>
<td>6.2</td>
<td>6.25</td>
<td>1.45</td>
<td>2.15</td>
<td>0.296</td>
<td>8.35</td>
<td>6</td>
<td>40.46</td>
<td>10</td>
<td>32193.55</td>
<td>1940.16</td>
</tr>
<tr>
<td>Diagram</td>
<td>5.5</td>
<td>6.2</td>
<td>3.7</td>
<td>1.2</td>
<td>0.406</td>
<td>9.63</td>
<td>7</td>
<td>6.60</td>
<td>0</td>
<td>9250.1</td>
<td>660.23</td>
</tr>
<tr>
<td>Elephant</td>
<td>6.65</td>
<td>6.35</td>
<td>1.35</td>
<td>4.9</td>
<td>1.106</td>
<td>4.80</td>
<td>8</td>
<td>12.85</td>
<td>0</td>
<td>26099.26</td>
<td>1747.21</td>
</tr>
<tr>
<td>Elk</td>
<td>6.2</td>
<td>6.5</td>
<td>1.3</td>
<td>3.35</td>
<td>0.746</td>
<td>7.05</td>
<td>3</td>
<td>1.43</td>
<td>4</td>
<td>9212.99</td>
<td>2.56</td>
</tr>
<tr>
<td>Elm</td>
<td>6.4</td>
<td>5.85</td>
<td>1.1</td>
<td>1.6</td>
<td>1.256</td>
<td>9.06</td>
<td>6</td>
<td>7.02</td>
<td>3</td>
<td>9024.43</td>
<td>61.87</td>
</tr>
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<td>1.75</td>
<td>4.7</td>
<td>0.436</td>
<td>7.42</td>
<td>6</td>
<td>1.31</td>
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Table 5.A 4 Final list of pseudowords utilised in the EEG/MEG experiment.
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Appendix 5.B  Univariate t-test results

Band-limited evoked analysis of word category comparisons

Figure 5.B 1 Raw F-values computed for condition (visual vs. auditory/hand) x band (Gamma vs. Alpha) interaction effects. These maps were used as input to the cluster-based permutation results shown in Figure 5.4.
Figure 5.B 2 Univariate t-test results of comparing each word category against pseudowords. These maps were used as input to the cluster-based permutation results shown in Figure 5.5.
EEG/MEG broad-band evoked analysis of word category comparisons

**Figure 5.B 3** Univariate t-test results of comparing word categories for data filtered between 0.1-30Hz. These maps were used as input to the cluster-based permutation results shown in Figure 5.6.
Appendix 5.C  Regions of interest analysis

EEG/MEG literature investigating the role of sensory-motor spokes in semantics originally examined the role of sensory-motor areas over the time axis by contrasting broad-band evoked brain responses for different word categories. For example, (Moscoso Del Prado Martín et al. 2006) investigated activations of parieto-occipital cortices in response to words with strong colour and shape attributes, and more recently (Moseley et al. 2013) reported a double dissociation for the action and object words in the fronto-central motor cortices and occipito-temporal visual areas, respectively. The timings of spokes activation in the previous literature have often been tested using regions of interest analysis and by means of broad-band ERP (Kiefer et al. 2008; Moseley et al. 2013). In this chapter, our whole-brain broad-band evoked analysis highlighted potential processor hub(s) but not sensory-motor cortices. However, it was of interest to explore whether by restricting the broad-band analyses to the sensory-motor areas (likewise in the aforementioned studies), we will be able to replicate and expand on some of the previous findings, in particular, the findings of (Moseley et al. 2013) for visual versus action words.

Materials and Methods

Localiser tasks

At the end of the main EEG/MEG experiment described in 5.2.2, subjects performed three localiser tasks of overall 5-minutes duration. These tasks were designed to help defining visual, auditory, and hand action regions of interests (ROI). The auditory localiser task consisted of 50 short beeps. Visual task consisted of shape versus scrambled shape judgement as well as distinguishing colour grids of dots versus grey scale grids of dots. Button presses using the index/ring fingers of the right hand in response to the visual localisers were used to localise the hand motor cortex in the left hemisphere.

Extracting ROI time course in source space

Source reconstruction was conducted as described in 5.2.6 and results were averaged in 17 consecutive time windows from 50ms to 450ms averaged in bins of length 25ms. Thereafter, we extracted time courses of three regions of interest (ROIs) in the visual, auditory and hand motor cortex which were manually defined based on the localiser tasks. In order to extract the ROI time courses, we used a mean-flipped approach. This approach computes a parcel time course by taking an average of sign-flipped signals of the vertices within that ROI. The flipping sign is determined based on the relative source orientation of each vertex within the ROI compared to the orientation of the first
principal component within that ROI. Positive sign indicates outward-flowing current. More details of this approach can be found in MNE-Python documentation.

Results and conclusions: replicating some of the previous findings

We compared broad-band evoked responses to different word categories in the aforementioned sensory-motor ROIs in visual, auditory and hand motor cortices. The average time courses for each condition and ROI across participants are shown in Figure 5.C.1. We examined 50ms-450ms interval averaged over 25ms time windows (i.e. 50ms-75ms, 75ms-100ms etc.) using a repeated measure ANOVA design with three factors and three levels per factor in order to examine the condition × ROI effects. After correction for multiple comparisons across time windows using cluster-based permutations, we found a marginally significant effect (p < 0.1) between 200-250ms. Thereafter, in order examine the interaction effect in pairwise comparisons, we used three post-hoc two-way repeated measure ANOVAs each with two factors and two levels per factor. For visual-hand word comparisons, the interaction effect was significant in a time window from 200ms-275ms (corrected p < 0.05 and between 150-175ms, uncorrected p < 0.05). For visual-auditory comparison, we found an effect between 325-350ms but it did not pass correction for multiple comparison tests. For hand-auditory comparison we found no significant differences. Additionally, we did not find any main effects of condition contrasts in the ROIs. Results are shown in Figure 5.C.1.
Therefore, our results show a marginally significant effect of ROI x condition interaction in three-by-three design and particularly highlight a cross-over interaction of visual and hand-action words in occipital and central cortices at around 200ms. These results replicate the findings of (Moseley et al. 2013) for visual versus action words, except that here we have utilised signed evoked responses while absolute power was computed in that study and therefore directions of responses cannot be compared. Unlike visual-hand contrast, our results for pairwise comparisons that contain auditory words are less consistent. Together with the main results of this chapter on spokes, we conclude that in order to study the role of spokes in semantics, it is important to take the relevant oscillations into account.

Figure 5.C 1 Statistical analysis of condition by ROI interaction effect. A significant interaction of visual/hand category by visual/motor cortices were found between 200-275ms. Red plots: Visual words, blue plots: auditory words, black plots: hand words. Solid lines: visual cortex, dashed lines: middle central (left) and superior temporal (right) cortices. The pairs shown in the legend represent condition-ROI respectively. The solid blue line marks significant time window after temporal cluster-based permutation. Dashed blue lines mark above-threshold (F-value=4.3) F-values that did not survive corrections for multiple comparisons.
Adaptive Cortical Parcellations for Source Reconstructed EEG/MEG Connectomes

One of the key objectives of the current thesis is to examine dynamic whole-brain semantic graphs and modulations of connectivity within and between integrator hubs and spokes by different semantic variables. Source reconstructed EEG/MEG provide spatio-temporo-spectral resolution required for this purpose. However, the problem of leakage between brain sources that arises when reconstructing brain activity from EEG/MEG recordings outside the head makes it difficult to distinguish true connections from spurious connections, even when connections are based on measures that ignore zero-lag dependencies. In particular, standard anatomical parcellations for potential cortical sources tend to over- or under-sample the real spatial resolution of EEG/MEG. By using information from cross-talk functions (CTFs) that objectively describe leakage for a given sensor configuration and distributed source reconstruction method, we introduce methods for optimising the number of parcels while simultaneously minimising the leakage between them. More specifically, we compare two image segmentation algorithms: 1) a split-and-merge (SaM) algorithm based on standard anatomical parcellations and 2) a region growing (RG) algorithm based on all the brain vertices with no prior parcellation. Interestingly, when applied to minimum-norm reconstructions for EEG/MEG configurations from real data, both algorithms yielded approximately 70 parcels despite their different starting points, suggesting that this reflects the resolution limit of this particular sensor configuration and reconstruction method. Importantly, when compared against standard anatomical parcellations, resolution matrices of adaptive parcellations showed notably higher sensitivity and distinguishability of parcels. Furthermore, extensive simulations of realistic networks revealed significant improvements in network reconstruction accuracies, particularly in reducing false leakage-induced connections. Adaptive parcellations, therefore, allow a more accurate reconstruction of functional EEG/MEG connectomes.
6.1 Introduction

Connectivity analyses of source estimated EEG/MEG can provide a millisecond-by-millisecond map of functional and effective interactions (Bastos & Schoffelen 2016; Greenblatt et al. 2012) among multiple brain areas in resting state as well as during task performance (Brookes et al. 2016; Colclough et al. 2016; Palva et al. 2010). Consequently, there has been growing interest in reconstructing the human brain connectome to obtain time- and frequency-resolved whole-brain networks (Palva & Palva 2012). Studies on anatomical and functional MRI connectomics have revealed important properties of the brain in health and disease, particularly concerning changes in “hubs” and the associated “rich club” of highly-connected regions (Bullmore & Sporns 2009; Crossley et al. 2014; van den Heuvel & Sporns 2011). The growing field of EEG/MEG connectomics is anticipated to take this approach further by vastly increasing the temporal and spectral resolution of the human connectome (Brookes et al. 2011b; de Pasquale et al. 2010). However, the spatial resolution of EEG/MEG data is limited, because several thousand sources of activation in the brain must be estimated from maximally a few hundred sensor recordings.

The limited spatial resolution causes the so-called leakage or cross-talk problem for linear and linearly constrained distributed EEG/MEG source estimation (Hauk et al. 2011; Lachaux et al. 1999; Schoffelen & Gross 2009) which poses serious challenges for the interpretation of connectivity results (Colclough et al. 2015). More specifically, abundant spurious leakage-induced connections contaminate EEG/MEG connectome reconstructions and e.g. might lead to finding spurious hubs in the networks. Most previous EEG/MEG studies have adopted parcellations from anatomical or fMRI research for whole-brain connectivity analysis (Brookes et al. 2016; Colclough et al. 2016; Tewarie et al. 2016). However, considering the leakage problem, anatomical parcellations may not be optimal for reconstruction of EEG/MEG connectomes and thus recent studies have suggested EEG/MEG-based parcellations to be more desirable (Brookes et al. 2016).

An ideal parcellation should provide the maximum coverage of the cortex at which parcels show high sensitivity (activity arising from themselves) and specificity (low leakage from other parcels). CTFs can be used to characterise leakage among different brain areas (Hauk et al. 2011; Liu et al. 1998). Some previous studies have suggested using CTFs to minimise leakage between a small number of ROIs. Wakeman (2013), for example, sub-selected a number of vertices as representative for each of a few ROIs that had minimal cross-talk with the other ROIs, while Hauk and Stenroos (2014) proposed a method that optimises spatial filters for source reconstruction in order to produce zero cross-talk among a small set of brain sources and minimal cross-talk from other sources.
While these methods are optimised for the case of few spatially distinct sources, their extension to whole-brain connectivity analysis is limited. Palva et al. (2010) introduced a parcellation for graph theoretical analysis of single subject data by taking into account the source-sensor geometry of EEG/MEG. They used a clustering algorithm to parcellate the cortex into 365 patches (equal to the number of sensors), based on phase synchrony values estimated from simulated data that were generated from white noise in source space. More recently, Korhonen et al. (2014) introduced sparse weights to collapse the source space based on the forward and inverse modelling of simulated noise in the source space. Their method aims at assigning optimal vertices to a fixed set of parcels and extracting the parcel time course as a weighted sum of the assigned vertices. This method utilises phase coherence between the true and estimated sources in order to maximise fidelity of the assigned vertices to the recipient parcel. Unlike the aforementioned Palva et al.’s (2010) method, the sparse weights approach is suitable for group as well as single subject analysis and is based on the anatomical parcellations. However, while the sparse weights approach provides a way of extracting parcel time courses based on the spatial limitations of EEG/MEG, obtaining an adaptive parcellation that can optimise both the number and location of parcels, as well as vertex selection within those parcels, has remained a challenge (Bullmore & Bassett 2011; Korhonen et al. 2014). Considering that one of the key objectives of the current thesis is to investigate connectivity between the hub(s) and spokes using data-driven whole-brain connectome reconstruction (more details in Chapter 1), obtaining suitable parcellations for source estimated EEG/MEG is desirable. Thus, in this chapter, we will develop adaptive cortical parcellations for EEG/MEG and in the next chapter (Chapter 7), they will be applied for reconstruction of semantic networks.

Here, we utilise CTFs as a direct measure of spatial leakage to address the limitations of the aforementioned methods systematically. For this purpose, we have implemented two CTF-informed image segmentation algorithms (Gonzalez & Woods 2006) that parcellate the cortical surface into the maximum number of distinguishable parcels. In the first approach, we started from standard anatomical parcellations and modified the parcels using a CTF-informed split-and-merge (SaM) algorithm. The main idea is to merge parcels that produce highly overlapping CTFs, split parcels that produce distinguishable patterns of cross-talk, remove parcels for which EEG/MEG show low sensitivity, and for each parcel, identify a group of representative vertices that show high sensitivity and specificity to that particular parcel relative to the rest of the brain. This approach is suitable for studies that require a particular anatomical labelling of parcels. In the second approach, we start from all the brain vertices with no prior parcellation. A CTF-informed region growing algorithm is used to create parcels around the vertices that show highest sensitivity and specificity of CTFs on the cortex.
These parcels are then optimised with respect to specificity and sensitivity using an SaM algorithm. This approach should prove useful for studies where no strict anatomical labels are required.

Both algorithms yield adaptive parcellations since CTF patterns may change depending on the choice of head models, inverse operators, measurement configurations (i.e. EEG, MEG or their combination) and signal-to-noise ratios (SNR) of the data. Additionally, the proposed algorithms can use data from multiple subjects and yield parcellations suitable for group analysis through morphing the cortical surfaces from single subjects to a standard average space (e.g. MNI space). We evaluate the performance of the proposed algorithms by measuring the sensitivity and specificity of the CTFs of the final parcels to themselves as compared to the rest of the brain, and comparing performance to those of two standard anatomical atlases in the Freesurfer software (Desikan-Killiany (Desikan et al. 2006) and Destrieux (Destrieux et al. 2010)). Furthermore, we compared the performance of different parcellations by means of spectral connectivity analysis of simulated event-related networks in source space, and under various conditions in terms of number and locations of active sources, percentage of connections among the sources and realistic SNRs of the data. We show that EEG/MEG-adaptive parcellations result in a more accurate network reconstruction for both zero-lag and non-zero-lag connectivity metrics.

6.2 Theory

6.2.1 EEG/MEG source estimation and spatial resolution

In Chapter 2, we elaborated EEG/MEG forward modelling, inverse solution, resolution matrix and cross-talk functions (CTFs), which are the basis for the parcellation algorithms described in the Methods section (6.3) of the current Chapter. In Chapter 2 we discussed how the ill-posedness of the EEG/MEG inverse solutions causes the leakage problem and how CTFs can be used to quantify leakage. Here, we will first use CTFs to illustrate how leakage affects sensitivity and specificity of anatomical ROIs for EEG/MEG. Thereafter, we will briefly elaborate on the effects of leakage on zero-lag and non-zero-lag connectivity measures.

6.2.2 Using CTFs to quantify limitations of anatomical atlases

Two main problems can arise from utilising anatomical parcellations with EEG/MEG, which we illustrate in Figure 6.1:

1) **Sensitivity Problem**: EEG/MEG may not be sensitive to activity from some parcels:
   - While for superficial parcels CTFs may peak within the parcel (e.g. Supramarginal Gyrus, Figure 6.1a left), deeper parcels may receive much larger cross-talk from areas close to the sensors than from themselves (e.g. Insula, Figure 6.1a right).
2) **Specificity Problem:** Anatomical boundaries might not correspond to the spatial resolution of EEG/MEG:

   a. Large parcels may be split into sub-regions with distinguishable CTFs (e.g. postcentral gyrus, Figure 6.1b).

   b. Some distinct anatomical parcels may produce highly similar CTFs, and are therefore indistinguishable from one another due to the limited spatial resolution or EEG/MEG measurements (e.g. Pars Orbitalis and Pars Triangularis, Figure 6.1c).

The examples in Figure 6.1 also highlight the usefulness of CTFs for the evaluation - and possible construction - of cortical parcellations for EEG/MEG connectivity analysis.

6.2.3 Both zero-lag and non-zero-lag connectivity are affected by leakage

Signal leakage causes activity in one area to be estimated in nearby areas with no time delay; thus there will be zero-lag phase difference between the actual activity and the leaked activity (Brookes et al. 2012; Hipp et al. 2012). Therefore, connectivity methods that are insensitive to zero-lag correlations such as phase lag index (PLI) or imaginary part of coherency (ImCOH), have been introduced to overcome the leakage problem to some extent (Nolte et al. 2004; Stam et al. 2007). However, as has been pointed out in some previous studies (Colclough et al. 2015), even though insensitivity to the zero-lag connections can alleviate the problem, non-zero-lag methods are still affected by leakage.

We illustrate the principle of this problem using CTFs in Figure 6.1d. Let us consider a case where activity in rostral middle frontal (RMF) cortex and middle temporal gyrus (MTG) show non-zero-lag connectivity. In an ideal scenario with no leakage, the whole-brain seed-based connectivity with seed in the RMF should only produce connectivity with MTG (blue area in the Figure 6.1d). However, in a realistic scenario with leakage, two outcomes are possible: 1) If a connectivity measure which is sensitive to zero-lag connections such as Pearson Correlation or Coherence is used, high connectivity will be found between the active sources as well as their leakage domain (Figure 6.1d middle); 2) If a non-zero-lag connectivity measure such as ImCOH is used, the spurious connectivity between RMF seed and its surrounding areas (i.e. RMF “realm”) will be resolved but results will still be affected by the “blurring” (referred to as inherited connectivity in (Colclough et al. 2015)) around the MTG source (Figure 6.1d right). This is due to the fact that the whole neighbourhood of MTG is in non-zero-lag connection to the RMF. It is worth noting that the same argument can be brought for the bivariate directed connectivity methods such as Granger Causality (GC); i.e. if RMF Granger-causes activity in MTG, it will show spurious GC to the neighbourhood of the MTG too. However, generalisation to the multivariate connectivity methods is less straightforward which is discussed in Appendix 6.A.
Figure 6.1 A CTF-based illustration of the limitations of the use of anatomical parcellations for EEG/MEG analysis in source space. a) CTFs (bottom) for some parcels (e.g. supramarginal gyrus, left) peak within the parcel, while for others (e.g. a deep parcel in the insula) the CTF’s peak may be at a significant distance from the parcel; b) A single postcentral parcel produces potentially multiple distinguishable CTFs; c) Pars-orbitalis and Pars-triangularis (yellow and blue, respectively) are anatomically separate but have largely overlapping CTFs; d) An illustration of how seed-based connectivity is affected by the leakage problem in a hypothetical task where only two regions in RMF (seed) and MTG (target) are active and non-zero-lag connected. Left: ideal scenario with no leakage. Middle: in the presence of leakage if a method of connectivity that is sensitive to the zero-lag connections (e.g. coherence) is used. Right: in the presence of leakage if a method of connectivity that is insensitive to the zero-lag connections (imaginary part of coherency) is used. This figure is based on theoretical predictions of CTFs of the connectivity results rather than simulations.

6.3 Materials and methods

6.3.1 EEG/MEG data acquisition and pre-processing

We used the same dataset and pre-processing pipeline as in Chapters 3, 4. Therefore, our results here are based on the real data collected from 17 healthy subjects who participated in an event-related visual word recognition experiment to obtain head-models and noise covariance matrices of pre-stimulus baseline intervals for source estimation. Other data properties are not of interest in this chapter.

6.3.2 Head model and source estimation

Details of forward modelling were presented earlier in Chapter 3. In order to compute the inverse operators for each subject, noise covariance matrices were computed and regularised in a single framework which computes the covariance using empirical, diagonal and shrinkage techniques and selects the best fitting model by log-likelihood and three-fold cross-validation on unseen data (Engemann & Gramfort 2015). Baseline intervals of 500ms duration pre-stimulus were used for the estimation of noise covariance matrices. The resulting regularised noise covariance matrices were
used to assemble the inverse operators for each subject using an L2 minimum norm (MNE) estimator with loose orientation constraint 0.2 (Lin et al. 2004) and no depth weighting.

6.3.3 EEG/MEG-adaptive parcellations

As outlined in the introduction, we aim to obtain a parcellation of the cortical surface into parcels that, according to their CTFs, are sensitive to activity originating from or around them, but are relatively insensitive to leakage from other parcels. In the first approach, we started from existing standard anatomical parcellations, and optimised them using a modified split and merge (SaM) algorithm. In the second approach, we started with no prior parcellation and created an optimal set of parcels using a region growing (RG) algorithm. Both SaM and RG belong to the so-called region-based family of image segmentation with relatively simple and robust implementations of algorithms (Gonzalez & Woods 2006). These algorithms were preferred over more complex and less frequently used methods and also over edge-based family as another simple and common family of segmentation algorithms (Dutta et al. 2016; Pham et al. 2000). The latter was due to the fact that edge-based algorithms aim to form contours around the distinguishable parts of an image by setting some criteria for edge detection (e.g. gradient). Therefore, clear boundaries are typically required and the algorithms are sensitive to the presence of noise (Pal & Pal 1993). Hence, since CTFs of different brain areas are not necessarily clearly separated and noise levels in the data can be high, region-based methods were preferred. Moreover, among the region-based algorithms, those that require a pre-specified number of regions (segments) such as clustering methods (Pham et al. 2000) were not suitable. Instead, one of the main purposes of the current study is to recruit algorithms that yield the optimal number of parcels in the brain. Both SaM and RG are simple, fast and robust against noise and can be expected to yield coherent focal regions in the brain. A flowchart of different steps of analyses is shown in Figure 6.2.

6.3.3.1 Leakage and Parcel Resolution Matrices (PRmat)

Starting point for our algorithms is the Parcel Resolution Matrix (PRmat). While the resolution matrix \( R \) (Equation 2.4 in Chapter 2) describes cross-talk among all vertices, PRmat describes normalised cross-talk among parcels. Below, we will describe the computation of PRmats. Let us assume that at one stage within our algorithms, we have \( N_{\text{parcel}} \) parcels with \( N_v \) overall vertices and \( N_p \) vertices per parcel \( p \).

