From Right to Left: Interhemispheric Interactions while Seeing Words and Hearing Sentences

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Department of Psychology
University of Toronto

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2018

Abstract

The corpus callosum is the largest fiber bundle in the human brain and mediates communication between cerebral hemispheres through a combination of excitatory and inhibition interactions. The balance between excitation and inhibition has been clearly defined for certain perceptuomotor processes, but not with language. This dissertation outlined the interhemispheric interactions involved in sentence comprehension in aphasia patients (studies 1 and 2) and word recognition in healthy adults (studies 3 and 4). Aphasia is commonly associated with right hemisphere activation, which has been attributed to both inhibitory and excitatory mechanisms. Study 1 demonstrated a positive relationship between left hemisphere dysfunction and right hemisphere language activation, which could have resulted from either disinhibition or excess recruitment of the right hemisphere. Study 2 examined these two hypotheses using Dynamic Causal Modelling of fMRI. Healthy controls showed no evidence for interhemispheric homotopic inhibition, but instead demonstrated excitatory right-to-left connectivity between primary auditory cortices. Critically, auditory connectivity was associated with language recovery in patients; the worst performing patients lacked typical right-to-left excitation, and showed atypical left-to-right excitation. Studies 1 and 2 provide two very interesting results: 1) healthy language processing requires asymmetrical right-to-left perceptual transfer and 2) right
hemisphere activation in aphasia results from atypical excitatory recruitment. Interhemispheric interactions between perceptual regions was further explored in study 3 using a laterized lexical decision task with MEG. In line with results from study 2 and the broader word recognition literature, the results showed an asymmetrical transfer of visual information from right to left hemisphere. Importantly, the results add to the current literature by demonstrating transfer between primary visual cortices, at one of the earliest processing stages of word recognition. Finally, study 4 showed that simultaneous bilateral word recognition was facilitated when word pairs were semantically related. These findings again suggest that the interhemispheric interactions in word recognition are primarily excitatory. The four studies in this dissertation found consistent evidence for interhemispheric excitation in language processing. While there is clear evidence for inhibition in some language processes, the current studies suggest that both sentence comprehension and visual word recognition are primarily associated with excitatory interhemispheric interactions.
Acknowledgements

This dissertation is the culmination of years of work that would not be possible without professional and personal support from a number of individuals in my life. I have benefitted greatly from the mentorship provided by incredibly knowledgeable, wise and patient people.

My first mentor was Dr. Michael Cusimano, who dedicated personal time and resources into showing the ropes to an undergraduate kid who knew nothing about research. Dr. Cusimano took me to observe my first (and only) pituitary tumor resection, let me shadow and conduct basic interviews during clinical rounds and advised me through my first research project. These initial experiences laid the foundation for my development as a researcher.

Next, I’d like to acknowledge the efforts of Dr. Steve Joordens in providing me with countless opportunities in and outside of academia. Dr. Joordens took a chance and accepted me as a Master’s student, despite our diverging research interests. While I eventually left his lab to finish my PhD, Dr. Joordens remained a critical member in my thesis advisory committee who, along with Dr. Phil Monahan, helped shape the direction of my research.

My final advisor, Dr. Jed Meltzer, played the most critical role in shaping my skills as a neuroscience researcher and helping me transition towards a career in data science. Dr. Meltzer and I (and most of the lab) are pretty big geeks for evaluating novel algorithms. The lab’s philosophy of using state-of-the-art neuroimaging analysis to answer fundamental neuroscience questions heavily influences my current approach towards data science. Dr. Meltzer’s continued support and contagious enthusiasm towards neuroimaging, and science in general, have been a huge positive influence on my career development.

I’d also like to thank Dr. Tali Bitan, who was heavily involved in the research in Chapter 3. At the start of the project, I had zero experience with fMRI analysis, let alone a complicated
beast like Dynamic Causal Modelling. With her technical expertise and a seemingly endless
supply of patience, Dr. Bitan dedicated several hours every week to walk me through the
standard fMRI analysis pipeline. This project (and thus the contents of Chapter 3) would not
have been possible without Dr. Bitan’s dedication towards research and pedagogy.

Finally, while we did not formally work on any research projects together, I’d like to
thank Dr. Douglas Bors, who spent countless hours discussing fundamental statistics with me.
My passion for data science and statistics is largely due to Dr. Bors’ enthusiastic descriptions of
topics like probability distributions, multicollinearity and “the tipping effect”. He is always
available to give advice and has played a critical role in developing my data science toolkit.

From my personal life, my family has been extremely supportive of my academic and
professional goals. I want to thank my parents, Lily and Sidney Chu, who never waivered in their
support, despite knowing very little about what I actually did for the last five years. I also want
to thank my sister, Diana Chu, for her consistent positivity and uplifting attitude. My
professional accomplishments would not be possible without the continual support from my
incredible family.

Finally, I want to thank all of the peers (ALT Lab, Meltzer Lab, fellow TAs, GAPS, and
UScientia) that have shaped both my personal and professional life over these years.

It’s been fun, neuroscience. Thanks for the memories.
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Chapter 1
General Introduction

1.1. Are you left-brained or right-brained?

This question that has permeated into popular culture incorrectly suggests that individuals preferentially use a single hemisphere. However, this over-simplification of hemispheric specialization is based on a very well-documented characteristic of human cognitive processing: some aspects of some tasks are highly lateralized. While it makes little sense to ask whether an individual is left or right-brained, a number of studies have asked whether a task is left or right-lateralized. Hemispheric specialization is especially relevant when studying language, a complex multi-step process that requires the two hemispheres to cooperate and compete. The current consensus is that some aspects of language, like phonological processing, are highly left-lateralized, while other aspects, like sentence comprehension are more bilateral (reviewed in Vigneau et al., 2006, 2011). Critically, this suggests that language involves a combination of excitatory and inhibitory interactions between the two hemispheres. The interhemispheric interactions involved in language processing are not clearly established and there is debate regarding when and where these interactions are excitatory or inhibitory. This dissertation outlines the interhemispheric interactions involved in two aspects of language processing: sentence comprehension and word recognition. The following section outlines a brief history of research regarding interhemispheric interactions, and presents a selective review of these interactions in the context of language processing.
1.2. Corpus callosum - Anatomy

The corpus callosum (CC) is easily the largest fiber bundle in the human brain, containing more than 300 million fibers (Hofer & Frahm, 2006). While most of the fibers serve to connect homologous brain regions, a number of heterotopic fibers exist to asymmetrically link different cortical areas (Jeffrey M. Clarke & Zaidel, 1994; de Lacoste, Kirkpatrick, & Ross, 1985; Witelson, 1974). Given the lack of clear anatomical landmarks within the CC, several partitioning schemes have been proposed to delineate the CC into specific subsections connecting different cortical homologues (Duara et al., 1991; Larsen, Höien, & Ødegaard, 1992; Rajapakse et al., 1996; Weis, Kimbacher, Wenger, & Neuhold, 1993; Witelson, 1974). One of the most influential schemes is Witelson’s (1974) classification, which defines five sections and their associated cortical connections: the anterior third, the anterior midbody, the posterior midbody, the posterior third and the posterior one-fifth. The anterior one-third mediates connections between prefrontal, premotor and supplementary motor cortical areas. Motor and posterior parietal regions are connected by the anterior and poster midbodies, respectively. Finally, the posterior one-third mediates temporal, parietal and occipital connections. This scheme is strictly geometric, with each subsection defined as a particular ratio of the total anterior-posterior extent of the CC.

Advances in diffusion weighted MRI sequencing (DTI) have since allowed for more precise classification based on the cortical termination points. Hofer & Frahm, (2006) measured CC DTI in eight participants and came up with a similar classification scheme of five regions that differ in extent and associated cortical areas. Region I connects prefrontal areas, region II connects premotor and supplementary motor areas, region III connects primary motor areas, region IV connects sensory areas and region V connections parietal, temporal and occipital areas.
The distinct cortical termination points of the CC subdivisions suggest that each section is functionally distinct. However, attempts to define the function of the CC have been contentious and span decades of research. In fact, the fundamental type of interaction that the CC serves, excitation or inhibition, is still widely debated. The history of research around CC function is extensive and quite fascinating. Researchers interested in neuropsychology, neuroplasticity, hemispheric specialization, visuomotor integration, and language have all encountered this structure in some way. As with many lines of inquiry in neuroscience, curiosity in the corpus callosum was piqued by observations of patients with peculiar symptomatology following damage, or in the case of the CC, disconnection.

1.3. Callosal function - Clinical history

Patient studies of CC function was based on two major patient populations: callosotomy (split-brain) patients who underwent surgical resection of the corpus callosum to impede seizure propagation (reviewed in Gazzaniga, 2000) and callosal agenesis patients, whose CC were never developed (Paul et al., 2007). These two patient populations offer very different perspectives on callosal functioning. Callosotomy patients provide insight into brain adaptations that result from the loss of function due to hemispheric disconnection, while callosal agenesis reflects the adaptation of a brain that was never connected since birth; these patients show few of the deficits that occur following surgical resection of the CC (M. S. Gazzaniga, 2000). As such, much of what we know regarding typical callosal function comes from the former patient group.

Studies of split-brain patients have highlighted the role of the corpus callosum for sensory integration by measuring responses to stimuli that are presented to a single hemisphere. Such studies have shown that high precision somatosensory processes are largely lateralized. For example, stereognostic information processed by one hand is available only to the contralateral
hemisphere (M. S. Gazzaniga, Bogen, & Sperry, 1963), while the presence of light or deep touch from both sides of the body can be detected by both hemispheres (Stein, Price, & Gazzaniga, 1989). Likewise, fine control of distal muscle groups in the hands is lateralized but control of proximal muscles groups in the shoulders, arms and legs can be handled by both hemispheres (M. S. Gazzaniga, Bogen, & Sperry, 1967).

Studies using visual hemi-field presentations have shown that, unlike with monkeys (M. S. Gazzaniga, 1966), visual information in humans is transferred exclusively through the corpus callosum. Split-brain patients are unable to integrate visual information between the two visual hemi-fields; the unstimulated hemisphere has no access to the information from the ipsilateral visual field. Given this separation of visual processing, patients can actually conduct visual search across the two half-fields independently and in parallel. Consequently, when items are distributed across the visual fields, reaction times for patients are actually faster than those for healthy controls (Luck, Hillyard, Mangun, & Gazzaniga, 1989, 1994). Subsequent research showed that the hemispheres were not only searching independently, but also adopting different strategies. The left hemisphere adopts a conscious guided strategy that is not available to the right hemisphere (Alan Kingstone, Enns, Mangun, & Gazzaniga, 1995), while the right hemisphere has the propensity to automatically shift attention, specifically towards the gaze of faces (A. Kingstone, Friesen, & Gazzaniga, 2000; Alan Kingstone et al., 1995).

These differences in visual search capabilities may reflect hemispheric differences in information processing that developed as an evolutionary consequence of left hemisphere specialization for language (P. M. Corballis, Funnell, & Gazzaniga, 2000; M. S. Gazzaniga, 2000). According to this hypothesis, the evolution of language resulted in the co-opting of left hemisphere cortical regions that were once dedicated to visuospatial processing. This resulted in
a left hemisphere specialization for linguistic processing and a right hemisphere specialization for visuospatial processing. Indeed, studies show that the two hemispheres are differentially specialized for processing visual information; the left hemisphere is superior for identity matching (Paul M. Corballis, Funnell, & Gazzaniga, 1999), while the right hemisphere is superior for perceptual grouping (Paul M. Corballis et al., 1999), and visuospatial matching (Paul M. Corballis et al., 1999; Funnell, Corballis, & Gazzaniga, 1999). The two hemispheres also differ in their capacity to process sequential information, with a left hemisphere advantage for high temporal frequency (M. C. Corballis, 1996; P. M. Corballis et al., 2000) and a right hemisphere advantage for low temporal frequency (M. S. Gazzaniga, 2000).

Hemispheric differences are especially evident in language processing. The isolated left hemisphere has the full capacity to produce and comprehend language while the right has little ability to process syntax and phonology, but can possess a mental lexicon. The isolated right hemisphere also struggles with understanding syntactical aspects such as pluralization, possessives and active-passive differences (Michael S. Gazzaniga, 1970), lacks the capacity to use word order to understand phrases (Michael S Gazzaniga, Nass, & Reeves, 1984), and struggles with aspects of phonological processing, such as phonemic categorization (Sidtis, Volpe, Wilson, Rayport, & Gazzaniga, 1981) and rhyme detection (E. Zaidel & Peters, 1981).

The clear left hemisphere dominance for most language functioning begs the question of the exact role that the corpus callosum plays in mediating this lateralization. Split-brain patients have shown that the CC mediates the transfer of basic perceptual (M. S. Gazzaniga, 1966), orthographic (K. Suzuki et al., 1998) and semantic information (Sidtis, Volpe, Holtzman, Wilson, & Gazzaniga, 1981). However, with regards to language lateralization, some researchers suggest that the role of the CC is exclusively excitatory and lateralization arises from
asymmetrical excitatory transfer (Nowicka & Tacikowski, 2011a; Weems & Reggia, 2004), while others suggest that the CC plays an active role in suppressing the non-dominant hemisphere through transcallosal inhibition (Kinsbourne, 1970; Moscovitch, 1976; Eran Zaidel & Schweiger, 1984). These opposing accounts of CC function in language are still very much debated; the following section will outline the core components and supporting evidence of each hypothesis.

1.4. Callosal function in language - Excitation, inhibition or both?

Physiologically, callosal axons depend primarily on glutamate as a neurotransmitter, and thus the direct connections are excitatory (Bloom & Hynd, 2005; Conti & Manzoni, 1994), but the presence of inhibitory interneurons allows the CC to inhibit neural activity (Jeffrey M. Clarke & Zaidel, 1994). Thus, physiological inhibition and excitation are both present, but the core question regarding the corpus callosum is about functional excitation and inhibition: whether processing in one region tends to activate or suppress processing of homologous regions in the contralateral hemisphere (Bloom & Hynd, 2005; Hellige, 1993).

The excitatory model suggests that the CC serves to share and integrate information across hemispheres (Geschwind & Galaburda, 1985), whereas the inhibitory model suggests that the CC acts to isolate the dominant hemisphere by blocking transcallosal information transfer or by actively inhibiting the contralateral hemisphere (Cook, 1986; Kinsbourne, 1975). While callosal function is often dichotomised as a question of inhibition or excitation (e.g., Bloom & Hynd, 2005; van der Knaap & van der Ham, 2011), it is evident that both forms of interactions exist, depending on the task and callosal subdivision involved. For example, excitatory
connections are clearly necessary for the transfer of basic visual information via posterior callosal fibres (Bloom & Hynd, 2005; M. S. Gazzaniga, 2000; van der Knaap & van der Ham, 2011), while inhibitory connections are necessary for motor coordination (Perez & Cohen, 2009).

The role of the CC in language is especially interesting given that language processing involves a wide sweeping network of brain regions from posterior perceptual to frontal control areas. Thus, transcallosal interactions that mediate each processing step will vary depending on the cortical regions involved and processing demands. This dissertation will delineate the transcallosal interactions that are involved in auditory sentence comprehension and visual word recognition, two tasks that span the extreme ends of language processing. Chapter 2 outlines the relationship between right hemisphere language processing and left hemisphere tissue dysfunction in post-stroke aphasia. Chapter 3 characterizes interhemispheric connectivity during sentence comprehension in healthy adults and changes in connectivity following left hemisphere damage. Chapter 4 presents an assessment of interhemispheric connectivity in healthy adults during lateralized lexical decisions. Finally, Chapter 5 assessed the interhemispheric transfer of semantic information in a bilateral word recognition task. The results from these studies suggest that 1) left hemisphere dysfunction is directly related to right hemisphere activation in stroke, 2) healthy sentence comprehension involves excitatory connectivity between auditory cortices, 3) interhemispheric interactions in the early stages of visual word recognition are primarily excitatory and asymmetrical, and 4) interhemispheric transfer of semantic information can facilitate lateralized word recognition. The remainder of this introduction will be a selective review of current state of the literature regarding interhemispheric interactions in aphasia and in visual word recognition in healthy adults.
1.5. Hemispheric processing in aphasia

Research regarding the role of interhemispheric interactions in aphasia can be broadly divided into three categories: 1) neuroimaging studies of language activation following left hemisphere damage, 2) rehabilitation studies looking at non-invasive brain stimulation, and 3) connectivity studies looking at interhemispheric interactions. The following section will summarize these three categories of research and highlight what they say about interhemispheric interactions in aphasia.

Aphasia is a language disability that typically results from ischemic damage to left hemisphere language regions. While there is a general correlation between lesion size and behavioral deficits, the key determinant of language impairment is damage to critical regions within the left hemisphere language network (Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004; Sims et al., 2016). Currently, the literature suggests that recovery in aphasia can result in the recruitment of left hemisphere perilesional tissue (Katri Cornelissen et al., 2003; W.-D. Heiss, Thiel, Kessler, & Herholz, 2003; Perani et al., 2003; Warburton, Price, Swinburn, & Wise, 1999a) or right hemisphere homologues of damaged language areas (Cao, Vikingstad, George, Johnson, & Welch, 1999; Jenny Crinion & Price, 2005; Leff et al., 2002; Musso et al., 1999a; Perani et al., 2003; Rosen et al., 2000; Sharp, Scott, & Wise, 2004; Weiller et al., 1995).

The large variability in this patient population regarding lesion size, lesion location, patient demographics and pre-existing conditions complicate attempts to identify conditions that would lead to one hemisphere taking over. Some researchers have demonstrated correlations between lesion size and language lateralization: right hemisphere activation is more likely with larger left hemisphere lesions (Sebastian & Kiran, 2011; Sims et al., 2016; Skipper-Kallal, Lacey, Xing, & Turkeltaub, 2017; Vitali et al., 2007). Vitali et al., (2007) studied two aphasic
patients who received training for severe phonological anomia. The training induced different activation patterns in the two patients. Left hemisphere activation and better behavioral performance was observed in one patient with a smaller lesion that spared Broca’s area, while right hemisphere activation and poor performance was observed in the other patient with a larger lesion that completely destroyed Broca’s area. This relationship between lesion size and hemisphere activation was later observed in a study of eight patients that involved both semantic judgments and picture naming (Sebastian & Kiran, 2011). Again, they reported that larger lesions led to more right hemisphere activation, but this was also dependent on lesion location and task activation in controls. Picture naming activated a bilateral network in both patients and controls, although the right hemisphere activation in patients was correlated with lesion size. Semantic judgments however, involved left frontal regions in controls and homologous right hemisphere activation was observed only in patients with damaged left frontal tissue. More recently, Sims et al., (2016) studied fourteen aphasia patients and measured the percentage of tissue spared in particular regions of interest (ROI), and then assessed correlations between that measure and the percentage of BOLD signal change across a number of bilateral ROIs. They found that damage to the left inferior frontal gyrus (LIFG), left middle temporal gyrus (LMTG) and left angular gyrus/supramarginal gyrus (LAG/SMG) was correlated with more bilateral activation during semantic processing. Together, these results suggest that damage to regions along the perisylvian language network is associated with greater right hemisphere activation.

The correlation between left hemisphere damage and right hemisphere activation suggests that the right hemisphere is recruited to compensate for damaged tissue. Chapter 2 further explores this relationship by looking beyond structural damage, and assessing the relationship between dysfunction of spared perilesional tissue and right hemisphere activation.
This first requires an appropriate measure of task-independent tissue dysfunction. Chapter 2 thus, focuses on two components, the first is an assessment of several electrophysiological markers of tissue dysfunction. These markers are then evaluated for correlation with task-based activation.

The results from Chapter 2 show that left hemisphere tissue dysfunction is indeed correlated with right hemisphere task-activation during sentence-picture matching. These results are in line with Sebastian and Kiran (2011) showing that right hemisphere activation in picture naming is associated with structural damage to the left hemisphere. These correlations suggest that right hemisphere activation is compensating for damaged and dysfunctional tissue in the left hemisphere. However, some researchers argue that right hemisphere activation is maladaptive. This debate is couched in the fundamental question of interhemispheric interactions in healthy language processing and following left hemisphere damage.

1.6. Right hemisphere activation in aphasia – Recruitment or Disinhibition?

Hemispheric activation associated with language recovery varies widely across patients; many studies have associated recovery with the activation of left hemisphere perilesional regions (Katri Cornelissen et al., 2003; W. D. Heiss et al., 1997; Postman-Caucheteux et al., 2010; Rosen et al., 2000; Warburton et al., 1999a) and many other studies have linked recovery with activation of right hemisphere homologues (Abo et al., 2004; Blasi et al., 2002; Cappa et al., 1997; Jenny Crinion & Price, 2005; W.-D. Heiss et al., 2003; Jed A. Meltzer, Wagage, Ryder, Solomon, & Braun, 2013; Ohyama et al., 1996; Perani et al., 2003; Thulborn, Carpenter, & Just, 1999a).
These studies vary widely in the task involved, and in some cases, studies using the same task show conflicting results. For example, performance in word stem completion has been correlated with activation in the left hemisphere (Rosen et al., 2000) and right hemisphere (Blasi et al., 2002). Regardless, there is evidence that the efficacy of the right hemisphere activation is dependent on the lateralization of the task itself; perilesional activation is best associated with performance in tasks that are typically left lateralized (W. D. Heiss et al., 1997; Postman-Caucheteux et al., 2010) while right hemisphere activation is advantageous for bilateral tasks (Jenny Crinion & Price, 2005; Jed A. Meltzer et al., 2013; Thulborn et al., 1999a).

The left hemisphere advantage for lateralized tasks was clearly shown by Postman-Caucheteux et al., (2010) with single-trial analyses of fMRI responses in three aphasic patients during a picture naming task. The single-trial approach allowed for the analysis of trial difficulty and brain activation. Difficult trials were those with targets that were acquired later in life and associated with a high number of alternative names. Task performance was at ceiling levels for controls, and activation was largely left lateralized, however the right hemisphere was recruited during the more difficult trials. Task performance in patients ranged from 53-75%, and accuracy was correlated with difficulty. Critically, while perilesional activation was present for both correct and incorrect trials, right hemisphere contralesional activation was exclusive to incorrect trials. These findings suggest that while right hemisphere activation in controls reflected adaptive recruitment for difficult trials, right hemispheric recruitment in patients was maladaptive.

Conversely, Crinion and Price (2005) analyzed brain activity during a more complicated sentence comprehension task in two groups of patients, one group with infarcts damaging the left temporal lobe and another group with lesions sparing the left temporal lobe. This task was associated with bilateral activation in controls and both patient groups. Interestingly, differences
in activation between controls and patients were exclusive to the left hemisphere, with controls showing greater LH activation. Critically, both patient groups showed a positive correlation between auditory sentence comprehension and activation in the right lateral anterior temporal lobe. These results demonstrate that right hemisphere activation is adaptive in typically bilateral tasks.