- First, we compute absolute values of CTFs at each vertex, as we are only interested in the amount of leakage. We will still refer to these as CTFs for simplicity.
• We arrange all CTFs for vertices within a parcel p as rows of a matrix $M_p$. Thus, $M_p$ is a sub-matrix of $R$, containing only those rows corresponding to vertices in the parcel p.

• We compute singular-value decomposition (SVD) along the rows of all the $M_p$ matrices. We then represent each parcel by the first eigenvector $CTF_p$ along the rows (i.e. across CTFs).

• Second, we define $PRmat$, where each element $PRmat_{ij}$ describes leakage from parcel i to parcel j, normalised by the amount of leakage it receives from all parcels:

$$PRmat_{ij} = \frac{1}{N_i} \sum_{k \in K_j} \frac{CTF_k^i}{\sum_{l=1}^{N_j} CTF_l^i} \quad (6.1)$$

where $K_j$ refers to the set of indices for vertices in parcel j and $CTF_p^i$ is the cross-talk of parcel p at vertex v. The normalisation ensures that values in $PRmat$ are between 0 and 1. The ideal $PRmat$ is an identity matrix, and our purpose is to obtain parcellations for which the similarities between the actual and an ideal $PRmat$ are maximised.

Figure 6.2 A flowchart of data analysis and parcellation algorithms. Pre-processing and localisation steps can change depending on the study and CTFs and subsequent steps will change and adapt accordingly. $M_p$: a subset of $R$ matrix corresponding to each parcel, $CTF_p$: CTFs of each parcel at all the brain vertices, PRmat: parcel resolution matrix, RG: Region Growing, SaM: Split and Merge.
6.3.3.2 A CTF-based split-and-merge (SaM) algorithm for parcellation

In this section we examined Desikan-Killiany (DKA, 68 parcels) and Destrieux (DA, 148 parcels) Atlases that are defined in the fsaverage space in the Freesurfer software. Two different parcellations were used since DKA provides a coarser sampling of the cortex while DA provides a more fine-grained sampling of the cortex. This enabled us to observe the effect of the initial parcel sizes on the final results of parcellation modifications. We modified the parcellations using a CTF-informed algorithm similar to the split-and-merge algorithm in digital image processing literature (Haralick & Shapiro, 1985; Gonzalez & Woods 2006). Split-and-merge algorithm typically starts from a whole image and utilises an iterative process to divide the image into as many “homogeneous” segments as possible. The homogeneity is defined based on the image properties, for example, one implementation of the algorithm might seek to segment an image based on constant standard deviation inside each segment. If the homogeneity criterion is not satisfied inside a segment, that segment will be split into several equal-sized sub-segments and the homogeneity criterion will be checked inside each of these new segments. This procedure is iterated until no further splitting is possible. At this point, the algorithm searches for the segments that might have been over-split during the splitting and merges them together. To this end, the segments that show similar properties based on some predefined criterion (e.g. pixel colour or intensity) will be merged in an iterative procedure until no more merging is possible.

Here, we have adapted a similar idea and have defined the split, merge and homogeneity criteria based on CTFs. On the one hand, parcels that are too large to be represented by one CTF should be split up. On the other hand, if CTFs of two parcels overlap substantially, those parcels cannot be distinguished using EEG/MEG (Figure 6.1b, c). Furthermore, if EEG/MEG is not sensitive to activity from a parcel, it should be omitted from the parcellation (Figure 6.1a). Therefore, CTFs and resolution matrices can be used to inform the splitting and merging in order to parcellate the cortex into the optimal number of distinguishable parcels. As will be elaborated in the next subsections, the SaM algorithm used in this study is a non-iterative version of the original SaM algorithm described above.

6.3.3.2.1 Splitting criterion

The purpose of the first step – splitting - was to identify large parcels (e.g. Figure 6.1b) and split them into several sub-parcels. For a particular parcel:

- We determined the number of principal components (PCs), \( N_{PC} \), needed to explain more than 90% of the variance of their CTFs (determined from an SVD of matrix \( M^p \) in 6.3.3.1).
- If $N_{PC} > 1$, we split the parcel into $N_{PC}$ sub-parcels along its longest spatial axis. This is done by finding the principal Eigen-axis of the label on the spherical surface, projecting all the coordinates of the label vertices on this axis, and dividing them at equal intervals.

- In order to obtain a fixed number of sub-parcels across hemispheres per subject as well as across all subjects in the data set, we added the following constraints:
  - In order to obtain consistency across hemispheres, the minimum of $N_{PC}$ for the corresponding parcels in the left and right hemispheres was assigned to both parcels. We consider the over-splitting of parcels, i.e. multiple parcels that contain the same information, as less desirable than under-splitting, i.e. a parcel that potentially covers a larger area than necessary.
  - In order to obtain one splitting number for each parcel across subjects, we looked at the distribution of $N_{PC}$ across subjects and assigned the mode (i.e. the most frequency number, the minimum number if multiple modes) of this distribution to the parcel.

These steps yielded a “split-parcel” parcellation, which was used for further processing.

6.3.3.2.2 Homogeneity criterion

After creating a parcellation consisting of split-parcels, we tested for all individual vertices whether we could reassign them to one of the split-parcels, whether we should drop them because no split-parcel was sensitive to them, or whether they were candidates for a later merging procedure. For this purpose, $CTF_p$s for the split parcels were computed and morphed to the average brain, in order to be averaged over subjects. Thereafter, we assigned each of the vertices in the average brain to a maximum of one split-parcel. A vertex was assigned to a split-parcel only if it was:

1) Sensitive to that split-parcel (sensitivity)
2) Significantly more sensitive to that split-parcel compared to all other split-parcels in the brain (specificity).

Sensitivity and Specificity were defined as follows.

Sensitivity: We removed the vertices that were not sensitive to any split-parcels. To this aim, for every vertex, we tested for every split-parcel whether the split-parcel’s $CTF_p$ value at this vertex was equal or more than half of the maximum of the split-parcel’s $CTF_p$ values anywhere in the brain. If this was the case, that vertex was considered sensitive to that split-parcel. Vertices that were not sensitive to any split-parcels in the brain were removed from further analysis.
Specificity: For every pair \((i,v)\) of split-parcel \(i\) and vertex \(v\), we quantified the relative cross-talk that vertex \(v\) receives from split-parcel \(i\) compared to all other \(N\) split-parcels as the z-score \(Z_{iv}\):

\[
Z_{iv} = \frac{CTF_i - \overline{CTF_v}}{\sigma_{CTF_v}} \quad (6.2)
\]

where \(\overline{CTF_v}\) denotes the average of \(CTF\) values of split-parcels at vertex \(v\), and \(\sigma_{CTF_v}\) denotes the standard deviation across \(CTF\) values from all split-parcels at vertex \(v\), respectively.

Based on these z-scores, we classified vertices into one of three categories:

a. Declined vertices: If no split-parcels showed a z-score above 3 for a vertex, it indicated that the vertex was not specifically sensitive to the \(CTF\)s of any of the split-parcels in the brain. These vertices were removed from further analysis.

b. Assigned vertices: Using a winner-takes-all approach, if the split-parcel with the highest z-score for a vertex had a z-score above 3 and at least 1 standard deviation higher than the runner-up, that vertex was assigned to this split-parcel.

c. Merge candidate vertices: vertices that showed similarly high sensitivity to two split-parcels were marked for the merging procedure (see sub-section 3.3.2.3 below). In other words, merge candidates consisted of a vertex (or a patch of vertices) that showed high z-score (>3) to a pair of split-parcels but the difference between the z-scores was less than 1.

6.3.3.2.3 Merging criterion

The aim of the third step was to create a set of merged-parcels based on the merge candidate vertices described above. For this purpose, for each pair of split-parcels in the brain, a group of vertices that were similarly highly sensitive to those split-parcels were clustered together as a new merged-parcel. These merged-parcels resulted from two scenarios:

1. If two original split-parcels were too finely separated and not distinguishable using EEG/MEG (e.g. parcels in Figure 6.1c), they were completely merged together.

2. If \(CTF\)s of two split-parcels were partially overlapping, a third region might have emerged from that overlapping region.

Of these new merged-parcels, those that were of equal-size or larger than the smallest original split-parcel in the brain were kept for further analysis. As an example, vertices that were equally
sensitive to both superior temporal and middle temporal gyri were clustered as a new merged-parcel called superior-temporal_middle-temporal.

6.3.3.2.4 Final homogeneity evaluation

The procedure above resulted in a new parcellation (consisting of the original split-parcels and the new merged-parcels shown in Figure 6.C 1 in Appendix 6.C), based on splitting, merging and homogeneity criteria. However, these criteria used CTFs based on the initial parcellation. We therefore need to optimise the new parcellation based on its own PRmat. Thus:

- Step 6.3.3.2.2 (homogeneity criterion) was repeated for the modified list of split- and merged-parcels. Those parcels that could win at least 10 vertices were kept and the rest of the parcels were declined.
- The PRmat was computed for the modified parcels and if any off-diagonal elements of a particular parcel were higher than the diagonal element, that parcel was removed.
- In order to obtain a consistent parcellation across hemispheres, those parcels that survived the above criteria in only one hemisphere were removed. Moreover, in order to obtain a symmetrical final parcellation, parcels were kept in the hemisphere that showed more coverage and mirrored to the opposite hemisphere.

6.3.3.3 A CTF-based region growing algorithm for parcellation

Region growing is another algorithm of image segmentation which typically starts by randomly selecting a voxel (pixel) as the first “seed” in an image. Then, based on a pre-specified similarity criterion (e.g. colour or intensity), neighbouring voxels are grouped together with the seed voxel, leading to a growing region around the seed until no more voxels can satisfy the similarity criterion to connect to the cluster (Gonzalez & Woods 2006)). Thereafter, a new seed outside the existing cluster is randomly selected in the image and the same procedure is iterated until all the voxels in the image are assigned to one cluster. In this section, we have adopted a similar idea and have used CTFs to define the similarity criterion to grow regions around the vertices in order to create and modify parcels in the brain. Therefore, we started the parcellation at the single-vertex level with no prior parcels and created parcels using the following steps:

6.3.3.3.1 Finding seed vertices

The main purpose of the first step was to identify the “seed vertices”, i.e. vertices that show high sensitivity based on the CTFs. Therefore:

- The resolution matrix (R) was computed for all the vertices (section 2.1.2) with rows representing CTFs at each vertex.
Sensitivity and specificity steps described in section 6.3.3.2.2 were applied to the rows of the resolution matrix in order to find the sensitivity of each vertex to leakage from all other vertices. In other words, every vertex was treated like a “split-parcel” in 6.3.3.2.2, and then we tested (i.e. using a winner-takes-all approach with significantly highest z-score > 3) whether other vertices will be grouped with each vertex. Those vertices that could “win” more than one vertex were marked as seeds.

6.3.3.3.2 Growing regions surrounding the seeds

The second step comprised of growing regions around the seeds. For this purpose, we sorted the seeds in a descending order with the first seed being the “strongest” and created regions in succession following this order.

- Seeds were sorted based on their sensitivity to themselves; i.e. the strongest seed (seed 1) had the highest z-score for itself (section 6.3.3.2.2).
- All vertices that showed sensitivity to seed 1, i.e. produced higher cross-talk in seed 1 than the half maximum of the CTF values of this seed, were clustered together as parcel 1.
- In an iterative procedure, parcel \( n+1 \) was created from the vertices outside all parcel \( i \) with \( i \leq n \), with the same half maximum criterion.
- To obtain an inter-hemispheric symmetry of the parcels, the created parcels of the hemisphere with more winner seeds were mirrored to the opposite hemisphere using MNI coordinates. These created parcels are shown in Figure 6.C 1 in Appendix 6.C.

6.3.3.3.3 Modifying the parcels

The same procedures as those described in 6.3.3.2 (except for the splitting step) were applied to the parcels created by the region-growing (RG) algorithm in order to obtain the final RG parcellation.

6.3.3.4 Theoretical metrics of the parcellation performances

We used PRmat to evaluate the performance of different original and modified parcellations in theory. As explained earlier, the PRmat is computed by finding the normalised CTF values produced by each parcel at the location of all other parcels. If a parcellation consists of fully distinguishable parcels, the PRmat should be an identity matrix. Here we introduce two metrics to evaluate a parcellation’s performance:

- Sensitivity Index \( (S_{\text{ind}}) \) measures the sensitivity of parcels to themselves by taking the mean of the diagonal elements of the PRmat.
\[ S_{\text{ind}} = \frac{1}{N} \sum_{i=1}^{N} PRmat_{ii} \quad (6.3) \]

where \( N \) is the number of parcels in the parcellation. The ideal value would be 1.

- The **Distinguishability Index** \( (D_{\text{ind}}) \) is the correlation between the actual \( PRmat \) and the identity matrix of the same dimensions.

\[ D_{\text{ind}} = \frac{\sum_i \sum_j (PRmat_{ij} - PRmat)(ij - I)}{\sqrt{\sum_i \sum_j (PRmat_{ij} - PRmat)^2} \sqrt{\sum_i \sum_j (ij - I)^2}} \quad (6.4) \]

where \( \bar{\cdot} \) denotes the average of matrix elements and \( I \) is the identity matrix.

Furthermore, we computed the rank and condition numbers of \( PRmat \)s to make comparisons between the original anatomical and modified parcellations. The computed rank of the resolution matrix is far lower than the ideal rank, i.e. the number of vertices. This means that the rows of \( R \), i.e. the CTFs for all vertices, are not linearly independent, and activity in all vertices cannot be estimated independently of each other. Therefore, the condition number of this matrix will be infinity. This is different for \( PRmat \), where the parcels were chosen to minimize overlap of CTFp. A low condition number (especially around the value 1) would indicate that all CTFp are non-overlapping, and that an inversion of \( PRmat \) (e.g. for leakage correction) would be stable.

Hence the number of degrees of freedom is smaller than the number of rows/columns. Considering that \( PRmat \) is scaled between 0 and 1, we computed the rank with a heuristic tolerance of 0.05. It is worth noting that this value is much higher that the numerical precision for rank computation, however, it shows that if similarities between one row of the \( PRmat \) and a linear combination of all other rows are higher than 95%, that row will not be considered as independent from other rows. A high condition number is indicative of an ill-conditioned parcel resolution matrix, i.e. the estimated sources (output) can be very sensitive to small changes in the actual sources (input). A high condition number indicates that if the \( PRmat \) was to be inverted (e.g. to perform leakage correction based on the final \( PRmat \)) the results will be unreliable.

Additionally, for each parcellation we computed the coverage which is the total number of vertices that are included in the parcellation.

### 6.3.4 Simulated connectomes with realistic levels of noise

In this section, we compare the performance of different parcellations for network reconstruction using simulated data with realistic levels of noise. For this purpose, we simulate several hundred realistic datasets in order to evaluate the performance of different anatomical and modified parcellations. To our knowledge, this provides the first comparison of the effect of the choice of various parcellations on the reconstruction of realistically simulated EEG/MEG networks. Our
simulations are based on head models, forward and inverse operators of the 17 subjects described in 6.3.1 and 6.3.2. We use coherence as the measure of connectivity (edge strength) to reconstruct the simulated networks based on each of the anatomical and modified parcellations. Finally, we estimate the significant connections in each network and compare the results to the simulated ground truths. Details of each step are outlined in the next subsections and a flowchart of different steps is depicted in Figure 6.3. All simulations were carried out in python, and where appropriate (e.g. forward and inverse modelling), we used the mne-python software package.

### 6.3.4.1 Network Construction

We simulated a range of networks by varying the number of active seeds (3, 5, 10, 15) in the brain, the percentage of connections among those seeds (25%, 50% and 100%) and SNR of the data (1.0 and 3.0). For each of these cases, 36 random datasets were created in two scenarios: absence of leakage (reference ground truth) and presence of leakage. Additionally, we simulated 36 null networks (i.e. random networks with no significant connectivity patterns) in order to find solely leakage-induced connections for each parcellation. These simulations yielded 1764 datasets overall, each consisting of 17 subjects.

#### 6.3.4.1.1 Location and size of active sources

Each network was initiated by randomly selecting N, seeds on the cortex (fsaverage space). We defined the active seeds by randomly drawing parcels from the cortical areas of the Brainnetome functional atlas of the brain ([Fan et al. 2016](#)) in Appendix 6.B. This approach of defining source locations has two main advantages: a) defining seeds based on a canonical functional atlas provides a realistic representation of size and location of likely functional seeds in the brain; b) the size
Figure 6.3 Flowchart of the simulation pipeline consisting of three main steps of network construction, network reconstruction and network reconstruction accuracy. AN: Active node, BF: Basis function, TPR: True positive rate, FPR: False positive rate, STD: standard deviation.

and locations of seeds are independent of the choice of parcellations that will later be used for network reconstruction. This prevents biases towards any of the parcellation approaches. It is worth
noting that some previous studies have tested their parcellations using sources that corresponded to active parcels in their parcellation (e.g. (Korhonen et al. 2014)) so as to obtain a one-to-one correspondence between active seeds and cortical parcels. However, in comparison between different parcellations with different number and locations of the parcels, which is the case in the current study, that approach would result in a bias in favour of one parcellation or the other.

6.3.4.1.2 Simulated signals and connectivity patterns

$N_s$ sinusoidal signals for 40 epochs (duration 725ms including 125ms baseline) were simulated in randomly selected seed locations. All of the vertices within each active node (AN) were assigned the same signal and the rest of the vertices in the brain were assigned noise. In order to systematically vary connectivity in our simulated networks, we created activation time courses at each AN as a weighted sum of a fixed set of basis functions:

a) For the basis functions (BFs), we first simulated $N_s$ signals, each across 40 epochs. These BFs, for each epoch, were arranged as rows $\mathbf{bf}_i^T$ of a matrix $\mathbf{M}_{BF}$ (size $N_s \times N_t$, $N_t$: number of time samples for each epoch, Equation 6.5), each defined based on a function $f_j(t)$.

b) The frequency of each BF was randomly selected from a list of frequencies obtained by dividing the interval of 10-40Hz into $N_s$ equally-spaced frequencies. The phase of each BF randomly varied across the epochs in order to minimise coherence between each pair of BFs (i.e. ensure orthogonality of BFs).

c) We then computed the activation time courses at each AN ($\mathbf{an}_j^T$, Equation 6.6, defined by functions $g_j(t)$) as a weighted sum of phase-shifted versions of these basis functions. Each AN was given a randomly selected phase ($\varphi_j$, Equation 6.8) which remained constant over epochs. Therefore, if two ANs share the same BFs, there will be significant connectivity between them. Then, signals of all ANs were arranged in a matrix $\mathbf{M}_{AN}$ (size $N_s \times N_t$, $N_t$: number of time samples for each epoch, Equation 6.6), such that:

$$
\mathbf{M}_{BF} = \begin{bmatrix} \mathbf{bf}_1, \mathbf{bf}_2, ..., \mathbf{bf}_{N_s} \end{bmatrix}^T \in \mathbb{R}^{N_s \times N_t} \quad (6.5)
$$

$$
\mathbf{M}_{AN} = \begin{bmatrix} \mathbf{an}_1, \mathbf{an}_2, ..., \mathbf{an}_{N_s} \end{bmatrix}^T \in \mathbb{R}^{N_s \times N_t} \quad (6.6)
$$

$$
A = \begin{bmatrix} a_{ij} \end{bmatrix} \in \mathbb{R}^{N_s \times N_s} \quad (6.7)
$$

$$
g_j(t) = \sum_{i=1}^{N_s} a_{ij} f_i(t - \varphi_j) \quad (6.8)
$$

$\mathbf{M}_{BF}$ is the matrix of BF signals of size $N_s \times N_t$, $\varphi_j$ is the phase shifts for the $j$th AN and $A$ is the desired connectivity matrix:
d) In the Equations 6.7 and 6.8, connectivity among ANs was defined by a binary matrix $A$ which is of size $N_s \times N_s$. Each row corresponds to one AN, and determines the contribution of each BF to its activation time course. Therefore, those BFs that are assigned ones in the row of $A$ that corresponds to each AN will contribute to that specific AN. We imposed the following constraints on matrix $A$:

i. The diagonal elements of $A$ were all set to one, thus, each BF is inherent to one of the ANs. This ensures that all ANs are active (i.e. none is flat or all-noise) even if all the off diagonal elements of a row of $A$ are zeros.

ii. Since we introduced random non-zero phase-shifts between the nodes, the resulting signals will have non-zero-lag connectivity.

iii. For each network scenario, 25%, 50% or 100% of all possible connections among the ANs were set to be non-zero. These included the connections obtained by setting the corresponding elements of $A$ matrix to one and connectivity through connections to a common third source. The latter is taken into account since if, for example, nodes AN$_1$ and AN$_2$ are both connected to AN$_3$ through sharing BF$_3$, the network reconstruction (see section 6.3.4.2 below) will reveal a significant connectivity between AN$_1$ and AN$_2$ even if the corresponding element of $A$ matrix is not set to one. It is worth noting that taking indirect connections into account is not conventional since matrix $A$ fully describes the connectivity patterns of the “constructed networks”. However, indirect connections will become important at the level of “network reconstruction” since our functional connectivity metrics cannot distinguish between direct connections and indirect connections through a third source (multivariate metrics might alleviate this problem but cannot solve it). Thus, if indirect connections are not taken into account when constructing the network, reconstruction of a network with e.g. 10 seeds and 50% of connections might look very similar to the reconstruction of a network with 10 seeds and 100% of connections and hence, comparisons between some percentages of connectivity among seeds becomes trivial. This is more important for higher number of active nodes (e.g. 10 and 15 seeds compared to 3 and 5).

iv. The relative phases of ANs, the elements of A matrix and the frequencies of each BF are selected randomly, hence, the values of coherence among the ANs vary between 0 and 1 depending on the noise level and number of connections, which we assume to be the case for realistic brain networks.
After simulating the sinusoidal signals of the ANs, we added noise to them. Furthermore, we simulated random noise in all the vertices outside the active source locations. These networks were constructed with two levels of SNR: 1.0 and 3.0 in order to explore the effect of noise on the parcellation performances. SNR was defined as the square root of mean square signal (i.e. after 0ms) divided by the standard deviation of noise.

Each network was constructed in two scenarios:

- In the presence of leakage: Sources were simulated in the fsaverage source space, morphed to the single subject source space, projected onto the sensor space using the individual forward models and projected back to the source space using the individual inverse operators (described in 6.3.2). Each vertex time course was extracted from the source component normal to the surface, and the obtained activation maps were morphed back to the fsaverage source space.

- In the absence of leakage (reference ground truth): The simulated sources in the brain were analysed directly, without the application of forward and inverse operators. This will serve as the ground truth against which the performance of parcellations will be compared.

6.3.4.1.3 Null Networks

In addition to the networks elaborated above, we constructed a set of null networks in order to study the performance of parcellations in the absence of true brain connectivity. For this purpose, we simulated noise in every vertex of the fsaverage brain. The simulated signals were morphed to individual head spaces, forward and inverse models were applied to these noise-induced networks in order to obtain leakage-induced networks. And finally, these leakage-induced networks were morphed back to the fsaverage space. Similar to the realistic networks with active nodes, 36 datasets were created from 17 subjects for each of the leakage-induced networks.

6.3.4.2 Network reconstruction

We used Magnitude-Squared Coherence (COH) and imaginary part of Coherency (imCOH) as two measures of connectivity to reconstruct the simulated networks and compare the performance of different parcellation methods for whole-brain network reconstruction. COH and imCOH are spectral measures of connectivity which can detect both amplitude and phase couplings (Greenblatt et al. 2012; Bastos & Schoffelen 2016). COH is sensitive to zero-lag connections while imCOH is not (Nolte et al. 2004; Bastos & Schoffelen 2016). We used imCOH as well as COH in order to evaluate the consequences of the theoretical issue discussed in 6.2.3; i.e., whether EEG/MEG-adaptive
parcellations are useful both for zero- and non-zero-lag connectivity measures. In order to reconstruct each network using these measures:

- We simulated signals in each of the scenarios outlined above which resulted in $N_e \times N_v \times t$ matrix of vertex time courses across epochs where $N_v$ is the number of vertices in the brain, $N_e$ is the number of epochs and $t$ is time. As the first step of reconstruction, we parcellated the fsaverage cortex using each of the anatomical and modified parcellations. Thus, each active node (i.e. each parcel of the Brainnetome atlas) contributes to all the parcels in the anatomical/adaptive parcellations that overlap with that source, depending on the number of spatially overlapping vertices. Therefore, the extracted time course for each parcel will be determined by the signal of the ANs that it overlaps with plus noise vertices inside that parcel.

- Next, we collapsed the matrix of vertex time courses to a matrix of parcel time courses, $TC$, of size $N_e \times N \times t$ where $N$ is the number of parcels, $N_e$ is the number of epochs and $t$ is time. In order to extract the parcel time courses, we used a mean-flipped approach. This approach computes a parcel time course by taking the average of the sign-flipped signals of the vertices within that parcel. The flipping sign is determined based on the source orientation at each vertex within the parcel, with positive indicating outward-flowing currents.

- Thereafter, we computed COH and imCOH on $TC$ and obtained an $N \times N$ connectivity matrix $M_{con}$. COH and imCOH were computed using a multitaper approach with adaptive weights in a broad band frequency of 8-55Hz.

6.3.4.2.1 Lower coverage of the cortex by the modified parcellations

In the steps described above, the “ground truth” of each parcellation is determined based on that specific parcellation in the absence of leakage. However, it is worth noting that, unlike the anatomical parcellations that cover the cortex fully, the modified parcellations provide only a sparse sampling, so it is likely that some of the randomly selected seed locations do not coincide with any of the parcels (Figure 6.B 1) and therefore they will be absent in the “ideal ground truth” as well as realistic scenarios in the presence of leakage. Therefore, we additionally recorded the number of connections in the $A$ matrix that were missed due to no coverage of the corresponding ANs using each of the modified parcellations. This will be taken into account in the computation of true positive rates below.

6.3.4.3 Network reconstruction accuracy

We used statistical analysis in order to evaluate the accuracy of network reconstruction based on each of the parcellations:
• Firstly, for each network, the average value of the absolute values of all connections within that network was used as the baseline and was subtracted from the absolute value of all the elements of the N × N connectivity matrix, $M_{\text{con}}$. Baseline correction was applied in order to obtain connectivity values that are distributed around zero and are suitable for statistical analysis. Therefore, the elements of connectivity matrix that are below average in some subjects and above average in other subjects are likely due to noise while the connectivity values that are consistently above average are unlikely to be merely due to the noise. Furthermore, the absolute values (relevant for ImCOH) were used because, regardless of the sign of connectivity between two areas, the strength of connections is important for evaluation of statistical significance. It is worth noting that the choice of threshold is often arbitrary and should ideally be tested for a range of different values (Rubinov & Sporns 2010b). However, in this study, since we are using average thresholds for both reconstructed networks (i.e. in the presence and absence of leakage (ground truth)) in order to make comparisons between the two, testing various thresholds is not strictly required. Furthermore, since the same procedure is applied to both adaptive and anatomical parcellations, we expect no bias in favour of any of the parcellations due to the thresholding.

• For each ground truth network in the absence of leakage, significant connections were identified using one-tailed permutation tests (i.e. only connections that are significantly higher than the baseline are of interest), which included correction for multiple comparisons across connections. These calculations yielded “true significant connectivity” among the parcels in each parcellation.

• Baseline correction and permutation tests were also applied to each realistic network, and then compared against the true connectivity matrix, with two groups of connections identified:
  o True positives: Significant connections that were identified accurately in the realistic networks divided by the overall number of true connections. Note that we included the number of missed connections due to no coverage of some ANs by the modified parcellations (see 6.3.4.2.1) in calculation of true connections.
  o False positives: non-existent connections in the ideal scenario that were incorrectly marked as significant in the realistic networks divided by the overall number of zero connections in the ground truth.
These metrics were computed for each random dataset and averaged across 36 iterations. All of the evaluation steps were applied to the results of connectivity from both COH and imCOH.

6.4 Results

6.4.1 Parcellation results

6.4.1.1 Split-and-Merge algorithm (SaM)

We tested the split-and-merge (SaM) algorithm (section 6.3.3.2) on two standard anatomical parcellations in Freesurfer: Desikan-Killiany and Destrieux Atlases that are shown in Figure 6.4a, c with the corresponding Parcel Resolution Matrices (PRmat: relative between-parcel leakage values, see 6.3.3.1) shown in Figure 6.4b, d, respectively.

6.4.1.1.1 Desikan-Killiany Atlas

The original Desikan-Killiany Atlas included 68 parcels with sensitivity index $S_{\text{ind}}$ of 0.47 (i.e. the leakage value that each parcel received from itself relative to the rest of the parcels in the brain) and distinguishability $D_{\text{ind}}$ of 0.50 (i.e. correlation between the PRmat and an ideal identity matrix) (Table 6.1). The SaM algorithm resulted in 316 parcels at the intermediate step (Figure 6.C 1a, b; Appendix 6.C), from which 74 regions survived to the final parcellation that is shown in Figure 6.5a together with the corresponding PRmat. Compared to the original parcellation, $S_{\text{ind}}$ and $D_{\text{ind}}$ increased by 38% and 22% and reached 0.65 and 0.61 respectively (Table 6.1) and provided a sparser sampling of the cortex including 4079 vertices.

6.4.1.1.2 Destrieux Atlas

The original Destrieux Atlas consists of 148 parcels and is shown in Figure 6.4c with PRmat in Figure 6.4d. In comparison to the Desikan-Killiany parcellation, the PRmat of this parcellation shows less similarity with an identity matrix, indicating a more blurred estimation of activity for each of the parcels (Table 6.1). This difference suggests that the original Desikan-Killiany is a better match to the EEG/MEG spatial resolution than Destrieux. $S_{\text{ind}}$ and $D_{\text{ind}}$ of Destrieux Atlas were 0.37 and 0.38, respectively, and improved to 0.7 and 0.65 for the 74 parcels that survived the parcellation modification, providing an 89% and 71% improvement in these indices, respectively. The parcellation covered 3084 vertices of the cortical surface. The intermediate and final parcellation/PRmat for the modified Destrieux Atlas are shown in Figure 6.C 1c, d and Figure 6.5b respectively. Comparison to Figure 6.4d, as reflected in increased $S_{\text{ind}}$ and $D_{\text{ind}}$ values above, shows a clear improvement. Note that in Figure 6.5b, parcels that showed maximum overlap with each of the modified parcels from the Desikan-Killiany are colour-matched to Figure 6.5a for visual comparison.
Despite having twice the number of initial parcels, the SaM algorithm converged at 74 parcels for both atlases. This can be considered as an indicator of the robustness of the parcellation algorithms against the initial choice of parcellation.

Table 6.1 A summary of the performance of the original and modified parcellations in theory.

<table>
<thead>
<tr>
<th>Parcellation</th>
<th>No. of parcels</th>
<th>PRmat Rank</th>
<th>PRmat CN</th>
<th>$D_{\text{ind}}$</th>
<th>$S_{\text{ind}}$</th>
<th>Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desikan-Killiany Atlas</td>
<td>68</td>
<td>49</td>
<td>1.26x10^3</td>
<td>0.50</td>
<td>0.47</td>
<td>18742</td>
</tr>
<tr>
<td>Destrieux Atlas</td>
<td>148</td>
<td>92</td>
<td>1.78x10^4</td>
<td>0.38</td>
<td>0.37</td>
<td>18742</td>
</tr>
<tr>
<td>Split-and-Merge DKA</td>
<td>74</td>
<td>73</td>
<td>114.38</td>
<td>0.61</td>
<td>0.65</td>
<td>4079</td>
</tr>
<tr>
<td>Split-and-Merge DA</td>
<td>74</td>
<td>74</td>
<td>70.82</td>
<td>0.65</td>
<td>0.70</td>
<td>3084</td>
</tr>
<tr>
<td>Region Growing</td>
<td>70</td>
<td>70</td>
<td>91.59</td>
<td>0.64</td>
<td>0.70</td>
<td>3086</td>
</tr>
</tbody>
</table>

$D_{\text{ind}}$: Distinguishability index, $S_{\text{ind}}$: Sensitivity index, PRmat: Parcel Resolution Matrix, CN: Condition number

6.4.1.2 Region Growing algorithm (RG)

The Region Growing Algorithm does not require an anatomical parcellation as a starting point, but creates a parcellation based on the resolution properties of all the vertices. The first step of RG algorithm identified 174 seed vertices (Figure 6.4 a) in the left hemisphere and parcels were grown surrounding each of these seeds using the criteria described in section 6.3.3.3. The split and merge criteria were applied to these created parcels and resulted in a 70-parcel parcellation with $S_{\text{ind}}$ of 0.7, $D_{\text{ind}}$ of 0.64 and a sparse sampling of the whole cortex, covering 3086 out of 20484 vertices in the brain.
The final parcellation showed notable similarities and differences to the parcellation modification of the anatomical atlases (Figure 6.5c). A direct comparison of the overlaps and differences of the final parcellations are conducted in section 6.4.2.

These results demonstrate that our algorithms improve sensitivity and specificity of the original anatomical parcellations. In the following sections, we will analyse features of our algorithms in more detail.
6.4.2 Effect of initial choice of parcellation

As can be seen in Figure 6.5, some of the final parcels, particularly in the occipital, temporal and frontal lobes show overlaps across the three parcellations, while other regions in the central and parietal lobes can vary notably. All final parcellations in Figure 6.5 are colour-matched to the first parcellation (modified Desikan-Killiany parcellation). To obtain a more direct comparison between the parcels, we computed the overlaps, normalised by the sizes of parcels (Figure 6.6). More specifically, we took the modified Desikan-Killiany parcellation as the reference and found the overlaps between the colour-matched parcels in Figure 6.5. Rows of the matrices in Figure 6.6 illustrate the overlaps between each of the parcels of the parcellation on the y-axis (Py) with all the parcels of the parcellation on the x-axis (Px: always modified Desikan-Killiany), which is normalised by the size of that parcel of Py. Therefore, if there is only one column corresponding to each row, it shows a one-to-one correspondence between the two intersecting parcels while several columns intersecting with each row show that one parcel in Py is overlapping with several regions in Px. If one row consists of only dark colours, that parcel in Py is not overlapping with any parcel in Px. As can be seen in Figure 6.6, we found that a majority of parcels show a one-to-one correspondence between the final parcellations, with different degrees of overlaps. However, there are also several cases where a parcel in one parcellation overlaps with a few parcels or cases where a parcel does not have any matches in another parcellation.

Figure 6.6 Normalised overlaps between the parcels obtained from different parcellation algorithms. Modified Desikan-Killiany parcellation is shown on the x-axis and is used as the reference, (the order of parcels on the x-axis corresponds to Figure 6.5a). Y-axis represents the parcels in a) modified Destrieux and b) RG parcellations. The rows correspond to the colour-matched regions of the x-axis and therefore the order is arbitrary in comparison to Figure 6.5b, c. The sums of the normalised overlaps in each row are also shown as the first column.
6.4.3 Rank and condition number of final PRmats and implications

Here we compared the rank and condition numbers of PRmats for the original and modified parcellations. The resolution matrix, as expected, was highly ill-conditioned and while the ideal rank was 20484 in our study, the calculated rank was only 118. Parcellations (anatomical or modified) downsampled the source space to a few hundred parcels and thus improved the rank. We found a rank of 49 (ideal 68) and 92 (ideal 146) for the Desikan-Killiany and Destrieux atlases respectively, which, in spite of showing an improvement compared to the original source space, are still not full-ranked. In contrast, the modified parcellations showed near-perfect performance where we found ranks of 73 (ideal 74), 74 (ideal 74) and 70 (ideal 70) for the modified Desikan-Killiany, Destrieux and RG parcellations respectively. Even though full-ranked matrix guarantees independence between the parcel signals in the modified parcellations, the output might still be very sensitive to small changes in the input; hence a small condition number is desired. The condition numbers for the Desikan-Killiany and Destrieux atlases were $1.26 \times 10^3$ and $1.78 \times 10^4$ which were significantly improved to 114.38, 70.82 and 91.59 for the modified Desikan-Killiany, Destrieux and RG parcellations respectively. However, it is worth noting that condition numbers around 100 in the modified parcellations are still high and invite other complementary approaches to be used together with the EEG/MEG-adaptive parcellations.

6.4.4 Simulation results

In this section, we investigated the performance of anatomical and modified parcellations for realistic simulations of source networks where the ground truth is known, in order to address the following questions:

1- If there is no significant connectivity among the brain areas, how likely are different parcellations to identify significant false connections? These potential false connections will be merely leakage-induced and can act as a measure of susceptibility of each parcellation to leakage.

2- If networks with random active node (AN) locations and connections are simulated in the brain and different parcellations are used to reconstruct those networks, what is the accuracy of network reconstruction for each of the anatomical and modified parcellations?

3- Non-zero-lag connectivity measures such as imaginary part of coherency are insensitive to zero-lag connections. Leakage-induced connections are zero-lag. Does utilisation of non-zero-lag measures obviate the need for modified parcellations?
6.4.4.1 Question 1: null networks

In order to compare different parcellations in the absence of true connectivity, we evaluated the null networks described in section 6.3.4.1.3. These networks include no active nodes and every vertex in the brain is given a random signal. Therefore, after network reconstruction and statistical analysis of the connectivity patterns, any significant connection is a false positive. It is worth noting that the False Positive Rate (FPR) of the simulated networks will have two underlying causes: 1- spurious connections due to leakage and 2- Type I error of statistical testing. The latter is corrected for multiple comparisons using permutation tests and is approximately 0.0001 (corresponding to 10000 permutations and uncorrected p-value of 0.05 (North et al. 2002)), for each simulated network, hence can be considered as a target FPR in the absence of leakage. Considering that this value is negligible compared to the observed FPR (Figure 6.7), the main observed FPR for the null networks can be attributed to the leakage. Results are shown in Figure 6.7. We computed the FPR for each null network by dividing the number of significant leakage-induced connections by the number of all possible connections for that network and computed the average FPR across 36 simulated datasets. The FPRs for Desikan-Killiany (DKA) and Destrieux (DA) atlases were 0.101 (231 out of 2278 possible connections for 68 parcels in DKA) and 0.081 (885 out of 10878 connections for 148 parcels in DA), respectively. The FPRs were reduced to 0.038 (101 out of 2701 possible connections for 74 parcels), 0.031 (85 out of 2701 connections) and 0.024 (60 out of 2415 connections for 70 parcels) for modified DKA, modified DA and RG respectively. Therefore, the modified parcellations’ FPRs were about one third of those of the anatomical parcellations.

![Figure 6.7](image-url) a) Significant connections of the null networks for the anatomical and modified parcellations (corrected for multiple comparisons). The ratios of the leakage-induced connections (false positives) to all
possible connections were found to be 0.101 and 0.081 in DKA and DA atlases that were reduced to 0.038, 0.031 and 0.024 in the modified DKA, modified DA and RG parcellations, respectively. Node colours correspond to the node colours in Figure 6.4 and Figure 6.5; b) Variations of FPRs for null networks of each parcellation across 36 simulated datasets (boxplots mark median (red lines), standard deviations (in blue), confidence interval (in black) and outliers (red cross).

6.4.4.2 Question 2: realistic networks with active nodes

We simulated hundreds of realistic datasets with varying numbers of ANs (3, 5, 10, 15), percentage of connections among ANs (25%, 50% and 100%) and SNR of the data (1.0 and 3.0). For each of these scenarios, 36 datasets each consisting of 17 subjects were simulated where the locations of ANs and connections randomly varied across datasets. ANs were random parcels selected from Brainnetome functional atlas (Fan et al. 2016, Figure 6.B 1, Appendix 6.B). Thereafter, we used bivariate coherence for network reconstruction and identified significant connections of each network across subjects using permutation tests. Significant connections of one example network with 5 ANs and 100% connections among the ANs is shown in Figure 6.8. It is worth noting, since the ANs are based on the Brainnetome atlas, each AN might show spatial overlap with several nodes in each parcellation and therefore the number of active parcels found in any simulated network might be higher than the number of ANs. Furthermore, some of the ANs did not overlap with any of the modified parcels due to the lower coverage of the cortex by these adaptive parcellations (Figure 6.B 1). Table 6.2 presents the average number of missed ANs and average number of parcels per AN for each parcellation. Approximately 20-30% of connections were missed due to no coverage by modified parcellations and average parcel per AN for anatomical parcellations was approximately two times that of modified parcellations.
Figure 6.8 Significant connections for an example network with 5 active seeds. The first row shows the ground truth in the absence of leakage, the second and third rows show the network in the presence of leakage under SNRs 3.0 and 1.0, respectively. Networks are reconstructed using coherence. Node colours correspond to the node colours in Figure 6.4 and Figure 6.5.

Table 6.2 Average ratios of missed nodes (no overlap between an AN from Brainnetome atlas and parcels of a parcellation), missed connections due to the missed nodes and parcels per AN across all the simulated scenarios with different numbers of ANs and connections. DKA: Desikan-Killiany Atlas, DA: Destrieux Atlas, RG: Region Growing, AN: Active Node.

<table>
<thead>
<tr>
<th></th>
<th>DKA</th>
<th>Mod DKA</th>
<th>DA</th>
<th>Mod DA</th>
<th>RG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missed Nodes</td>
<td>0</td>
<td>0.19</td>
<td>0</td>
<td>0.26</td>
<td>0.28</td>
</tr>
<tr>
<td>Missed Connections</td>
<td>0</td>
<td>0.19</td>
<td>0</td>
<td>0.26</td>
<td>0.30</td>
</tr>
<tr>
<td>Parcels per AN</td>
<td>2.91</td>
<td>1.63</td>
<td>3.87</td>
<td>1.4</td>
<td>1.41</td>
</tr>
</tbody>
</table>

Here, we compared parcellation-specific ground truths (e.g. first row in Figure 6.8) in the absence of leakage to the realistic networks in the presence of leakage. Figure 6.9 summarises the proportions of true positive (TPR) and false positive rates (FPR) for each of the parcellations and in each of the simulated scenarios. Note that since the modified parcellations in Figure 6.5 do not cover some of the functional seeds of the Brainnetome Atlas (Figure 6.B 1) and the locations of active seeds are selected randomly, some seeds are missing in both ground truth and realistic scenarios of the adaptive parcellations. We identified the missing seeds and the corresponding connections for each modified parcellations using the procedure described in 6.3.4.2.1 and included them in the computation of TPRs. Thus, a parcellation that covers the AN in the Brainnetome atlas may have a chance to recover it, which would contribute to its TPR. However, if it mis-localises activity from this
AN or is insensitive to it, it will count towards the FPR or reduce TPRs. For a parcellation that does not cover the AN at all, it will automatically contribute to (reduction of) TPR. Table 6.3 presents the details of statistical comparisons between average TPRs and FPRs of each pair of parcellations across different numbers of seeds and connections. The p-values in this table are obtained using Kruskal-Wallis test in order to account for the potential non-normalities in the distributions of the variables.

Figure 6.9 True positive and false positive rates of coherence analysis of networks based on the anatomical and modified parcellations at SNRs 1.0 and 3.0. The reference for each parcellation is the reconstructed network in the absence of leakage. TPRs (left) and FPRs (right) are obtained by comparing each reconstructed network in the presence of leakage to the reference network for the same parcellation. COH: Coherence, SNR: Signal-to-noise ratio, DKA: Desikan-Killiany atlas, DA: Destrieux atlas, mod: modified, RG: Region Growing.

TPR: As shown in Figure 6.9, anatomical and modified parcellations showed comparable TPRs that were reduced as the number of seeds/connections increased. At SNR 3.0 and for the anatomical parcellations, starting from ~0.7 true positives for 3 seeds, TPRs were reduced to ~0.5 for 5 seeds, and then dropped sharply to 0.3 or less for 10 and 15 seeds. We found a similar trend for the modified parcellations, except that on average, modified DKA showed significantly higher TPRs than anatomical parcellations (refer to Table 6.3 for details). We found no significant improvements for the TPRs of modified DA and RG compare to anatomical parcellations. At SNR 1, we found a similar trend, but not surprisingly (as elaborated in Table 6.3), the TPRs at SNR 1 where on average lower than SNR 3, for
both anatomical and modified parcellations. Furthermore, as shown in Figure 6.9, the gap between TPRs of anatomical and modified was larger for SNR 1 compared to SNR 3.0 and both modified DKA and DA showed significantly higher TPR compared to anatomical parcellations.

**FPRs:** Even though TPRs were improved for some of the modified parcellations, we observed the main improvements in the FPRs. Anatomical parcellations showed substantially lower specificity compared to all the modified parcellations, by a factor of 2 or more (Table 6.3). We found that anatomical DKA showed significantly higher FPRs compared to anatomical DA and modified DKA showed significantly higher FPR compared to modified DA and RG. Moreover, we found that for 5, 10 and 15 seeds, FPR peaked when 100% of connections among seeds were present, suggesting that fuller networks might be more affected by leakage-induced false positives. At SNR 1, we found very similar trends as SNR 3 for both anatomical and modified parcellations. FPR was reduced at SNR 1, probably because low SNR results in larger variability and generally decreased detection of connections.