Interestingly, adaptive right hemisphere activation is not limited to language homologues. This was demonstrated by Meltzer et al., (2013) during a sentence-picture matching task which induced bilateral activation in both patients and controls. Again, right hemisphere activation in controls was positively correlated with task performance. However, the regions involved were not right hemisphere language homologues, but dorsal fronto-parietal regions more typically involved in working memory. The task itself did require a working memory component, as there was a brief memory delay, suggesting that patients were activating task-relevant, non-language networks to compensate for the damaged left hemisphere language network.

These studies show that right hemisphere activation can be adaptive or maladaptive depending on the demands of the task, and may reflect different mechanisms of interhemispheric interactions. Cases of adaptive right hemisphere activation may reflect excitatory transcallosal recruitment of right hemisphere language homologues, while cases of maladaptive right hemisphere activation may result from disinhibition of the right hemisphere due to damage to the left hemisphere. These competing theories make different predictions with regards to the efficacy of excitatory/inhibitory brain stimulation on patient rehabilitation. Many studies have assessed different brain stimulation protocols for rehabilitation in aphasia, and as with the activation studies, the results are conflicting.
1.7. Brain stimulation and Aphasia

Two noninvasive brain stimulation techniques have been used to facilitate rehabilitation in aphasia, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). TMS utilizes magnetic pulses generated directly above the scalp to induce electrical currents in specific brain regions (Pascual-Leone, Walsh, & Rothwell, 2000). Technological advances in the early 1990s allowed for the delivery of multiple repetitive pulses (rTMS) at a specified frequency, intensity and duration. This rTMS technique has been used to modulate the overall excitability of affected cortex, with the effect lasting for a period of time after stimulation (Brignani, Manganotti, Rossini, & Miniussi, 2008; Pascual-Leone et al., 1998). While low frequency repetitions at 1Hz frequency can decrease cortical excitability, high frequency repetitions, between 5-20Hz, can increase excitability (Margaret A. Naeser et al., 2010). Similar to rTMS, tCDS is another technique that can modulate cortical excitability by delivering a weak current through a sponge electrode placed on the scalp (Priori, Hallett, & Rothwell, 2009). The directionality of current flow determines whether neural excitability is increased (anodal tDCS) or decreased (cathodal tCDS) (Nitsche et al., 2008).

Naeser et al., (2010) presented a series of studies that demonstrated the efficacy of inhibitory rTMS over the right hemisphere to facilitate recovery in nonfluent aphasia. Nonfluent aphasia is characterized by a deficit in speech production, which is typically left lateralized in controls (Cai, Haegen, & Brysbaert, 2013), and RH activation amongst these patients has been shown to be maladaptive (Belin et al., 1996; Margaret A. Naeser et al., 2004; Perani et al., 2003; Rosen et al., 2000). The first study presented in Naeser et al., (2010) assessed the effects of rTMS over the right hemisphere frontal ROIs and demonstrated significant naming improvements at 2 months and 8 months after rTMS treatment. The next study looked at fMRI
activation in two non-fluent aphasia patients before and after rTMS treatment. One patient showed good response to rTMS with positive naming improvements and exhibited a shift from right hemisphere activation before rTMS to left hemisphere perilesional activation 16 months post-TMS. The other patient had no change in naming following rTMS and showed no new perilesional LH activation in any following assessment. The third study demonstrated the efficacy of rTMS combined with constraint-induced language therapy in one patient with mild nonfluent aphasia and another with severe nonfluent aphasia. Together, these studies suggest that inhibitory stimulation over the right hemisphere can improve cases of non-fluent aphasia by shifting activity back towards the perilesional tissue.

More recently Otal et al., (2015) reviewed nine randomized clinical trials, involving 215 participants, that used rTMS or inhibitory c-tDCS over the right hemisphere to facilitate rehabilitation. All studies paired stimulation with speech language therapy (SLT) and used accuracy in naming, another left lateralized task, as the outcome measure. The results showed that SLT combined with inhibitory stimulation over the right hemisphere improved naming above and beyond SLT alone. Interestingly, inhibitory c-tDCS over the left hemisphere has also been shown to improve naming accuracy (A. Monti et al., 2008). This finding was interpreted as c-tDCS decreasing the excitability of inhibitory circuits in the damaged left hemisphere, thereby increasing the excitability of the perilesional tissue (Alessia Monti et al., 2013). As evidence for this, Kanjiro Suzuki et al., (2012) demonstrated increased excitability of damaged left hemisphere motor cortex following c-tDCS.

While there is considerable evidence for the efficacy of inhibitory right hemisphere stimulation for naming, the results are not always consistent. For example, Flöel et al., (2011) demonstrated improvements in anomia following excitatory a-tDCS over the right hemisphere,
and a recent meta-analysis of six randomized clinical trials questioned the validity of reported behavioral improvements after a reanalysis with standardized effect sizes (Elsner, Kugler, Pohl, & Mehrholz, 2015).

The results for speech comprehension, a typically bilateral process, are even more variable. A recent meta-analysis of seven studies, four of which measured language comprehension, showed mixed results regarding the efficacy of inhibitory rTMS over the right IFG: improvements were observed with the Token Test for receptive problems in aphasia, but not the comprehension subtests of the Aachen Aphasia Test (AAT) and Boston Diagnostic Aphasia Examination (BDAE) (Ren et al., 2014). Other studies have also failed to find evidence for right hemisphere rTMS effects on speech comprehension (Li, Qu, Yuan, & Du, 2015; Thiel et al., 2013a).

The findings that inhibitory rTMS to the right hemisphere can improve left lateralized verbal processes support the claim that right hemisphere activation is maladaptive and results from disinhibition. However, the inconsistent effects of right hemisphere inhibition for bilateral processes like speech comprehension support the notion that right hemisphere activation is adaptive and results from excitatory recruitment. These two interhemispheric mechanisms cannot be disentangled with stimulation alone, but advances in connectivity analyses provide new insights into transcallosal interactions in language processing.

1.8. Interhemispheric Connectivity in Language and Aphasia

A number of studies have assessed changes in inter and intrahemispheric connectivity in aphasia (Griffis, Nenert, Allendorfer, & Szaflarski, 2016; Kiran, Meier, Kapse, & Glynn, 2015; Marcotte, Perlberg, Marrelec, Benali, & Ansaldo, 2013; Meier, Kapse, & Kiran, 2016; Schofield et al., 2012; Teki et al., 2013; Warren, Crinion, Lambon Ralph, & Wise, 2009; Zhu et al., 2014).
Studies of resting-state functional connectivity have found a positive association between language performance and interhemispheric connectivity (Marcotte et al., 2013; Zhu et al., 2014). Marcotte et al., (2013) assessed overall connectivity within the default-mode network (DMN) in patients before and after intensive Semantic Feature Analysis (SFA) therapy. Patients who underwent SFA exhibited increased functional connectivity within the posterior subnetwork of the DMN, which included bilateral temporal regions. Zhu et al., (2014) also reported a positive correlation between resting state frontal interhemispheric connectivity and language comprehension. Furthermore, Warren et al., (2009) measured task-related functional connectivity and found that connectivity between left and right superior temporal cortices was associated with word and sentence comprehension.

Together, these studies show that interhemispheric connectivity is critical for language recovery. However, measures of functional connectivity can not distinguish between excitatory and inhibitory connections, nor can they reveal the direction of information flow. More recently, studies have looked to effective connectivity measures, like Dynamic Causal Modelling (DCM), to better characterize interhemispheric interactions in aphasia (Kiran et al., 2015; Schofield et al., 2012; Teki et al., 2013). Schofield et al., (2012) assessed effective connectivity between bilateral medial geniculate bodies, bilateral Heschl’s gyri (HG), and bilateral planum temporale (TP) during speech perception in patients with moderate and severe aphasia. The control group showed mutual positive interhemispheric coupling between bilateral HG and bilateral PTs while moderate aphasia patients showed significantly reduced coupling from right-to-left HGs. Teki et al., (2013) assessed effective connectivity between bilateral superior temporal gyri (STG) and bilateral HGs during an auditory oddball task using verbal stimuli. Patients exhibited greater left-to-right excitatory coupling between the HGs and phonemic discrimination ability was positively
correlated with left-to-right coupling between the STGs. Finally, Kiran et al., (2015) found evidence that bilateral interhemispheric connectivity between frontal ROIs in some patients was significantly modulated by training in a semantic feature-based naming intervention. However, these results did not generalize to the group level analysis due to large variability in both lesion size and location.

These DCM studies demonstrate again, that aphasia is associated with disrupted interhemispheric connectivity, which is correlated with the magnitude of language disruption. Interestingly, inhibitory interhemispheric connectivity was not observed in any of the above studies, although some DCM studies with healthy controls have demonstrated interhemispheric inhibition in certain tasks.

Seghier et al., (2011) looked at interhemispheric connectivity of bilateral dorsal and ventral frontal ROIs during a semantic decision task using words and pictures. They reported that semantic decisions on words led to negative coupling from the left-to-right dorsal ROIs. Interestingly, Kawabata-Ducan et al., (2014) presented evidence for both excitation and inhibition when studying lexical decisions for Kana and Kanji. Specifically, they reported bilateral excitation between left and right vOTs and asymmetrical right-to-left inhibition at the IFGs.

Other studies of healthy participants have found only evidence for interhemispheric excitation. Stephan et al., (2007) assessed young controls during both spatial and letter detection using lateralized presentations of words. They found that letter detection was associated with an asymmetric excitatory connectivity from the right-to-left hemisphere, only when stimuli were presented to the left visual field, suggesting an asymmetrical transfer of information. Carreiras et al., (2008) also demonstrated mutual excitatory connectivity along bilateral angular gyri, as well
as negative feedback connectivity to occipital ROIs when comparing single word reading vs. object naming.

Thus far, the studies of DCM in healthy participants provide evidence for interhemispheric inhibition between frontal regions (Seghier et al., 2011; Kawabata-Duncan et al., 2014) and excitation between posterior regions (Stephan et al., 2007; Carreiras et al., 2008; Kawabata-Duncan et al., 2014). Furthermore, frontal inhibition seems to be related to more complicated tasks that involve response competition (Kawabata Duncan et al., 2014; Seghier, Josse, Leff, & Price, 2011a), while posterior excitation is necessary for sharing of basic perceptual information (Carreiras et al., 2009; Kawabata Duncan et al., 2014; Klaas E. Stephan et al., 2007).

Chapter 3 continues this line of research and uses Dynamic Causal Modelling (DCM) to characterize the interhemispheric interactions in sentence comprehension. In line with the other studies of effective connectivity, the results fail to find any evidence for homotopic inhibition in either controls or patients. Instead, controls exhibited feedback inhibitory connections from the LIFG to both HGs and excitatory right-to-left modulation between HGs. While these connections were not significant on the group level in patients, they do correlate significantly with language performance. Patients with connections that were in the opposite direction from controls (e.g., inhibition when controls show excitation) performed worse in measures of language comprehension. These results suggest that language deficits in aphasia result from a loss of feedback connectivity from the LIFG and disrupted excitatory transfer of perceptual information between hemispheres.

While the stimulation studies have typically focused on canonical language regions such as Broca’s and Wernicke’s areas, the results from Chapter 3 and other DCM studies show that
some language deficits may result from disrupted interhemispheric transfer of perceptual information, an area that has received less attention in language research. Chapter 4 focuses on basic perceptual information transfer in lateralized visual word recognition.

1.9. Transcallosal interactions in Visual Word Recognition

The study of transcallosal interactions in visual word recognition started with behavioral studies using tachistoscopic presentations of verbal stimuli presented to a single visual field. This methodology takes advantage of the lateralized nature of the human visual system: stimuli presented to one visual field are projected to the contralateral hemisphere (Bourne, 2006). Decades of research have consistently demonstrated that verbal stimuli are processed faster and more accurately when presented to the right visual field / left hemisphere (RVF-lh) (eg., Barca et al., 2011; D. B. Boles, 1983; David B. Boles, 1987; D.B. Boles, 1995; Bourne, 2006; Bradshaw & Nettleton, 1983; Hellige, 1993, 1993; Hines, 1976; Hunter & Brysbaert, 2008; Iacoboni & Zaidel, 1996; Leiber, 1976; McKeever, 1971; McKeever & Hulling, 1971; Nazir, 2000; Nazir, Ben-Boutayab, Decoppet, Deutsch, & Frost, 2004; Nicholls & Wood, 1998; Seitz & McKeever, 1984; Selpien et al., 2015; Weems & Zaidel, 2004). This RVF-lh advantage is thought to reflect the direct projections from the right side of the retina (in both left and right eyes) to the language-dominant left hemisphere (Banich, 2003; Bourne, 2006; Bradshaw & Nettleton, 1983; Hellige, 1993; Hunter & Brysbaert, 2008; though see Ducrot & Grainger, 2007; Nazir, 2000; Nazir et al., 2004 for an alternative account).

Compelling evidence for the left hemisphere dominance account of the RVF-lh advantage was recently reported by Hunter and Brysbaert (2008). The study included 26 left-handed individuals, a population with a higher percentage of bilateral language representation (Knecht et al., 2003). Following a diagnostic lateralized naming task, three subsets of
participants were selected based on their degree of behavioral lateralization and participated in a follow-up fMRI assessment of language lateralization using a mental word generation task. The results from these participants showed a clear correlation between the behavioral VF advantage and the lateralization of responses at bilateral IFG ROIs: participants with greater RVF-lh advantages showed more left lateralized responses. This shows that the RVF-lh advantage is directly linked to the lateralization of language processing at frontal regions, suggesting that at some point, LVF-rh stimuli needs to be transferred from the right-to-left hemispheres. However, the precise stage for this transfer is unclear, with some studies suggesting that the transfer is very early between occipital regions, while others suggest that transfer occurs between homologous regions located at the posterior ventral occipitotemporal cortex (vOT).

The role of the left vOT in reading has been studied since 1892, when Dejerine first reported the case of a patient who selectively lost the ability to read following a lesion to the left vOT. Dejerine hypothesized that, for reading, visual information is processed independently in each hemisphere, but a position invariant representation of the word is eventually transferred to the left vOT. Evidence for this claim can be found from a number of studies showing lesions to the posterior corpus callosum lead to alexia but only for words presented to the LVF-rh (Abe, Nakamura, Sugishita, Kato, & Iwata, 1986; L. Cohen & Dehaene, 1996; Damasio, Chui, Corbett, & Kassell, 1980; Degos et al., 1987; Sidtis, Volpe, Holtzman, et al., 1981; Sugishita, Iwata, Toyokura, Yoshioka, & Yamada, 1978; Kanjiro Suzuki et al., 2012; Trescher & Ford, 1937).

More recently, Cohen et al., (2000) provided neuroimaging evidence for this hypothesis in a combined fMRI-EEG study of lateralized word naming in two patients with lesions to the posterior corpus callosum, which disconnected the posterior hemispheres. In controls, bilateral extrastriate occipital areas responded more strongly to contralateral stimuli, reflecting the
contralateral projections of the visual system. However, a region along the posterior left vOT was equally responsive to LVF-rh and RVF-lh stimuli. This left hemisphere region was also activated in the disconnected patients, but only for RVF-lh stimuli. These results led the authors to suggest that this so called Visual Word Form Area (VWFA) takes part in processing position-invariant representations of visual word forms and acts as a gateway from the visual system to the left hemisphere language network. The activation of the VWFA in response to words has been replicated many times since (Cai et al., 2013; L. Cohen et al., 2003, 2003; Laurent Cohen et al., 2002; Dehaene & Cohen, 2011; Devlin, Jamison, Gonnerman, & Matthews, 2006; Pammer et al., 2004), though the response specificity of this region to just words has been questioned by authors citing findings of VWFA responses to pictures and pseudowords (Dehaene & Cohen, 2011; Devlin et al., 2006). The finding that the VWFA is responsive to stimuli from both visual fields inspired a basic model of visual word perception wherein visual information is processed independently in each hemisphere before converging at the VWFA (McCandliss, Cohen, & Dehaene, 2003).

More recently, evidence against the claim of position-invariant VWFA processing was presented by Rauschecker et al., (2012). Participants made lexical decisions to stimuli that were presented at various eccentricities along the horizontal meridian. fMRI responses from the primary visual cortex (V1/V2), the left VWFA, the right hemisphere homologue of the VFWA (rVFWA) and Broca’s area were used to predict the horizontal position of target stimuli. As expected, fMRI responses from the V1/V2 led to very high decoding accuracy of 94%, and responses from Broca’s area, which does not encode any position information, led to chance-level decoding accuracy. Critically, using the combined responses from the VWFA and rVFWA, the classifier predicted horizontal position with 92% accuracy. These results demonstrate that the
VWFA and its right hemisphere homologue do indeed process information regarding a stimulus' location on the retina. This led Rauchecker et al., (2012) to propose a circuit diagram for visual word recognition in which each hemisphere processes basic visual information independently, with each hemisphere’s VWFA acting as a gateway to the left hemisphere language system. According to this model, the bilateral VWFAs are the first regions involved in interhemispheric interactions.

The research into the VWFA led to the development of models in which basic visual information is processed independently at each hemisphere (McCandliss, Cohen, & Dehaene, 2003; Rauschecker et al., 2012). However, recent neuroimaging studies provide evidence for earlier interhemispheric transfer between the occipital lobes (Barca et al., 2011; Selpien et al., 2015). Barca et al., (2011) reported MEG responses collected during a lateralized word naming that were source localized to three ROI pairs, bilateral middle occipital gyri (MOG), bilateral VWFAs and bilateral precentral gyri. Responses at both MOGs were stronger for contralateral stimuli, but the response to ipsilateral stimuli was greater for the left MOG, suggesting an asymmetrical transfer of visual information from the right-to-left hemisphere. Similarly, the responses at the VWFAs were greater for contralateral stimuli, but there was no difference in response to ipsilateral stimuli. These results provide evidence for very early asymmetric hemispheric transfer between occipital regions.

Selpien et al., (2013) measured EEG responses to a lateralized lexical decision with stimuli presented horizontally or rotated vertically. Vertical stimulus orientation was included to disrupt the typical perceptual processes involved in normal reading. The behavioural results showed a typical RVF-Lh advantage, but only for horizontal stimuli. Furthermore, visual field differences in neural responses to horizontal words were localized to the left BA19 (V4), left
angular gyrus and left supramarginal gyrus, while visual field differences for vertical words were localized to the left angular gyrus and left supramarginal gyrus. Together, these results suggest that left ventral occipital cortex is selectively responsive to verbal stimuli presented in a canonical horizontal orientation, and that this region is more responsive to stimuli from the contralateral visual field.

Together, the results from Barca et al., (2011) and Selpjen et al., (2013) provide evidence against the models suggesting that each hemisphere processes basic visual information separately (McCandliss et al., 2003; Rauschecker et al., 2012). Further evidence against the idea of independent hemispheric visual processing can be found in the phenomenon of the bilateral effect. Several studies have shown that under bilateral presentation conditions, responses to LVF-rh verbal stimuli are asymmetrically impaired (David B. Boles, 1987; D.B. Boles, 1995; Fernandino, Iacoboni, & Zaidel, 2007; Iacoboni & Zaidel, 1996; Olk & Hartje, 2001; Perrone-Bertolotti, Lemonnier, & Baciu, 2013; Seitz & McKeever, 1984; Weems & Zaidel, 2004, 2005; Wey, Cook, Landis, Regard, & Graves, 1993). Critically, studies have recently demonstrated that the magnitude of this bilateral effect depends on stimulus characteristics of the contralateral distractor. Perrone-Bertolotti et al., (2013) used a lexical decision task (word / nonword judgment) tested several types of distractors and found that the bilateral effect was a function of the perceptual and lexical overlap between the target and distractor: lexically incongruent distractors (e.g. DOG - BEP) created the most interference, semantically related distractors (DOG - CAT) created less interference, and distractors that were identical to the target (DOG - DOG) abolished the RVF-lh advantage. Similarly, Fernandino et al., (2007) showed that perceptual distractors (e.g., XXXX) created less interference than word and pseudoword distractors. These studies demonstrate that the bilateral effect can result from
perceptual, lexical, and semantic distractors, suggesting that interhemispheric interactions occur at multiple stages of word recognition.

Chapter 4 looks at the precise stage of interhemispheric transfer and interference during a bilateral lexical decision task. Neural responses, and inter and intrahemispheric connectivity were measured between four regions of interest, bilateral middle occipital gyri (MOG) and bilateral VWFA. The results show that for unilateral trials, there was an asymmetrical interhemispheric transfer between right-to-left MOGs that was present only for LVF-rh trials. Behavioral analysis of the bilateral trials showed a typical bilateral effect, with accuracy most impaired for bilateral trials with LVF-rh targets. Interestingly, bilateral trials led to reduced neural responses along all four regions of interest and reduced interhemispheric connectivity, irrespective of target visual field. Together these results suggest that interhemispheric transfer and interference occurs early in the processing stream between occipital regions.

The results from Chapter 4 provide further evidence for excitatory transcallosal transfer between posterior occipital regions. While perceptual processing typically necessitates integration between hemispheres, transcallosal inhibition may play a role in downstream processes that are associated with response competition. Chapter 5 explores the interhemispheric interactions related to semantic processing in a bilateral word recognition task.

1.10. Interhemispheric interactions in Semantic Processing

Semantic processing of verbal information involves a widespread bilateral network (Vigneau et al., 2011), with the two cerebral hemispheres specialized to process different types of semantic relationships (e.g., Beeman, 1993; Deacon et al., 2004; Federmeier, 2007). However, the role of interhemispheric communication in semantic processing is uncertain. According to
the two accounts of interhemispheric interactions, semantic information from the contralateral hemisphere can either facilitate processing through excitatory priming (Collins & Coney, 1998) or cause inhibitory response competition (Cook, 1986). Studies using simultaneous bilateral displays have demonstrated that the presence of interhemispheric semantic inhibition or excitation is contingent on task demands. Compared to unilateral presentations, bilateral presentations can facilitate responses for relatedness judgments in the Dimond paradigm (reviewed in, Leblanc-Sirois & Braun, 2014) and hinder responses during lateralized lexical decisions (Fernandino et al., 2007; Iacoboni & Zaidel, 1996; Olk & Hartje, 2001; Perrone-Bertolotti et al., 2013; Weems & Zaidel, 2004; Wey et al., 1993).