Therefore, we observed a substantial improvement in the FPRs and some improvement in the TPRs in comparison of modified and anatomical parcellations. It is worth noting that since modified parcellations do not cover some of the functional seeds of the Brainnetome Atlas (Figure 6.B 1), two separate factors influence TPRs: 1- missing seeds; 2- sensitivity score for the areas that are covered by the modified parcellations. In order to tease these two factors apart and focus on number 2, we also computed TPRs without taking the missing sources into account. This was done by comparing each network in the presence and absence of leakage (e.g. first vs. second rows of Figure 6.8). Results are shown in Figure 6.B 2 and Table 6.B 1 in Appendix 6.B. These results are informative since they show sensitivity in the areas that are covered by each parcellation (Figure 6.B 1) and additionally correspond to the parcellation performance indices provided by the PRmat that are also based on the “covered parcels” only.

<table>
<thead>
<tr>
<th></th>
<th>True Positives</th>
<th>False Positives</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coherence SNR 3</td>
<td>Coherence SNR 3</td>
</tr>
<tr>
<td></td>
<td>mean±std</td>
<td>mean±std</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>p-value</td>
</tr>
<tr>
<td></td>
<td>DKA  DA Mod DKA Mod DA RG</td>
<td>DKA  DA Mod DKA Mod DA RG</td>
</tr>
<tr>
<td>DKA</td>
<td>0.41±0.06</td>
<td>0.15±0.011</td>
</tr>
<tr>
<td></td>
<td>NA  0.21  0.002  0.87  0.07</td>
<td>NA  1.7×10⁻¹²  2.9×10⁻¹³  2.9×10⁻¹³  2.9×10⁻¹³</td>
</tr>
<tr>
<td>DA</td>
<td>0.42±0.04</td>
<td>0.12±0.01</td>
</tr>
<tr>
<td></td>
<td>0.21  NA  0.027  0.40  0.002</td>
<td>1.7×10⁻¹²  NA  2.9×10⁻¹³  2.9×10⁻¹³  2.9×10⁻¹³</td>
</tr>
<tr>
<td>Mod DKA</td>
<td>0.45±0.15</td>
<td>0.08±0.006</td>
</tr>
<tr>
<td></td>
<td>0.02  0.027  NA  0.006  1.2×10⁻⁵</td>
<td>2.9×10⁻¹³  2.9×10⁻¹³  NA  6.3×10⁻⁶  9.6×10⁻⁷</td>
</tr>
<tr>
<td>Mod DA</td>
<td>0.41±0.07</td>
<td>0.07±0.007</td>
</tr>
<tr>
<td></td>
<td>0.87  0.40  0.006  NA  0.07</td>
<td>2.9×10⁻¹³  2.9×10⁻¹³  6.3×10⁻⁶  NA  0.67</td>
</tr>
<tr>
<td>RG</td>
<td>0.38±0.16</td>
<td>0.07±0.006</td>
</tr>
<tr>
<td></td>
<td>0.07  0.002  1.2×10⁻⁹  0.07  NA</td>
<td>2.9×10⁻¹³  2.9×10⁻¹³  9.6×10⁻⁷  0.67  NA</td>
</tr>
<tr>
<td></td>
<td>Coherence SNR 1</td>
<td>Coherence SNR 1</td>
</tr>
<tr>
<td></td>
<td>mean±std</td>
<td>mean±std</td>
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<tr>
<td></td>
<td>p-value</td>
<td>p-value</td>
</tr>
<tr>
<td></td>
<td>DKA  DA Mod DKA Mod DA RG</td>
<td>DKA  DA Mod DKA Mod DA RG</td>
</tr>
<tr>
<td>DKA</td>
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<td>0.10±0.008</td>
</tr>
<tr>
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<td>0.08±0.008</td>
</tr>
<tr>
<td></td>
<td>0.26  NA  2.6×10⁻⁶  0.015  0.87</td>
<td>4.1×10⁻¹⁰  NA  4.1×10⁻¹³  2.9×10⁻¹³  2.9×10⁻¹³</td>
</tr>
<tr>
<td>Mod DKA</td>
<td>0.41±0.05</td>
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<tr>
<td></td>
<td>1.4×10⁻⁹  2.6×10⁻⁶  NA  0.002  7.0×10⁻⁴</td>
<td>2.9×10⁻¹³  4.1×10⁻¹³  NA  2.0×10⁻⁶  8.5×10⁻⁵</td>
</tr>
<tr>
<td>Mod DA</td>
<td>0.36±0.07</td>
<td>0.05±0.006</td>
</tr>
<tr>
<td></td>
<td>0.001  0.015  0.002  NA  0.11</td>
<td>2.9×10⁻¹³  2.9×10⁻¹³  2.0×10⁻⁶  NA  0.23</td>
</tr>
<tr>
<td>RG</td>
<td>0.34±0.07</td>
<td>0.05±0.006</td>
</tr>
<tr>
<td></td>
<td>0.21  0.87  7.0×10⁻⁶  0.11  NA</td>
<td>2.9×10⁻¹³  2.9×10⁻¹³  8.5×10⁻⁵  0.23  NA</td>
</tr>
</tbody>
</table>

6.4.4.3 Question 3: imaginary part of Coherency

In this section, we investigated whether or not non-zero-lag connectivity measures such as imaginary part of coherency will also benefit from E/MEG-informed parcellation modifications. Figure 6.10 displays the TPRs and FPRs for the ImCOH (similar to Figure 6.9 for Coherence). We found TPR and FPR patterns that resembled the Coherence results. FPRs were generally higher for the anatomical compared to the modified parcellations. TPRs did not differ between the anatomical and modified parcellations. Therefore, modified parcellations also improve the ImCOH results. Both TPRs and FPRs were lower for ImCOH compared to COH. Lower TPR is presumably due to the fact that true zero-lag connections were not detectable using ImCOH, and ImCOH also attenuates near-zero-lag connections. Additionally, lower TPRs and FPRs might be attributed to the fact that ImCOH ignores the real part of the signal and thus yields smaller connectivity values that are more likely to become obscured by the presence of noise in the data.
Discussion

We used cross-talk functions (CTFs), which describe the spatial resolution of linear or linearly constrained distributed source models, to create EEG/MEG-adaptive parcellations of the cortex as a basis for connectivity analysis of EEG/MEG data in source space. We implemented two CTF-based algorithms – split-and-merge (SaM) and region growing (RG) – which differed with respect to the starting points of the parcellation process. For SaM, we started from two different standard anatomical parcellations with different average sizes of parcels (Desikan-Killiany (Desikan et al. 2006) and Destrieux (Destrieux et al. 2010) Atlases) and modified the parcels so as to comply with the spatial resolution of EEG/MEG. For RG, we started with no prior parcellation and created a parcellation from all the brain vertices. We used metrics for distinguishability and sensitivity based on parcel resolution matrices (PRmat) to quantify the performance of different parcellations, using a dataset consisting of combined EEG and MEG measurements. All three analyses yielded approximately 70 distinguishable parcels in the brain, suggesting that this reflects the general resolution limits of the utilised measurement configuration and source estimation methods. All approaches provided a sparse sampling of the cortex, and significantly improved the parcellation performance compared to the
anatomical parcellations with respect to sensitivity and distinguishability of parcels, while at the same time maximising the number of distinguishable parcels in the brain.

Furthermore, using extensive realistic simulations, we showed that: a) when there are no true connections among the brain areas, the ratio of false leakage-induced connections detected by the modified parcellations were improved by a factor of two or more compared to the anatomical parcellations; b) in the presence of active sources and connections, adaptive parcellations showed comparable sensitivity (in spite of lower coverage of the cortex) and substantially higher specificity (up to improvement factor of 2); and c) modified parcellations improved the network reconstruction accuracy using both zero-lag and non-zero-lag connectivity measures.

6.5.1 Adaptive parcellations for the spatial limitations of EEG/MEG

EEG/MEG studies typically adopt anatomical or fMRI-based functional parcellations. For example, Hillebrand et al. (2012) used the Talairach Daemon Database for the parcellation of the brain, Colclough et al. (2015, 2016) used the Harvard-Oxford anatomical parcellation and ICA-based fMRI parcellation, while several other studies have used the Automatic Anatomical Labelling (AAL) atlas (Brookes et al. 2016; Tewarie et al. 2014, 2016). Nevertheless, as described in the theory section, anatomical parcels are unlikely to be optimal for EEG/MEG analysis. Therefore, in the current study we introduced EEG/MEG-adaptive parcellations. For this purpose, we used a state-of-the-art measurement configuration containing EEG and MEG sensors, realistic individual boundary element (BEM) models (Fuchs et al. 2002) and L2 minimum norm (MNE) source estimation that makes minimal assumptions about the source configuration (Hämäläinen & Ilmoniemi. 1994; Hauk 2004) and introduced novel approaches for parcellating the cortex.

The parcellation algorithms implemented here are adaptive and can change depending on the choices of EEG/MEG measurement configuration, head model and source estimation methods. Therefore, since it has been shown previously that combining EEG and MEG provides higher spatial resolution (Fuchs et al. 1998; Henson et al. 2009; Molins et al. 2008), it can be expected that EEG or MEG on their own will result in a smaller number of surviving parcels and/or coverage of the cortex than for their combination. Moreover, we have used a common BEM model in our forward computations (Hämäläinen & Sarvas 1989; Mosher et al. 1999). It can be expected that using other multi-layer headmodels or Finite Element Models (FEMs) (Buchner et al. 1997) may also change the parcellations. Furthermore, different source estimation methods will result in different CTFs. It is important to note that all CTFs, regardless of the linear inverse methods used, are linear combinations of the leadfields. Thus, CTFs that are not in the space of the leadfields cannot be achieved by any method. In this study, we used L2 MNE that results from the minimisation of the difference between
the resolution matrix and the identity matrix (Dale & Sereno 1993; Hauk 2004) and yields an optimum source localisation when no further specific modelling constraints are applicable. However, it is worth noting that a bias towards superficial sources is often associated with L2 MNE which might have resulted in the exclusion of deeper brain areas in the adaptive parcellations. Nevertheless, in studies where other constraints are justified, e.g. when other families of spatial filters such as beamformers (Barnes et al. 2006; Van Veen et al. 1997) or weighted MNE are used, different parcellations of the cortex and possibly more coverage of deeper brain areas can be expected. It is also worth noting that in the current study with unweighted L2 MNE source localisation which depends on the data only through regularisation by the noise covariance matrix, the final number of parcels in a parcellation is relatively independent of the degrees of freedom in the data. However, the final number of parcels would be expected to have stronger data-dependence if e.g. beamformers were used.

### 6.5.2 Different parcellation approaches: similarities and differences

Our proposed parcellation algorithms addressed the three theoretical issues of using anatomical parcels with EEG/MEG that were discussed in the Theory section (Figure 6.1). Firstly, adaptive parcellations identified and omitted vertices that our source estimation methods provided a low sensitivity to. More specifically, we found a limited sensitivity to the signals that are produced in deeper brain areas. All three parcellations (Figure 6.5) showed almost no coverage of the medial view of the cortex indicating the relative insensitivity of our source estimation to these deeper brain cortices. It is worth noting that while the locations of the cortices with low sensitivity might change depending on measurement configuration and source localisation, our results suggest that the proposed algorithms can identify those vertices successfully. Secondly, the specificity of the anatomical parcellations did not match that of the EEG/MEG parcellations: On the one hand, some fine-grained neighbouring areas were not distinguishable. For example, the four areas pars-triangularis, pars-orbitalis, pars-opercularis and lateral orbitofrontal cortex from the Desikan-Killiany atlas (Figure 6.4a) were merged into two areas in the anterior and posterior inferior frontal gyrus in the modified version of this atlas (Figure 6.5a). On the other hand, large parcels such as pre- and post-central gyri were split into smaller parcels (e.g. compare Figure 6.4a and Figure 6.C 1a).

The two SaM and RG approaches showed highly overlapping final parcels for all three final parcellations, which indicates the robustness of the proposed algorithms with respect to the initial choice of parcellation. This indicates that the final parcellation of the cortex is mostly influenced by the choices of measurement configuration, head model and source estimation method. However, as shown in section 6.4.2, we observed notable differences as well, in that not all the parcellations provide a similar sparse sampling of all the brain areas. For example, as can be seen in Figure 6.5, while
the final RG parcellation includes several parcels in the temporal lobe, the modified Destrieux parcellation provides a better coverage of centro-parietal cortices. Furthermore, as shown using simulated networks and as a result of different samplings of the cortex, modified parcellations provided different sensitivity and specificity of network reconstructions. More generally, the SaM approach is based on anatomically defined regions and thus provides a better solution for optimising the number of a priori selected parcels or testing specific hypotheses. In contrast, the RG approach is most distinct from anatomical labels and limitations that they could impose on detection of functional networks. Therefore, it might be more desirable for data-driven whole brain connectivity analyses, e.g. for resting state networks.

6.5.3 Effect of parcellations on reconstruction of realistic networks

Our simulations were set up to investigate the effects of different parcellations on the accuracy of network reconstructions in several scenarios by varying the number and locations of active sources in the brain, percentage of connections among those sources as well as SNR of the data. Active sources were defined by randomly selecting functional parcels from the Brainnetome atlas (Fan et al. 2016) so as to obtain a realistic representation of the size and locations of functional nodes in the brain. We found that adaptive parcellations show up to three times less false leakage-induced connections among the parcels. This was found by investigation of a) null networks with realistic levels of noise and no active sources as well as b) realistic networks with multiple active sources. Furthermore, we observed improvements in detection of true connectivity among the sources. This was interestingly in spite of the fact that approximately 20% of connections were missed by the modified parcellations since the corresponding seeds of the Brainnetome atlas were not covered by the modified parcellations and thus the maximum true positive rates that could have been achieved using adaptive parcellations were approximately 0.8. Even so, the overall true positives detected by the modified parcellations were at a same level or higher than the anatomical parcellations. This was particularly evident for lower SNR (SNR 1.0 compared to 3.0), suggesting that optimal parcellation is more crucial in the presence of higher levels of noise. Therefore, our investigation of sensitivity and specificity depict that if the spatial resolution of EEG/MEG and source localisation methods do not allow for inclusion of some the brain cortices, including them in the model will reduce the specificity substantially while it does not allow for improvements in sensitivity.

Comparing the performance of different adaptive parcellations, we found that modified DKA showed higher sensitivity compared to modified DA and RG while modified DA and RG showed higher specificity. Modified DKA is based on the Desikan-Killiany atlas which includes 68 parcels that is of the same order as the final adaptive parcellations. In other words, it can be considered a good starting
point for initiation of the parcellation algorithms. Therefore, the modification procedure resulted in fewer changes in this parcellation and higher overall coverage compared to modified DA and RG. In contrast, modified DA and RG yielded the most distinct parcels in the brain and higher specificity at the expense of less coverage. Therefore, even though as discussed in section 6.5.2 different parcellations provided highly overlapping results, differences in network reconstructions suggest that depending on the purpose of a study and locations of the networks of interest, one initial point and/or algorithm might prove more useful.

Another finding involved the trend of changes in the sensitivity and specificity as a function of changes in the number of simulated active sources/connections in the brain. The sensitivity for all anatomical and adaptive parcellations decreased with increases in the number of active sources/connections in the brain. In particular, we observed a sharp change from 5 seeds to 10 seeds. This shows that the accuracy of network detection drops substantially for widespread or highly dense networks. However, it is worth mentioning that the number of seeds is not equal to the number of active parcels since the seeds are derived from the Brainnetome atlas and parcels of this atlas might overlap with several parcels in the parcellations. As a matter of fact, 10 active seeds might actually correspond to 20 active parcels or more. On the other hand, the false positives showed a trend that was similar among different parcellations. Unlike true positive rates, FPRs were fluctuating more depending on the percentage of connections among the seeds rather than the number of active nodes. For example, keeping 100% of connections resulted in higher FPRs compared to 25% of connections for any number of seeds, suggesting that fuller networks are more prone to the leakage problem.

6.5.4 Non-zero-lag connectivity does not obviate the need for EEG/MEG-adaptive parcellation

Non-zero-lag connectivity measures have been introduced to alleviate the leakage problem (Nolte et al. 2004; Stam et al. 2007). We investigated whether using non-zero-lag connectivity can resolve the need for an adaptive parcellation for whole-brain network analysis. We used magnitude-squared coherence (COH) and imaginary part of coherence (imCOH) as spectral measures of synchrony (Bastos & Schoffelen 2016; Greenblatt et al. 2012). While COH is sensitive to zero- as well as non-zero-lag connections, imCOH is only sensitive to the latter. We argued (section 6.2.3) that even bivariate and multivariate non-zero-lag connectivity measures are affected by leakage. Furthermore, we showed that long-range spurious connections between a seed and a target can occur due to leakage to the target (i.e. inherited connectivity (Colclough et al. 2015)). By means of realistic simulations we found that ImCOH: a) resulted in fewer false positives as expected but did not resolve the FPR problem.
In fact, FPRs obtained from imCOH for anatomical parcellations were comparable to FPRs obtained from COH using adaptive parcellations; b) showed substantially lower FPRs for modified compared to anatomical parcellations and c) showed notably less TPRs for both anatomical and modified parcellations. The latter can be attributed to the fact that imCOH does not detect true zero-lag connections and attenuates near-zero-lag connections. Additionally, lower TPRs and FPRs might be attributed to the fact that imCOH ignores the real part of the signal and thus yields smaller connectivity values that are more likely to become obscured by the presence of noise in the data. Therefore, it appears that using imCOH with anatomical parcellations can reduce false positives at the expense of lowering true positives while utilising COH with adaptive parcellations can result in comparable reductions in FPRs without compromising the TPRs. Additionally, if having low FPRs is of main interest in a study, or zero-lag connections are assumed unlikely or irrelevant in a dataset, combining imCOH with adaptive parcellations can result in a high suppression of FPRs.
Appendix 6.A  Effect of leakage on multivariate connectivity

We can generalise the bivariate (two-ROI) example discussed in section 6.2.3 to multivariate methods for estimating the unique (partial) covariance between pairs of ROIs in a network of connections between three or more ROIs. In Figure 6.1d, consider a seed in the RMF (region Y), a target in the MTG (region Z) and a new region X within the leakage realm of MTG. Let us assume that the true source in Z co-varies with Y, but true connectivity between X and Y is zero. Let us further assume, for the sake of simplicity, that the whole network only consists of these three regions and Y does not receive/send leakage from/to any other ROIs. Therefore, considering the linear and time-unvarying effects of leakage, the estimated X and Z signals will be a linear combination of true signals at these regions (X’ and Z’ respectively) while the estimated Y activity equals the true source activity Y’ and can be written as:

\[ X = \alpha_1 X' + \beta_1 Z' \]
\[ Z = \alpha_2 X' + \beta_2 Z' \]
\[ Y = Y' \]  

(6.A 1)

where \( \alpha_1 \) and \( \beta_1 \) are the amount of leakage that X receives from itself and true Z’ source respectively and \( \alpha_2 \) and \( \beta_2 \) are the amount of leakage that Z receives from true X’ source and itself respectively. Therefore, in the scenario outlined above, \( \text{COV}_{XY} = 0 \) and in order for the partialising of covariance to overcome leakage, it should yield \( \text{COV}_{X|Z} = 0 \).

\[ \text{COV}_{XY} = \text{COV}_{YZ} - \text{COV}_{XZ} \]  

(6.A 2)

\[ \text{COV}_{XY} = E[(X - \mu_X)(Y - \mu_Y)] = E[(\alpha_1 X' + \beta_1 Z' - \alpha_1 \mu_X' - \beta_1 \mu_Z')(Y - \mu_Y)] = \alpha_1 \text{COV}_{XY} + \beta_1 \text{COV}_{ZY} = \beta_1 \text{COV}_{ZY} \]

\[ \text{COV}_{YZ} = E[(Z - \mu_Z)(Y - \mu_Y)] = E[(\alpha_2 X' + \beta_2 Z' - \alpha_2 \mu_X' - \beta_2 \mu_Z')(Y - \mu_Y)] = \alpha_2 \text{COV}_{XZ} + \beta_2 \text{COV}_{ZZ} = \beta_2 \text{COV}_{Z'Z} \]

\[ \text{COV}_{XZ} = E[(X - \mu_X)(Z - \mu_Z)] = E[(\alpha_1 X' + \beta_1 Z' - \alpha_1 \mu_X' - \beta_1 \mu_Z')(\alpha_2 X' + \beta_2 Z' - \alpha_2 \mu_X' - \beta_2 \mu_Z')] = \alpha_1 \alpha_2 \sigma_X^2 + \beta_1 \beta_2 \sigma_Z^2 + (\beta_2 \alpha_1 + \alpha_2 \beta_1) \text{COV}_{XZ} \]  

(6.A 3)

\[ \text{COV}_{X|Z} = \beta_1 \text{COV}_{Z|Y} - \beta_2 \text{COV}_{Z|X} (\alpha_1 \alpha_2 \sigma_Z^2 + \beta_1 \beta_2 \sigma_Z^2 + (\beta_1 \alpha_2 + \alpha_2 \beta_1) \text{COV}_{Z|X}) \]  

(6.A 4)

Therefore, \( \text{COV}_{X|Z} \neq 0 \). The only exceptional case is when the true source X’=\( \mu_X \) (i.e. inactive), \( \beta_1 = \beta_2 = 1 \) (i.e. Z and X are equally influenced by the leakage from Z), Z’ has unit variance and, thus, \( \text{COV}_{XY} = 0 \). Even though the second condition (\( \beta_1 = \beta_2 = 1 \)) might be obviated using normalised measures of co-variation, the first and third conditions are unlikely to be true for the whole brain network analysis. This argument, might be generalised to time-lagged connectivity measures (e.g. multivariate autoregressive modelling).
Even though the above examples argue that leakage cannot be resolved using non-zero-lag or multivariate connectivity measures, Equations 6.A 2-4 show that quantifying leakage between ROIs (i.e. coefficients $\alpha_1, \alpha_2, \beta_1, \beta_2$) and combining them with multivariate connectivity measures might provide a more accurate reconstruction of whole brain networks using source reconstructed EEG/MEG data. In this study we concentrated on the former.

Appendix 6.B Simulations supplementary materials


![Brainnetome Atlas](image1)

Figure 6.B 1 a) Brainnetome functional atlas from which the active nodes (ANs) of the simulated networks were randomly drawn. Parcels of the Brainnetome atlas that showed overlap with any of the parcels of the modified b) Desikan-Killiany, c) Destrieux and d) Region Growing parcellations are shown in colour and parcels with no overlaps are masked in white.