The Dimond paradigm requires participants to make relatedness judgments between two visual stimuli that are simultaneously presented to one or both visual fields. Studies using this paradigm have reported a bilateral advantage when making semantic relatedness judgements of Chinese synonyms (Zhang & Feng, 1999) and semantically related pictures (Koivisto, 2000, Koivisto & Revonsuo, 2003) and word pairs (Koivisto & Revonsuo, 2003; Davis et al., 2012; 2015). While semantic relatedness judgements benefit from bilateral displays, studies of lexical decision show that bilateral displays can asymmetrically impair processing of targets presented to the LVF-rh (Fernandino et al., 2007; Iacoboni & Zaidel, 1996; Olk & Hartje, 2001; Perrone-Bertolotti et al., 2013; Weems & Zaidel, 2004; Wey et al., 1993).

These conflicting effects of bilateral displays suggest that interhemispheric interactions can be either interfering or facilitative depending on the task. In the case of the Dimond paradigm, the task requires the integration of stimuli from both visual fields, while with the bilateral effect, one visual field is attended to, and the other must be ignored. Chapter 5 extended this body of research on bilateral displays using a bilateral word recognition task, in which
participants were asked to identify two words that are briefly presented in the two visual fields. This design was implemented to assess how semantic information from the contralateral hemisphere can influence target identification in a task that required the independent identification of words presented to both visual fields.

The results from Chapter 5 provide further evidence for the excitatory transfer of semantic information between hemispheres. Specifically, words are easier to identify when a semantically related word is presented to the contralateral visual field. The results also provided some evidence for an asymmetry in this semantic transfer, with the LVF-rh preferentially receiving priming from the RVF-lh. As with the previous chapters, the results failed to find evidence for interhemispheric inhibition.

The following chapters in this dissertation outline the interhemispheric interactions that are involved in various stages of language processing. Chapter 2 demonstrates that the right hemisphere language activation is associated with the magnitude of tissue dysfunction within the perilesional region. These findings could have resulted from either disinhibition or maladaptive recruitment. Chapter 3 further investigates this, looking at interhemispheric effective connectivity in the same group of patients doing the same task with fMRI. The results show no evidence of homotopic inhibition, but instead indicate that a loss of feedback inhibition from the LIFG to both A1s is associated with language difficulties. Furthermore, healthy language processing was also associated with an asymmetrical excitatory transfer from the right-to-left auditory cortices, and disrupted language processing was associated with disruption of this interaction. The asymmetrical transfer of perceptual information was further explored in Chapter 4 in the context of lateralized word recognition. Contrary to the current models of word recognition, the results indicate that interhemispheric transfer occurs very early and
asymmetrically between the occipital lobes. Finally, interhemispheric transfer of semantic information was explored in Chapter 5 using a bilateral word recognition task. As with previous chapters, the results show evidence for excitatory transfer but no interhemispheric inhibition. Together the studies on this dissertation outline the role of excitatory transfer across multiple stages of language processing.
Chapter 2
MEG-based detection and localization of perilesional dysfunction in chronic stroke

2.1. Introduction

Stroke causes profound disturbances to cognition, and is a leading cause of adult disability. One of the most debilitating cognitive impairments is aphasia, which typically occurs following damage to language networks in the left hemisphere. As stroke-induced cortical lesions are essentially permanent, language recovery is thought to proceed from processes of reorganization and neural plasticity occurring in structurally intact brain tissue. Specifically, reorganization of the language network after stroke is associated with the recruitment of structurally intact, perilesional tissue (K. Cornelissen et al., 2003; Warburton, Price, Swinburn, & Wise, 1999b) and contralateral homotopic language areas (Musso et al., 1999b; Thulborn, Carpenter, & Just, 1999b; Tillema et al., 2008). Although both perilesional and contralesional activity are thought to play a role in recovery, recruitment of perilesional areas is associated with a better long-term outcome (W.-D. Heiss & Thiel, 2006), and a shift from right-to-left hemisphere activation has been observed to occur during spontaneous recovery (D. Saur et al., 2006) and with treatment (Wilson et al., 2012). With the advent of noninvasive brain stimulation as a viable treatment for aphasia and post-stroke motor disorders, positive results have been obtained from efforts to induce a shift from contralesional to perilesional activity, either through excitatory stimulation of the affected hemisphere or through inhibition of the unaffected hemisphere (Kang, Kim, Sohn, Cohen, & Paik, 2011; Marangolo et al., 2013; M. A. Naeser et al., 2005; J. P. Szaflarski et al., 2011). It is still unkown why perilesional tissue remains
underactivated in some patients. In some cases, patients may have large lesions that engulf most of the left hemisphere language areas; as such, language processing must be relegated to right hemisphere homologues. Indeed, studies have reported a correlation between left hemisphere tissue damage and right hemisphere language activation (Sebastian & Kiran, 2011; Sims et al., 2016; Vitali et al., 2007). However in other cases, perilesional tissue may be structurally intact, but ‘functionally lesioned’ (Hofmeijer & van Putten, 2012) representing an ideal target for intervention. Therefore, noninvasive methods to identify functional abnormalities in perilesional tissue will help guide physiological interventions to target the most relevant areas, and to assess their effectiveness. The current study demonstrates that spectral and nonlinear analyses of source localized MEG signals can be used to identify dysfunctional perilesional tissue.

One of the most prominent indices of tissue dysfunction following stroke is a change in spontaneous oscillatory activity measured by spectral analyses of MEG/EEG signals. Studies have found increased low frequency (Butz et al., 2004a; Harmony, Fernandez-Bouzas, et al., 1995; C. Machado et al., 2004; M. Meinzer et al., 2013; F. Zappasodi, Tombini, Milazzo, Rossini, & Tecchio, 2007) and attenuated high frequency (Cuspineda et al., 2009) spontaneous activity, localized to perilesional areas. Importantly, improved functional outcomes are associated with a reduction in perilesional low frequency amplification (M. Meinzer et al., 2004, 2008; F. Zappasodi et al., 2007) and increase in perilesional alpha-band functional connectivity (Westlake et al., 2012). Thus, low frequency amplification and high frequency attenuation are promising indicators of dysfunctional perilesional tissue.

Although most characterizations of pathological spontaneous activity in stroke have centered on spectral analyses, researchers have also applied techniques from the field of nonlinear dynamics towards analysis of brain signals in other disorders (for review, see Stam,
Measures based on the concept of entropy have been especially useful. The various algorithms incorporating this term estimate the complexity of neural dynamics, with complexity indicating a rich temporal structure that is neither random (e.g. white noise) nor strictly periodic. In this study, we examine multiscale entropy (MSE; Costa et al., 2002, 2005), an increasingly popular technique that assesses time series complexity across multiple time scales, reducing the arbitrariness inherent in pre-selecting a specific time scale (see methods for details). Reduced MSE has recently been demonstrated in brain injury (A. Raja Beharelle, Kovačević, McIntosh, & Levine, 2012), Autism (Bosl, Tierney, Tager-Flusberg, & Nelson, 2011; Catarino, Churches, Baron-Cohen, Andrade, & Ring, 2011) and Alzheimer’s disease (Hornero, Escudero, Fernández, Poza, & Gómez, 2008; J-H. Park, Kim, & Kim, 2007).

Given the success of MSE to characterize dysfunctional physiological signals, the current study aimed to compare MSE with the more traditional measures of spectral power in their ability to characterize perilesional dysfunction. In the present study, we used beamforming analysis of MEG data to localize and quantify abnormal perilesional activity in patients who have had a stroke in the left hemisphere of the brain. The patients were participating in a MEG study of language processing, aiming to identify networks that are recruited to support language comprehension in post-stroke aphasia (J. A. Meltzer, Wagage, Ryder, Solomon, & Braun, 2013). In the present study, we analyzed spontaneous aspects of the MEG data collected from these patients, focusing on the intertrial interval of the language comprehension task, but obtaining very similar results from data extracted from task periods. We hypothesized that, irrespective of engagement in a cognitive task, altered neural dynamics would be present in perilesional tissue, compared to other brain regions and compared to the same brain regions in healthy control participants. We used both spectral-based and entropy-based measurements, and report here the
similarities and differences found in these approaches. Specifically, the measures were compared along two levels, 1) the spatial extent of abnormal spontaneous activity detected by these measures and 2) the degree to which spontaneous perilesional activity predicted language activation in right hemisphere homologues, a frequently observed consequence of damage or dysfunction in left hemisphere language areas (J. Crinion & Price, 2005; D. Saur et al., 2006; Sebastian & Kiran, 2011; Sims et al., 2016; Thompson & den Ouden, 2008; Vitali et al., 2007).

The above questions were addressed with four different analyses. To address the first question, we 1) computed voxel-based comparisons of source localized relative power and MSE between patients and controls. To illustrate the differences in power spectra that drove the differences between groups seen in the whole-brain maps, we 2) additionally computed power spectra in selected regions of interest (ROI). To address the second question, we 3) computed task activation maps and 4) assessed correlations between task activation in the right hemisphere and characteristics of spontaneous signals in the left hemisphere. Finally, we 5) computed single subject maps to demonstrate the clinical utility of this approach for detecting tissue dysfunction within individual patients. Additionally, to further characterize the relationships between the nonlinear and spectral measures, we examined across-subjects correlations between MSE and relative power in different bands.

2.2. Methods

2.2.1. Participants

MEG data was obtained from three groups of participants, who had participated in studies of language comprehension (Meltzer and Braun, 2011; Meltzer et al., 2013). These included 25 patients (11 female, 2 left-handed) with aphasia, resulting from a single left-hemisphere ischemic
stroke which occurred at least 6 months prior to testing (0.7-24.3 years, mean 5.8 years). Patients ranged in age from 34-72 years (mean 57). The study was approved by the Institutional Review Board of the NIH Intramural Program (NIH protocol 92-DC-0178). Participants were financially compensated.

Imaging data from aphasic participants were compared with data from two control groups. First, there was a young control group, consisting of 24 healthy subjects (12 female, aged 22-37, mean 27). Additionally, to control for the effects of aging, we recruited an older control group, consisting of nine healthy subjects matched in age to the aphasic patients (range 44-71, mean 53). All young and age-matched controls were right-handed. None of the participants reported any developmental language difficulties.

The aphasic patients and the older control subjects underwent an extensive battery of cognitive and neurolinguistic assessments in addition to MEG and structural MRI, while the younger controls only completed the neuroimaging components. All older control subjects tested were within normal limits on all cognitive and linguistic tests, while the aphasic patients exhibited deficits consistent with their diagnosis of post-stroke aphasia. More details regarding lesion characteristics and neuropsychological profiles of the patients can be found in Meltzer et al., 2013.

The smaller number of age-matched controls reduced the power of our contrasts to reveal aging-related changes. However, as demonstrated in the results, both young and age-matched controls demonstrated comparable differences relative to aphasic patients, localized to perilesional regions, although the effects were stronger for young controls. Critically, the age-matched controls served to confirm that the current findings were related to stroke and not aging.
2.2.2. **Sentence picture-matching paradigm**

Participants performed a sentence picture-matching task during MEG scanning. Complete details of the sentence and picture materials can be found in previous reports (J. A. Meltzer & Braun, 2011; J. A. Meltzer et al., 2013). A brief description of the paradigm is as follows. On each trial, subjects heard a sentence, spoken at a natural rate, while viewing a fixation cross. After the sentence, the fixation cross remained during a three-second memory delay. Next, the cross was replaced by two pictures. Subjects indicated which picture correctly depicted the action described in the sentence, by pressing the left or right button on a fiber optic response box. Pictures remained on screen for four seconds, and were followed by an inter-trial interval of 2.1-2.25s. Trials were presented in seven runs of 36 trials each, and subjects were allowed to rest in between runs if desired. Total time for the experiment was approximately one and a half hours, including preparation.

Triggers were inserted into the MEG acquisition stream to allow for analysis of the MEG signal during each time period of the task. In the present study, we assessed spontaneous aspects of perilesional neural activity by analyzing data from the intertrial interval, using data epochs consisting of one second prior to sentence onset. Thus, analyses are based on 252 one-second epochs per participant. Data from the intertrial interval reflects a state of seated relaxation but high alertness, as participants were engaged in a cognitive task but were not actively processing sensory or cognitive information at the time. Possible implications of this selection of data as opposed to “true rest” are addressed in the discussion.

2.2.3. **Anatomical MRI**

Each patient underwent an anatomical MRI session, for purposes of MEG source localization and lesion delineation. MRI was acquired on a General Electric Signa 3-Tesla
scanner with an 8-channel head coil, using parallel imaging with ASSET reconstruction. Scans included a T1-weighted 3D high-resolution MPRAGE (1mm isotropic resolution, Fast Spin-Echo T2, T2 and FLAIR (both 3.5mm thick slices)). T1 images were skull stripped by applying a stripping procedure to the T2-weighted image, applying the resulting mask to the T1 image, and making further manual adjustments. This procedure produces better results than stripping the T1 image directly, due to the presence of large lesions that appear dark on T1 contrast.

Lesion borders were delineated using segmentation tools in FSL and ROI drawing tools in AFNI, based on a T1 intensity threshold followed by manual adjustments. Regions of gliosis were included in the lesion on the basis of hyperintense signal seen in a co-registered T2-FLAIR image. T1 images were spatially normalized by computing a 12-parameter affine registration between the individual patient brains and the "Colin brain" in Talairach space. Nonlinear registration algorithms produced slightly better registrations in some cases, but were not reliable for all patients in the presence of large lesions, so affine registration was adapted for consistency across the cohort. Cost-function masking was applied using the individual lesion masks to exclude the lesioned area from the warp computation. Using the computed affine matrices, both T1 anatomical images and lesion masks were warped into Talairach space for group analysis of lesion characteristics and source-localized MEG activation.

For the display of activation maps derived from patient data, we constructed a “composite lesion underlay” to indicate damaged regions with the greatest overlap across patients. The spatially normalized T1-weighted anatomical images of the 25 patients were averaged together. The resulting image was further darkened by subtracting a percentage of the signal proportional to the number of patients having a lesion at each voxel.
2.2.4. MEG acquisition and analysis

MEG was recorded with a CTF Omega 2000 system, comprising 275 first order axial gradiometers. For environmental noise reduction, synthetic third-order gradiometer signals were obtained through adaptive subtraction of 33 reference channels located inside the MEG dewar far from the head. Signals were digitized at 600 Hz with an anti-aliasing filter at 125 Hz. Head position was tracked continuously using coils placed at three fiducial points on the head (McCubbin et al., 2004). The average head position over the entire experiment was used for source localization, and coregistered with the same fiducial points marked on the anatomical MRI using adhesive marker disks. In no cases did the total root-mean-square of movement for any coil exceed 1 cm.

2.2.4. Synthetic aperture magnetometry

MEG source analysis was conducted using Synthetic Aperture Magnetometry (Vrba & Robinson, 2001) (SAM), as implemented in CTF software (CTF, Port Coquitlam, British Columbia, Canada). SAM is a beamformer technique that can be used to compute the full time course of virtual channels at selected individual locations, or on a regular grid of locations (voxels) spread across the brain. SAM is a scalar beamformer, in which a nonlinear optimization technique is used to select one direction of current flow at each voxel to maximize dipole power. In short, SAM provides a series of weights for each voxel; the weights are computed so as to pass signal from a dipole located in the target voxel, while minimizing signal power from all other locations. We computed weights on a whole-brain grid of locations spaced 1 cm apart. These weights were then multiplied with the original sensor time series data to yield a new, spatially filtered, time series signal at each voxel (1 cm³). Normalized weights were used to render virtual signals in dimensionless units of signal-to-noise ratio, with noise power estimated
as the lowest singular value of the sensor covariance matrix (Vrba & Robinson, 2001). This weight normalization step is commonly used to compensate for the depth-bias inherent in beamforming. However, because all our analyses are scaled to the signal strength, this step does not affect the results of the study at all. Signals were filtered at 0-80 Hz prior to beamforming.

2.2.4. Exploratory Analysis of Perilesional Abnormalities

As mentioned above, we are presenting a reanalysis of data from an experiment originally designed to assess adaptive right hemisphere activation in aphasia (Meltzer et al., 2013). The present study evaluates new methods for characterizing abnormal spontaneous activity in perilesional tissue in stroke patients. Although all statistical maps are corrected for multiple comparisons across voxels, we did not conduct additional correction across the multiple signal quantities (e.g. relative delta power, theta power, multiscale entropy, etc.) assessed in this study. As such, the following analyses are exploratory in nature, and the methods identified as being the most sensitive and specific may be used in future confirmatory studies in which study design and statistical power are optimized to test specific hypotheses about perilesional electrophysiological abnormalities, such as their relationship to other indices of pathology (e.g. blood flow, metabolism, white matter disconnection).

2.2.5. SAM Maps - Spontaneous Activity During the Intertrial Interval

We tested for changes in the frequency content of spontaneous MEG signals using spectral analysis. At each voxel, the power spectrum of the virtual signal for each data epoch was computed using Welch’s method in Matlab (Fast Fourier Transform of 500ms Hamming windows with 50% overlap). Power spectra were averaged across epochs.

To evaluate quantitative parameters related to slowing of spontaneous activity, we computed measures of relative power from the resulting power spectra. Relative power of the
Delta (1-4Hz), Theta (4-7Hz), Alpha (8-12Hz) and Beta (15-30Hz) frequency bands were calculated as the ratio of the power of each specific frequency band divided by the total power across 0-80Hz. Computing relative power over the frequency spectrum avoids potential confounds introduced by the normalized beamformer weights (Luckhoo, Brookes, & Woolrich, 2014) and effectively bases the analysis on spectral shape rather than levels of absolute power.

Besides measures based on the power spectrum, we also calculated MSE from the time series signal at each voxel; a detailed explanation of MSE calculations can be found in Costa et al., (2002). MSE is an increasingly popular technique from a family of techniques that have included approximate entropy (ApEn), introduced by Pincus (1991), and the later refinement sample entropy (SampEn; Richman and Moorman, 2000). Most entropy estimation methods are dependent on a choice of parameters, the most critical of which is the time scale on which successive samples are compared. MSE addresses the problem of time scale selection by successively averaging the signal across progressively larger scales, and computing SampEn at each scale, denoted by a scaling parameter. The original sampled time series is generally the finest time scale, while increasingly coarser scales are obtained by averaging successive values. Sample entropy is the negative natural logarithm of the conditional probability that two sequences of m consecutive data points, within a tolerance r, will remain similar following the addition of the next consecutive data point. The tolerance value r is a threshold for a binarized decision on whether two sequences are sufficiently similar to constitute a “match,” and is commonly scaled by the standard deviation of the time series. Put simply, lower values of SampEn indicate time series that have more self-similarity: the shape of successive values centered around one time resembles that centered around other times. Both periodic and completely random signals (e.g., white noise) are low in sample entropy, while complex
aperiodic signals (e.g., 1/f noise) are higher in sample entropy (M. Costa, Goldberger, & Peng, 2005; Madalena Costa, Goldberger, & Peng, 2002).

Sample entropy was calculated with the parameters $m = 2$ and $r = 0.2$ from scales 1-12, which corresponded to times scales of approximately ~1.5-20ms. The entropy values averaged across the 12 time scales were used for the MSE maps. There are no clear guidelines for choosing parameter values, though $r$ values typically range between 0.1 and 0.25 and $m$ values are either 1 or 2 (see Lake et al., 2002 for a discussion of the optimal choices for $m$ and $r$).

These methods produced whole-brain 3D-maps (including the infarcted regions) of relative power in each frequency band, and MSE. The maps were then warped into Talairach space by applying the transformation computed on anatomical images (see above), and interpolated to a final resolution of 5 mm$^3$. The maps for patients and controls were compared using voxel-wise independent sample t-tests implemented in AFNI. All of the maps were thresholded at $p < 0.005$, with a minimum cluster size of 10 voxels to keep the family-wise error rate at $p < 0.05$. This threshold was based on Monte Carlo simulations from the 3dClustSim tool in AFNI using a FWHM of 8, as calculated previously with the same data (Meltzer et al., 2013).

2.2.6. SAM Maps - Task Activation

The SAM technique can also be used to map task-related neural activity using a pseudo-T statistic, which is a normalized measure of the difference in oscillatory power in a given frequency range between two time windows (Vrba & Robinson, 2001). Previous results have demonstrated that task-induced neural activity generally results in decreased oscillatory power in the 8-30 Hz range, both in simple sensory and complex cognitive paradigms (Brookes et al., 2005; Hillebrand, Singh, Holliday, Furlong, & Barnes, 2005; Singh, Barnes, Hillebrand, Forde, & Williams, 2002). Thus, we created single subject, pseudo-T SAM maps which quantified the
change in 8-30Hz power between the sentence listening period and the baseline intertrial interval. The values from these pseudo-T maps were subjected to group level analysis to assess neural activity related to sentence processing between patients and controls, as well as ROI analyses in patients to assess the correlation between perilesional spontaneous activity and task-induced activation of the homologous contralesional cortex.

2.2.7. ROI analyses

Voxel-wise statistical maps provide a good overview of differences between patients and controls, but are potentially affected by variability in the lesion extent across patients. To directly test the hypothesis that perilesional regions generate abnormal physiological activity, we analyzed changes in relative band power and MSE within specific regions of interest in both hemispheres.

To quantitatively assess the degree of dysfunction detected by spectral and nonlinear measures we selected two atlas-based regions that consistently tended to border the anterior and posterior portions of lesions in most of the patients. To do so, we visually inspected the map of lesion overlap (see Meltzer et al., 2013 Figure 4a), and compared it with an atlas of 90 macroanatomical regions (Eickhoff et al., 2005). From this inspection we identified the middle frontal gyrus as an ideal anterior ROI. Two regions from that atlas, labeled as “angular gyrus” and “inferior parietal lobe,” were combined into a posterior ROI in each hemisphere. In each patient, the ROI was masked by the lesion maps in order to exclude lesioned voxels. On average, 22.67% (SD = 25) of posterior ROI and 19.15% (SD = 19.46) of the anterior ROI were excluded due to lesion overlap.

The atlas-based ROIs provide a means to assess signal characteristics in consistent locations across subjects, but they are not truly “perilesional” in all subjects due to variability in
lesion location and extent. Therefore, we also constructed customized perilesional and contralesional ROIs for each aphasic patient. The voxels immediately surrounding the lesion mask (downsampled to 1cm resolution) were identified in each participant, and as a control, the same region was defined in the undamaged right hemisphere by reflecting the perilesional mask across the sagittal axis in Talairach space and warping it back to individual space. Areas exhibiting FLAIR hyperintensity were not generally included in the perilesional ROIs, as they were included in the original lesion tracings. Only voxels containing a majority of gray matter were included in the perilesional ROIs, as estimated by automated anatomical segmentation of high-resolution T1 scans, performed in FSL software. This procedure produced ROIs containing structurally intact cortical tissue in all patients, even those with mainly subcortical infarcts.

Relative power and MSE values were then averaged across all included voxels within these ROIs and univariate ANOVAs were conducted to compare the averaged values between groups. Post-hoc comparisons were conducted using Tukey’s HSD test.

The SAM analysis revealed that relative to young controls, both patients and age-matched controls exhibited increased right hemisphere rolandic beta power compared to younger controls (Figure 2.1). To further investigate the signal characteristics in the rolandic region, we extracted averaged power spectra from bilateral rolandic ROIs which consisted of the pre and post central gyri as defined by the macroanatomical atlas.

2.2.8. Correlations with Activity

To test whether perilesional abnormalities predict task-induced activation of homologous regions in the right hemisphere, we calculated Pearson correlations of intertrial MSE and relative power at left perilesional ROIs with subsequent task-related activation at respective contralateral homologous ROIs. We have observed in previous studies that task demands in language
experiments tend to induce power decrease (also known as "event-related desynchronization," or "ERD") in a frequency range of approximately 8–30 Hz (Kielar, Meltzer, Moreno, Alain, & Bialystok, 2014; Kielar, Panamsky, Links, & Meltzer, 2015; J. A. Meltzer & Braun, 2011; J. A. Meltzer et al., 2013). Thus, task-relevant activation was defined as the magnitude of 8-30Hz power decrease during the sentence listening period of the task compared to the baseline inter-trial interval.

2.2.9. Single Subject Maps

One objective of the current study is to present a methodology to identify dysfunctional tissue within each individual patient. Thus, we present two approaches for creating single subject maps.

In one approach, we adopted a methodology used in Muhlau et al., (2009) for voxel-based morphometry of individual patients. Briefly, unequal two-sample t-tests were performed at each voxel comparing an individual patient’s score against the mean of each control group. To calculate the t-score at each voxel, the difference between each patient’s score and each control group’s mean was divided by a pooled variance estimate. This resulted in two t-maps for each patient: one vs. young controls and one vs. age-matched controls. These maps were overlaid on top of the individual structural MRI to identify dysfunctional perilesional tissue on the individual subject level.

We also present an alternative approach for single subject mapping that does not require data from a control group. Specifically, z-score maps were created by comparing each voxel within an individual’s brain against the mean and standard deviation calculated from all voxels within the brain (including the lesioned area). This approach highlights areas in which brain
electrical activity differs strongly from the rest of the brain, and in our experience, does not show patterns of significant alterations within the brains of healthy control subjects.

2.2.10. Correlations between measures

To better understand the general relationship between spectral band power and MSE, as measures of neural activity, we calculated Pearson’s correlations between MSE and relative power at each frequency band and between MSE and the ratio low (delta + theta) to high (beta) frequency power. In controls, the whole cortex was used as an ROI. We also tested whether the relationship between spectral power and MSE would change as a result of brain pathology, by computing the correlations within the perilesional ROI.

2.3. Results

2.3.1. Voxel-wise Maps - Aphasia vs. Controls

Figure 2.1 presents the comparison maps of relative power and MSE between groups and Table 2.1 summarizes these results for each hemisphere. Voxels with significant differences are coloured, overlaid on an artificially darkened average anatomical image representing the lesion distribution across patients; darker regions correspond to areas with greater lesion overlap. Highest lesion overlap occurred in left inferior frontal and superior temporal areas, consistent with typical infarct patterns resulting from left middle cerebral artery occlusion, the most common cause of aphasia (Phan, Donnan, Wright, & Reutens, 2005). Figure 2.1 presents maps estimated from the baseline intertrial period and from the sentence listening and memory delay period of the task. Visual inspection indicates that the estimates from the two periods revealed very similar patterns of results, with slightly more sensitivity associated with the estimates from
the baseline period. As such, the following section will focus on the findings from the baseline period, which represents a better estimation of spontaneous neural activity.

**Baseline**

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<td>Multiscale Entropy</td>
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**Sentence Listening**

<table>
<thead>
<tr>
<th></th>
<th>A) Aphasia vs. Young Controls</th>
<th>B) Aphasia vs. Age-Matched Controls</th>
<th>C) Age-Matched vs. Young Controls</th>
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Figure 2.1 - **Voxel-wise contrasts from baseline (upper) and sentence listening (lower) periods of the task.** T-test maps of relative power and MSE overlaid on top of an artificially darkened render representing the lesion distribution across patients; darker regions correspond to areas with greater lesion overlap. The maps contrast patients minus young controls (A), patients minus age-matched controls (B), and age-matched controls minus young controls (C). Active voxels are color coded according to the magnitude of difference and thresholded at p<0.05, corrected.
Table 2.1 – Table summarizing results from the SAM analysis of spontaneous activity within each hemisphere. ‘Increased’ indicates the contrast yielded at least one significant cluster of positive voxels (p < 0.05, correct), ‘decreased’ indicates the opposite; Ns. = no significant clusters.

### 2.3.2. Patients vs. Young Controls

In the left hemisphere patients exhibited significantly increased delta and theta power and significantly reduced beta power and MSE posterior to the region of maximal lesion overlap. Patients also exhibited reduced beta power and MSE anterior to the region of maximal lesion overlap.

In the right hemisphere, patients exhibited significantly reduced delta and theta power in superior temporal, inferior parietal and rolandic regions. Patients also exhibited increased rolandic beta.

### 2.3.3. Patients vs. Age-Matched Controls

In the left hemisphere patients exhibited significantly increased delta and theta power and significantly reduced beta power and MSE posterior to the region of maximal lesion overlap. Patients also exhibited reduced beta power and MSE anterior to the region of maximal lesion overlap.
There were no significant difference between patients and age-matched controls in the right hemisphere.

### 2.3.4. Voxel-wise Maps - Age-Matched vs. Young controls

In general, both control groups exhibited similar relative power values across the whole brain. Differences were noted in the delta, theta, and beta bands. Specifically, age-matched controls exhibited decreased left hemisphere delta power in posterior temporal areas and significantly decreased right hemisphere theta power in inferior parietal, rolandic and inferior frontal areas, relative to younger controls. Age-matched controls also exhibited bilaterally increased beta power in rolandic regions (precentral and postcentral gyri).

#### 2.3.5. Task Activation

Figure 2.2(a-c) presents the group level activation maps for patients and controls; activation is reflected as the magnitude of 8-30Hz power reduction (desynchronization). Young and age matched controls exhibited primarily left lateralized ventral activation. In patients, left hemisphere activation is localized to perilesional tissue anterior to the lesion while right hemisphere activation in patients was localized to contralateral homologues of lesioned and perilesional tissue. These maps are thresholded by activation magnitude (effect size), as the average pseudo-T value across subjects. An arbitrary effect size threshold of 0.5 is used here to avoid differences in the extent of statistically significant activation related to different numbers of subjects in the three groups. The activation magnitude maps are shown here to demonstrate the increased degree of right hemisphere activation in stroke patients, as the region of interest analysis (see below) examined correlations between perilesional dysfunction and compensatory activation of the right hemisphere.
Figure 2.2(d-f) present statistical maps comparing task-related 8-30Hz desynchronization between groups. Compared to young and age-matched controls, patients exhibited a significant deficit in desynchronization (Figure 2.2(d-e); reflected by positive t-values) in the temporoparietal junction. Increased right hemisphere activity in patients reached statistical significance relative to young controls (Figure 2.2d) but not compared to age-matched controls (Figure 2.2e). The presence of right-hemisphere activation was highly variable across patients. Therefore, we conducted subsequent ROI-based correlation analyses to assess possible associations between the degree of left-hemisphere perilesional dysfunction and right-hemisphere task activation. Age-matched controls exhibited increased left hemisphere rolandic desynchronization relative to young controls.
Figure 2.2 - **Task activation maps.** Pseudo-T maps (left panel) presenting 8-30Hz event related desynchronization during the sentence listening period of the task for patients (A), young controls (B) and age-matched controls (C). These maps represent the average magnitude of activation across subjects (effect size), and are thresholded at an arbitrary level of 0.5, to avoid differences related to different numbers of subjects in the groups. T-test maps (right panel) contrast patients minus young controls (E), patients minus age-matched controls, and (F), age-matched minus young controls. Active voxels are color coded according to the magnitude of difference and thresholded at p<0.05, corrected.

### 2.3.6. Regions of Interest Analyses

#### 2.3.6.1. **Atlas-based anterior ROI**

Figure 2.3(a-b) presents the power spectra extracted from the four atlas-based ROIs. In the left hemisphere anterior ROI, there was a significant main effect of group for relative beta power, $F(2,55) = 5.840, p < 0.01$. Post-hoc analyses using Tukey’s HSD test revealed that beta power was significantly lower in patients ($M = 0.185, SEM = 0.011$) when compared to young ($M = 0.218, SEM = 0.011$) and age-matched controls ($M = 0.253, SEM = 0.018$). The main effects of relative delta, $F(2,55) = 1.767, p = 0.181$, theta, $F(2,55) = 2.409, p = 0.099$ and alpha, $F(2,55) = 0.538, \ p = 0.587$, were not significant.

There was also a main effect of MSE, $F(2,55) = 6.240, p < 0.01$; MSE was significantly lower in patients ($M = 1.784, SEM = 0.012$) when compared to young ($M = 1.837, SEM = 0.013$) and age-matched controls ($M = 1.852, SEM = 0.021$).

In the right hemisphere, there were no significant main effects of relative delta, $F(2,55) = 1.711, p = 0.190$, relative theta, $F(2,55) = 2.006, p = 0.144$, relative alpha, $F(2,55) = 0.171, p = 0.844$, relative beta, $F(2,55) = 1.643, p = 0.203$, or MSE, $F(2,55) = 0.730, p = 0.487$. 
Figure 2.3 - **Power spectra averaged across all voxels from the atlas-based (top), perilesional and contralateral (middle), and rolandic (bottom) ROIs.** Spectra from homologous ROIs are plotted together: left hemisphere in blue and right hemisphere in red. Spectra are plotted separately for patients (A), young controls (B), and age-matched controls (C). Spectra from the perilesional and contralateral ROIs, averaged across all subjects, are plotted together (D): left hemisphere in blue and right hemisphere in red. The displayed lesion and perilesional ROIs are from a single example subject. (E) Averaged spectra from the three groups are plotted together for the left (top) and right (bottom) rolandic ROIs. Shaded regions represent the standard error of the mean power estimate.
2.3.6.2. Atlas-based posterior ROI

In the left hemisphere posterior ROI, there were significant main effects of relative power in the delta, \( F(2,55) = 5.992, p < 0.01 \), theta, \( F(2,55) = 12.331, p < 0.001 \) and beta, \( F(2,55) = 10.106, p < 0.001 \), frequency bands. Post-hoc analyses revealed that delta power was significantly higher in patients (\( M = 0.110, \text{SEM} = 0.001 \)) when compared to young (\( M = 0.090, \text{SEM} = 0.001 \)) and age-matched controls (\( M = 0.073, \text{SEM} = 0.011 \)). Theta band power was also significantly higher in patients (\( M = 0.115, \text{SEM} = 0.005 \)) when compared to young (\( M = 0.090, \text{SEM} = 0.005 \)) and age-matched controls (\( M = 0.076, \text{SEM} = 0.008 \)). Patients also exhibited significantly reduced relative beta power (\( M = 0.160, \text{SD} = 0.010 \)) when compared to young (\( M = 0.210, \text{SD} = 0.010 \)) and age-matched controls (\( M = 0.237, \text{SD} = 0.017 \)). There were no significant group differences in relative alpha power, \( F(2,55) = 0.544, p = 0.446 \).

There was also a significant main effect of MSE, \( F(2,55) = 9.636, p < 0.001 \). Patients exhibited significantly decreased MSE (\( M = 1.755, \text{SEM} = 0.011 \)) when compared to young (\( M = 1.843, \text{SEM} = 0.011 \)) and age-matched controls (\( M = 1.821, \text{SEM} = 0.017 \)).

In the right hemisphere ROI, there was a marginally significant main effect of group for relative delta power, \( F(2,55) = 2.796, p = 0.069 \). However, post-hoc analyses with Tukey’s HSD test revealed no differences between patients (\( M = 0.078, \text{SEM} = 0.005 \)), young (\( M = 0.092, \text{SD} = 0.005 \)) and age-matched controls (\( M = 0.076, \text{SEM} = 0.008 \)). There were no main effects of group in the theta, \( F(2,55) = 2.338, p = 0.106 \), alpha, \( F(2,55) = 0.310, p = 0.310 \) and beta, \( F(2,55) = 2.113, p = 0.131 \), frequency bands. The main effect of MSE was also not significant, \( F(2,55) = 0.100, p = 0.905 \).
2.3.6.3. **Perilesional ROI**

The location of a perilesional ROI and its contralesional mirror ROI in one example subject are shown in Figure 2.3d, and the average power spectra across subjects in the two ROIs in Figure 2.3d. Note that the ROI does not appear perfectly symmetrical in both hemispheres due to the distortion of left hemisphere structures by the lesion. Paired t-tests revealed that the perilesional ROI exhibited significantly increased delta, \( t(24) = 5.15, p < 0.001 \), and theta power \( t(24) = 7.051, p < 0.001 \) as well as significantly reduced beta power, \( t(24) = 11.475, p < 0.001 \), compared to the contralesional ROI produced in each patient by reflecting the perilesional rim into the right hemisphere. The difference in relative alpha power was not significant, \( t(24) = 1.464, p = 0.156 \).

The left hemisphere perilesional ROI also exhibited significantly reduced MSE, \( t(24) = 6.578, p < 0.001 \), when compared to the contralateral mirror ROI.

2.3.6.4. **Rolandic ROI**

Figure 2.3d presents the average power spectra from the bilateral rolandic ROIs for all groups. Across both hemispheres, differences between spectra are most notable along the beta band. Specifically, right hemisphere beta power is increased for patients and age-matched controls, while left hemisphere beta is increased only for age-matched controls.

2.3.6.5. **Correlations with homologue task activation**

Figure 2.4 presents scatterplots of right hemisphere homologue task activation as a function of intertrial MSE and relative power in left hemisphere perilesional areas. Perilesional relative delta power was positively associated with right hemisphere homologue task activation \( (r(23) = 0.516, p < 0.01) \), while perilesional MSE was negatively associated with right hemisphere homologue activation \( (r(23) = -0.540, p < 0.01) \). There were no significant
correlations between right hemisphere task activation and perilesional relative theta (r(23) = 0.321, p > 0.118), relative alpha (r(23) = -0.164, p = 0.433), and relative beta (r(23) = -0.271, p = 0.191).

Figure 2.4 - The magnitude of contralateral homologous task activation (8-30Hz ERD) plotted as a function of perilesional relative delta, theta, alpha, beta, and MSE (B). Pearson’s correlations are presented with each figure. Significant at *p <0.05.

2.3.7. Single Subject Mapping

Thresholded single subject maps of relative theta power and MSE are shown in Figure 2.5 for one patient with a perisylvian lesion and one patient with a subcortical lesion. For both patients, MSE was reduced and theta was increased. The magnitude and spatial extent of perilesional dysfunction as detected by the t-score and z-score methods were comparable. To illustrate the sensitivity of the different measures for single subject mapping, and to estimate the incidence of detectable abnormalities in perilesional tissue in individual patients, we calculated the proportion of voxels that exhibited significant t-scores vs. age-matched controls (p<0.05, uncorrected), within each individual’s perilesional ROI (Figure 2.6).
Figure 2.5 - **Single Subject Maps.** Maps of baseline relative theta (right) and MSE (left) are presented for a patient with a left hemisphere perisylvian lesion (A) and a patient with an anterior subcortical lesion (B). T-score maps were computed by comparing the single subject’s value at each voxel vs. the mean and standard deviation of the young (upper) and age-matched (middle) control group. Z-score maps (lower) were computed by comparing each voxel vs. the mean and standard deviation of all voxels in the individual’s brain. Active voxels are color coded according to the magnitude of difference and thresholded at p<0.05, uncorrected.
Figure 2.6 - **Bar graph illustrating the proportion of participants with significant perilesional changes in relative power and MSE compared to age-matched controls (significant single subject t-scores; p<0.05, uncorrected).** The colored bars represent different proportions of the perilesional ROI with significant voxels.

### 2.3.8. Correlations between MSE and spectral band power

Table 2.2 presents correlations of MSE and relative band power across the entire cortex for controls and in the perilesional areas of patients. In young controls there were significant negative correlations between MSE and relative delta, $r(22) = -0.638$, $p < 0.01$, relative theta power, $r(22) = -0.702$, $p < 0.01$, and the (delta + theta)/beta ratio, $r(22) = -0.828$, $p < 0.01$. MSE also positively correlated with relative beta power, $r(22) = 0.815$, $p < 0.01$. MSE did not correlate with relative alpha power, $r(22) = 0.043$, $p = 0.849$. As demonstrated in Table 2.1, the same pattern of correlations between MSE and spectral power was also present in age-matched controls and in perilesional tissue.
Table 2.2 – Correlations of MSE and relative power. Table of correlations across subjects between MSE and relative delta, theta, alpha & beta averaged across the whole cortex for patients and controls. * p <0.05; **p< 0.01

<table>
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<th>Young Controls</th>
<th>Age-Matched Controls</th>
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<tbody>
<tr>
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<td>-0.638**</td>
<td>-0.785*</td>
<td>-0.856**</td>
</tr>
<tr>
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<td>-0.828**</td>
<td>-0.851**</td>
<td>-0.938**</td>
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2.4. Discussion

This study illustrates a novel approach to the characterization of altered spontaneous electrical activity generated by perilesional areas following stroke. Building on previous EEG and MEG studies, both spectral and nonlinear analyses of electrophysiological data revealed robust group differences between patients with stroke and healthy controls, and between the affected and unaffected hemispheres (e.g., Finnigan et al., 2004; Finnigan and van Putten, 2013; Tecchio et al., 2006, 2005). Whereas previous studies of spontaneous electrical activity in stroke have largely focused on increased low-frequency signals, the present study presents a method for source analysis of low-amplitude high-frequency activity, and characterization of signals using nonlinear algorithms in source space.

The analysis of different signal measures in a common source space allowed us to evaluate differences in sensitivity between them. For example, SAM maps of reduced MSE and relative beta in patients vs. controls revealed significant voxels in areas anterior and posterior to the areas of maximal lesion overlap, while maps of increased relative theta and delta revealed significant voxels only posterior to the lesion zone. This is further confirmed by ROI analyses.
demonstrating that MSE, delta, theta, and beta measures were sensitive to changes in the posterior ROI, while only MSE and beta power were sensitive to dysfunction in the anterior ROI. This particular distinction between anterior and posterior regions most likely reflects the idiosyncratic nature of the present sample of patients, whose lesions were distributed in various areas centered on left perisylvian cortex. However, these results suggest that reductions in MSE and beta power may be equally or even more sensitive than the more commonly used measures of low-frequency power increase.

Some limitations apply for this study, and suggest directions for future research. One limitation is that true “resting” MEG data was not available in these patients. Patients were originally recruited for an MEG study of language processing, and the timing of the procedures was optimized to maximize sensitivity for that study. In the present reanalysis of that MEG data, we examined “spontaneous” data from the intertrial interval of the language task. Similar results were obtained from data in the task periods. Thus, there is some concern that the brief intertrial intervals included task-related neural activity ‘spilled over’ from the previous trial. However, given that neural activity results in a decrease in 8-30Hz power (Brookes et al., 2005; Hillebrand et al., 2005; Singh et al., 2002), such spillover would result in reduced 8-30Hz power for active tissue relative to inactive tissue. Our results demonstrated the opposite: perilesional tissue exhibited reduced beta-band power (15-30Hz) relative to healthy tissue from both control groups. These findings were replicated in a follow-up study with 5 minutes of rest collected from a separate sample of 19 aphasia patients (Kielar et al., 2016). The results further validated both low-frequency oscillatory power and MSE as sensitivity measures detecting tissue dysfunction. Furthermore, MEG measures of perilesional dysfunction correlated with hypoperfusion, as measured by arterial spin labelling.
Another limitation of the present study is the difficulty in conducting group statistical analysis in a heterogeneous sample of patients. The patients did have some commonalities: all had a single left-hemisphere stroke impinging on perisylvian language regions, leading to aphasia. But there was also considerable variability in aphasia symptoms, and lesion location and extent. We dealt with this heterogeneity by conducting several complementary analyses, based on whole-brain mapping, consistent atlas-based ROIs, and customized perilesional ROIs. Each had drawbacks: the whole-brain mapping ignores the lesion location; the atlas-based ROIs are perilesional in some subjects but not others, and the customized perilesional ROIs have widely variable size and location across participants. Fortunately, all analyses converged on the same conclusions: perilesional tissue consistently exhibited reduced high-frequency activity and MSE, and in some regions also showed increased low-frequency activity. In fact, we anticipate that the methods presented in this paper will ultimately be more useful for analysis of individual patients in a clinical / therapeutic context (see section 4.3), obviating the problems associated with group analysis.

Together, the findings support the utility of both spectral and nonlinear time series measures in source space to identify neural dysfunction in perilesional tissue, and suggest that identification of increased delta-range activity alone may provide an incomplete characterization of altered spontaneous neural dynamics after stroke.

2.4.1. Relationship between spectral and nonlinear measures

While there were differences between maps based on spectral measures and multi-scale entropy, they were overall quite similar, raising the question of whether these techniques provide complementary information, or instead represent two ways of quantifying essentially the same phenomenon. Besides the visual comparison of statistical maps generated from both techniques,
we also assessed direct correlations between MSE and spectral power across subjects in the young control group and the patients, testing whether there was a close association between these measures in normal, healthy tissue. In both groups, MSE was positively correlated with beta power, but negatively with delta and theta power, and not significantly correlated with alpha power (note that we did not assess correlations in the older controls simply because there were fewer of them, reducing the power to detect a correlation). Thus, MSE seems to closely covary with the ratio of higher frequencies to lower frequencies in an electrophysiological signal, at least at the timescales that we assessed. This intuition was confirmed by directly assessing the correlation between MSE and the (delta + theta)/beta power ratio, which was stronger than the correlation with any individual frequency band. A similar conclusion was reached by Bruce et al., (2009) who compared SampEn and spectral measures in EEG obtained from adults during wakefulness and sleep, and also obtained similar results from simulated EEG signals.

One difference noted between the spectral measures and MSE related to the effects of aging, and deserves some special scrutiny. We did not observe any differences in MSE between the younger controls and the age-matched controls (Figure 2.1c). However, age-matched controls exhibited bilateral increased relative beta power, and decreased delta/theta power, which seemed to be a general effect of aging rather than an indicator of disease-related pathology. This general speeding of the signal is also present in the unaffected right hemisphere of patients, when compared to young controls. Furthermore the power spectra from the right rolandic ROI (Figure 2.3e) clearly shows increased beta power for both patients and age-matched controls.