6.B.2. Supplementary simulation results

In the results section, under question 2 section 6.4.4.2, we evaluated the performance of different parcellation algorithms using simulated networks with different number of ANs and connections. Here, we aim to observe the sensitivity of each parcellation to the areas covered by each parcellation. Motivations are brought in 6.4.4.2 and results are presented in Figure 6.B 2 and Table 6.B 1.
Figure 6.B 2 TPRs and FPRs before taking the missed connections due to no coverage of some parts of the cortex in adaptive parcellations into account. That is, we compared parcellation-specific ground truths (e.g. first row in Figure 6.8) in the absence of leakage to the realistic networks in the presence of leakage (i.e. without considering calculations in 6.3.4.2.1). Left panel, TPRs: a) at SNR 3.0 (top), TPRs were reduced as the number of seeds/connections increased. For the anatomical parcellations, starting from ~0.7 true positives for 3 seeds, TPR was reduced to ~0.5 for 5 seeds, and then dropped sharply to 0.3 or less for 10 and 15 seeds. We found a similar trend for the modified parcellations, except that 1) for all the seeds/connections, modified parcellations showed significantly higher TPRs than anatomical parcellations (c.f. Table 6.B 1 for details) and 2) for 3 and 5 seeds, the TPR remained relatively constant at around 0.75 and then dropped to 0.4 or less for 10 seeds or more. We found no significant difference between the TPRs of the three modified parcellations. c) Both SNRs showed a similar trend, but (as elaborated in Table 6.B 1), the TPRs at SNR 1.0 where on average lower by approximately 10% and 6% compared to those at SNR 3.0, for anatomical and modified parcellations, respectively. b, d) FPRs: FPRs are the same as Figure 6.9 and are presented here for the sake of completeness.
Table 6.B 1  Statistical comparison of average TPRs and FPRs of the anatomical and modified parcellation considering ANs covered by the modified parcellations only. Blue shading: adaptive parcellations significantly improved compared to anatomical. Grey shading: significant differences among the adaptive parcellations.

<table>
<thead>
<tr>
<th>True Positives</th>
<th>False Positives</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coherence SNR 3</td>
</tr>
<tr>
<td></td>
<td>mean±std</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
</tr>
<tr>
<td>DKA</td>
<td>0.41±0.06</td>
</tr>
<tr>
<td></td>
<td>5.6×10⁻¹¹</td>
</tr>
<tr>
<td></td>
<td>2.1×10⁻⁹</td>
</tr>
<tr>
<td></td>
<td>2.6×10⁻⁸</td>
</tr>
<tr>
<td>DA</td>
<td>0.42±0.04</td>
</tr>
<tr>
<td></td>
<td>1.6×10⁻¹⁰</td>
</tr>
<tr>
<td></td>
<td>6.2×10⁻⁹</td>
</tr>
<tr>
<td></td>
<td>1.8×10⁻⁷</td>
</tr>
<tr>
<td>Mod DKA</td>
<td>0.54±0.06</td>
</tr>
<tr>
<td></td>
<td>5.6×10⁻¹¹</td>
</tr>
<tr>
<td></td>
<td>1.6×10⁻¹⁰</td>
</tr>
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</tr>
<tr>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td>Mod DA</td>
<td>0.54±0.07</td>
</tr>
<tr>
<td></td>
<td>2.1×10⁻⁸</td>
</tr>
<tr>
<td></td>
<td>6.2×10⁻⁹</td>
</tr>
<tr>
<td></td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>0.26</td>
</tr>
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</tr>
<tr>
<td></td>
<td>1.8×10⁻⁷</td>
</tr>
<tr>
<td></td>
<td>0.07</td>
</tr>
</tbody>
</table>

|               | Coherence SNR 1  | Coherence SNR 1  |
|               | mean±std         | mean±std         |
|               | p-value          | p-value          |
| DKA            | 0.31±0.05        | 0.1±0.008        |
|                | 6.2×10⁻¹³        | 4.1×10⁻¹⁰        |
|                | 2.7×10⁻¹⁰        | 2.9×10⁻¹³        |
|                | 1.6×10⁻¹¹        | 2.9×10⁻¹³        |
| DA             | 0.33±0.04        | 0.08±0.008       |
|                | 9.3×10⁻¹³        | 4.1×10⁻¹⁰        |
|                | 1.5×10⁻⁹         | 2.9×10⁻¹³        |
|                | 1.2×10⁻¹⁰        | 2.9×10⁻¹³        |
| Mod DKA        | 0.50±0.06        | 0.06±0.007       |
|                | 6.2×10⁻¹³        | 2.9×10⁻¹³        |
|                | 9.3×10⁻¹³        | 4.1×10⁻¹³        |
|                | NA               | NA               |
|                | 0.31             | 2.0×10⁻⁶         |
|                | 0.01             | 8.5×10⁻⁵         |
| Mod DA         | 0.48±0.09        | 0.05±0.006       |
|                | 2.7×10⁻¹⁰        | 2.9×10⁻¹³        |
|                | 1.5×10⁻⁹         | 2.9×10⁻¹³        |
|                | 0.31             | 2.0×10⁻⁶         |
|                | 0.24             | NA               |
| RG             | 0.46±0.08        | 0.05±0.006       |
|                | 1.6×10⁻¹¹        | 2.9×10⁻¹³        |
|                | 1.2×10⁻¹⁰        | 2.9×10⁻¹³        |
|                | 0.01             | 8.5×10⁻⁵         |
|                | 0.24             | 0.23             |
|                | NA               | NA               |
Appendix 6.C  Initial results of the parcellation algorithms

Figure 6.C 1 shows the initial split and merged parcels which were used as input to the final parcellation procedure.

Figure 6.C 1 Initial results of the parcellation algorithms. a) Split and b) merged parcels from the Desikan-Killiany Atlas. The primary splitting procedure for this parcellation resulted in 194 split parcels and merging procedure resulted in 122 merged parcels; these sets of parcels formed an intermediate parcellation that was input into the final homogeneity check for final vertex assignment (section 6.3.3.2). From this figure, it can be seen that larger parcels (e.g. pre-/post-central and temporal regions) were split into several sub-parcels. Additionally, vertices that are located at the intersection of adjacent parcels were typically clustered together to form merged parcels. While some of these clusters survive as new parcels in the final parcellation (Figure 6.5a), others are removed, leaving gaps between the neighbouring parcels which results in a sparse sampling of the cortex to maximise the distinguishability in the final parcellation. c) split and d) merged parcels from Destrieux Atlas. The initial splitting procedure for this parcellation resulted in 428 parcels and merging procedure in 280 extra parcels (overall 708 parcels) compared to 316 parcels for the Desikan-Killiany atlas. e) “Created” parcels from the region growing algorithm. These created parcels were mirrored to the right hemisphere using MNI coordinates and where put through an SaM algorithm as described in section 6.3.3.3.
Embodied Conceptome: Dynamic Brain Networks Underlying Concept Retrieval Comprise Interacting Supramodal and Sensory-Motor Areas

Fast dynamic connectivity between the nodes of semantic networks while a concept is retrieved in the brain remains largely unknown. To tackle this, in this chapter we proposed an unprecedented translation of the predictions of the hub(s)-and-spokes framework into quantifiable concepts of network community and modularity in graph theory. For this purpose, we utilised the spatio-temporo-spectral resolution of source-estimated EEG/MEG and reconstructed whole-brain connectomes based on the adaptive parcellations introduced in Chapter 6. Thereafter, using a data-driven permutation-based statistical approach, we examined differences between networks underlying words with strong visual (e.g. sun), auditory (e.g. whistle) and hand-action (e.g. wrench) attributes in three frequency bands of Alpha, Beta and Gamma and three time windows of 50-250ms, 150-350ms, and 250-450ms. We found: (i) Eight consensus functional modules across time windows, frequencies, conditions and subjects in the cortex. Interestingly, while the left anterior temporal lobe (ATL), posterior middle temporal (pMTG) and angular gyrus (AG) were clustered together and formed a single temporo-parietal module, the right ATL, pMTG and inferior parietal cortices were identified as stand-alone modules; (ii) Right ATL, right pMTG and right parietal modules were identified as potential integrator semantic hub modules; (iii) Bilateral occipital and left parietal modules were identified as visual spokes, bilateral central module as hand spoke and left temporo-parietal module as well as bilateral frontal cortices as auditory spokes; (iv) We found modulations of three types of inta-/inter-modular connections including hub-hub, spoke-spoke, and hub-spoke connectivity. These results provide the first evidence for global integrator hubs, spokes, and connectivity among them. Together with the results of the previous chapters, these results suggest distinct roles for the left versus right-hemispheric semantic hubs as well as different temporo-spectral profiles for the involvement of ATL and parietal cortex as integrator semantic hubs.
7.1 Introduction

In the previous Chapters, we discussed that most recent theories of semantic cognition suggest a network of heteromodal (hub) and unimodal (spoke) brain areas underlie semantic representation and retrieval. Therefore, three types of connections can be expected to underpin the formation of this network: hub-hub, spoke-spoke and/or hub-spoke. However, to the best of our knowledge, no model of semantic networks to date has presented explicit hypotheses about all of these types of connectivity and instead, different models have typically highlighted one type only. For example, firstly, strong embodiment views emphasise connectivity between semantic spokes as a key aspect of semantic networks. While some of these theories acknowledge the involvement of the core language areas to some extent (Pulvermüller 1999), others consider spoke-spoke connectivity to be necessary and sufficient (Glenberg & Kaschak 2003). Secondly, some other models have emphasised interactions among the heteromodal semantic areas as a key aspect of semantic retrieval (Lau et al. 2008). And thirdly, the hub-and-spokes model (Patterson et al. 2007; Rogers et al. 2004) proposes a hierarchical network where the hub area (as the topmost node of the network) should express differential connections to sensory-motor-limbic cortices depending on the sensory-motor-limbic attributes of a concept in order to enable the integration of lower-level information provided by the semantic spokes. Thus, words like “sun”, “whistle” and “wrench” that refer to concepts with strong visual, auditory and hand-movement attributes, are predicted to increase connections between the integrator hub area(s) and visual, auditory and motor cortices, respectively.

Emerging connectivity research has identified the anterior temporal lobe (ATL) (Guo et al. 2013; Jackson et al. 2016; Papinutto et al. 2016; Zhao et al. 2016), angular gyrus (AG) (Hagmann et al. 2008; Seghier et al. 2010; Tomasi & Volkow 2011) and middle temporal gyrus (MTG) (Binney et al. 2012; Catani et al. 2005; Fang et al. 2015) as potential integrator semantic hubs predominantly based on fMRI and DTI connectivity analyses (see Chapter 1 for more details). These cortices have been shown to express rich connectivity to numerous brain areas and thus, in principle, provide suitable candidates for integrator hubs. Despite this emerging evidence for connectivity patterns of the candidate hubs, modulations of hub-hub, hub-spoke and spoke-spoke connectivity by different semantic variables have been much less investigated (Chow et al. 2014; Jackson et al. 2016). Importantly, fast dynamic connectivity of semantic networks, using EEG/MEG, for example, have remained largely unexplored and thus unknown. In this chapter, for the first time, we propose to translate some of the predictions of the hub(s)-and-spokes framework into quantifiable graph-theoretical concepts in order to test these predictions explicitly.
The growing field of source-reconstructed EEG/MEG connectomics has provided a unique opportunity to study dynamics of the brain networks (Brookes et al. 2011b; Liu et al. 2017) and has revealed valuable properties such as temporal switching between the brain states (Baker et al. 2014), spectral properties of the brain networks (Brookes et al. 2016), direction of information flow in the brain networks (Hillebrand et al. 2016), and temporal hierarchy of the brain networks (Vidaurre et al. 2017). In addition, measures of graph theory provide powerful tools for summarising the key features of the whole-brain connectomes (Bullmore & Sporns 2009). In particular, identification of functional modules has detected network communities in the brain through which segregated and integrated information processing are made possible (Bullmore & Sporns 2012). More specifically, local and functionally specialised brain subnetworks (e.g. sensory areas) that are densely connected, have been shown to interact through sparse long-range connections to facilitate large-scale flow and integration of information in the brain (Sporns & Betzel 2016).

We propose that functional modules and connectivity among them can be used to efficiently identify the integrator semantic hub(s) and spokes and connectivity among them through clustering the highly connected local nodes as independent modules and modelling modulations of intra-/inter-modular connections. In particular, we hypothesise interactions among these modules to play a key role in constructing concepts in the brain. For this purpose, these connections are predicted to be modulated by contrasts of different categories of words. For example, while primary and secondary sensory areas might form spoke modules, higher-order nodes in temporal or parietal cortices are predicted to be clustered as integrator hub modules and intra-/inter-modular connectivity is predicted to be modulated by semantic variables.

These analyses are expected to take the next step following our connectivity investigations in Chapters 3 and 4 where we provided novel evidence for the potential role of the left ATL and AG as integrator hubs: a) within the heteromodal part of the semantic network in the left hemisphere (DCM analysis) and b) based on seed-based functional connectivity to all the brain vertices (Coherence analysis). However, by focusing on the left-hemispheric hubs, the role of the right-hemispheric semantic areas and interhemispheric connectivity were not covered sufficiently in those chapters. Nevertheless, given the well-established widespread activation of numerous brain areas in response to different concepts (Binder et al. 2009; Huth et al. 2016), these connections are likely to subserve important aspects of the semantic networks. Therefore, a data-driven whole-brain graph-theoretical approach is expected to yield a more comprehensive picture.

In order to test the aforementioned hypotheses about semantic modules, in this chapter, we examine time-varying semantic networks using source-reconstructed EEG/MEG. We use a semantic
target detection task in a visual word recognition paradigm and contrast modular presentations of the connectomes derived from different word categories including words with strong visual (e.g. sun), auditory (e.g. whistle) and hand-action (e.g. wrench) attributes (using the same data as Chapter 5). Thereafter, we evaluate these contrasts using statistical tests in order to address the following aspects of the semantic networks:

1. Can we identify consensus functional modules across conditions, times, frequency bands and subjects for this dataset and which brain areas are clustered to form independent modules?

2. In a modular network, nodes that show high between-module connectivity and act as links between several modules are referred to as connector hubs. We predict that one property of an integrator semantic hub is to act as a link between the heteromodal language modules and sensory-motor modules and thus appear as a connector hub for differentiation of categories of concepts;

3. We hypothesise that while integrator hub modules should be involved in all the three pairwise comparisons included in this study (i.e. visual/hand, visual/auditory and auditory/hand contracts), spoke modules for each sensory-motor modality should only be modulated in the two pairwise comparisons that involve their corresponding category. We aim to identify the integrator hub and spoke modules based on these criteria;

4. We highlight three types of connections including hub-hub, spoke-spoke, and hub-spoke connectivity and seek to identify the type(s) that are predominantly modulated in contrasts of semantic conditions.

In order to address these points, following the predictions and findings about timings and frequency bands in the previous Chapters 3, 4 and 5, we focus our analyses within 450ms post-stimulus, on Alpha, Beta and Gamma frequency bands, and employ a data-driven cluster-based permutation approach for statistical analysis.

7.2 Materials and methods

7.2.1 Word lists

We compare brain responses to three categories of word lists with strong sensory-motor associations to either vision, audition or hand-actions. The word rating study utilised to select these words and the final lists were described in Chapter 5.
7.2.2 EEG/MEG acquisition, pre-processing and source localisation

Details of EEG/MEG acquisition, experimental procedures, pre-processing and localisation were elaborated in Chapter 5. It is worth noting that filtering of this analysis was similar to the subsection of oscillatory dynamics in Chapter 5; i.e. data were filtered between 0.1-45Hz before projection to the source space (more details in sections 5.2.3 and 5.2.4). After pre-processing and source estimation, we investigated semantic networks by means of whole-brain connectome reconstruction and for this purpose, we used adaptive cortical parcellations introduced in Chapter 6 (details in the following subsections). A flowchart of different steps of pre-processing, connectivity estimation and graph-theoretical analyses is shown in Figure 7.1.

![Flowchart](image)

Figure 7.1 A flowchart of different steps of preprocessing, source estimation, connectivity and graph-theoretical analysis. biCOH: bivariate Coherence.

7.2.3 Optimal connectivity method for whole-brain connectome

In Chapter 2, we reviewed numerous connectivity metrics that have been introduced for neurophysiological signals, and discussed how each of these methods can reflect one or a few aspects of connectivity (Greenblatt et al. 2012). In Chapter 4, we compared Coherence, Pairwise Phase Consistency and Mutual Information for whole-brain seed-based connectivity analysis of a concreteness decision task using a novel approach based on the principal component analysis (PCA),
and identified magnitude squared Coherence as the most suitable connectivity metric. Considering the high similarities of the current dataset and data in Chapter 4 (i.e. concurrent EEG/MEG recordings of healthy young participants performing visual word recognition tasks with similar data preprocessing and localisation methods), we used coherence measures in this chapter. Further theoretical advantages of using Coherence for the questions of this thesis were discussed earlier in the Theory section of Chapter 4.

Furthermore, in Chapter 4 we argued that multivariate connectivity methods are theoretically most suitable for whole-brain parcellation-based connectivity analyses (Bastos & Schoffelen 2016; Greenblatt et al. 2012). This is due to the fact that multivariate measures find connectivity between a pair of regions after regressing out the effect of all other regions on the pair. For example, in multivariate coherence, this is achieved through subtraction of the linear projections of all other brain areas before computing coherence between each pair of interest. Therefore, multivariate coherence will improve specificity but will reduce sensitivity by compromising the SNR. In Appendix 7.A, we compared the performance of bivariate (biCOH) versus multivariate coherence (mulCOH) for whole-brain connectome reconstruction in order to make an informed decision about the optimal connectivity method. For this purpose, we used realistically simulated networks in the presence of leakage with an SNR similar to that of the real data and utilised forward models and inverse operators of the same 19 subjects included in the real data analyses. We compared the accuracy of network reconstructions based on biCOH and mulCOH using Receiver Operator Curves (ROC), and found that in spite of the theoretical preference of mulCOH for whole-brain connectomes, biCOH showed higher performance in practice.

7.2.4 Whole-brain semantic networks

We used biCOH for connectome reconstructions. In order to reconstruct the connectome for each subject, we first applied the inverse operator to single trials in order to project them into the source space and morphed the time courses from individual head space to an average brain. Next, we parcellated the cortex and extracted parcel time courses. Thereafter, we computed all-to-all parcel connectivity matrices in the time windows of interest. Details of these steps are elaborated below.

1. Single trials of data, filtered between 0.1-45Hz, were projected onto the source space the same way as for the evoked responses explained in Chapter 5 (section 5.2.6), except that instead of using SNR = 3.0, we used SNR = 1.0 for applying the inverse operator to single epochs. Thereafter, time courses of the brain vertices for each subject were morphed to the standard average brain in Freesurfer (aka. fsaverage5). This yielded an \( N_v \times N_v \times t \) matrix of
vertex time courses across epochs where \( N_v \) is the number of vertices, \( N_e \) is the number of epochs and \( t \) is time.

2. The fsaverage cortex was parcellated using modified Desikan-Killiany Atlas (mod-DKA adaptive to EEG/MEG spatial resolution introduced in Chapter 6). Next, the matrix of vertex time courses was collapsed to a matrix of parcel time course so that each parcel will be presented by one time series. The matrix of parcel time courses, \( \mathbf{M}_{\text{TC}} \), was of size \( N_e \times N \times t \) where \( N = 74 \) is the number of parcels, \( N_e \) is the number of epochs and \( t \) is time. In order to extract parcel time courses, we identified a vertex inside each parcel that showed the highest sensitivity (i.e. highest value of the cross-talk function) to the signal of that parcel and used that vertex as the representative. This approach was further elaborated in Chapter 3 (section 3.2.4).

3. BiCOH was computed on \( \mathbf{M}_{\text{TC}} \), yielding an \( N \times N \) connectivity matrix \( \mathbf{M}_{\text{con}} \). It was computed using a multitaper approach with adaptive weights in three frequency bands of Alpha (8-12 Hz), Beta (13-30 Hz) and low Gamma (31-45 Hz) (Engel & Fries 2010), and in three time windows of interest 50-250ms, 150-350ms and 250-450ms. It is worth noting that we did not include higher Gamma in the analyses considering that the ability of EEG/MEG to detect high Gamma is less clear to date (Muthukumaraswamy 2013). Furthermore, we excluded Theta band from our connectivity analyses since: a) given the short epoch lengths in this experiment, Theta band connectivity is prone to computation inaccuracies; b) considering the oscillatory dynamics that are hypothesised to play crucial role for different spokes (Chapter 5), we were predominately interested in Alpha/Beta and Gamma bands and c) in the seed-based connectivity analyses of the previous dataset (Chapter 4), we only found higher frequency bands.

7.2.5 Graph theory: identifying modules and connector hubs

We used measures of graph theory to summarise some of the key properties of the reconstructed connectomes in 7.2.4. For this purpose, we considered parcels as nodes and connectivity among the parcels as edges of the weighted graphs. We used Brain Connectivity Toolbox (BCT) (Rubinov & Sporns 2010a) in MATLAB for the graph analyses.

7.2.5.1 Consensus modules

We started by identifying modules on the cortex following a procedure similar to the previous studies (Cole et al. 2014; Geerligs et al. 2015). Briefly:

1. In order to find modules, we examined the reconstructed connectivity matrices \( \mathbf{M}_{\text{con}} \) per subject, condition, frequency band and time window and identified community structures of each \( \mathbf{M}_{\text{con}} \) using Louvain approach (Blondel et al. 2008). This method of community detection
divides the whole network into non-overlapping modules such that within-module connectivity is maximised while between-module connectivity is minimised and yields an N × 1 vector of module assignment for N graph nodes. We used a multi-iterative generalisation of Louvain algorithm as implemented in the BCT.

2. Louvain community detection is initiated by randomisation; thus, every iteration of the algorithm on the same data will yield different modules. Therefore, we repeated the previous step 100 times and obtained a P matrix of numerical module assignments which was of size N × 100. This matrix was then converted to a so-called agreement matrix D of size N × N where each element ij showed the number of times out of 100 iterations that nodes i and j were assigned to the same module.

3. Matrix D can be thought of as a new connectivity matrix, where each element shows the probability of co-occurrence of two nodes in a single module. Therefore, as the next step, we fed D back to step 1 (used as M_{con}) and repeated steps 1 and 2 until the resulting matrix D_{final} did not change anymore. This convergence point was the point where clustering parameters were optimised such that every pair of nodes was always assigned to the same module. Thus, D_{final} consisted of ones and zeros only. Module assignment vector p_{final} that corresponds to D_{final} was extracted as a result of this iterative process.