This finding is in line with previous reports of age-related speeding of electrical activity. Bruce et al., (2009) found decreased relative delta and increased relative beta associated with aging during wakefulness and sleep. Fienburg and Campbell (2003) also found reduced delta
associated with aging during sleep, while Mann and Roschke (2004) found a significant negative correlation between age and delta/theta power measured during sleep. This speeding of the frequency spectrum may seem contrary to behavioral and electrophysiological studies demonstrating age-related increases in the latency of response time and ERPs (Rossini, Rossi, Babiloni, & Polich, 2007). However, Hong and Rebec (2012) proposed that the speeding of the frequency spectrum may actually reflect compensatory speeding of firing rates. Specifically, the authors suggest that aging associated increases in conduction delays will progressively increase the phase difference between synchronized neurons until they are in antiphase. To compensate, one neuron must double the firing rate to realign their excitability peaks. This compensatory speeding will be reflected as a shift of the frequency spectrum from low to high frequencies. It should be noted that the authors hypothesized aging related increases in gamma power while we observed increased beta. This is likely due to the fact that the speeding was observed in rolandic regions where idle beta activity is dominant (Ritter, Moosmann, & Villringer, 2009). Our findings are consistent with a previous report of increased relative and absolute beta power in older adults compared to younger adults (Holschneider and Leuchter, 1995).

Notably, the MSE measures were not significantly affected by this increase in relative beta power present in older participants. Therefore, it is possible that MSE could provide a more specific indicator of perilesional dysfunction in stroke, dissociable from effects of aging. Future studies including larger groups of participants at various age levels are needed to fully dissociate the role of aging in altered neural dynamics commonly seen in patients with neurological disorders.
Compensatory Right Hemisphere Activation

The activation maps presented here converge with a multitude of studies demonstrating right hemisphere language activation in chronic aphasia (Musso et al., 1999b; Thulborn et al., 1999b; Tillema et al., 2008). Specifically, we found greater right hemisphere activation in aphasic patients during language processing. Despite the bilateral pattern seen in patients, increased right-hemisphere activation in patients as a group was not statistically significant compared to age-matched controls (Figure 2.2e). This may be due to the low power resulting from a smaller group of older controls, but is also related to the high degree of variability across the patient group in lesion characteristics and right-hemisphere activation. In our previous study with this cohort, we characterized the relationship between language comprehension performance and differential activation to sentences of varying difficulty levels, finding a correlation between right hemisphere activation and successful comprehension (Meltzer et al., 2013). However, in that study, positive correlations with performance were not generally in homologous regions to those associated with comprehension performance based on lesion analysis; this suggests that compensatory activity may reflect adaptive recruitment of alternative strategies rather than homologous takeover of the same cognitive functions.

In the present study, we examined a simpler contrast of sentence listening vs. the prestimulus baseline, to test whether there was any association between the degree of right hemisphere activation present in each patient and the degree of perilesional dysfunction detected during the intertrial period. We did find such an association: perilesional dysfunction (increased slowing and reduced entropy) was correlated with task activation in the right hemisphere homolog of the perilesional tissue. Thus, the current results provide evidence for homologous takeover during basic sentence processing, which is modulated by the magnitude of left
hemisphere dysfunction. Some authors have suggested that activation of right hemisphere homologues of language areas may reflect a release of transcallosal inhibition from the damaged left hemisphere (Martin et al., 2004; Thiel, Schumacher, et al., 2006a). However, right hemisphere activation can also result from uncontrolled excitatory input from the perilesional region, resulting in maladaptive activation through the introduction of irrelevant information (Chiarello & Maxfield, 1996; J. M. Clarke, Luflkin, & Zaidel, 1993). The study presented a relationship between left hemisphere dysfunction and right hemisphere activation, but was not designed to test the possible mechanism behind relations; Chapter 3 explored effective connectivity analyses to directly test the hypotheses regarding transcallosal interactions following stroke.

2.4.3. Identifying targets for non-invasive stimulation-base intervention

The role of right hemisphere activation in residual language processing is still debated though evidence suggests that the best outcome is associated with a reintegration of surviving perilesional regions into the language network (D. Saur et al., 2006). Therapeutic studies of noninvasive brain stimulation typically aim to increase the activation of structurally intact perilesional cortex, either by direct excitatory stimulation of that tissue (Marangolo et al., 2013; J. P. Szafarski et al., 2011), or by inhibitory stimulation to the contralateral hemisphere (Abo et al., 2012; C. H. Barwood et al., 2011; C. H. S. Barwood et al., 2013; Kakuda, Abo, Momosaki, & Morooka, 2011; Kindler et al., 2012; Medina et al., 2012; M. A. Naeser et al., 2010; Margaret A. Naeser et al., 2005a; Thiel, Habedank, et al., 2006; Thiel et al., 2013b; Waldowski, Seniów, Leśniak, Iwański, & Członkowska, 2012; Weiduschat et al., 2011; Winhuisen et al., 2007). However, there is also evidence of beneficial outcomes associated with excitatory right hemisphere stimulation (Flöel et al., 2011b). It is likely that a multitude of factors contribute to
the overall relationship between stimulation site and behavioral outcome, including lesion size, location, pre-stroke laterality and structural and functional integrity of the perilesional tissue.

The methods demonstrated here provide a means to identify dysfunctional perilesional tissue potentially suitable for physiological interventions such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). The fact that stimulation of the perilesional cortex can improve behavioral outcomes suggests that dysfunctional perilesional tissue has the capacity for successful reintegration into the language network. Critically, such regions may be ideal targets for intervention as numerous studies have demonstrated that the best clinical outcome in aphasia is associated with reactivation of perilesional tissue. The single subject mapping approaches presented here provide a means to identify tissue within an individual patient that is most likely to benefit from non-invasive stimulation, and could also allow researchers to assess both short-term and long-term changes in cortical activity induced by the stimulation. It should be noted that the single subject maps from some patients did not show perilesional dysfunction. As such, it stands to reason that these patients may not benefit from direct perilesional stimulation. The clinical utility of the single subject maps lies in its ability to identify ideal candidate patients and brain regions for stimulation-based rehabilitation. Thus, mapping of perilesional dysfunction is likely to play an important role in the future development of physiologically informed neurorehabilitation programs in stroke.
Chapter 3
Interhemispheric interactions during sentence comprehension in patients with aphasia

3.1. Introduction

This study examines the role of interhemispheric connections in recovery from aphasia. One of the most prevalent questions in brain plasticity research considers the involvement of the right hemisphere (RH) in recovery from aphasia and specifically whether it plays a compensatory or maladaptive role in language processing after stroke. This question has clinical implications as well as theoretical significance for the understanding of brain lateralization in healthy individuals, and of mechanisms underlying brain plasticity after unilateral damage.

The adaptive account suggests that increased RH activation in post-stroke patients reflects compensatory recruitment of intact regions homologous to the lesioned areas, facilitating language processing and thus enhancing recovery (Cappa, Perani et al. 1997; Blasi, Young et al. 2002; Abo, Senoo et al. 2004; Winhuisen, Thiel et al. 2005). In contrast, other studies argue that the RH involvement in language processing in post-stroke patients is maladaptive (Postman-Caucheteux, Birn et al. 2010) and is the result of a release from transcallosal lateral inhibition (Heiss, Thiel et al. 2003; Naeser, Martin et al. 2004; Price and Crinion 2005). According to this view, activity in the left hemisphere (LH) of the intact brain suppresses homotopic areas in the contralateral hemisphere via transcallosal pathways, resulting in the typical left lateralized pattern of activation in language tasks (Kinsbourne 1974). When the LH is lesioned, transcallosal inhibition on the RH is released, resulting in increased RH activation (Selnes 2000; Thiel, Schumacher et al. 2006). In turn, this increase in RH activation suppresses homotopic areas in the LH via transcortical inhibition, further interfering with language performance and impeding
recovery (Naeser, Martin et al. 2004; Price and Crinion 2005). However, it should be noted that maladaptive involvement of the RH in post-stroke aphasia is not necessarily mediated by direct transcallosal inhibition on LH homotopic regions. A negative effect of RH activity on language performance can also be a result of inefficient processing occurring in the RH and interfering with LH processing through excitatory coupling of both homotopic and heterotopic connections (Clarke, Lufkin et al. 1993; Chiarello and Maxfield 1996). Therefore, directly measuring interhemispheric connectivity is important for understanding the role of the RH in aphasia recovery.

Recently, several studies have measured task-related interhemispheric connectivity in patients with aphasia (Schofield, Penny et al. 2012; Teki, Barnes et al. 2013; Kiran, Meier et al. 2015; Meier, Kapse et al. 2016), and focused on naming tasks or on single word judgment tasks. In contrast to these tasks, which are typically left lateralized, sentence comprehension relies on bilateral activation in healthy individuals (Price 2010; Friederici 2011; Vigneau, Beaucousin et al. 2011). Differences in lateralization between tasks are very likely to affect the value, strength, and direction of interhemispheric interactions in both healthy and brain damaged individuals (Price and Crinion 2005). The current study examines interhemispheric connectivity in a sentence comprehension task performed by patients with chronic aphasia, seeking to clarify the role of the RH in language recovery.

Numerous neuroimaging studies show enhanced RH activation during language tasks in patients with aphasia following LH lesions (Basso, Gardelli et al. 1989; Buckner, Corbetta et al. 1996; Ohyama, Senda et al. 1996; Thulborn, Carpenter et al. 1999; Calvert, Brammer et al. 2000; Gold and Kertesz 2000; Rosen, Petersen et al. 2000; Blank, Bird et al. 2003; Abo, Senoo et al. 2004). The finding that such RH activation is correlated with better language performance in
patients (Cappa, Perani et al. 1997; Blasi, Young et al. 2002; Abo, Senoo et al. 2004; Winhuisen, Thiel et al. 2005) supports the view that the RH plays a compensatory role in language recovery. Furthermore, it was shown that compensatory changes in RH activation following language therapy in these patients are more likely in RH regions homologous to the LH lesion (Abel, Weiller et al. 2015). In contrast to these findings, other neuroimaging studies suggest that recovery-related language reorganization in patients with aphasia occurs only in perilesional areas in the LH, while RH activation during language tasks is an epiphenomenon which does not contribute to performance (Heiss, Karbe et al. 1997; Warburton, Price et al. 1999; Rosen, Petersen et al. 2000; Thiel, Herholz et al. 2001). For example, a magnetoencephalography (MEG) study that used a sentence comprehension task showed that although aphasic patients activated RH areas homologous to the lesioned temporal area, this was not correlated with comprehension performance. Instead, performance was correlated with activation in left dorsal fronto-parietal regions (Meltzer, Wagage et al. 2013). This conclusion is also supported by structural connectivity measures (Geva, Correia et al. 2015). Moreover, RH activation has been associated with incorrect naming responses in patients with LH lesions, suggesting that RH activation is actually interfering with recovery in some patients (Fridriksson, Baker et al. 2009; Postman-Caucheteux, Birn et al. 2010). The apparent contradiction between findings supporting the compensatory or the maladaptive accounts may be settled by other explanatory factors such as the time since injury (Fernandez, Cardebat et al. 2004; Saur, Lange et al. 2006), the specific RH regions involved (Crosson, McGregor et al. 2007), or the nature of the tasks used for measuring language recovery (Heiss, Thiel et al. 2003; Price and Crinion 2005). Price and Crinion (2005) suggest that RH activation is compensatory in speech comprehension tasks (Sharp, Scott et al. 2004), but plays a maladaptive role in speech production tasks (Heiss, Karbe
et al. 1997; Rosen, Petersen et al. 2000; Fernandez, Cardebat et al. 2004; Saur, Lange et al. 2006; Postman-Caucheteux, Birn et al. 2010).

Neuroimaging studies using PET and FMRI can only provide correlational findings, so even a negative correlation between RH activation and language recovery across participants does not provide causal evidence for a maladaptive role of the RH. Increased RH involvement may be the consequence of a more severe or extensive LH damage which results in a poor outcome for recovery not directly caused by the RH (W. D. Heiss et al., 1997; Karbe et al., 1998; Sebastian & Kiran, 2011; Sims et al., 2016; Vitali et al., 2007). In contrast, numerous transcranial brain stimulation studies in the last decade overcome this weakness by showing a causal effect of RH inhibitory or excitatory stimulation on language function within subjects (Naeser, Martin et al. 2005; Winhuisen, Thiel et al. 2005; Floel, Rosser et al. 2008; Monti, Cogiamanian et al. 2008; Baker, Rorden et al. 2010; Sandars, Cloutman et al. 2016). For example, a meta-analysis of 9 randomized control trials, including 215 patients with post-stroke aphasia, tested the effect of inhibitory stimulation with low frequency repetitive Transcranial Magnetic Stimulation (rTMS) or cathodal Transcranial Direct Current Stimulation (tDCS) over the right hemisphere as an adjunct to speech language therapy (Otal, Olma et al. 2015). The results show a significant improvement in naming accuracy across studies, suggesting that these RH areas play a maladaptive role in naming in patients with aphasia, so that inhibiting them can improve performance. However, even within naming studies the results are not always consistent. For example, results of a study showing that anodal tDCS (an excitatory stimulation technique), rather than cathodal tDCS over the right temporo-parietal cortex improves naming in patients with aphasia (Floel, Meinzer et al. 2011), are more consistent with a compensatory role for some regions in the RH.
Speech comprehension studies show even more variable results. A meta-analysis across 160 patients shows that low frequency rTMS over the right IFG improves performance in various language tasks including speech comprehension (Ren, Zhang et al. 2014). However, other studies using rTMS over the right IFG do not find clear evidence for improvement in speech comprehension tasks (Thiel, Hartmann et al. 2013; Li, Qu et al. 2015). Interestingly, a tDCS study using cathodal (inhibitory) stimulation to the right superior temporal gyrus as adjuvant to therapy, found improved auditory verbal comprehension in subacute stroke patients (You, Kim et al. 2011), highlighting possible differential effects for different anatomical areas within the RH.

It is important to remember that even causal evidence linking inhibitory right hemisphere stimulation and behavioral recovery cannot explain how the RH plays this maladaptive role in recovery. A case study of a patient with a LH lesion reported evidence of both compensatory and maladaptive effects of the RH within the same patient (Turkeltaub, Coslett et al. 2012). Although the patient’s performance improved after suppression of the right IFG pars Triangularis using rTMS, a subsequent lesion to the RH resulted in worsening of the aphasia, suggesting that while some RH regions may support recovery, others interfere with it. Importantly, the study showed that the improvement in performance following rTMS to the right Triangularis was associated with reduced activation in the right Triangularis, but with no increase in activation in the LH. These results are not consistent with the hypothesis that transcallosal suppression induced by RH regions on perilesional regions in the LH underlie the maladaptive role of the RH in recovery (Naeser, Martin et al. 2004; Price and Crinion 2005). An alternative hypothesis is that the output from ineffective processing in the RH is integrated with the information processed in the LH through excitatory coupling, thus reducing performance (Chiarello and Maxfield 1996). In order to find more direct evidence for transcallosal suppression or other mechanisms underlying the
recruitment of the RH in patients with aphasia it is therefore necessary to examine inter-hemispheric connectivity in this population.

Resting state connectivity studies in healthy individuals are based on the assumption that positive connectivity reflects coordination and integration between hemispheres whereas negative connectivity reflects segregated or competing systems (Fox, Snyder et al. 2005; Fair, Dosenbach et al. 2007; Gee, Biswal et al. 2011). Although several studies examined intra- and inter-hemispheric functional connectivity in post stroke patients with aphasia (Schofield, Penny et al. 2012; Marcotte, Perlberg et al. 2013; Teki, Barnes et al. 2013; Kiran, Meier et al. 2015; Griffis, Nenert et al. 2016; Meier, Kapse et al. 2016), there is still no clear evidence that RH activation in these patients results from a release from transcallosal inhibition induced by the LH, or that RH regions suppress perilesional areas in the LH. An association between decreased activation in the LH and increased activation in the RH in patients with LH lesions was demonstrated in a SPECT study (Uruma, Kakuda et al. 2010). This association was also demonstrated in an fMRI study measuring activation during a verb generation task in chronic stroke patients with aphasia (Griffis, Nenert et al. 2016). The results showed that theta-burst stimulation enhancing activation in left IFG was associated with decreased activation in right IFG and decreased connectivity from right-to-left IFG. Activation in right IFG was negatively correlated with improvements in a fluency task following stimulation suggesting that activation in right IFG and its input to left IFG are maladaptive for word generation.

In the area of speech perception, inter-hemispheric connectivity following LH lesion was measured by two studies that focused on low level auditory and temporal cortices. An fMRI study showed enhanced reliance on the RH when patients with auditory comprehension deficits following LH lesions listened to word pairs (Schofield, Penny et al. 2012). Patients showed
weaker bidirectional connectivity between right and left primary auditory cortices (A1) compared to controls, and asymmetric right-to-left excitatory connectivity at the level of the planum temporale, suggesting increased reliance on the RH. A MEG study with LH lesioned patients performing a phonemic task (Teki, Barnes et al. 2013) also showed evidence for greater reliance of patients on the RH, but this was reflected in stronger connectivity in the other direction (from the lesioned to the contralesional A1 LA1 – RA1) in patients compared to controls. Importantly, patients also showed a negative correlation between performance on a phonemic discrimination task and left-to-right connectivity (LSTG - RSTG) (Teki, Barnes et al. 2013). Although these results suggest that the involvement of the RH is not beneficial for phonemic processing, they do not constitute evidence for transcallosal inhibition.

The present study examined the role of inter-hemispheric connectivity in language performance in patients suffering from aphasia following LH lesion, in order to shed light on the mechanisms underlying compensation and recovery of language function. Previous studies that found negative correlations of performance with RH activation (Postman-Caucheteux, Birn et al. 2010), and improved performance after inhibiting RH regions (Ren, Zhang et al. 2014; Otal, Olma et al. 2015) suggested that these effects can be explained by transcortical suppression between homotopic regions, but there has not been direct evidence for interhemispheric suppression from functional connectivity studies. In the present study, we measured interhemispheric connectivity using fMRI during a sentence comprehension task, which typically relies on both hemispheres (Price 2010; Friederici 2011; Vigneau, Beaucousin et al. 2011), and is therefore expected to show strong inter-hemispheric connectivity in both patients and controls. Inter- and intra-hemispheric connectivity was examined in a network comprising four regions of interest involved in sentence comprehension in typical adults, namely bilateral A1, and bilateral
IFG. In order to identify the direction of the effects (right-left vs. left-right) we used Dynamic Causal Modeling (DCM) analysis, which quantifies task-dependent effective connectivity (Friston, Harrison et al. 2003).

Previous studies have shown increased involvement of the RH in language processing in patients compared to controls and suggested that this is a result of release from transcallosal inhibition exerted from the LH on homotopic regions in the RH, especially in IFG (Heiss, Thiel et al. 2003; Naeser, Martin et al. 2004; Price and Crinion 2005). If the transcallosal inhibition account of RH activation is true, we would expect three findings: 1) increased involvement of the RH in language processing and stronger connectivity emanating from the RH in patients compared to controls; 2) there should be stronger negative coupling from the LH to the RH in controls and release from this inhibition in patients, especially in IFG; 3) as previous studies that examined speech perception tasks showed a compensatory role for lower level auditory processing regions in the RH (Schofield, Penny et al. 2012; Teki, Barnes et al. 2013), we expect that interhemispheric connectivity at the level of primary auditory cortices (A1) will be excitatory and positively correlated with performance.

3.2. Methods

3.2.1. Participants

Patient and control participants in this study also participated in a previously published MEG study using a similar task (Meltzer et al. 2013). fMRI data was collected for twenty patients with aphasia. Each had suffered a single left-hemisphere ischemic stroke at least six months previously, resulting in mild to moderate aphasia confirmed by a research Speech-Language Pathologist. Five participants were excluded due to insignificant activation in at least
one of the regions of interest. Of the remaining fifteen participants, nine (ages 34-71, mean=55, five females) showed adequate model fit (>10%) and were included in the final DCM analysis. DCM analyses from the full group of fifteen patients are also reported to confirm that the results from the included and full groups do not differ significantly. Table 3.1 presents participants’ lesion extents relative to the volume of the left hemisphere, their performance on standardized language assessments, and performance on the experimental task for the nine patients included in the final DCM analysis and the six excluded due to low model fit. Figure 3.1 presents the lesion overlap of these groups of patients. No differences were found between the two groups of patients in lesion size, demographics or any behavior measures.

Twenty-four young adults participated in the study as a control group. fMRI activation data from the young adults were previously published in Meltzer et al. (2010). Five participants were excluded due to insignificant activation in at least one of the regions of interest and one participant was excluded due to poor model fit; the data from 18 young adults (ages 22-36, mean=27, nine females) were entered into the final analysis. Seven age-matched controls also participated in the study. Two participants were excluded due to insignificant activation in at least one of the regions of interest; the data from five age-matched controls (ages 42-49, mean = 46, four females) were entered into the DCM analysis. No age-matched control participants were excluded for low model fit in the DCM analysis.
Table 3.1 - Characteristics of individual patients. Patients included in the DCM analysis and those excluded due to low model fit are presented separately.

Repetition Composite Score: Average of scores from the Nonwords Repetition subtest (#8) of the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA) and Sentence Repetition subtest of the Western Aphasia Battery (WAB).

Receptive Composite Score: Average of scores from the Auditory Word Recognition subtest of the WAB and three subtests of the PALPA (#5, Auditory Lexical Decision, #47, Spoken Picture Matching, and #49, Auditory Synonym Judgment).

Expressive Composite Score: Average scores on Object Naming subtest from the WAB, and the Druks and Masterson Action and Object naming batteries.

PAL Sentence-Picture Matching: a measure of sentence comprehension taken from the Psycholinguistic Assessment of Language.

WAB:AVC: Score of the Auditory Verbal Comprehension subtest from the WAB.

% of Left Cortex Damage: computed based on the overlap between Left Hemisphere Cortex mask and individual Lesion masks warped into Talairach space.

Aphasia diagnosis: given by a speech pathologist (author JR from Meltzer et al., 2013).

Task performance - These scores are chance corrected with the formula [1 - 2(proportion incorrect)], yielding performance ranges from 0 (chance) to 100%; scores below chance are negative. The condition of reversible object-embedded clause-containing sentences is excluded from the behavioural measure, as aphasic patients performed consistently at chance in this condition (Meltzer et al., 2013).