4. Columnar vectors p_{final} were obtained for different conditions, time windows, frequency bands and subjects, concatenated along the y-axis and fed to step 2 as matrix P. The same procedure was repeated until a consensus partition of the cortex was achieved (P_{grand}). This procedure of obtaining consensus modules is almost identical to (Lancichinetti & Fortunato 2012).

5. It is worth noting that final results of this procedure depend on a resolution parameter (γ) set in step 1 that determines the average size of modules. In order to obtain an optimal γ, we repeated steps 1-4 for various γ’s from 1 to 3 with 0.2 increments (similar to Geerligs et al. 2015) and identified the γ for which the average normalised mutual information of the corresponding P_{grand} to the P_{grand}’s of all other γ’s was maximised. This most consistent P_{grand} (highest average mutual information) was found to correspond to γ = 2.8.

7.2.5.2 Connector hubs

We hypothesised that one possible property of an integrator semantic hub is to act as a linking node between multiple higher-level and lower-level modules in the cortex. In graph theory, this property is reflected in the so-called connector hubs; i.e. nodes that are characterised by high between-module connectivity and thus can link several modules together. We used a measure named participation coefficient that computes the diversity of between-module connections for each node.
(Guimera & Amaral 2005) in order to identify the connector hubs that differentiate between different semantic conditions.

7.2.6 Statistical analysis

The $P_{\text{grand}}$ corresponding to $\gamma = 2.8$ identified 8 modules in the brain (see Results section 7.3.1). We collapsed the node-node connectivity matrix $M_{\text{con}}$ of size $74 \times 74$ into a module-module connectivity $M_{\text{mod}}$ matrix of size $8 \times 8$. In order to conduct statistical testing, the $M_{\text{mod}}$ matrices were compared for pairwise contrasts of different conditions (i.e. visual/hand, visual/auditory and auditory/hand contrasts) in different frequency bands (Alpha, Beta, and Gamma) and time windows (50-250ms, 150-350ms and 250-450ms). As the first step, paired t-tests were computed for each matrix element of contrasts of $M_{\text{mod}}$'s across subjects. Thereafter, in order to correct for 84 multiple comparisons (i.e. $\frac{8 \times (8-1)}{2}$ × time-windows), we utilised a topology-based clustering approach similar to the Network-Based Statistics (NBS) approach (Zalesky et al. 2010). The core idea of the NBS is similar to other cluster-based statistical tests: after computation of t-tests (e.g. for each matrix element), raw t-values are thresholded at a predefined $T_{\text{thresh}}$ and above-threshold neighbouring elements are clustered together. Permutation tests are then conducted in order to identify the significant clusters (see Chapter 3 for more details of cluster-based permutations). Nonetheless, unlike other cluster-based statistics, the NBS defines neighbours based on topological properties of a graph. That is, instead of clustering matrix elements based on their spatial adjacency, it clusters edges of a graph that are topologically connected (i.e. connected through one or more above-threshold edges) and thus finds the so-called connected components in a graph. However, the original NBS approach, that has typically been used for static graphs, does not include the time axis. Here, we adapted the same idea with an exception of accommodating the time axis. For this purpose, the components were defined as edges connected to the same node over one or more time windows.

7.3 Results

We examined the reconstructed connectomes and identified modules in order to address the four key aspects of the semantic networks outlined in the Introduction.

7.3.1 Aspect 1: number, sizes and locations of modules

We found consensus modules across subjects, conditions, frequency bands and time windows in order to determine the number of functional modules and areas that were clustered together. For this purpose, as elaborated in the methods section, we reconstructed a whole-brain connectome by means of biCOH. Next, we used the Louvain approach (Blondel et al. 2008) to identify modules and a method similar to (Lancichinetti & Fortunato 2012) in order to identify consensus modules based on
the weighted graphs. 8 modules were identified on the cortex bilaterally (Figure 7.2). We assigned the following labels to these modules: 1- bilateral visual and left parietal; 2- right parietal and parieto-occipital junction; 3- left temporal cortex; 4- right posterior temporal cortex; 5- bilateral central cortices; 6- right anterior temporal lobe; 7- bilateral prefrontal and left superior/inferior frontal cortices; 8- right superior/inferior frontal cortex.

Two key aspects can be noticed from these modules: a) right-hemispheric modules were more fine-grained and confined to one hemisphere while predominantly left-hemispheric modules were larger and some of them also contained a few nodes in the right hemisphere. For example, occipital and superior frontal modules were bilateral, even though predominantly left-hemispheric; b) as a consequence of property (a), while right ATL, middle temporal and parietal cortices formed distinct modules, left ATL, posterior temporal and angular gyri were clustered together, forming a large left-hemispheric temporo-parietal cluster.

![Figure 7.2](image-url)

**Figure 7.2** a) 8 modules identified on the cortex based on the average $M_{con}$ connectivity matrices across subjects, conditions, frequency bands and time windows. Green arrow marks the identified connector hub (see section 7.3.2 for details); b) Average $M_{con}$ matrix rearranged according to the modules. Modules boundaries are marked with dashed lines.

7.3.2 Aspect 2: connector hub nodes

We calculated participation coefficients for each node of the network in order to identify the connector hub nodes that differentiated between word categories. Connector hubs are the nodes that link several modules in the brain. Inspired by the ideas of the hub-and-spokes model, we predicted that one possible property of an integrator semantic hub areas could be to act as links between heteromodal language modules and sensory-motor modules, and show significantly different participation coefficients for different conditions. Participation coefficient measures the diversity of the inter-modular connections of each of the 74 nodes of the networks.
The only such area found after corrections for multiple comparisons across 74 nodes and 3 time windows was the right anterior part of MTG/ITG (aMTG/ rh-ITG, one of the two nodes in right ATL module). In visual/auditory contrast, we found significantly (spatio-temporally corrected p<0.05) higher aMTG/rh-ITG participation coefficient for visual words in Alpha and Beta bands in 150-350ms and 250-450ms. In hand/auditory contrast we found marginally significant (spatio-temporally corrected p<0.1) higher aMTG/rh-ITG participation coefficient for hand words in Beta band in 150-350ms and 250-450ms time windows. Therefore, these results support aMTG/rh-ITG as a connector hub (marked with a green arrow in Figure 7.2). However, we found no such potential connector hubs for visual/hand contrasts. We also computed node strengths (sum of connectivity to all other nodes) as a measure of centrality, which is independent of the module definitions. However, none of the results survived spatio-temporal corrections for multiple comparisons.

It is worth noting that results of this section are focused on single nodes (i.e. hub nodes), while aspects 3 and 4 outlined below are focused on modules which are the main focus of the results. Thus, connector hub nodes were computed as extra analysis to the main module investigations and the main conclusions will be drawn from the latter.

7.3.3 Aspect 3: “hub” and “spoke” modules

One of the key hypotheses of this chapter was that modules appearing for all the semantic contrasts (i.e. visual/auditory, visual/hand and auditory/hand contrasts- for at least one frequency band and/or time window) can be considered as “integrator hub modules” while modules appearing for specific contrasts that include one specific category (i.e. contrasts that involve only one of the visual, auditory and hand categories) can be considered as “spoke modules”. In order to identify these two types of modules, we conducted pairwise comparisons of the $8 \times 8$ between-module $M_{mod}$ matrices for visual/auditory, visual/hand and auditory/hand contrasts. We investigated the contrasts in three frequency bands of Alpha, Beta, Gamma as well as in three time windows of 50-250ms, 150-350ms and 250-450ms. Results were temporo-topologically corrected for multiple comparisons as elaborated earlier in section 7.2.6.

7.3.3.1 Integrator hub modules

We found that right ATL, right posterior MTG and right parietal cortices (surprisingly all in the right hemisphere) appeared in all the pairwise comparisons for at least one frequency band and/or time window and thus matched our predictions for integrator hubs. We further observed that while the hubness of the right ATL and pMTG modules were more evident in the Alpha/Beta bands and in various time windows spanning 50-450ms, the hubness of the right parietal module was more notable in the Gamma band and was more evident at slightly later time windows (150ms onwards and 250-
450ms in particular). As will be discussed in the discussion section, this may reflect a distinction of stages and/or oscillatory dynamics that underlie the role of these areas as semantic hubs. A summary of the significant results is shown in Figure 7.3.

7.3.3.2 Spoke modules

For the visual, auditory and hand spokes, respectively, we found:

- Visual spokes: we found that bilateral occipital, as well as left-hemispheric parietal modules appeared only for the contrasts that involved visual words, matching our criteria for visual spokes. The visual spokes were differentially connected to the right ATL module in Alpha and Beta bands for visual/hand contrast and to the right pMTG, right parietal/parieto-occipital as well as bilateral prefrontal modules in Beta and Gamma bands for visual/auditory contrast. Therefore, right ATL can be considered crucial for the former contrast while fronto-parietal networks seem to be more important for the latter.

- Auditory spokes: left temporo-parietal module as well as bilateral superior and inferior frontal modules appeared only for the contrasts that involved auditory words and matched our criteria for the auditory spoke. For the auditory/visual contrast, the auditory spokes showed modulated connections to the right pMTG in Beta band and bilateral inferior/superior frontal modules in Gamma band. For auditory/hand contrast, only the latter connections were modulated.

- Hand spokes: bilateral central module appeared only once in the earliest time window, in the Gamma band and for the hand/auditory contrast. It showed differential connections to the right frontal module, one of the identified auditory spokes. The central module matched our predictions for the hand-action spoke, but it did not appear in any of the hand/visual contrasts. We conducted an ad-hoc test in order to further explore whether lack of such finding might be due to the low statistical power given the strict correction for multiple comparisons. For this purpose, we focused on the connections of the central module (module 5) and the earliest time window (50-250ms) only. After a more lenient correction at $p < 0.01$ for this specific module and time window, we found a modulation of connections between modules 5 and 1 (bilateral occipital, the identified visual spoke) in Alpha band for hand/visual contrast. Therefore, central module is differentially connected to one of the auditory spokes for auditory/hand contrast and to the visual spoke for visual/hand contrast.
Figure 7.3 A summary of significant connections for pairwise comparisons of different word categories. Modules 2 (right ATL), 4 (right posterior MTG) and 6 (right parietal) matched our predictions for hub areas since they appeared in all pairwise comparisons (for at least one frequency band and/or time window). Module 1 (bilateral occipital) appeared only for the contrasts that involved visual words and matched visual spoke. Modules 3 (left temporo-parietal cortex), 7 and 8 (bilateral superior and inferior frontal) appeared only for some of the contrasts that involved auditory words and matched auditory spoke. Module 5 (bilateral central) appeared in the earliest time window for the hand/auditory and hand/visual contrasts, with the latter appearing in the ad-hoc test explained in the text and shown in pale red here. FC: Full Correction for multiple comparisons across nodes and times. NTC: No Temporal Correction: a more lenient procedure that corrects for multiple comparisons across 64 elements of $M_{mod}$ connectivity matrix contrasts but considers every time window separately and does not correct for the three time windows.
Figure 7.4 a) Comparison of module-by-module connectivity matrices ($M_{mod}$) between visual and hand words. Module 6 (right ATL) was the only module found to be of key importance in differentiating the two conditions, and in the Alpha and Beta bands. Effects started early (i.e. in 50-250ms time window) but some persisted until later time windows. All significant results were obtained from strict FC (full correction) for multiple comparisons and the more lenient NTC (no temporal correction) procedure did not yield additional results (see Figure 7.3 caption for details); b) The strongest connections (above half maximum) obtained after subtracting visual – hand networks and averaging across subjects. Note that only results of FC correction are visualised.
7.4 Aspect 4: intra-/inter-modular connectivity of hubs and spokes

Connectivity of the semantic networks was hypothesised to be reflected in hub-hub, hub-spoke and/or spoke-spoke connections. We found modulations of all the three types of connections in semantic contrasts. More specifically:

- For visual-hand contrast, hub-hub connections included rh-ATL to rh-pMTG and rh-PL in the Alpha and Beta bands as well as intra-modular connections of the rh-ATL in the Beta band. Spoke-spoke connections included bilateral central to bilateral occipital in the Alpha band. Hub-spoke connections included the rh-ATL to the bilateral occipital in the Alpha and Beta bands. Connections were found in multiple time windows (see Figure 7.4 for details).

- For auditory-hand contrast, hub-hub connections included rh-ATL to the rh-pMTG and rh-PL in the Alpha and Beta bands as well as intra-modular connections of the rh-ATL in the Beta band. Spoke-spoke connections included fronto-central and fronto-frontal connections in the Gamma band. Hub-spoke connections included rh-ATL to the left temporo-parietal and bilateral prefrontal modules in the Beta band as well as rh-pMTG to the rh-frontal modules. Connections were found in multiple time windows (see Figure 7.5 for details).

- For visual-auditory contrast, the hub-hub connections included rh-ATL to the rh-pMTG in the Beta band. Spoke-spoke connections included bilateral prefrontal to the bilateral occipital and left temporo-parietal modules in the Gamma band. Hub-spoke connections included rh-pMTG to the left temporo-parietal and bilateral occipital modules in the Beta band, rh-pMTG to the rh-frontal in the Gamma band as well as rh-PL to the bilateral occipital and bilateral frontal modules in the Gamma band. Connections were found in multiple time windows (see Figure 7.6 for details).
Figure 7.5 a) Comparison of module by module connectivity matrices ($M_{\text{mod}}$) between auditory and hand words. Module 6 (right ATL) was found to be of key importance in differentiating the two conditions in the Beta band. Module 8 (right superior/inferior frontal cortex) was found to be important in the Gamma band. Effects started early (i.e. in 50-250ms or 150-350ms time window) but some persisted until later time windows. Cells that are marked with asterisks show the results of strict FC (full correction) for multiple comparisons while those marked with unfilled circles mark the more lenient NTC (no time correction) procedure (see Figure 7.3 caption for details). b) The strongest connections (above half maximum) obtained after subtracting auditory – hand networks and averaging across subjects. Note that only results of FC correction are visualised.

Figure 7.6 a) Comparison of module by module connectivity matrices ($M_{\text{mod}}$) between visual and auditory words. Modules 2 (right parietal and parieto-occipital junction) and 7 (Bilateral prefrontal and left superior/inferior frontal cortices) were found to differentiate the two conditions in the Gamma band. Module 4 (right posterior temporal) was found to differentiate the conditions in the Beta band. All effects started early (i.e. 50-250ms time window) but some remained until later time windows. Cells that are marked with asterisks show the results of strict FC (full correction) for multiple comparisons while those marked with unfilled circles mark the more lenient NTC (no time correction) procedure (see Figure 7.3 caption for details). b) The strongest
connections (above half maximum) obtained after subtracting visual – auditory networks and averaging across subjects. Note that only results of FC correction are visualised.

7.5 Discussion

This study provides the first evidence for time-varying brain networks that underpin single word semantic processing, uncovering that these networks consist of interacting supramodal (hub) and modality-specific sensory-motor (spoke) cortices, including hub-hub, hub-spoke and spoke-spoke connectivity. This novel evidence supports the notion that higher-level integrator semantic hubs in the temporo-parietal cortices bind and mediate modality-specific semantic information represented in lower-level spokes. Importantly, these results were obtained through an unprecedented translation of the predictions of the hub(s)-and-spokes framework regarding connectivity within semantic networks into quantifiable concepts of network community and modularity in graph theory. In order to test these hypotheses, we used source-estimated EEG/MEG connectomes (using adaptive parcellations introduced in Chapter 6) and compared the brain responses to three pairwise comparisons of concrete words with either visual (e.g. sun), auditory (e.g. whistle) or hand-action (e.g. wrench) attributes using data-driven statistical approaches.

The key findings were: 1) Modules: eight functional modules were identified on the cortex, with larger modules in the left hemisphere (some also including right-hemispheric nodes) and smaller self-contained modules in the right. In particular, while the left anterior temporal lobe (ATL), posterior middle temporal (pMTG) and angular gyrus (AG) were clustered together and formed a single temporo-parietal module, the right ATL, pMTG and inferior parietal cortices were identified as stand-alone modules; 2) Hubs: importantly, based on these modules, right ATL, right pMTG and right parietal modules were identified as potential integrator semantic hubs that appeared in all the three aforementioned pairwise comparisons of word categories and consequently were supposed to be involved in modality-general semantics. Additionally, we found a node in the right inferior middle ATL (a node of the right ATL module) as a potential central connector hub involved in visual/auditory and auditory/hand contrasts but not visual/hand contrast; 3) Spokes: bilateral occipital and left parietal modules were identified as the visual spokes, bilateral central module as the hand spoke and left temporo-parietal module as well as bilateral frontal cortices as the auditory spokes. Each of these spoke modules were specifically involved in two of the pairwise comparisons that included their corresponding word category (i.e. modality-specific semantics); 4) Connections: we found modulations of three types of intra-/inter-modular connections including hub-hub, spoke-spoke and hub-spoke connectivity. Therefore, locations of the integrator semantic hubs (ATL, pMTG, parietal cortex) and some of the spoke modules (bilateral occipital, bilateral central and left temporo-parietal) matched our predictions. However, the finding of right-hemispheric hubs was somewhat unexpected,
but as we will discuss below may reflect different connectivity profiles of the language-dominant left compared to the right hemisphere.

7.5.1 Left versus right hemisphere: representation versus coordination?

Community detection algorithms in this study clustered the key heteromodal hub candidates in the left hemisphere (i.e. ATL, pMTG and AG) as a single super module, while right-hemispheric counterparts of these cortices appeared as stand-alone modules. Importantly, while fine-grained right-hemispheric candidate hubs showed rich connectivity to numerous cortices and were thus revealed as global integrator hubs, the temporo-parietal super module in the left hemisphere appeared more secluded.

The role of left versus right-hemispheric language areas in semantic processing has been a long-lasting matter of debate. It is well-established that unilateral damage/resection of either of ATLs introduces much less severe symptoms compared to the bilateral damage (Snowden et al. 2017). In particular, it has been argued that progressive loss of conceptual knowledge in semantic dementia might in fact be a consequence of the bilateral nature of the disease. It has therefore been suggested that bilateral ATLs act as one interconnected system that underlies semantic representation (Lambon Ralph et al. 2016). However, the more specific role of each ATL within this system has remained ambiguous. Patient studies have shown that asymmetrical higher deterioration of the left compared to right (L>R) ATL is associated with more deficits in remembering names and performing verbal tasks while R>L is associated with difficulty recognising faces/voices and performing picture naming tasks (Woollams & Patterson 2017).

Our results suggest that heteromodal semantic areas in the left hemisphere might form a super module with dense intra-modular connections that, as suggested in the previous studies (Woollams & Patterson 2017), might play a principal role in verbal and symbolic representation of concepts but shows little inter-modular connectivity. As a complementary, right-hemispheric integrator semantic hubs, e.g. ATL and AG, might underlie embodied (e.g. pictorial) representations of concepts through connections with spokes. Consequently, full meaning comprehension is likely to be accomplished though dynamic connectivity between these two sub-parts of the semantic networks. However, this latter property was not highlighted in our investigations. Overall, these results can be interpreted as the initial evidence for distinct roles of left and right heteromodal semantic areas, an interpretation that is also in line with some theoretical proposals in the previous literature (Gainotti 2015; Gainotti & Gainotti 2015). It is worth noting that spoke modules, as will be elaborated below in 7.5.3 were mostly found to be bilateral and thus such discussions are specific to the semantic hubs.
7.5.2 Integrator semantic hubs

One key role of a semantic hub, which we have referred to as integration hubness, is to integrate and mediate sensory-motor-limbic attributes of a concept that are supposedly provided by primary/secondary sensory cortices (Binder 2016; Lambon Ralph et al. 2016). In this study, we found modules in the right ATL, right pMTG and right parietal lobe (PL) as potential integrator hubs.

7.5.2.1 Right anterior and posterior temporal modules

We found connectivity patterns of the hub modules in the right ATL and pMTG to be modulated in Alpha and Beta bands and during earlier and later time windows (i.e. 50-250ms, 150-350ms and 250-450ms). While connectivity of the right ATL to several brain areas including itself, surrounding fronto-temporal cortices and long-distance sensory cortices was found to be modulated, right pMTG was predominantly involved through modulation of its connections to the right ATL (see e.g. Figure 7.4 and Figure 7.5). Additionally, anterior MTG-ITG (a node of the right ATL module) was the only region identified as a connector hub (that links multiple modules) to differentiate visual/auditory (Alpha and Beta bands) and auditory/hand (Beta band) words but not visual/hand words. Therefore, plausibly, while ATL might play the role of a central integrator hub, pMTG might act as a supporting convergence zone that performs a role in semantic representation/control through modulation of its connections to the ATL.

This interpretation is also in line with some recent findings in the literature. On the one hand, while pMTG (including the Wernicke’s area) has traditionally been considered as a key region for language comprehension (Martin et al. 2014), some recent TMS studies have suggested this area to be involved in semantic control rather than semantic representation per se (Hallam et al. 2017; Jefferies 2013). Furthermore, given the location of this area and strong connections to the visual and auditory streams, it has also been proposed to act as a semantic interface zone for convergence of information from multiple sensory areas (Visser et al. 2012). On the other hand, growing evidence based on connectivity analyses in recent years suggests bilateral ATLS as potential semantic hubs in healthy participants as well as semantic dementia (Guo et al. 2013; Lambon Ralph et al. 2016). For example, a series of fMRI studies with novel distortion correction techniques have provided evidence for a graded functional specialisation within ATL and between bilateral ATLS (Binney et al. 2016; Jackson et al. 2016; Lambon Ralph et al. 2016; Rice et al. 2015a). These studies suggest that ATLS consist of a central ventrolateral amodal core that, together with the surrounding cross-modal medial, ventral and superior temporal sub-regions, form a graded hub for semantic processing (Binney et al. 2016; Jackson et al. 2016). The latter peripheral sub-regions of ATL have been shown to be functionally and structurally connected to different parts of the language and sensory-motor-limbic cortices, a
property that makes this region an ideal candidate for an integrator hub (Jackson et al. 2016). These recent findings, together with the previous findings of the current thesis (Chapters 3 and 4), suggest the role of ATL as an integrator semantic hub and pMTG as a potential supporting convergence zone for multisensory integration (Beauchamp et al. 2004a).