<table>
<thead>
<tr>
<th>Group</th>
<th>Age</th>
<th>Gender</th>
<th>Years Post-Stroke</th>
<th>Education</th>
<th>Reception Composite 100</th>
<th>Lexical Recreational Composite 100</th>
<th>Lexical Expressive Composite 100</th>
<th>PAL Sentence-Picture Matching 100</th>
<th>WAB:AVC 100</th>
<th>% Left Cortex Damage</th>
<th>SLP</th>
<th>Reversible Sentence Performance</th>
<th>Irreversible Sentence Performance</th>
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<td>mild anomic aphasia</td>
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<td>95</td>
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<td>38%</td>
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<td>190</td>
<td>11%</td>
<td>mild anomic aphasia</td>
<td>28%</td>
<td>46%</td>
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</table>
3.2.2. Behavioral Assessment

Prior to the fMRI experiment, all aphasic and age-matched control participants were administered an extensive test battery to assess behavioral deficits, including the Western Aphasia Battery (WAB) (Kertesz 1982), selected tests from Psycholinguistic Assessments of Language Processing in Aphasia, (PALPA) (Kay, Coltheart et al. 1992) and the Object & Action Naming Battery (Druks and Masterson 2000). Three composite scores were computed from the different subtests and are reported in Table 3.1. Table 3.1 also reports participants’ scores on the
Auditory Verbal Comprehension (AVC) subtest of the WAB, used as a general measure of comprehension ability. Finally, for an offline measure of grammatical sentence comprehension, we administered a sentence picture matching task consisting of 40 sentences of various structures (Psycholinguistic Assessment of Language- PAL; Caplan, 1992). This task resembles the task performed in the scanner but samples a wider range of syntactic structures. Further details on the behavioral tests can be found in Meltzer et al. (2013). Performance on all language measures was at ceiling for age-matched controls. Young controls did not undergo cognitive testing, but performed at or near ceiling on the experimental task conducted in the scanner.

3.2.3. fMRI Task

Patients performed a sentence picture-matching task during fMRI scanning, providing a measure of BOLD activity related to comprehension of sentences. The fMRI task comprised a sentence picture-matching paradigm, in which a subject first heard a spoken sentence and then viewed 2 pictures, selecting the matching picture via a button press. Registration of the subject's choice was confirmed by highlighting the selected picture in a green box, but no accuracy feedback was given. A jittered event-related design was used, in order to distinguish between activity related to auditory sentence perception and picture selection. Despite the fact that picture selection always followed sentence presentation, it was possible to disentangle the hemodynamic responses related to the 2 task stages using linear regression (Miezin, Maccotta, Ollinger, Petersen, & Buckner, 2000), along with 2 techniques that served to reduce the correlation between the hemodynamic responses of the 2 stages: temporal jitter and partial trials (Ollinger, Corbetta, & Shulman, 2001). Subjects were informed that a random subset of the sentences would be followed by a picture-matching trial, and instructed to attend to each sentence in preparation for a possible response. Subjects were informed that they could forget about the
proceeding sentence as soon as a new one began. Accordingly, only 50% of the sentences were followed by a picture-matching trial. The delay between each stimulus event, either sentence or picture, was jittered as 6, 8, or 10 s.

The experiment manipulated two factors, syntactic complexity and semantic reversibility, but the current analysis focused only on general sentence comprehension, and collapsed across all trial types. Reversible sentences involved humans as both subjects and objects and were constructed so that both were plausibly interchangeable (e.g., “The boy is pushing the girl” or “The girl is pushing the boy”). Irreversible sentences on the other hand involved a human and an inanimate object, and thus the subject and object were not plausibly interchangeable (e.g., “The boy is eating a sandwich”). The Syntactic complexity factor included three types of sentences that increased in difficulty by using embedded clauses and manipulation of agent-patient word order: simple active sentences ("The boy is pushing the girl out of the way"), subject-embedded relative clauses ("The boy who is pushing the girl wants to win the race"), and object-embedded relative clauses ("The girl who the boy is pushing wants to win the race"). Altogether, there were six sentence types (2-reversibility x 3-complexity). However, the goal of the current study was to assess the connectivity pattern associated with general sentence comprehension, irrespective of sentence type. As such, the six sentence conditions were collapsed together for all analyses.

Patients’ overall task performance are presented in Table 3.1. Performance for the young control group (M=92.34%, SD=6.21%) and the age-matched control group (M=85.75%, SD=7.88%) were both at ceiling.

### 3.2.4. fMRI Acquisition

Whole-brain gradient-echo echo-planar imaging (EPI) data were acquired on a 3-T GE Signa scanner with an 8-channel head coil (repetition time [TR]=2000ms, echo time=30ms, flip
angle=90, 64x64 matrix, field of view 224 mm, 38 slices, 3.5 mm thick, obliquely aligned to the plane between the anterior and posterior commissures). A 1-mm isotropic magnetization prepared rapid acquisition gradient echo (MPRAGE) image was also acquired. Two hundred and twenty-six volumes were acquired in each run (preceded by dummy scans to achieve steady-state magnetization), with 7 runs total. Auditory stimuli were presented through pneumatic headphones (Avotec, Inc., Stuart, FL) at an individually adjusted volume level.

3.2.5. Image Analysis

Univariate analysis of task activation was performed using the General Linear Model implemented in SPM12b (http://www.fil.ion.ucl.ac.uk/spm). Functional images were spatially realigned to the first volume to correct for head movements. No individual runs had greater than 4 mm of displacement, with an average of 1.2 mm per individual run. 2nd Degree B-Spline interpolation was used to minimize timing errors between slices. The functional images were co-registered with the anatomical image and normalized to the standard T1 template volume (Montreal Neurological Institute). Normalization was accomplished using the updated unified segmentation procedure in SPM12b, which segments, bias corrects and normalizes all in the same model (Ashburner and Friston 2005). The normalized images were then smoothed with a 6 mm FWHM Gaussian kernel and resliced to an isotropic voxel size of 2 mm.

Statistical analyses at the first level were calculated using an event-related design, in which sentence onsets were modeled as ‘miniblocks’ rather than point events, with a duration of 3.45 s, representing the mean auditory sentence length. We modeled the six linguistic conditions separately: three levels of syntactic complexity x two levels of reversibility (reversible vs. irreversible sentences). A high-pass filter with a cutoff period of 128 s was applied. Six motion realignment regressors and six picture onset regressors (for the six linguistic conditions) were
included in the model as covariates of no interest. Statistical analyses at the first level were
calculated using an event-related design, with the six linguistic conditions as contrasts of interest.
Group results were obtained using random effects analyses by combining subject-specific
summary statistics across the group as implemented in SPM12b. An all-sentence contrast, which
included activation for all sentence types, was entered into the second level analysis to identify
peaks for the group. These group analyses were used to determine the location of volumes of
interest (VOIs) for the effective connectivity analysis.

3.2.6. VOI selection

Table 3.2 presents the MNI coordinates for the four VOIs chosen for the effective
connectivity analysis. The bilateral Inferior Frontal Gyri (IFG) were chosen as regions of interest
because these regions (on the left hemisphere) are typically involved in sentence comprehension
(e.g., Fiebach, Friederici et al. 2002; Friederici, Ruschemeyer et al. 2003; Meltzer and Braun
2011), and were strongly activated by healthy participants in this task in a previous study
(Meltzer, McArdle et al. 2010). Moreover, these areas are typical targets for stimulation studies
(e.g., Naeser, Martin et al. 2004; Price and Crinion 2005) and are therefore potential sources of
transcallosal suppression. Bilateral primary auditory cortices (A1) VOIs were selected as the
locations of the auditory driving input. In the current study, we were interested in measuring
intrinsic connectivity between homologous VOIs to test the hypothesis of altered
interhemispheric inhibition in post-stroke aphasia.

To select the IFG and A1 VOIs at the individual level, we first computed the group-level
contrast of all sentences vs. baseline, and thresholded it at a familywise error rate of p<.05,
according to Gaussian random field theory. All four VOIs showed above threshold group
activation for all groups in this contrast. The peak coordinates of activation in the appropriate
regions were identified separately for each group. Individual VOIs were 6mm spheres centered on the individual peak activations in the same contrast from the first level analysis, thresholded at $p<0.1$ with a minimum of four active voxels (Richardson, Seghier et al. 2011), within a 10mm search radius of the group peak. Anatomical masks defined by the WFU PickAtlas in SPM12b were used to ensure that the IFG VOIs were spatially constrained to the three IFG subdivisions. A 10mm search radius was chosen to account for the large anatomical variability in patients.

Principal eigenvariate of hemodynamic time-series within each 6mm sphere were used for VOI extraction. Because the utility of DCM analysis depends on the region showing above threshold activation in the relevant contrast, only participants in which all four VOIs showed enough activation were included in the final analysis. Six patients, five young controls and two age-matched controls were excluded due to insignificant activation in at least one of the VOIs.
### Table 3.2 - Spatial coordinates and Brodmann areas for the four VOIs across the three different groups.

<table>
<thead>
<tr>
<th></th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>BA</th>
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<tr>
<td><strong>Young Controls</strong></td>
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<tr>
<td>LIFG</td>
<td>-42</td>
<td>14</td>
<td>20</td>
<td>44</td>
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<tr>
<td>RIFG</td>
<td>38</td>
<td>14</td>
<td>22</td>
<td>44</td>
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<tr>
<td>LA1</td>
<td>-54</td>
<td>-20</td>
<td>4</td>
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<tr>
<td>RA1</td>
<td>56</td>
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<td><strong>Age-matched Controls</strong></td>
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<tr>
<td>LIFG</td>
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<tr>
<td>RIFG</td>
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<tr>
<td>LA1</td>
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<tr>
<td>RA1</td>
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<td>-12</td>
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<td><strong>Included Patients</strong></td>
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<tr>
<td>LIFG</td>
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<td>RIFG</td>
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<td>LA1</td>
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<td>RA1</td>
<td>58</td>
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L = Left, R = Right, IFG = Inferior Frontal Gyrus, A1 = Primary Auditory Cortex, BA = Brodmann Area

### 3.2.7. Bayesian Model Selection

Effective connectivity between VOIs was examined using the Dynamic Causal Modeling (DCM) tool in SPM12b. Two sets of parameters were estimated: 1) the direct influence of all sentences on regional activity; and 2) the intrinsic connections between regions across all experimental conditions; (Mechelli, Price et al. 2003). DCM describes the interactions between a network of neuronal populations, which are estimated from the observed hemodynamic response. The resulting parameter estimates of intrinsic connectivity, measured in Hz, reflect the
underlying strength of neuronal coupling between two regions of interest. Typically, the absolute values of DCM connectivity range from 0.1 Hz to 1 Hz for non-trivial connections (K. J. Friston, Kahan, Biswal, & Razi, 2014).

Sixteen models were included in model space to compare intrinsic interhemispheric homotopic connections between left and right IFG and between left and right A1 (Figure 3.2). The models differed in the presence of the four homotopic connections between right and left IFG and between right and left A1; their combinations resulted in 16 models. All other possible connections, including self-connections, intra-hemispheric connections, and heterotopic-interhemispheric connections were fixed across the models, and bilateral A1’s were the sources of the driving input. Participants whose best fitting model did not explain at least 10% of the variance in the data were excluded from the analysis. Six patients and one participant young-control group were excluded due to low model fit. The demographic information of these patients and lesion extent are presented separately on Table 3.1 and Figure 3.1.

Figure 3.2 - Model Space. Arrows indicate the direction of driving input and intrinsic connections. Dashed lines represent the four parameters manipulated across the 16 models; solid lines represent connections that were held constant across all 16 models.
Model comparison involved Bayesian model selection (Klaas Enno Stephan, Penny, Daunizeau, Moran, & Friston, 2009) which compared the exceedance probabilities of each of the 16 models, separately for each group. The BMS procedure revealed the same winning model for all three groups, the model with all four homotopic connections turned on (Figure 3.3). Parameter estimates from this model were used in all subsequent analyses.

The individual parameter estimates from the winning model were subjected to one sample t-tests separately for each group, which tested the null hypothesis that a given parameter estimate was zero across individuals in the group, and independent sample t-tests to compare between patients and each one of the control groups (Stephan, Penny et al. 2010). We then assessed the correlations between these parameter estimates and three independent estimates of language comprehension ability. First, each parameter estimate was correlated with an overall measure of task performance. However, because of the acoustic noise in the scanner, this performance may underestimate participants’ ability, as was evident by better performance of these patients in the same task in an MEG experiment (Jed A. Meltzer et al., 2013). Therefore, correlation was also tested between parameter estimates and two offline measures. The auditory-verbal comprehension score on the Western Aphasia Battery (WAB:AVC) was used as a general offline measure of language comprehension, which was shown to be correlated with performance in the experimental task (Meltzer, Wagage et al. 2013). The WAB is a very common neuropsychological test battery of general language ability that is broken into eight subscales. Most relevant to the current study is the auditory verbal comprehension subtest which measures a patient’s ability to answer general and environmental questions, recognize auditory words, and execute auditory sequential commands (Turkstra, 2011).
In addition, performance on the sentence-picture matching task from the Psycholinguistic Assessment of Language (PAL; Rochon et al., 1994) was used as an offline measure of sentence-picture matching ability. This offline measure is very similar to the task performed in the scanner, but includes a wider sample of syntactic structures. Bonferroni correction was applied to all three sets of tests by multiplying each p-value by eight, to account for all eight interhemispheric connections that were correlated with these measures.

![Figure 3.3 - Exceedance probabilities. Probability of individual models across the three participant groups and one additional group of fifteen patients that included all six patients with low model fit.](image)

### 3.3. Results

#### 3.3.1. GLM Analysis

The group activation maps from the second level analysis for the contrast of all sentences vs. baseline in the final analysis are presented in Figure 3.4. As expected, given that participants’ selection criterion for inclusion in the DCM analysis was above threshold activation in all VOIs, all groups exhibited bilateral perisylvian activation, including in our selected VOIs: bilateral IFG and A1. Figure 3.4 also shows a comparison between patients with adequate model fit to be
included in the DCM analysis and those with low model fit (<10% variance explained) which were therefore excluded from the analysis. This comparison shows similar activation between the two patient groups.

![fMRI activation maps](image)

**Figure 3.4 - fMRI activation maps.** Four maps contrast all sentence conditions minus baseline within each group and one map (right-most column) contrasts activation between patients included in the DCM analysis and patients excluded due to poor model fit. One-sample t-test within each group is thresholded at p uncorrected < 0.0001, group comparison: p uncorrected < 0.005.

### 3.3.2. DCM Analysis

**Model selection:** Bayesian model selection of all 16 models showed one consistent winning model for all groups, the model with all homotopic connections turned on. This was also the winning model for age-matched controls, but a second model with the LIFG→RIFG connection turned off had a comparable exceedance probability. A within-group analysis of parameter estimates for both of these models within age-matched controls yielded the same results, as such, the analyses will focus on the universal winning model across the three groups.
Parameter estimates: Intrinsic connections: Parameter estimates from the winning model within each group were subjected to one-sample t-tests. Figure 3.5a presents significant intrinsic parameter estimates for the young controls. The reported p-values were corrected for sixteen connections (including intra- and inter-hemispheric connections as well as self-connections). The young control group shows a significant driving input into the right A1 (p<0.05, corrected) from which excitatory coupling goes into left A1 (p<0.05, corrected) and from there into left IFG (p<0.05, uncorrected). LIFG sends an inhibitory signal to both left (p<0.05, uncorrected) and right A1 (p<0.05, corrected). In the age-matched control group too, right A1 receives excitatory driving input (p<0.05, uncorrected) and inhibitory coupling from the left IFG (p<0.05, uncorrected) (Figure 3.5b). Analyses from the group of included patients and from the full patient group yielded no significant parameters. None of the between-group comparison of parameter estimates were significant.

Figure 3.5 also presents, within the age-matched control and included patient groups, the parameters estimates of non-significant connections that were significant in young controls. The magnitude and sign of these parameter estimates demonstrate that the connectivity pattern in age-matched controls and patients is similar to that of young controls. The lack of statistical significance of these parameters is likely due to the small sample size in the age-matched control group and the inherent variability in the patient group.
3.3.3. Correlations of parameter estimates and behavior

In order to examine the contribution of inter-hemispheric connections to language performance and to recovery from aphasia we tested the correlation between parameter estimates of the eight interhemispheric intrinsic connections in patients with performance in the experimental task and with offline measures of general language comprehension (the WAB:AVC score), and performance on sentence comprehension in a sentence-picture matching task (the PAL score).

Figure 3.6 presents all significant correlations from the included patient group. Offline sentence picture matching ability is negatively correlated with coupling from LIFG to LA1 [$r(7) = -0.742$, $p<0.05$, uncorrected] and with coupling from LIFG to RA1 [$r(7) = -0.843$, $p<0.05$,
General language comprehension, as measured by the WAB:AVC score, is positively correlated with coupling from RA1 to LA1, \[r(7) = 0.672, p<0.05, \text{uncorrected}\] and negatively correlated with coupling from LA1 to RA1, \[r(7) = -0.745, p<0.05, \text{uncorrected}\]. There were no significant correlations between parameter estimates and overall task performance.

Figure 3.6 - **Behavioral correlations from included patient group.** Plots present correlations between parameter estimates of intrinsic connections A) PAL score; B) WAB:AVC. Correlations are significant at **p<0.05 (corrected) and * p<0.05 (uncorrected).**

Figure 3.7 presents correlations from the full patient group. As with the previous analysis, offline sentence picture matching ability is negatively correlated with coupling from LIFG to LA1 \[r(13) = -0.615, p<0.05, \text{uncorrected}\] and with coupling from LIFG to RA1 \[r(13) = -0.707, p<0.05, \text{corrected}\]. The correlation between RA1 to LA1 coupling is only marginally positively correlated with WAB:AVC \[r(13) = 0.5039, p<0.1, \text{uncorrected}\]. However, the negative correlation between LA1 to RA1 coupling and WAB:AVC is stronger in this group, and
survived multiple comparison correction [$r(13) = -0.680, p<0.05$, corrected]. There were no significant correlations between parameter estimates and overall task performance.

In summary, the pattern of correlations was very similar between the two patient groups. We note that adding in the six patients with poor model fit improved the statistical significance of some correlations by increasing the sample size, but it likely did not contribute new information to the analysis, because the estimated connection parameters for the patients with poor model fit are at or near zero, as can be seen from the group of points clustered around the x-axis origin in Figure 3.7. Therefore, we believe that the analysis restricted to the nine patients with satisfactory model fits is the most accurate one, despite the fact that not all of the participants could be included in the analysis.

A) PAL

B) WAB:AVC
3.4. Discussion

The current study examined inter-hemispheric connectivity in patients suffering from chronic aphasia following a LH lesion, during the performance of a sentence comprehension task. The patients were compared to two groups of healthy controls: a young control group and an age-matched control group. Effective connectivity was measured using Dynamic Causal Modeling (DCM) which estimated intrinsic connectivity during sentence comprehension. All estimated models included two symmetrical pairs of regions in the two hemispheres: A1 and IFG. Sixteen models were compared that manipulated the intrinsic connectivity between left and right IFG and between left and right A1. Across all three groups, the winning model had all of the homotopic connections turned on.

An interesting pattern of intrinsic connectivity emerged; some connections which were significant in control groups, also showed correlations with performance in patients. Specifically, the young control group showed a significant driving input into the right A1 from which the excitatory information flow continued into left A1, and from there into left IFG. A feedback loop is then closed with inhibitory top-down connections emanating from left IFG into both left and right A1 (see Figure 3.5a). The most significant of these connections (LIFG-to-RA1) is also found in the smaller age-matched control group (Figure 3.5b). In patients, these connections are not significantly different from zero across the group, but the strength of some of the same interhemispheric connections is correlated with their individual level of language performance. Specifically, a strong negative correlation was found between the connection from left IFG into right A1 and performance on the PAL sentence-picture matching task, so that high performing
patients showed an inhibitory connection, similar to controls, while patients with poor
performance show zero or excitatory connectivity. A similar correlation was found in a post-hoc
analysis for the intra-hemispheric connection LIFG-LA1 (see Figure 3.6). We also found a
positive correlation between the homotopic connection from right-to-left A1 and performance on
an independent test of auditory verbal comprehension (WAB: AVC). Here too, patients with
good performance showed an excitatory connection, similar to controls, while poor performing
patients showed inhibitory coupling. Note that in all of these correlations, the pattern of
connectivity in high performing patients was similar to healthy individuals, whereas altered
connectivity was associated with poor performance. Finally, patients also showed a negative
correlation between language performance (WAB: AVC) and LA1-to-RA1 coupling, which was
not significant in controls; poor performing patients showed positive coupling from the left-to-
right hemisphere.

The analyses revealed no significant correlations between parameter estimates and
overall task performance. It should be noted that the same patients who participated in this study
performed much better in a similar MEG experiment using the same task (Jed A. Meltzer et al.,
2013). We posit that noise from the MRI scanner contributed additional difficulty for patients,
given previous findings that patients with cortical lesions frequently have exaggerated difficulty
understanding speech in noise (Häusler & Levine, 2000). As such, we believe that the
WAB:AVC and PAL are more appropriate measures of language ability. The following sections
focus on the connections that showed significant correlations with these offline measures in
patients.
3.4.1. Interhemispheric connectivity between homotopic regions

Our results show no evidence of transcallosal inhibition between homotopic regions in controls. On the contrary, young controls show excitatory homotopic connections from RA1-to-LA1. This finding is consistent with previous studies showing transfer of sensory information from right-to-left in language perception tasks (Nowicka, Grabowska et al. 1996; Krumbholz, Hewson-Stoate et al. 2007; Bitan, Lifshitz et al. 2010). This asymmetric flow of information may reflect transfer of information from the non-language-dominant hemisphere to the language dominant LH for more specialized processing (Hugdahl, Carlsson et al. 1997; Gazzaniga 2000). For patients, the connection from RA1-to-LA1 was not significant across the group, but positively correlated with performance on the WAB:AVC, which is consistent with our hypothesis (#3; see Figure 3.7b). Importantly, patients with good comprehension showed excitatory connectivity, similar to controls, while two patients with poor comprehension showed inhibitory connectivity from right-to-left A1. This positive correlation is consistent with previous findings (Andoh and Zatorre 2013) and suggest that cooperation between hemispheres at the level of the auditory cortex is beneficial for auditory verbal comprehension. Furthermore, a recent speech perception study reported more positive right-to-left coupling between auditory VOIs in healthy controls, when compared to patients (Schofield, Penny et al. 2012).