7.5.2.2 Right parietal module

Inferior parietal cortex, and the angular gyrus in particular, has been identified as one of the key heteromodal regions involved in semantic cognition (Binder et al. 2009). Being one of the main areas of the default mode network, and located at the intersection of the parietal, temporal and occipital cortices, AG retains rich structural and functional connections to various regions in the frontal, temporal, central, parietal and occipital cortices (Seghier 2012; Seghier et al. 2010). Among various functions proposed for this region, semantic representation has been suggested as possibly the most consistent role (Seghier 2012). However, AG has been shown to play a more important role for concrete concepts compared to abstract concepts (Fernandino et al. 2016b; Handjaras et al. 2017; Wang et al. 2010). For example, in a recent study, Fernandino et al. (2016) examined 900 words and showed that a set of heteromodal cortices including AG sit at the overlap of the areas that encode colour, shape, visual motion, sound, and manipulation attributes of the words. In another study, Lin et al. (2017) showed that areas responding to imageability and sociability effects overlap in AG. Based on these findings, these studies have suggested that AG can be placed at a higher level of hierarchy of the semantic networks compared to the primary and secondary sensory-motor areas (Lin et al. 2017). Our results, in line with these recent findings, provide further evidence for the hubness of this area for concrete concepts. Together with the results of Chapter 4, our results suggest the important role of AG, particularly for integration of sensory-motor attributes of concrete words.

7.5.2.3 Distinct mechanisms underlying the role of temporal and parietal modules?

Based on the hub evidence discussed so far, we conclude that right anterior temporal and right parietal cortices serve as global integrator semantic hubs in whole-brain connectomes through rich modulations of connections to multiple unimodal and cross-modal cortices. This finding is consistent with the main two competing hub candidates in the most recent literature (i.e. ATL and AG) (Binder 2016; Lambon Ralph et al. 2016). However, the specific role of each area is unknown and has been largely a matter of debate in recent years. Interestingly, examining our results more closely (section 7.3.3), it can be noticed that while the hubness of the ATL was more pronounced in lower Alpha/Beta bands, parietal module was more important in higher Beta/Gamma bands. Additionally, while the former was modulated from the earliest time window (50ms onwards), the latter came into
play later (150ms or 250ms onwards). Putting these together with the predictions of the hub-and-spokes model on the role of the hub, the following novel interpretation of the specific role of the anterior temporal and inferior parietal cortices seems plausible: when we see the word “apple”, ATL might be the first area that becomes modulated (as the processor hub, evidence in Chapters 3 and 5), it may then make connections to visual/gustatory spokes in order to stimulate them in the same way as when one encounters “apple” in the real world. This will re-activate colour/shape/taste signals associated with “apple” and the object will be reproduced in a “bottom-up” manner. From this stage onwards, parietal cortex might play role for coordination and integration of these bottom-up signals (as a node placed higher in the network hierarchy) that are continuously sent back to the ATL until the meaning is fully retrieved. Therefore, further to the distinction between processor and integrator hubs suggested in Chapters 3 and 4, results of the current chapter suggest distinct temporal and oscillatory profiles for these integrator hubs.

7.5.3 Semantic spokes

We found bilateral occipital and left-hemispheric parietal modules as visual spokes, left temporo-parietal (including but not restricted to the auditory cortex) module as well as bilateral superior and inferior frontal modules as auditory spokes, and bilateral central module as a potential hand-action spoke. Interestingly, all the identified spoke modules were found to be involved from early time windows of exploration (i.e. 50ms or 150ms) and most frequently in the Gamma and Alpha bands. Different theories of semantic networks more or less agree on the localisation of the spokes in the primary/secondary sensory-motor areas. Accordingly, we predicted occipital modules, superior temporal modules and central modules to act as visual, auditory and hand-action spokes, respectively.

Therefore, the obtained results, particularly for visual and hand spokes showed a good match to the predictions. However, results for auditory spokes were less conclusive: we found temporo-parietal as well as frontal modules as auditory spokes. Firstly, bilateral superior/inferior/prefrontal cortices were not hypothesised as auditory spokes. Nonetheless, the involvement of frontal cortex (in particular inferior frontal regions) in some aspects of auditory perception such as pitch and music perception has been often reported in the literature (Koelsch & Siebel 2005; Zatorre et al. 1992, 1994). Thus, even though not hypothesised as a classic auditory spoke in the previous literature, these results might suggest some nodes of frontal cortex might, in fact, represent auditory-specific semantic information. Alternatively, one could attribute this finding either to the fact that auditory words in this study were less accurately identified as words or due to the significantly lower rating on concreteness scale compared to visual and hand words (see word rating study in Chapter 5). These two differences might have resulted in the differential involvement of the attentional brain system in
the frontal cortices that is not specific to auditory-specific semantic representation. Secondly, due to the adjacency of the main auditory spokes in the superior temporal cortex to other temporo-parietal language areas involved in semantics, community detection algorithms clustered these areas together as a single module (particularly in the left hemisphere). Therefore, even though the left temporo-parietal module was identified as an auditory module, it is not straightforward to attribute this finding to the superior temporal auditory cortex.

Overall, considering the strict data-driven analysis conducted in this study, and medium sample size compared to the norm of studies on brain graphs (typically 100 or more (Cole et al. 2014; Geerligs et al. 2015; Váša et al. 2017; Whitaker et al. 2016)), these results can arguably provide strong (and first) evidence for differential connectivity patterns of sensory-motor spokes for modality-specific semantic representation. In particular, involvement of these areas from early stages of semantic processing onwards, in line with findings of Chapter 5, supports the notion of embodied representation of concepts. However, considering the less conclusive results for the auditory words, these findings should ideally be followed up using imaging methods with high spatio-temporal accuracy such as intracranial recordings.

7.5.4 Hub(s) and spokes connectivity

Our investigations of intra-/inter-modular connectivity revealed three types of connections within the identified semantic networks: a) hub-hub connectivity such as connections of right ATL-pMTG pair or right ATL-PL pair; b) spoke-spoke connectivity such as connections of pairs of central-occipital and frontal-occipital cortices and c) hub-spoke connectivity such as connections of the right ATL to the occipital and frontal cortices. Theories of semantics have typically focused on one of these types of connectivity. For example, strong embodiment views emphasise connectivity between semantic spokes (Glenberg & Kaschak 2003) while the hub-and-spokes model highlights hub-spoke connectivity as an essential aspect of the semantic networks (Patterson et al. 2007). Accordingly, previous connectivity analyses of static semantic networks (using fMRI or DTI) have focused on the hub connectivity to other heteromodal and unimodal semantic areas (Jackson et al. 2016). Results of the current study reveal for the first time that all three types of the aforementioned connections are crucial in the formation of dynamic semantic networks. Therefore, in addition to supporting the general framework of heteromodal integrator hubs and multiple unimodal spokes, these results reveal novel aspects of connectivity between and within subnetworks of semantics.

7.5.5 Caveats and future directions

We used state-of-the-art community detection algorithms in order to find semantic modules in the brain. However, these approaches to date have been specifically designed and applied to
structural and functional MRI and thus the identified modules are static. In this study, we adopted similar approaches and applied them with no modification. Thus, the identified modules were collapsed across time windows, frequency bands and semantic conditions using state-of-the-art methods for identification of consensus modules. The key advantage of this approach is that results are readily comparable across times, frequencies and contrasts. Nonetheless, the main drawback is that some of the subtle dynamic changes due to semantic word categories might have been averaged out. For example, in this study, nodes of auditory spoke in the superior temporal cortex were clustered together with several candidate hub regions in the temporo-parietal cortex. While such clustering might be optimal in general, it is likely to be sub-optimal for specific frequencies (e.g. Alpha or Gamma) and for the auditory words. To the best of our knowledge, no adaption of these algorithms have been proposed to accommodate temporal fluctuations in community detection and hence it remains a challenge as to how to include these variations while retaining the possibility to make comparisons across different times, frequencies, etc.

Additionally, in this study, we utilised a fully data-driven approach for statistical comparisons of graphs. While this approach can arguably increase the reproducibility of the results, considering the medium sample size of the experiment (19 subjects), it increases the risk of Type II error. While this problem might have less impact on the identifications of hub(s) and spokes, the more specific identification of the types of connections involved in each contrast (i.e. hub-hub, spoke-spoke and hub-spoke) might be more affected. More specifically, while our results provide the first empirical evidence that all the three aforementioned types of connections are involved in semantic retrieval, they are inconclusive about which of these connections are more important. Graph theoretical studies that have applied similar approach typically utilise a large sample size (e.g. 100 participants or more (Cole et al. 2014; Geerligs et al. 2015; Whitaker et al. 2016)) in order to obtain a higher statistical power. Therefore, replication and further specification of the results of this chapter using a larger sample size will be desirable. Alternatively, focusing on a few of the identified hub(s) and spokes using an imaging modality with higher spatio-temporal resolution (e.g. intracranial EEG) can further strengthen these conclusions.
Appendix 7.A  Bivariate versus multivariate coherence

We compared bivariate (biCOH) versus multivariate coherence (mulCOH) for whole-brain EEG/MEG network reconstruction using adaptive Desikan-Killiany atlas introduced in Chapter 6. This comparison was included because even though multivariate methods are theoretically more suitable for all-to-all parcellated connectivity analyses, they are more susceptible to low SNRs which is an inevitable property of non-invasive EEG/MEG data. Therefore, it was of interest to compare these two methods using realistically simulated data (with the same forward model and inverse operators as the real data) in order to make an informed decision for applying the most suitable connectivity method to the real data.

Materials and methods

We simulated 36 realistic datasets and compared the accuracy of network reconstruction for biCOH and mulCOH. This simulation pipeline was a simplified and somewhat modified version of the more comprehensive simulations described in Chapter 6 (6.3.4) which will be described briefly in this section. Similar parts will be mentioned briefly and differences will be elaborated below; otherwise, the reader is referred to the aforementioned chapter for more details.

Network construction

We simulated 36 datasets, each based on the same forward and inverse models of the same 19 subjects as in the main study (see 5.2.2 for details). Each network was simulated at SNR 3.0 (realistic for event-related data) and consisted of 5 active seeds randomly drawn from the Brainnetome functional atlas of the brain ((Fan et al. 2016) details similar to 6.3.4.1). The percentage and locations of connections were randomly selected from a range of 10% to 100% (hereafter referred to as C%) with 10% increments.

Simulated signals and connectivity patterns

N, sinusoidal signals for 40 epochs (duration 725ms including 125ms baseline) were simulated in randomly selected seed locations. In order to systematically vary connectivity in our simulated networks, we created activation time courses at each active node (AN) as a weighted sum of a fixed set of orthogonal basis functions (BF). Connectivity among ANs was defined by a binary matrix $A$ which was of size $N_A \times N_A$. Each row of $A$ corresponded to one AN, and determined the contribution of each BF to that AN’s activation time course. Therefore, those BFs that were assigned ones in the row of $A$ that corresponded to each AN contributed to that specific AN. We imposed the following constraints on matrix $A$: a) the diagonal elements of $A$ were all set to ones, thus, each BF was inherent to one of
the ANs; b) since we introduced random non-zero phase-shifts between the nodes, the resulting signals had non-zero-lag connectivity; c) for each network scenario, C% of all possible connections among the ANs, i.e. the corresponding element in $A$, were set to one. It is worth noting that one key difference between simulations here compared to Chapter 6 was that in the latter, indirect connections through a shared third source were counted towards the C% while in this chapter they were not. In other words, in order to achieve C% connections among the seeds, C% of the off-diagonal elements of the upper triangle of the $A$ matrix were set to one. This ensured no bias in favour of bivariate measures in the later reconstruction steps since bivariate measure are more susceptible to spurious connections through a shared third source while multivariate measures are designed to alleviate this issue; d) the relative phases of ANs, the elements of $A$ matrix and the frequencies of each BF were selected randomly. Hence, the values of coherence among the ANs varied between 0 and 1 depending on the noise level and number of connections, which we assumed to be the case for the realistic brain networks.

After simulating the sinusoidal signals of the ANs, we added noise to them. Furthermore, we simulated random noise in all the vertices outside the active source locations. These networks were constructed at a relatively high SNR of 3.0. Note that higher SNR increases sensitivity but also enunciates the effects of leakage. Thus, while multivariate coherence (less sensitive to leakage but lower sensitivity) becomes more likely to identify true connections as SNR increases, bivariate coherence (sensitive to leakage) becomes more likely to identify spurious connections.

In the next step, we parcellated the cortex using modified Desikan-Killiany Atlas (mod-DKA) for network reconstruction, as described in Chapter 6. Therefore, here we recorded the parcels in the mod-DKA that overlapped with each of the ANs and connection values in the $A$ matrix that corresponded to these ANs. This yielded the ground truth connectivity matrices against which the later reconstructions were compared. Note that this method of defining ground truth is another key difference of these simulations to Chapter 6.

Network reconstruction

We used bivariate and multivariate Magnitude-Squared Coherence (biCOH and mulCOH) as two measures of connectivity in order to reconstruct the simulated networks and compare the performance of these two measures. biCOH and mulCOH are spectral measures of connectivity which can detect both amplitude and phase couplings (Greenblatt et al. 2012; Bastos & Schoffelen 2016). biCOH is sensitive to zero-lag connections as well as indirect connections through connectivity to a shared third source while mulCOH is less susceptible to both issues (see Chapter 2 for details). In order to reconstruct each network using these measures we simulated each dataset as outlined above and,
for each subject/frequency band in each dataset, obtained an $N_v \times N_e \times t$ matrix of vertex time courses across epochs where $N_v$ is the number of vertices in the brain, $N_e$ is the number of epochs and $t$ is time. Thereafter, we parcellated the fsaverage5 cortex using mod-DKA, extracted parcel time courses using mean-flipped approach and computed biCOH and mulCOH on matrices of connectivity among parcels ($M_{con}$ matrices). Details of network reconstruction are similar to section 6.3.4.2 in Chapter 6.

**Network reconstruction accuracy and receiver operator curves (ROC)**

We used ROC in order to compare network reconstruction accuracies of biCOH and mulCOH. For this purpose, each realistic network was compared against its own ground truth. The accuracy of network reconstruction was evaluated using the steps below (note the procedure has some key differences to the network reconstruction accuracy step in Chapter 6):

- Firstly, we identified significant connections in each realistic network. For this purpose, each network was thresholded at P% of the highest connections. Connections that were significantly higher than the threshold were of interest. Therefore, significant connections were identified using one-tailed t-tests, and results were Bonferroni corrected for multiple comparisons.

- Secondly, significant connections identified from each network reconstruction were compared against the corresponding ground truths and two groups of connections were identified:
  - True positives (sensitivity): Significant connections that were identified accurately in the realistic networks divided by the overall number of true connections. Note that we included the number of missed connections due to lack of coverage of some ANs by the modified parcellations (see section 6.3.4.2.1 in Chapter 6 for details) in the calculation of true connections.
  - False positives (1-specificity): non-existent connections in the ideal scenario that were incorrectly marked as significant in the realistic networks divided by the overall number of zero connections in the ground truth.

- Finally, we varied P% threshold from 5 to 100 and repeated steps 1, 2 in order to obtain the ROCs by plotting true positives as a function of false positives.

These metrics were computed for each random dataset and averaged across 36 iterations. All of the evaluation steps were applied to the results of connectivity from both biCOH and mulCOH and ROC curves are compared below.
Results

We simulated 36 datasets each consisting of the same 19 subjects included in the real study with 5 active nodes randomly selected based on the Brainnetome atlas and random number and patterns of connectivity among the active nodes. The same forward models and inverse operators as the main study as well as realistic SNRs were used so that generalisation of the results to the real data can be justified. When compared the accuracy of network reconstructions using biCOH and multCOH, as shown in Figure 7.A 1, the former showed a higher area under the ROC and hence a higher network reconstruction accuracy. Therefore we used biCOH for reconstruction of the networks from real data. It is worth noting that the reason none of the measures in Figure 7.A 1 reached the ultimate sensitivity of 1 is due to the fact that adaptive DKA does not cover the whole cortex whereas the Brainnetome atlas includes parcels everywhere (see Chapter 6 section 6.3.4.2.1 for details).

Figure 7.A 1
Comparing receiver operator curves (ROC) obtained from bivariate COH and multivariate COH analysis of simulated networks. The accuracies of network reconstructions were found to be higher for biCOH.
8 General Discussion

The current thesis provides novel evidence for some of the core predictions of the hub(s)-and-spokes framework, supporting the general framework but also suggesting modification and further specification of the original model, in particular with respect to the semantic hubs. Details of these findings will be summarised and discussed in the following sections. Investigation of the spatio-temporal/oscillatory dynamics and time-varying connectivity using source-estimated EEG/MEG in this thesis was proved essential for uncovering the previously unknown aspects of the semantic networks. Importantly, these results were obtained using novel approaches for connectivity analyses of the source-estimated EEG/MEG and connectome reconstruction.

8.1 Semantic networks

Results of the current thesis provide novel evidence towards addressing the following ongoing debates regarding the organisation of semantic networks in the brain:

Q1. Single hub or multiple hubs (aka. convergence zones)?

A1. In order to address this question, it is important to draw a distinction between different roles of a hub, namely processing and integration hubness, and test hypotheses as to how each role can be quantified at different times of semantic word retrieval. We found that:
A2. Bilateral ATLs (predominantly left) served as the processor hubs: this property was reflected in modulation of activation amplitudes by contrasts of semantic variables with multiple degrees of specificity (Chapters 3, 5);
A3. ATL and AG played the role of integrator hubs (predominantly early versus predominantly later hubs, respectively): this property was reflected in the modulation of the connectivity of the integrator hubs to other semantic areas (Chapters 3, 4, 7).
It is noteworthy that temporal resolution was of fundamental importance to tease apart different stages of word semantic retrieval (more details below in 8.1.1) and thus identification of different types of hubs.

Q2. What is the mechanism of semantic representation in the unimodal spokes?

A1. Temporal and oscillatory dynamics of semantic spokes suggest a recruitment of these areas as in perception and action as of the early stages of semantic word retrieval;
A2. Modulations of hub-spoke and spoke-spoke connections from early stages of word meaning comprehension suggest an involvement of spokes in semantic retrieval through widespread cortico-cortical connections.

Q3. How are the semantic networks organised in the whole-brain graphs?

A1. Semantic networks were found to be formed of hub-hub, spoke-spoke and hub-spoke connections;
A2. Left and right-hemispheric integrator hubs were found to play potentially distinct yet overlapping roles.

8.1.1 Different types of semantic hubs: four stages of semantic retrieval

In the literature review of Chapter 1, we outlined the historical development of the theoretical models of the semantic networks in the brain. While a decade ago the key question was to address whether semantic representation is symbolic or embodied (Mahon & Caramazza 2008; Pulvermüller et al. 2005a), accumulation of neuroimaging evidence converged on involvement of both heteromodal and modality-specific semantic representation (Hauk & Tschentscher 2013; Lambon Ralph et al. 2016; Meteyard et al. 2012). Therefore, contemporary models of the semantic networks, and hub-and-spokes model in particular, have concentrated on further specification of the role of different unimodal and heteromodal semantic areas, mechanisms of their involvement in meaning comprehension and importantly, interactions between these semantic sub-systems (Patterson et al. 2007; Rogers et al. 2004). The hub-and-spokes model, as discussed thoroughly in the earlier chapters, proposes a hierarchy of semantic processing with lower-level information provided by the unimodal sensory-motor-limbic systems (semantic spokes) being mediated and integrated by a higher-level heteromodal semantic hub. However, it has remained controversial as to whether a single-hub is sufficient to fulfil the tasks of the higher-level layer of the semantic network hierarchy or whether several nodes are required (Binder 2016; Lambon Ralph et al. 2016). Throughout this thesis, we proposed that further clarification of the hubness definition and examination of different tasks of a hub through different stages of semantic retrieval using appropriate and objective tools can be expected to advance this debate. More specifically, we proposed that it is essential to investigate
processing and integration as the two key roles of a semantic hub through different stages of word semantic retrieval.

Overall, our results of Chapters 3, 4, 5 and 7 suggest four distinct yet highly overlapping key stages through which semantic hub(s) support word meaning comprehension (Figure 8.1):

- **Stage 1 early processing**: One property of a semantic hub is to serve as the topmost node of the network hierarchy, orchestrating all other semantic areas. In order to fulfil this task, as the first step, a hub is expected to be the first area that receives input from the sensory cortices (e.g. from the visual cortex in the case of visual stimulus presentation) and gets modulated by semantic variables. We found this property reflected in early modulation of the ATLs’ activation to a range of semantic contrasts with different degrees of specificity, including: different word categories against pseudowords (Chapter 5), concrete versus abstract words (Chapter 3) and different categories of concrete words with various sensory-motor attributes (Chapter 5). Interestingly, while the lateralisation and sub-regions of the ATLs differed depending on the contrast, ATLs (predominantly left) were found to be the only cortices appearing in early stages of all the tested contrasts. Therefore, we conclude ATLs as the early processor hubs.

- **Stage 2 early integration**: As the second step (initiating shortly after stage 1 and occurring highly in parallel to that stage), a hub was hypothesised to stimulate lower-level unimodal and multi-sensory cortices that correspond to sensory-motor-limbic attributes of a concept such that these areas will reproduce the concept (i.e. in a bottom-up manner). In order to do so, hub(s) were hypothesised to show differential connections to distributed semantic areas. Our DCM investigations of Chapter 3 uncovered left ATL as an early integrator hub within the heteromodal semantic sub-network in the left hemisphere and the whole-brain investigations of graphs in Chapter 7 revealed right ATL as the main early integrator hub in the semantic connectome (both within 250ms). Furthermore, our investigations of Chapter 4 uncovered ATL and AG as integrator hubs from 150ms onwards (but predominantly in later time windows of 250-450ms, see stage 3 below).

- **Stage 3 later integration**: As the third step, continuing on stage 2 on reproduction (i.e. simulation) of a referent of a word in the distributed semantic networks, later integrator hub(s) were predicted to come into play for coordination and integration of the simulated bottom-up signals (as nodes placed one level higher than unimodal cortices in the network hierarchy). Our DCM investigations of Chapter 3 showed left AG as the main integrator hub within the left-hemispheric heteromodal semantic subnetwork (up to 450ms) and whole-brain graphs in Chapter 7 suggested this area (and right parietal cortex in general) as the key
global integrator hub, particularly during later stages of word processing (200ms onwards). It is worth noting that while both ATL and AG were identified as integrator hubs during earlier and later stages of semantic processing, they were shown to be more important in either early or later stages, respectively. Therefore, we conclude ATL and AG as predominantly early and late integrator hubs, respectively.

- **Stage 4 later processing:** After integration of the lower-level information from unimodal cortices, a supramodal abstract representation of concepts in the processor hubs during later stages of semantic processing (i.e. around N400 time window) was found. At this stage, the word meaning is supposedly abstracted away from the sensory-motor attributes and thus can, for example, be generalised or integrated into a context (Taylor et al. 2011). For this purpose, the amplitudes of the processor hub(s) activations were hypothesised to be modulated. In Chapter 5 we found left-hemispheric fronto-temporo-parietal cortices to act as processor hubs for general semantic contrasts (word categories versus pseudowords) and in Chapters 3 and 5 we found ATLs and anterior IFGs as later processor hubs. Interestingly, in spite of variability in lateralisation and sub-regions, the later processor hubs overlapped at ATLs, suggesting the involvement of other cortices to be specific to a condition or a contrast. Thus we conclude ATLs as the later supramodal processor hub.