The current results also showed a negative correlation between LA1-to-RA1 coupling and performance on the WAB:AVC (see Figure 3.7b), reflecting poor sentence comprehension in patients with excitatory LA1-to-RA1 coupling. Increased LA1-to-RA1 coupling in aphasia, was also reported by Teki et al., (2013), however this was not correlated with task performance. Instead, they found negative correlations between LSTG-to-RSTG coupling and three tests of phonemic discrimination, further supporting the hypothesis that the behavioral implications of
atypical interhemispheric interactions are task-specific (Heiss, Thiel et al. 2003; Price and Crinion 2005). Together, these results suggest that impaired sentence comprehension in aphasia is associated with two forms of atypical homotopic interactions between the auditory cortices: reduced right-to-left coupling and increased left-to-right coupling.

3.4.2. **Interhemispheric connectivity between heterotopic regions**

The results of the young control group show inhibitory interhemispheric connections between non-homotopic regions; namely, from left IFG to both A1s (Figure 3.5c). The top-down connection LIFG-RA1 is particularly interesting because it is also found in the age-matched control group (Figure 3.5b). These inhibitory top-down connections may be part of a feedback loop through which high level language areas modulate the sensory input based on prior knowledge and expectation and increase speech clarity (Sohoglu, Peelle et al. 2012; Wild, Davis et al. 2012). Moreover, in patients, there was a very strong negative correlation between LIFG-to-RA1 connectivity and performance on the PAL, an offline measure of sentence-picture matching (see Figure 3.7a). Namely, patients with good performance showed inhibitory connectivity, like controls, while poor performance was associated with zero or excitatory connectivity. However, a post-hoc analysis shows that this correlation was not unique for the inter-hemispheric connections, but was also found for the intra-hemispheric top-down connection LIFG-LA1. These findings suggest that inhibitory top-down influence from left IFG to left and right auditory cortices are necessary components in the network involved in sentence comprehension in both healthy individuals and patients. When this inhibition is released due to LH damage, this is associated with impaired task performance. Although this findings is consistent with our prediction of release from left-right inhibition following LH damage (#2), which is based on motor and naming studies (Selnes 2000; Thiel, Schumacher et al. 2006;
Rehme, Eickhoff et al. 2011), it shows this pattern for a heterotopic connection which is part of a feedback loop from a higher level region in the lesioned hemisphere to both ipsilesional and contralesional sensory areas.

3.4.3. Limitations

The main limitation of the current study is the small number of patients (9) included in the final analysis. Although a much larger sample of 20 patients were scanned, the data from many of them could not be included in the DCM analysis because they showed no activation in at least one of the VOIs (5 patients) or because the best fit model explained less than 10% of the variance in the data (6 patients). These limitations are inherent to the DCM analysis method, and are used to increase the validity of the DCM parameters. Although the small sample size does not increase the risk for type I error, and therefore does not undermine the reliability of effects found to be significant in the current study, it does increase the risk of type II error (rejecting true parameters). Therefore, the small sample size may explain the fact that some parameter estimates did not reach corrected levels of statistical significance in the control groups (Figure 3.6).

In order to test whether our exclusionary criteria may have biased our results, we compared patients included in the DCM analysis with those excluded from the DCM analysis due to low model fit. No differences were found in lesion size, demographics or behavioral performance on standardized measures or the experimental task. We have also compared the two groups of patients in their activation patterns and found no differences. Furthermore, a separate set of DCM analyses that included all 15 patients with adequate VOI activation showed the same results for model selection, parameter estimates and behavioral correlations. However, the parameter estimates for connections in patients with poor model fit were all at or near zero, suggesting that their inclusion contributes little information to the analysis. Thus, we believe that
the analysis restricted to patients with satisfactory model fit is the most accurate one for
determining the directionality and functional role of neural connections in aphasia recovery. The
reason for the failure of model fit in some patients is unknown. One contributing factor may be
the total loss of structural connections between areas due to stroke-induced lesions. However,
this is unlikely to explain all cases, some control subjects without lesions were also excluded for
lack of model fit.

3.5. **Conclusions**

Previous studies have suggested that the increased involvement of the RH in language
processing in patients with aphasia following LH damage was a consequence of release from
left-to-right transcallosal suppression between homotopic regions (Selnes 2000; Thiel,
Schumacher et al. 2006). This model has been supported by animal studies (Buchkremer-
Ratzmann and Witte 1997; Reinecke, Lutzenburg et al. 1999) and studies of human patients with
motor disorders following unilateral brain damage (Shimizu, Hosaki et al. 2002; Rehme,
Eickhoff et al. 2011), although the role of the unaffected hemisphere in cortical reorganization
after stroke is still highly controversial even within the motor domain (Fridman, Hanakawa et al.
2004; Butefisch, Kleiser et al. 2005; Gerloff, Bushara et al. 2006). Within the language domain
there was a lot of indirect evidence in support of this model, but this was mainly from studies of
naming and word generation tasks (Naeser, Martin et al. 2005; Monti, Cogiamanian et al. 2008;
Otal, Olma et al. 2015) with less consistent support from speech perception studies (Thiel,
Hartmann et al. 2013; Li, Qu et al. 2015).

Our study showed that inter-hemispheric homotopic connections are not necessarily
inhibitory in healthy controls. The excitatory homotopic connectivity found in the current study
can be attributed to the nature of the sentence comprehension task, which requires integration of different types of processes for which both hemispheres specialize. Our results further demonstrate three types of changes to the interhemispheric connectivity in patients with aphasia following LH lesion, all of which are associated with poor performance: a) typical excitatory right-to-left homotopic coupling (RA1-LA1) becomes inhibitory; b) an emergence of a new left-to-right homotopic excitatory coupling (LA1-RA1); and c) release from left-to-right inhibitory coupling which is part of a top-down feedback loop emanating from a high level regions in the lesioned hemisphere onto sensory cortex of both hemispheres (LIFG-RA1; LIFG-LA1). All of these changes were associated with poor language recovery. Although these are correlational findings, they demonstrate how changes in both excitatory and inhibitory connections between hemispheres can be maladaptive. Cooperation between hemispheres in a typically bilateral sentence comprehension task depends on a specific division of labor and an intricate network of excitatory and inhibitory interactions in both directions. When this balance is disrupted due to damage to the left hemisphere, this results in poor performance.
Chapter 4
Interhemispheric Connectivity in Lateralized Lexical Decision

4.1. Introduction

For most right-handed individuals, words presented to the right visual field, and therefore to the left hemisphere (RVF-lh), are processed faster and more accurately than words presented to the left visual field and right hemisphere (LVF-rh). There is a general agreement that this advantage is related to the direct projections from the RVF-lh to the language dominant left hemisphere (Banich, 2003; Bourne, 2006; Bradshaw & Nettleton, 1983; Hellige, 1993; though see Ducrot & Grainger, 2007 for a review of alternative accounts). As such, this long-established RVF-lh advantage has been the foundation for several behavioural (Fernandino et al., 2007; Iacoboni & Zaidel, 1996; Olk & Hartje, 2001; Perrone-Bertolotti et al., 2013; Weems & Zaidel, 2004, 2005) and neuroimaging studies (Barca et al., 2011; Doron, Bassett, & Gazzaniga, 2012; Rauschecker et al., 2012; Selpien et al., 2015; Klaas E. Stephan et al., 2007) looking to further delineate the underlying interhemispheric interactions in language processing.

In behavioral work, many studies have reported a ‘bilateral effect’ for lateralized lexical decision: LVF-rh targets are asymmetrically sensitive to interfering stimuli from the contralateral visual field (Fernandino et al., 2007; Iacoboni & Zaidel, 1996; Olk & Hartje, 2001; Perrone-Bertolotti et al., 2013; Weems & Zaidel, 2004, 2005). Bilateral effect studies use a lateralized lexical decision task, in which targets are presented randomly to either visual field. As with many other lateralized language tasks, the typical RVF-lh advantage is observed. More importantly, in some of trials, a lexically incongruent distractor is presented to the contralateral visual field (e.g., a RVF-lh word target would be accompanied by a LVF-rh pseudoword...
These bilateral trials typically impair accuracy, but only for LVF-rh targets, indicating that the RVF-lh is resistant to interference from the contralateral hemisphere.

The presence of interference with bilateral trials is a clear demonstration that interhemispheric interactions are involved in lateralized word recognition. However, the exact stage for this interaction is unclear. Studies have shown that the bilateral effect is significantly weaker with perceptual distractors (e.g., XXXX) (Fernandino et al., 2007; Perrone-Bertolotti et al., 2013) and unaffected by response hand (Olk & Hartje, 2001; Weems & Zaidel, 2005). As such, interhemispheric interactions likely exist at the stage of lexical access, following pre-lexical perceptual processing but prior to post-lexical response generation (Fernandino et al., 2007; Perrone-Bertolotti et al., 2013; Weems & Zaidel, 2005).

Rauschecker et al., (2012) proposed that the earliest stage for interhemispheric interactions occurs between the visual word form area (VWFA) and its right hemisphere homologue (RVFWA). The VWFA is a well-studied left hemisphere region, located at the posterior ventral occipitotemporal cortex. This area was initially thought to hold position-invariant representations of visual word forms, and as such, act as a gateway from the visual system to the left hemisphere language network (L. Cohen et al., 2000, 2003; Laurent Cohen et al., 2002; McCandliss et al., 2003). However, Rauschecker et al., (2012) recently demonstrated that both the VFWA and RVFWA encode retinotopic information. fMRI activation patterns from the left inferior frontal gyrus (LIFG) and homologous ROIs located in the visual cortex (V1/V2) and VWFA were used to predict the position of words presented along the horizontal meridian. Activation from V1/V2 and VWFA homologous pairs accurately predicted stimulus horizontal positions with 94% and 92% accuracy, respectively, while IFG activation performed at chance. These findings counter the hypothesis of position-invariant encoding within the VWFA and led
the authors to propose a systems-level circuitry model for lateralized reading. They suggested that visual information is processed independently in each hemisphere and interhemispheric interactions occur between the left and right VWFAs.

Evidence against this model can be found in recent connectivity studies of MEG and fMRI (Doron et al., 2012; Klaas E. Stephan et al., 2007). Doron et al., (2012) assessed MEG connectivity across sensors during a lateralized lexical decision task. Analyses of low-frequency amplitude envelope correlations showed that LVF-rh targets led to a greater density of interhemispheric connectivity when compared to RVF-lh targets. This LVF-rh specific increase in interhemispheric connectivity was observed 100ms after stimulus onset along posterior sensors. The authors suggest that this reflects a very early transfer of visual information, though the exact locus for this transfer could not be confirmed with analyses in sensor space.

Interhemispheric connectivity in language has also been explored with Dynamic Causal Modelling of functional Magnetic Resonance Imaging (DCM-fMRI) data (Klaas E. Stephan et al., 2007). The study looked at interhemispheric connectivity during both spatial and letter judgments using lateralized presentations of letter strings. The authors focused on three regions of interest in each hemisphere: bilateral middle occipital gyri, lingual gyri, and fusiform gyri. They reported that letter judgements but not spatial judgements were associated with asymmetric excitatory connectivity from the right lingual and fusiform gyri to their left hemisphere homologues. These results suggest that letter judgements are associated with asymmetric transfer of perceptual information along the ventral visual stream starting as early as the lingual gyrus.

The results from Stephan et al., (2007) suggest that letter detection starts with transfer from the right lingual gyrus, but does this hold for word recognition as well? Recent electrophysiological studies have provide evidence for asymmetrical transfer between occipital
ROIs (Barca et al., 2011; Selpien et al., 2015). Barca et al., (2011) analyzed source-localized MEG responses during a lateralized passive reading task. Event-related fields from left and right occipital ROIs (i.e., $x = 35, y = 85, z = 13$ and $x = 27, y = 96, z = 9$) showed two main findings: 1) the response at each ROI was greater for contralateral vs ipsilateral stimuli, and 2) there was a clear response in the left hemisphere to LVF-rh stimuli but not vice versa. The authors took this as evidence for asymmetrical transfer of information between visual areas.

More recently, Selpien et al., (2015) used a lateralized lexical decision task to localize the earliest visual ERP component associated with left hemisphere language dominance, the N100. Stimuli were presented to either visual field in horizontal and vertical orientations. With horizontal presentations, the typical RVF-lh reading advantage was observed and visual field differences in N100 were localized to the left extrastriate cortex (BA19) and left angular gyrus. However, when words were rotated vertically, the RVF-lh behavioral advantage was abolished and visual field differences in the N100 were localized to the left angular gyrus and supramarginal gyrus, but not the extrastriate cortex. These findings suggest that the N100 asymmetries found under natural (horizontal) reading conditions, are driven by the left ventral extrastriate cortex.

The proposal of independent hemispheric processing up until the VWFA (Rauschecker et al., 2012) is at odds with neuroimaging studies showing asymmetrical transfer between visual areas (Barca et al., 2011; Doron et al., 2012; Selpien et al., 2015; Klaas E. Stephan et al., 2007). The current study explores these conflicting accounts and provides evidence that both are correct; interhemispheric transfer occurs early between primary visual regions, but LVF-rh stimuli are also transferred intrahemispherically to the RVWFA. We combined the lateralized lexical decision task described above with connectivity analyses of source localized MEG signals
to explore the connectivity pattern in bilateral regions of interest along the ventral occipitotemporal stream. Specifically, this study combined MEG with a bilateral lexical decision task to 1) identify the first stage of interhemispheric transfer in visual word recognition using connectivity analyses of homologous occipital and VWFA ROIs and 2) determine the stage of interhemispheric interference from the RVF-lh by comparing the neural responses to unilateral and bilateral trials.

4.2. Methods

4.2.1. Participants

Nineteen right-handed, healthy adults participated in the experiment (12 females; mean age = 25.47 ± 3.8 years). Participants were recruited through advertisements from Greater Toronto Area and the University of Toronto community. All were native speakers of English, with normal hearing and normal or corrected-to-normal vision. None had history of neurological or psychiatric illness, neurological injury, or use of psychotropic medication. Participants gave informed consent and were financially compensated for their time.

4.2.2. MEG Experimental Procedures

Participants were seated in a padded chair inside a magnetically shielded room containing the MEG instrument. Visual cues were displayed on a screen located approximately 75cm from the participant’s face. Participants were seated with their right hand on a response pad with the index and middle fingers to respond.

The experiment included 12 different conditions in a 2(Visual Field: Left vs Right) x 3 (Condition: Unilateral vs. Bilateral Congruent vs. Bilateral Incongruent) x 2(Lexicality: Word vs Pseudoword) design. The visual field factor determined the visual field of the target and the
condition factor determined the type of distractor: no distractor for the unilateral trials, a lexically congruent distractor for the bilateral congruent conditional (e.g., a word distractor for a word target) and a lexically incongruent distractor for the bilateral incongruent trials (e.g., a pseudoword distractor for a word target). There were 50 trials for each condition, adding up to a total of 600 trials for the entire experiment; there was an equal number of word and pseudoword target trials. The session was divided into 12 runs of 50 trials each, allowing for a brief rest period between runs. The total time for the MEG session was approximately 120 min, including setup and instructions.

4.2.3. Stimulus selection

To ensure sufficient power in our MEG analyses, there were 50 trials for each of the twelve conditions. Four of the twelve conditions were unilateral and eight were bilateral, thus requiring a total of 1000 unique stimuli (4 x 50 + 8 x 100 = 1000; 500 words and 500 pseudowords). 500 monosyllabic, regular words of length 4-6 characters and celex frequency greater than 10 occurrences per million were selected from the CELEX database. 500 pseudowords were then generated and matched to the words using the Wuggy pseudoword generator (Keuleers & Brysbaert, 2010). Each pseudoword was matched to its word counterpart according to length, number of phonemes and the OLD20 measure of orthographic distance (Keuleers & Brysbaert, 2010). These 500 words and 500 pseudowords were then separated into 20 distinct sublists, all matched according to length, number of phonemes, bigram and trigram frequency, OLD20 and for words, word frequency. All lexical variables were provided by the N-watch stimulus selection program (C. J. Davis, 2005). Latin square counterbalancing was used to assign each of the 20 sublists to be presented in a specific condition and visual field across each
of 10 experimental lists. Participants were then pseudorandomly assigned without replacement to one of the 10 experimental lists.

4.2.4. Task

Participants performed a lateralized lexical decision task while in the MEG. Figure 4.1 outlines the stimulus presentation sequence for a typical trial. Every trial begins with a fixation cross lasting 3000ms. This is followed by a 200ms presentation of the target screen which includes the target, and arrow pointing towards the target visual field, and a distractor for bilateral trials. The screen is then masked for 200ms, and participants are then cued to respond as to whether the target was a word or pseudoword. Participants are given up to 3000ms to respond, and are given feedback immediately after each response.

Target visual field was randomized across trials so participants could not predict the location of each upcoming target. This presentation method was chosen specifically to minimize eye movements within the time period of data analysis (Hunter & Brysbaert, 2008). Targets and distractors (for bilateral trials) were all presented along the horizontal meridian with the inner edge subtending 1.5 degrees from the center of the screen.
Figure 4.1 - Example of an incongruent bilateral trial. A fixation cross is presented for 3000ms. This is followed the stimulus screen for 200ms and a 200ms mask. The central arrow from the stimulus screen points to the visual field of the target (CAT). Participants are then given up to 3000ms to respond, and provided with feedback.

4.2.5. MRI acquisition and processing

Each subject underwent a structural MRI session on a 3-Tesla scanner (Siemens TIM Trio) located at Baycrest Health Sciences. A high resolution T1-weighted anatomical scan was used to construct a head model for MEG source modeling (MPRAGE, 1mm isotropic voxels). To construct head models for MEG analysis, the locations of the fiducial points were marked manually in AFNI software, and the T1-weighted MRI was spatially transformed into the coordinate space of the MEG data. The skull was stripped using Brain Extraction Tool, and a 3D convex hull approximating the inner surface of the skull was constructed using the software package Brainhull (http://kurage.nimh.nih.gov/meglab/Meg/Brainhull). Taking into account the position of the head relative to the sensors, a multi-sphere model (Huang et al., 1999) was computed. To normalize MEG source estimates into MNI space, we computed a nonlinear warp of each subject's brain to MNI152 standard-space T1-weighted average structural template image, using the software package ANTS (Avants et al., 2011).

4.2.6. MEG acquisition

MEG signals were acquired with a 151-channel whole-head system with axial gradiometers (VSMMedTech, Coquitlam, Canada). MEG was recorded continuously at a sampling rate of 625 Hz, with online synthetic 3rd-order gradient noise reduction (Vrba and Robinson, 2001). After acquisition, continuous signals were cut into epochs corresponding to each trial. Head position with respect to the MEG helmet was monitored using three coils placed at anatomical landmarks of the head (nasion, left and right pre-auricular points). The head position was measured before and after each run, and averaged across runs for source analysis.
The average maximum root-mean-square motion of the fiducial points over the entire 12 runs was 0.5 cm.

### 4.2.7. Source Localization

For source localization of the MEG signal we applied the adaptive beamforming technique Synthetic Aperture Magnetometry (SAM). For each voxel in the brain, SAM constructs an optimized spatial filter that estimates a virtual signal of electromagnetic activity generated at the target location while attenuating activity arising from anywhere else (Van Veen et al., 1997; Vrba and Robinson, 2001). The spatial filter is constructed from the data covariance matrix and a lead field map derived from the MRI head model. This technique was used to localize activity for both whole-brain SAM maps of brain activity and for time-frequency analysis localized to specific ROIs.

### 4.2.8. Source Localization - Whole-Brain SAM Maps

For each subject, at a regular grid of locations spaced 7 mm apart throughout the brain, we computed the pseudo T-statistic, which is a normalized measure of the difference in signal power between two time windows (Vrba and Robinson, 2001). Due to this “dual-state” analysis approach, multi-subject statistical maps were derived from subtractive contrast images computed on the single-subject level, not from individual conditions. These “dual-state” maps contrasted 1-5Hz oscillatory power from an active window 100 to 300ms after stimulus onset against a baseline from -300ms to -100ms before stimulus onset. This time frequency-window was based on the results from ROI analyses showing an early peak in oscillatory power and phase locking peaked within the 1-5Hz range (Figure 4.4). Maps of pseudo t-values throughout the brain were spatially normalized to MNI space by applying the nonlinear transforms computed by ANTS (by warping the T1-weighted MRI to an MNI template at 5mm resolution), enabling random-effects
analysis at the group level. Group statistics on SAM results were computed in a similar fashion as is customary in fMRI studies. For each experimental comparison, the spatially normalized whole-brain map of pseudo t-values was submitted to a voxel-wise one-sample t-test across subjects.

4.2.9. Source Localization - ROI Analysis

For ROI analysis, weights for each subject were computed for a 3-dimensional grid of 10^3 mm voxels across the entire brain. The weights that corresponded to the four regions of interest (Figure 4.2) were then used to estimate virtual signals in the bilateral middle occipital gyri (MOG), left visual word form area (VWFA), and their right hemisphere homologues. To delineate the bilateral MOG, we used the automated anatomical labelling atlas in MNI space (Tzourio-Mazoyer et al., 2002). Because the VWFA does correspond to a distinct anatomical landmark, the VWFA ROIs were placed as 10mm spheres centered on coordinates derived from the literature. The location of the left VWFA was taken from the study of McAndliss et al., (2003) (x = -43, y = -54, z = -12), while the right VWFA was centered on the same coordinates with the X-axis flipped (x = 43, y = -54, z = -12).

Given that each ROI spanned multiple voxels, we further used a principle component analysis (PCA) to extract a single time series from each ROI that captured the greatest amount of variance across voxels within the ROI. This PCA method was conducted separately within each ROI and for each participant. Weights for each of the voxels within an ROI were extracted and matrix-multiplied by the time series from the 151 sensors for each of the 600 trials (12 conditions x 50 trials each), leading to 600 source-localized time series for each voxel. At each voxel, the 600 time-series were then concatenated into a single column vector. All the resultant column vectors, one for each voxel, were then combined into a single matrix for the PCA. The principal
Component coefficients for the first principal scores were then extracted and used as weights to reduce the set of multiple voxel-wise time series into a single set of 600 time-series for each ROI and each participant. This procedure effectively summarizes the coherent electrophysiological activity across multiple adjacent voxels, and accounts for the fact that beamforming algorithms can arbitrarily assign different polarities to current dipoles placed in different voxels. Reversal of dipole polarity can cause cancellation of relevant signals if time series are simply averaged across voxels, whereas PCA will simply assign positive and negative weights to voxels according to their polarity. On average, the variance explained by the first principle component of each of the four ROIs were as follows: LMOG - 41% (SD = 2), RMOG - 47% (SD = 10), LVWFA - 86% (SD = 10), RVWFA - 87% (SD = 11). All subsequent analyses were conducted on these source-localized time-series.