It is worth noting that referring to these four stages independently does not imply sequential non-overlapping activation of one after the other. On the contrary, as illustrated in Figure 8.1 these stages were shown to be highly overlapping with soft and fuzzy boundaries.

### 8.1.1.1 Hub lateralisation

Our investigations of the processing and integration roles of the semantic hub(s) suggest that while the former is predominantly dependent on the left-hemispheric hub candidates, the latter might rely more on the right-hemispheric areas. On the one hand, we found amplitude modulations of the temporo-parietal semantic areas in response to word/pseudoword contrasts (Chapter 5) in the left hemisphere, differentiation of concrete/abstract words (Chapter 3) was initiated in the left ATL and spread to bilateral ATLs and IFGs only in later time windows (~400ms), and effects of the fine-grained categories of words (Chapter 5) were confined to the left ATL for two of the contrasts (visual/hand and auditory/hand) and to the right ATL for one the contrasts (visual/auditory).

On the other hand, whole-brain connectome investigations (Chapter 7) revealed modules in the right ATL and parietal cortex as the key global semantic hubs with numerous connections to other heteromodal as well as sensory-motor semantic modules. Importantly, while the key candidate hubs in the right hemisphere were identified as independent modules, their left-hemispheric counterparts
were clustered together in a super module. Our earlier DCM investigations in Chapter 3 had identified the potential structure of a time-varying subnetwork within this super module. Therefore, it is likely that a large processing hub with internal connections in the left hemisphere is principally involved in the symbolic representation of concepts as the topmost node of the network hierarchy while right hemispheric hubs underlie embodied representation of concepts and orchestrating distributed semantic networks. With this interpretation, interactions between left and right-hemispheric hubs are expected to become vital in construction of the concepts in the brain. Nonetheless, we did not find such interactions in our investigations. It is worth highlighting that assigning distinct roles to the left
and right-hemispheric hubs does not imply mutually exclusive roles. Instead, as has been suggested in the previous research, a graded functionality seems more likely (Rice et al. 2015a).

8.1.2 Oscillations and dynamic connectivity specified semantic representation in spokes

The specific role of the spokes in semantics is less clear than for the hubs (Hauk & Tschentscher 2013; Meteyard et al. 2012). In fact, as elaborated in Chapter 1, until a few years ago, it was an intense matter of debate as to whether these lower-level cortices are at all necessary in semantic processing (Mahon & Caramazza 2008; Pulvermüller et al. 2005a). More recent evidence has suggested their involvement in different stages of semantic retrieval (Moseley et al. 2013). Nevertheless, the empirical evidence for the specific role of these areas remains highly ambiguous. In this thesis, we demonstrated novel aspects of temporal and oscillatory dynamics as well as time-varying connectivity of the semantic spokes that further specifies their role in the earlier and later stages of semantic retrieval. More specifically, we showed that neural oscillations that are involved in perception and action are invoked during semantic processing of the words that contain those sensory-motor attributes (Chapter 5). Additionally, spoke-spoke and hub-spoke connectivity were shown to be modulated by the sensory-motor attributes of different concepts (Chapters 4, 7). These results shed light on some of the potential mechanisms of the involvement of the spokes in the aforementioned stages 2, 3 (early and late integration) of concept retrieval. In particular, we suggest that during stage 2, spokes might be stimulated by the early integrator hub(s) through modulation of hub-spoke connectivity. Subsequently, in stages 2 and 3, amplitudes of the spokes in their characteristic frequencies (e.g. visual gamma or hand mu) might be modulated by semantic contrasts, providing lower-level information that is necessary to build up concepts in the brain (referred to as ingredients in the hub-and-spokes model). This information is continuously sent back to the later integrator hubs for mediation and integration.

8.1.3 Dynamic connectivity of semantic networks

To the best of our knowledge, modulations of connectivity among semantic areas for different semantic word categories or words versus pseudowords are essentially unknown to date. Therefore, a major scope of this thesis was to shed light on the connectivity within the semantic networks for contrasts of semantic variables and variations of these connections over the time course of semantic word processing. Furthermore, through investigations of these connections, as summarised in the previous subsections, we aimed to further specify the mechanisms of involvement of the hub(s) and spokes in semantic retrieval. We found three types of connections among the semantic brain areas: hub-hub, hub-spoke and spoke-spoke connections.
Firstly, hub-hub connections were observed using DCM analysis of a heteromodal subnetwork of semantics in the left hemisphere (Chapter 3), where ATL and AG were identified as integrator hubs that received input from the visual word form area and established connections to other key candidate hubs (e.g. IFG and MTG) within 250ms and 450ms post-stimulus, respectively. Additionally, hub-hub connections were observed in the whole-brain graphs underlying contrasts of concrete words with different sensory-motor attributes such as auditory, hand-action and visual-relatedness (Chapter 7). Secondly, hub-spoke connections were found between ATL and limbic cortices as well as AG and somatosensory cortices based on the whole-brain seed-based connectivity of the contrast of concrete and abstract words (Chapter 4). Moreover, hub-spoke connections were found in the whole-brain graphs that subserved differentiations of different categories of concrete words (Chapter 7). Thirdly, spoke-spoke connections were also observed in the contrasts of the whole-brain graphs for different word categories (Chapter 7). These three types of connections were observed in multiple time windows spanning the course of semantic word retrieval and in the higher frequency bands (i.e. alpha, beta and gamma).

These results show that all three types of connections are modulated in the semantic networks. This was particularly of interest considering that most prominent theories of semantic networks typically emphasise only one type of these connections and eliminate the other types or do not make explicit hypotheses about them. For example, strong embodiment views propose connections among spokes as necessary and sufficient to build up concepts in the brain without any need for an integrator hub (Glenberg & Kaschak 2003). On the contrary, in the hub-and-spokes model, hub-spoke connectivity is a fundamental aspect of the model, while the model does not make explicit predictions about the other types of connections (Lambon Ralph et al. 2016). Therefore, through highlighting multiple types of dynamic connections, our results suggest a more complex semantic network in the brain. However, as the first step towards quantification of these dynamic networks, this thesis opens up numerous questions for future research. Some of these questions and potential approaches for tackling them will be discussed in the Future Directions.

8.1.4 Time-varying hub(s)-and-spokes model

Overall, our investigations of the hubs, spokes and interactions among them suggest modifications and updates to the current hub-and-spokes model. More specifically, the most recent version of the hub-and-spokes model (referred to as graded hub-and-spokes shown in ) postulates a core amodal hub area in the ventrolateral subregion of the ATls, encompassed by modality-specific medial, superior temporal and other subregions of the ATls that subserve establishing connections to the distributed spokes. Therefore, this model predicts that ATls are the first areas to be modulated.
by the input, establish connections to the spokes, integrating modality-specific information provided by the spokes until a word meaning is retrieved. Our results suggest three key modifications to this model: 1) Distinct yet overlapping heteromodal areas underlie processor and integration hubness with ATL being predominantly responsible for the former while both ATL and AG subserving the latter; 2) Semantic network is time-varying and thus, depending on the stage of concept processing, different hub(s), spokes and brain oscillations play role; 3) Not only hub-spoke connections but also hub-hub and spoke-spoke connections underpin semantic representation. The proposed modified model is illustrated in Figure 8.2, where the early processor hub is the first to get modulated by the input. It then establishes connection to the early integrator hubs that establish connections to the spokes. Sensory-motor-limbic information re-produced in spokes is then integrated by the later integrator hub and sent back to the later processor hub for a higher-level abstract representation of a concept (details of each stage were elaborated earlier in 8.1.1).

8.2 Method development for EEG/MEG connectivity

Considering the main cognitive objectives and the key findings of the current thesis, time-varying connectivity and whole-brain connectome reconstructions have been of fundamental importance in the characterisation of the semantic networks. However, optimal connectivity estimations of the EEG/MEG data in source space in general, and whole-brain graphs in particular, are still methodologically challenging (Bastos & Schoffelen 2016; Colclough et al. 2015, 2016). The following two issues were considered as being especially relevant for the cognitive interpretability of the results of the current thesis and thus we proposed methods to address them.
Firstly, the precise neuronal mechanisms through which semantic areas are orchestrated are not known. Consequently, quantification of the connectivity among these areas based on the complex EEG/MEG signals becomes challenging. This is due to the fact that different EEG/MEG connectivity metrics propose different qualitative and quantitative definitions of connectivity (reviewed in Chapter 2) and arguably no single method can capture all possible aspects of neuronal connectivity. Therefore, in order to obtain connectivity estimations that are cognitively interpretable, ideally a knowledge of the underlying mechanisms is required. Given that such mechanisms are not known for semantic networks, in Chapter 4, we proposed a novel method based on the principal component analysis that received results of multiple connectivity metrics for a dataset as input and determined the most suitable connectivity (MSC) metric based on the maximum explained variance. Comparing three methods of Coherence, Pair-wise Phase Consistency and Mutual Information, each representing one core idea for connectivity estimation, Coherence was identified as the MSC for the datasets of this thesis.

Figure 8.2 Left: Graded hub-and-spokes model proposed in Lambon-Ralph et al. 2016, where ventrolateral ATL has been suggested as the amodal hub that is responsible for supramodal semantic representation while peripheral ATLs (e.g. medial or superior temporal) play the role of modality-specific hub through connections to the semantic spokes (three out of several spokes shown here as example). Right: modified and further specified time-varying hub(s)-and-spokes model proposed based on the results of the current thesis. Early/later processor/integrator hubs were elaborated in Three types of connections were identified in our studies: hub-spoke, hub-hub, and spoke-spoke that are shown with different shades of green (from dark to bright, sequentially). Circled arrows show cross-modal (solid line) and modality-specific (dashed line) processing within hubs and spokes. Note that, as elaborated in the text, distinct yet overlapping areas were identified as the processor and integrator hubs. The overlaps are not illustrated to avoid unnecessary graphical complexity (see Figure 8.1 for details).
Secondly, signal estimations in EEG/MEG source space and consequently connectivity estimation among these sources are contaminated by the so-called leakage problem. That is, connectivity between two brain areas is not only reflective of the connectivity between the sources they encompass, but also a by-product of the leakage of activity from the surrounding areas. The source leakage becomes a serious source of inaccuracies in the whole-brain connectome reconstructions if parcels of a parcellation exchange substantial amounts of leakage and thus are not distinguishable using EEG/MEG source localisation methods. In order to alleviate this problem for the reconstruction of the semantic graphs, in Chapter 6 we proposed automated algorithms based on the cross-talk functions (CTFs) for linear distributed source models of EEG/MEG in order to optimise sizes, locations and number of parcels in a parcellation. This framework yielded cortical parcellations that are adaptive to the limitations of the spatial resolution of the source reconstructed EEG/MEG data. An example of how these parcellations improved sensitivity and distinguishability of the parcels in a parcellation and reduced false leakage-induced connections in the simulated random networks is illustrated in Figure 8.3.

Figure 8.3 Comparison of the performance of an example of anatomical (left) and adaptive (right) cortical parcellations for reconstruction of source estimated EEG/MEG connectomes (based on Destrieux atlas). Top row shows the ideal parcel resolution matrices (PRmats) for each parcellation, with sizes and colours of the nodes (i.e. parcels) showing ideal normalised CTF that each node should receive from itself (i.e. 1.0). Bottom row shows realistic PRmats where the sizes and colours of the nodes represent normalised CTF of each parcel at itself and colours of the edges show between-parcel CTFs. Furthermore, significant leakage-induced connections (corrected for multiple comparisons) that each parcellation has identified from the null noise networks is illustrated. Note that in an ideal scenario in the absence of leakage, null networks should produce no significant connections and thus more connections in these figures show higher susceptibility to the leakage. It is worth noting that this figure is mainly for illustration purposes and the reader is referred to Figure 6.4, Figure 6.5 and Figure 6.7 and relevant sections in Chapter 6 for more details.
8.3 Future directions

8.3.1 Semantic networks

Based on the evidence presented in the current thesis, new aspects of the semantic hubs and spokes were revealed and mechanisms of their involvement in word semantic retrieval were further specified. Importantly, this work presents new insight into the dynamic connectivity within and between semantic hubs and spokes. However, as the first step towards quantification of the dynamic semantic networks, these investigations also raise new questions for the future research.

Throughout the current thesis, we employed a data-driven approach in order to identify the large-scale properties of the semantic networks. Therefore, in order to keep the results tractable, we limited the connectivity analyses to a few time windows and considering the length of these time windows (200ms or more), we assumed bidirectional connections among the semantic areas. However, as the next step, some of the proposed hub mechanisms in 8.1.1 might be further tackled through the observation of the direction of information flow among the brain areas. For example, in the early integration stage (stage 2), we predict that the direction of connections will be predominantly from the hubs to the spokes while in stage 3 the direction is expected to be reversed. The current thesis provided the first evidence towards definition and timing of these stages as well as hub and spoke cortices involved in each stage. Therefore, focusing on specific stages and/or specific hubs and spokes in the future research might further pinpoint the direction of information flow among the semantic areas.

Moreover, we identified three types of connections within the semantic networks including hub-hub, hub-spoke and spoke-spoke connectivity. However, bivariate connectivity metrics utilised for graph-theoretical analysis are prone to indirect connections through a third shared source (see Chapter 2). Therefore, some of the identified connections are likely to be indirect connectivity. For example, it is not unlikely that some of the identified spoke-spoke connections are in fact due to the connectivity of the pair of spokes to a single hub. In Chapter 2, we discussed that multivariate connectivity metrics have been proposed to alleviate this problem (even though arguably no method can completely resolve the problem without removing true connections). However, in the process of removing indirect connections, SNR of the data can be substantially compromised, particularly for the whole-brain parcellated connectivity with numerous parcels with highly correlated time courses. Our simulations in Chapter 7 showed that at an SNR comparable to that of the source estimated EEG/MEG data, bivariate measures are overall more cost efficient for the reconstruction of realistically simulated connectomes in the presence of leakage. Therefore, we utilised bivariate coherence for reconstruction of the whole-brain semantic graphs. However, if this drawback can be addressed using different
imaging modalities with higher SNRs and/or through innovative experimental manipulations that obviate indirect connections, different types of connectivity among semantic areas can be determined with more accuracy.

Importantly, our connectivity estimations were constrained to within-frequency band interactions. However, a number of studies (Canolty et al. 2006; Jensen & Colgin 2007; Voytek 2010) in the past decade have proposed phase-amplitude cross-frequency couplings as a key mechanism of orchestrating long-range connections between higher-level fronto-temporal cortices and lower-level sensory-motor areas. In particular, phase of lower frequency bands such as Theta have been proposed to modulate amplitude of the higher frequencies such as Gamma (Canolty & Knight 2010; Heusser et al. 2016). Translating these findings in the context of the hub-and-spokes model, it is possible that while hub-hub and spoke-spoke interactions are reflected in within-frequency interactions, hub-spoke connections might be reflected in cross-frequency couplings. More specifically, it does not seem unlikely that phase of the low frequency bands (e.g. Theta) in integrator hubs might interact with the amplitude of the higher frequency bands (e.g. action Mu, auditory Tau and visual Gamma) in spokes such that hub areas can coordinate multiple spokes through long-range connections. Such analysis, in spite of providing an exciting scope for the research on hubs and spokes, could not be accommodated within the experiments of this thesis because phase-amplitude coupling with source-estimated EEG/MEG are not methodologically established (Voytek et al. 2013) and most of the previous studies have recruited intracranial recordings (i.e. higher SNRs seem to be strongly required). More importantly, the length of the epochs (~500ms) was well below the minimum epoch length required for a reliable estimation of the phase-amplitude couplings that involve Theta (i.e. typically several seconds) (Dvorak & Fenton 2014; Tort et al. 2010). Subject to resolving these issues, this notion can potentially provide a breakthrough in our understanding of the semantic networks.

Crucially, we proposed potential bottom-up versus top-down mechanisms during different stages of word semantic retrieval. Aforementioned directionality of information flow as well as further specification of the oscillatory mechanisms can be used to validate this proposal. In particular, a vast body of literature on sensory processing have proposed gamma and beta/alpha bands to underlie bottom-up and top-down information processing, respectively (Engel & Fries 2010; Fries 2009; Siegel et al. 2012). Our results of Chapter 7 (refer to 7.5 for discussion) are suggestive of the ATL as the top-down integrator hub (earlier time windows in stage 2, predominantly Alpha/Beta) and AG as the bottom-up integrator hub (later time windows in stage 3, predominantly Gamma). However, further specification of these results by focusing on each hub/time window/frequency band, ideally using imaging modalities with high spatio-temporal resolution such as the intracranial recordings can strengthen these arguments substantially.
Moreover, as elaborated earlier, our results suggest distinct yet overlapping roles for the left and right hemispheric hubs with the former playing a more important role as a processor semantic hub while the latter being more important for the integration of category-specific information that is supposedly provided by the more distributed semantic networks. In this view, inter-hemispheric connectivity of the hub areas is expected to play an essential role in word meaning processing. However, our results did not highlight these connections. Therefore, further specification of such connections in the future research is desirable.

Last but not least, our results proposed modifications to the state-of-the-art graded hub-and-spokes model. However, it is worth noting that while the spatial resolution of fMRI has allowed identification of the subregions of ATL and AG in the previous studies and their involvement in semantic networks, source reconstructed EEG/MEG does not allow for examination of those subregions (see Chapter 6). Subsequently, we found ATL as a whole to subserve processing and integration hubness and inferior parietal cortex to subserve the latter. Nonetheless, we were unable to pinpoint if different subregions might have played a more important role for each task at different time windows. This remains an intriguing question for the future research.

8.3.2 Next steps on method developments

8.3.2.1 PCA-based ensemble connectivity

The PCA approach utilised in Chapter 4 can be considered as a novel ensemble method for source reconstructed EEG/MEG connectivity that can identify either the most suitable connectivity method or the most consistent pattern of connectivity across multiple metrics. Additionally, unlike precedent ensemble connectivity approaches that rely on simulated signals in the absence of leakage (Wang et al. 2018), it is based on real data and thus the effect of leakage on individual connectivity metrics is taken into account. However, considering that the extent of leakage contribution to the identification of the most consistent connectivity metric remains unclear, it can be argued that the “most robust” connectivity patterns of connectivity in source space might in fact be the leakage patterns. This is particularly plausible considering that leakage is inherent to the EEG/MEG source localisation and ill-posedness of the inverse solution (see Chapter 2). Thus, stable patterns of spurious zero-lag connectivity that are fairly independent of time, frequency, etc. can be expected. Therefore, application of robustness tests that are suitable for DTI/fMRI such as test-retest reliability and existing ensemble connectivity approaches (including PCA approach in this study) to EEG/MEG with no adaptation, might in fact identify the leakage pattern as one of the most reliable connectivity patterns across subjects, conditions, etc. Therefore, it remains an intriguing question for the future research as
to how to “customise” the reliability criteria for the EEG/MEG data so that the leakage-driven reliability will be minimised.

8.3.2.2 Adaptive cortical parcellations

In Chapter 6 we showed that obtaining EEG/MEG-adaptive cortical parcellations can improve sensitivity and distinguishability of the parcels in the brain, both in theory using resolution matrices and in practice using simulated networks. However, it is worth noting that the proposed algorithms depend on the choice of forward model and inverse solution and are consequently sensitive to the potential modelling errors. The degree to which the proposed algorithms are sensitive to the modelling errors should be evaluated in future research. Moreover, current implementations of our algorithms are mostly suitable for studies on homogeneous cohorts of participants. This is due to the fact that depending on the choice of source localisation methods, adaptive parcellations are to some degree data-dependent. For example, L2 MNE depends on the noise-covariance matrix of the data and is somewhat data-dependent (depending on the regularisation parameter) and beamformers depend on the data covariance and are strongly data-dependent. Therefore, if the relevant data properties (e.g. noise covariance or data covariance) change significantly between different groups under investigation (e.g. patients and healthy participants), different parcellations might be obtained for different groups. This can result in significant differences in the functional networks. Thus, generalisation of current approaches to inhomogeneous groups could be explored in the future studies. These outstanding questions provide opportunities for the future research on adaptive parcellations.

Furthermore, the final parcel resolution matrices and simulation results suggest that network reconstruction accuracy has been notably improved in adaptive parcellations. However, the presence of off-diagonal elements in PR mats (specifically reflected in the results of simulated null networks, Figure 8.3) allow for using adaptive parcellations together with complementary methods from the previous literature that can be expected to further improve network reconstruction accuracies. One such complementary method might be to combine adaptive parcellations with multivariate connectivity. In the theory section and Appendix 6.A of Chapter 6, we discussed how multivariate and non-zero-lag connectivity methods can be affected by the leakage, and considering the linear nature of CTFs and based on the multivariate covariance as an example, we discussed that leakage coefficients could be taken into account in order to quantify the effects of CTFs on multivariate connectivity analysis. These leakage coefficients can be extracted from the PR mats. Therefore, we suggest that modified parcellations and PR mats might be used together with multivariate and time/phase-lagged estimates of connectivity, in order to get more direct and directed measures of whole-brain graphs. It is worth noting that computing PR mats for any given parcellation (e.g.
anatomical parcellations) to inform the multivariate connectivity analysis might not result in an accurate reconstruction of whole-brain networks. This is due to the fact that standard anatomical parcellations are likely rank-deficient (section 6.4.3) which indicates that signals of one or more parcels can be explained as a linear combination of other parcels in the brain and cannot be estimated accurately. On the contrary, the parcellation algorithms in this study improved this issue, suggesting that one can derive N independent signals for N parcels yielded by the parcellation algorithms. Therefore, obtaining distinguishable CTF-based parcels is an essential first step and how to combine these adaptive parcellation methods with different connectivity methods will be an important question for future studies.

8.4 Conclusions

Results of the current thesis provided new evidence for further specification of different types of semantic hubs, suggesting that distinct yet overlapping brain systems might underlie processing and integration hubness through different stages of semantic word retrieval. Furthermore, potential mechanism and content of semantic representation in the unimodal spokes was revealed through observation of temporo-oscillatory responses in these cortices. Crucially, complex and time-varying hub-hub, hub-spoke and spoke-spoke connectivity were found to subserve the formation of semantic networks. These three key findings support the general hub(s)-and-spokes framework through providing new evidence for some of its previously unresolved predictions, but also suggest updates to the model. Importantly, these results were obtained using novel approaches for EEG/MEG connectivity analyses, particularly adaptive cortical parcellations for the whole-brain connectomes.


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