![Figure 4.2 - Size and locations for regions of interest.](image)

The VWFA ROIs are 10mm spheres based on coordinates from McCandliss, Cohen, and Dehaene, (2003) for the LVWFA and the same coordinates with the x-axis flipped for the RVWFA. The bilateral MOG ROIs are based on the macrolabels automated anatomical labelling atlas (Tzourio-Mazoyer et al., 2002).

### 4.2.10. ROI Analyses

The source-localized time-series were subjected to three analyses: 1) event-related fields (ERF) were computed to assess the low-frequency evoked responses that were time-locked to stimulus presentation at each ROI separately, 2) time-frequency analyses were computed to
assess induced changes in oscillatory power at each ROI separately, and 3) the time-frequency spectra of the weighted-phase locking index (wPLI) was computed across the two intrahemispheric connections and the two homologous interhemispheric connections, for a total of four different connections.

4.2.10.1. Event-Related Fields (ERF)

For ERF analyses, we first low-pass filtered the raw sensor data at 5Hz. The filtered single-trial data were then localized with beamforming to voxels within the ROIs and submitted to the principle component analysis described above. The resulting set of individual trial time-series were then averaged within their respective conditions, resulting in twelve ERF time-series for each of the four ROIs and for each participant. Prior to statistical analysis and plotting, each participant’s set of ERFs were subjected to normalization across conditions, separately at each ROI in a manner similar to Barca et al., (2011), to address the wide variability in response strength observed across participants and regions of interest. Normalization involved first squaring the time-series, then subtracting the squared series by the mean and dividing by the standard deviation of the squared response for a period of 0-1000ms post stimulus onset across all twelve conditions. This results in responses that are standardized to a mean zero and unit standard deviation across that time period, but preserves differences in response strength between conditions.

4.2.10.2. Time-Frequency Analysis

Time frequency analyses were computed by first low-pass filtering the raw sensor data at 40Hz. The filtered trial data were then localized and submitted to the principle component analysis described above. Changes in oscillatory power time-locked to the stimulus presentation, a.k.a. time-frequency responses (TFR) centered on -500ms to 1000ms post stimulus onset were
computed using a sliding Hanning window of 500ms in length implemented in the Fieldtrip toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2010).

4.2.10.3. **Weighted-Phase Locking Index (wPLI)**

Connectivity analyses were computed by first low-pass filtering the raw sensor data at 40Hz. The filtered trial data were then localized and submitted to the principle component analysis described above. Connectivity between ROIs were measured using the Weighted Phase Lag Index (wPLI) (Vinck, Oostenveld, van Wingerden, Battaglia, & Pennartz, 2011). This index measures the extent to which one signal consistently leads another signal in phase at a given frequency, and is similar to the older measure Phase Lag Index (Cornelis J. Stam, Nolte, & Daffertshofer, 2007), with exception that wPLI is weighted by the magnitude of the imaginary component of the cross-spectrum between the two time-series. This weighting results in a measure that is more robust to noise and has a greater sensitivity to detect true lagged interactions, while remaining insensitive to influence from common sources projecting to both signals through volume conduction. wPLI was computed using a sliding window of 500ms in width centered on each timepoint from -500ms to 1000ms post stimulus onset, resulting in matrices of wPLI values at each time point and frequency. These time-frequency responses were computed for four ROIs pairs: LMOG-RMOG, LVWFA-RVWFA, LMOG-LVWFA, and RMOG-RVFWA.

4.2.10.4. **Statistical Analysis**

Statistical analyses for the ERF and wPLI time-series were conducted in two ways. The first set of analyses computed paired t-tests at each time point to assess the effect of visual field for unilateral word trials. The second set of analyses computed repeated-measures ANOVAs at each time point, and included only words in a two-way, 2(Visual Field: Left vs. Right) x 2
(Condition: Unilateral vs Bilateral Congruent) design; the incongruent trials were excluded from this analysis due to the chance level performance for incongruent LVF-rh targets (Figure 4.3). Together, these two sets of analyses address the two main questions of this study: 1) where does interhemispheric transfer occur for unilateral parafoveal stimuli, and 2) where does perceptual interference from contralateral stimuli occur?

To provide the flexibility necessary to reveal effects of interest while protecting against type-1 error given multiple comparisons across time points, we employed a cluster-based analysis approach to identify significant differences across conditions, a technique adopted from Maris and Oostenveld (2007). Briefly, a paired t-test or repeated measures ANOVA was conducted at each time point, and t or f-values exceeding a threshold of \( p < .05 \) were clustered based on adjacent time bins. Cluster-based corrected p-values were produced by randomly permuting the assignment of individual subject’s values to the four conditions 1000 times, and counting the number of permutations in which larger clusters (defined by the total t or f-values of all timepoints exceeding \( p < .05 \)) were obtained than those in the correct assignment of conditions.

Both the ERF and wPLI analyses focused on activity below 5Hz. Figure 4.4 shows the full time-frequency responses of wPLI, averaged across all conditions. The results showed that most of the connectivity occurred at the lower frequency bands, as such cluster-based wPLI was restricted to the low frequency band (1-5Hz).

### 4.3. Results

#### 4.3.1. Behavioral Analysis

Accuracy and inverse reaction time (Whelan, 2008) were analyzed using three-way ANOVAs with a 2(Visual Field: Left vs. Right) x 3 (Condition: Unilateral vs. Bilateral...
Congruent vs. Bilateral Incongruent) x 2 (Lexicality: Word vs. Pseudoword) design. All follow-up pairwise comparisons between left and right visual fields are corrected for the six possible comparisons within each measure.

4.3.2. Accuracy

Figure 4.3a presents accuracy across all twelve conditions of the experiment. The three-way ANOVA revealed a significant main effect of condition \( [F(2,36) = 16.148, \text{MSe} = 0.009, p < 0.001, \eta^2 = 0.473] \), driven mainly by superior accuracy in the unilateral condition, especially for LVF-rh words. There was also a main effect of visual field \( [F(1,18) = 15.9, \text{MSe} = 0.021, p < 0.001, \eta^2 = 0.469] \), with better accuracy for RVF-lh words compared to LVF-rh words. The results also showed significant two-way interactions between condition and visual field \( [F(2,36) = 5.8, \text{MSe} = 0.004, p < 0.01, \eta^2 = 0.244] \), and between visual field and lexicality \( [F(2,36) = 5.8, \text{MSe} = 0.004, p < 0.01, \eta^2 = 0.244] \). Finally, there was a significant three-way interaction between condition, visual field and lexicality \( [F(2,36) = 7.723, \text{MSe} = 0.007, p < 0.01, \eta^2 = 0.300] \).

The three-way interaction was further examined with Bonferroni corrected pairwise t-tests of left vs. right visual field at each level of condition and lexicality. The results revealed significant visual field differences for word targets in congruent \( [t(18) = 4.7083, p < 0.005, \text{corrected}] \) and incongruent \( [t(18) = 5.625, p < 0.005, \text{corrected}] \) trials. There was also an effect of visual field for unilateral word trials that did not survive correction \( [t(18) = 2.8095, p < 0.05, \text{uncorrected}] \). In all three cases, RVF-lh accuracy was higher. Furthermore, there was an effect of visual field for congruent pseudoword trials that did not survive Bonferroni correction \( [t(18) = 2.1818, p < 0.05, \text{uncorrected}] \). In this case, accuracy was higher for LVF-rh trials.
To summarize, the three-way interaction reflects the difference in visual field advantages across presentation conditions, which are themselves different for word and pseudoword targets. With word targets, there is a consistent RVF-lh advantage that is exaggerated for bilateral trials, as performance degrades in the LVF-rh as the interference from the RVF-lh increases (interference being lowest in the unilateral condition, higher in bilateral congruent, and highest in bilateral incongruent), whereas performance in the RVF-lh for word stimuli remains consistently high across all three conditions. With pseudoword targets, the pattern is very different. With pseudowords, there is a slight LVF-rh advantage that is significant only for the bilateral congruent trials.

4.3.3. Reaction time

Figure 4.3b presents inverse reaction time for across all twelve conditions of the experiment. The three-way ANOVA of reaction time revealed significant main effects of condition \( [F(2,36) = 32.613, MSe = 0.098, p < 0.001, \eta^2 = 0.644] \), visual field \( [F(1,18) = 8.015, MSe = 0.317, p < 0.05, \eta^2 = 0.308] \), and lexicality \( [F(1,18) = 6.104, MSe = 0.094, p < 0.05, \eta^2 = 0.253] \). These results indicate that performance is faster for unilateral compared to bilateral stimuli, for RVF-lh compared to LVF-rh stimuli, and for for words compared to pseudowords. The results also showed significant two-way interactions between condition and visual field \( [F(2,36) = 7.037, MSe = 0.019, p < 0.005, \eta^2 = 0.281] \), and between condition and lexicality \( [F(2,36) = 4.445, MSe = 0.029, p < 0.05, \eta^2 = 0.198] \).

The two-way interactions between condition and visual field and between condition and lexicality were further explored with post-hoc pairwise t-tests of left vs right visual field after collapsing across lexicality and visual field, respectively. T-tests after collapsing across lexicality showed a significant effect of visual field for unilateral trials \( [t(18) = 3.3297, p < 0.05, \eta^2 = 0.308] \).
corrected]. There were also uncorrected effects of visual field for congruent [t(18) = 2.2581, p < 0.05, uncorrected] and incongruent [t(18) = 2.23704, p < 0.05, uncorrected]. In all cases, inverse reaction time was higher (faster) for RVF-lh trials. T-tests after collapsing across visual field showed one uncorrected effect of lexicality for unilateral trials [t(18) = 2.7971, p < 0.05, uncorrected]; inverse reaction time was higher (faster) for words.

To summarize, the two-way interaction between visual field and condition reflects differences in visual field advantages across conditions, that are present for both word and pseudoword trials. Specifically, there is a right visual field advantage to reaction time for all conditions, but this advantage is greatest for unilateral trials. Furthermore, the two-way interaction between lexicality and condition shows that participants respond faster to words than pseudowords for unilateral trials specifically, whereas this lexicality advantage was attenuated under conditions of bilateral stimulus presentation.

Figure 4.3 - Behavioral results. Plots present accuracy (top) and inverse reaction time (bottom) separately for words (left) and pseudowords (right). Significant differences between left and
right visual field are thresholded at: *p<0.05 (uncorrected), **p<0.05 (corrected), ***p<0.01 (corrected).

### 4.3.4. Time Frequency Maps

Figure 4.4a presents time-frequency responses averaged across the four conditions of interest (i.e., unilateral left words, unilateral right words, bilateral congruent left words, bilateral congruent right words) within the four ROIs. The results show three main effects: an early event-related synchronization (ERS, or power increase) in low frequencies, approximately 1-5 Hz, a later event-related desynchronization (ERD, or power decrease) in higher frequencies spanning the alpha and beta bands (10-20Hz), and a late beta (15-30Hz) ERS. Figure 4.4b presents the time-frequency decomposition of wPLI averaged across the four conditions within each of the four ROI pairs of interest. The results show that wPLI is concentrated in the low frequencies, and coincides with the initial low frequency ERS observed with the time-frequency responses. As such, the subsequent ERF and wPLI analyses will focus on activity in the low frequency, 1-5Hz, range.
**Figure 4.4 - Time-frequency responses.** Plots presents the percentage change in oscillatory power (left) and the standardized change in wPLI (right) compared to a baseline period of -300 to -100ms before stimulus onset. Both plots are averaged across all 12 conditions of the experiment.

4.3.5. SAM Maps

Figure 4.5 presents the pseudo-T maps for unilateral and bilateral trials comparing 1-5Hz activity from 100-300ms post-stimulus onset vs. baseline. In all conditions, peak activation was localized to the contralateral hemisphere (Unilateral RVF-lh: x = -7.5, y = -85.5, z = 5.5; Unilateral LVF-rh: x = 2.5, y = -80.5, z = 5.5; Bilateral RVF-lh: x = -32.5, y = 59.5, z = 5.5; Bilateral LVF-rh: x = 22.5, y = -80.5, z = 10.5).

**Figure 4.5 - Source-localized activation maps.** Maps present 1-5Hz oscillatory activity for unilateral and bilateral word trials from 100-300ms post-stimulus onset against a baseline period of -300ms to -100ms before stimulus onset. All maps thresholded at p<0.001, uncorrected
4.3.6. ROI Analysis - Unilateral Trials

4.3.6.1. Event-related fields

Figure 4.6 presents event-related fields localized to the four ROIs. Cluster analysis comparing unilateral LVF-rh and unilateral RVF-lh trials for words revealed two significant differences at the RMOG (p<0.05) and RVWFA (p<0.05), both showing a greater response to LVF-rh trials. Two other effects that did not reach significance from the cluster analysis are worth mentioning. In the LMOG, there are two sequences of consecutively significant timepoints, one effect showing a stronger response to RVF-lh trials followed by another effect showing a stronger response to LVF-rh trials. Together, these results suggest that LVF-rh stimuli lead to greater responses along right hemisphere ROIs, while left hemisphere ROIs are equally responsive to both visual fields. Furthermore, they suggest that the LMOG receives input from the LVF-rh at a later latency than from the RVF-lh, whereas the response in the LVWFA is similar for both visual fields.
**Figure 4.6 - ERF plots for unilateral trials.** Plots present the normalized ERF responses that were time-locked to stimulus onset, and low-pass filtered at 5Hz. Responses are localized to the LMOG (top left), RMOG (top right), LVWFA (bottom left), and RVWFA (bottom right). Horizontal ticks indicate significant visual field differences from the cluster-based permutation analysis. Significance is thresholded at: .p<0.01, *p<0.05

**4.3.6.2. Weighted-Phase Lag Index (wPLI)**

Figure 4.7 presents 1-5 Hz wPLI across the four channel pairs. Cluster analysis comparing unilateral LVF-rh and unilateral RVF-lh trials showed significant effects at the LMOG-RMOG (p<0.05) and RMOG-RVWFA (p<0.05) channel pairs; in both cases wPLI was greater for LVF-rh trials. These results indicate that LVF-rh targets induce two specific forms of connectivity in an early time period (~0-200 ms) that are not present when stimuli are presented to the dominant hemisphere as RVF-lh. First, there appears to be an early transfer of visual information, presumably from the right to the left hemisphere, reflected in the LMOG-RMOG connection. Second, there seems to be independent intrahemispheric processing of LVF-rh stimuli in a right-hemisphere pathway, reflected in the RMOG-RVWFA connection.

Additionally, although the following effects did not reach the criteria for statistical significance, it should be noted both the LMOG-RMOG and RMOG-RVWFA channel pairs showed a later peak in wPLI for RVF-lh trials compared to LVF-rh trials, in a time range of approximately 300-500 ms. These effects may reflect the output of linguistic computations in the dominant left hemisphere being shared with the nondominant right hemisphere. The LMOG-RMOG connection seems to reflect a late transfer of visual information, whereas the RMOG-RVWFA seems to reflect a late independent stream of processing in the nondominant right hemisphere for RVF-lh words, even though such processing is unlikely to be necessary for successful performance.
Figure 4.7 - **wPLI for unilateral trials.** Plots present raw wPLI values between LMOG-RMOG (top left), LVWFA-RVWFA (top right), LMOG-LVWFA (bottom left), and RMOG-RVWFA (bottom right) channel pairs. Horizontal ticks indicate significant visual field differences from the cluster-based permutation analysis. Significance is thresholded at: .p<0.1, *p<0.05

### 4.3.7. ROI Analysis - Unilateral and Bilateral Trials

#### 4.3.7.1. Event-related fields

Figure 4.8 presents the ERFs localized to the four ROIs. Cluster analyses comparing condition and visual field, in a 2(Visual Field: Left vs. Right) x 2 (Condition: Unilateral vs Bilateral Congruent) design, revealed significant main effects of condition at the LMOG (p<0.005), LVWFA (p<0.05), and RVWFA (p<0.005), all reflecting reduced responses for bilateral trials compared to unilateral trials. There were also significant interactions in the RMOG (p<0.01) and RVWFA (p<0.05). In both cases, the interactions reflect stronger responses
for unilateral LVF trials compared to all other conditions. Together, these results show that the bilateral trials are associated with reduced ERF responses at both hemispheres.

**Figure 4.8 - ERF plots for unilateral and bilateral trials.** Plots present the normalized ERF responses that were time-locked to stimulus onset, and low-pass filtered at 5Hz. Responses are localized to the LMOG (top left), RMOG (top right), LVWFA (bottom left), and RVWFA (bottom right). Horizontal ticks indicate significant main effects of visual field (black), condition (red), and significant interactions (blue) from the cluster-based permutation analysis. Significance is thresholded at: *p<0.05, **p<0.01, ***p<0.005.

### 4.3.7.2. Weighted-Phase Lag Index

Figure 4.9 presents wPLI across the four channel pairs. Cluster analyses comparing effects of condition and visual field, in a 2(Visual Field: Left vs. Right) x 2 (Condition: Unilateral vs Bilateral Congruent) design, showed a significant main effect of visual field at the LMOG-RMOG (p<0.05), reflecting greater wPLI for LVF-rh trials in an early time period (~100-300 ms). This finding suggests that in both unilateral and bilateral conditions, LVF-rh targets induce early visual information transfer from the nondominant right hemisphere to the dominant left hemisphere. A significant main effect of visual field was also found at the RMOG-
RWFA (p<0.05), reflecting greater wPLI for RVF-lh trials in a later time period (~400-600 ms). Although there was not a significant interaction effect, inspection of Figure 4.9d suggests that the main effect of visual field is driven mainly by a later wave of intrahemispheric connectivity within the nondominant right hemisphere, especially with unilateral RVF-lh targets but also, to a smaller degree, with bilateral RVF-lh targets. This finding suggests again that the results of left-hemisphere computations may be "shared" with the right hemisphere in a later time period after the left hemisphere has completed its linguistic analysis of the input.

The analyses also revealed significant effects of condition at the LMOG-LVVFA (p<0.05), LMOG-RMOG (p<0.05; p<0.005), LVWFA-RVWFA (p<0.005) pairs, reflecting reduced connectivity for bilateral trials. Together, these results indicate that bilateral trials result in reduced interhemispheric homotopic connectivity. Presumably, provision of a visual-linguistic stimulus to both hemispheres causes each hemisphere to engage in its own independent processing, with less interaction between them, whereas unilateral stimulation leads to the stimulated hemisphere sharing its information with the unstimulated hemisphere more easily. Notably, the strength of intrahemispheric connections did not vary appreciably between unilateral and bilateral conditions. In the left hemisphere, LMOG-LVVFA connectivity was similar in all four conditions, reflecting a relatively invariant role of the left hemisphere ventral stream in lexical decision. In the right hemisphere, RMOG-RVVFA connectivity was similar in the early (~100-300 ms) time period for all conditions except for unilateral RVF-lh, the one condition in which the right hemisphere receives no direct sensory input. However, in this condition, a later wave of connectivity is seen, most likely due to delayed influence from the left hemisphere.
4.4. Discussion

This study examined interhemispheric interactions during the early stages of lateralized word recognition. The experiment was designed to identify the location for the interhemispheric transfer of LVF-rh stimuli and examined the ostensibly contradictory findings of interhemispheric transfer between posterior visual areas (Barca et al., 2011; Selpien et al., 2015) and the position sensitivity of the left VWFA and its right hemisphere homologue (Rauschecker et al., 2012).

The behavioral results are in line with previous studies; word targets showed a clear interaction between visual field and presentation condition. In all cases, accuracy was higher for RVF-lh trials, an advantage that was greater for bilateral congruent trials and greatest for
bilateral incongruent trials. These results replicate previous findings of asymmetrical interference of LVF-rh stimulus processing from the contralateral hemisphere (Fernandino et al., 2007; Iacoboni & Zaidel, 1996; Perrone-Bertolotti et al., 2013). Interestingly, the results for pseudowords were reversed, showing an LVF-rh advantage for bilateral congruent trials. Given that we were specifically interested in hemispheric communication during word reading, the neuroimaging analyses included only word trials.

Two sets of neuroimaging analyses were conducted to address the main questions of the study: 1) where does interhemispheric transfer occur for unilateral trials? and 2) where does interhemispheric interference occur for bilateral trials? The first question was answered by looking at differences in ERF responses and brain connectivity for unilateral word trials only. The ERF responses to unilateral words provide evidence of asymmetrical interhemispheric transfer between the bilateral MOGs (Figure 4.6). At the LMOG there are two clear peaks, one for RVF-lh trials and another for LVF-rh stimuli, the LVWFA was equally responsive to both visual fields. However, both right hemisphere ROIs were uniquely responsive to LVF-rh trials. This pattern of results is in line with previous studies showing an asymmetrical transfer between early visual areas (Barca et al., 2011; Selpien et al., 2015), and also in line with Rauschecker et al., (2012), showing that the RWVFA is uniquely responsive to LVF-rh stimuli. Furthermore, Barca et al., (2011) also demonstrated that both VWFAs were more responsive to the contralateral visual field. Together, these results suggest that LVF-rh stimuli are initially processed by the RMOG, immediately transferred across the corpus callosum to the LMOG but also transferred within the right hemisphere to the RVFWA. This is supported by connectivity analyses showing that LVF-rh trials lead to greater wPLI between the LMOG-RMOG and between the RMOG-RVFWA (Figure 4.7).
Greater interhemispheric connectivity for LVF-rh stimuli was also found by Doron et al., (2012). The study used a standard laterialized lexical decision task with unilateral trials and analyzed the low-frequency amplitude envelope correlation between sensors. In line with the current results, the authors found a higher density of interhemispheric connections for LVF-rh trials immediately following stimulus onset. Furthermore, results show that the interhemispheric network density peaked later for RVF-lh trials, eventually surpassing the density for LVF-rh trials at 400ms after stimulus onset (Doron et al., 2012, Figure 2). Similarly, we see that wPLI for RVF-lh trials between LMOG-RMOG and between RMOG-RVWFA, also peaked later at around 400ms, after stimulus onset. While the size difference of this peak relative to the wPLI signal for LVF-rh trials did not reach statistical significance, it is noteworthy that both the current study and the results from Doron et al., (2012) show that lateralized displays lead to increased low frequency connectivity early for LVF-rh trials and later for RVF-lh trials.

The second analysis addressed the question of interhemispheric interference. As mentioned above, several behavioral studies show that the LVF-rh is asymmetrically susceptible to interference from the contralateral hemisphere (Fernandino et al., 2007; Olk & Hartje, 2001; Perrone-Bertolotti et al., 2013; Wey et al., 1993). While we see a clear asymmetry of interference in the behavioral data, the imaging results suggest that the interference is mutual. The ERF analyses showed that responses to bilateral trials were reduced across all ROIs regardless of visual field (Figure 4.8). Furthermore, bilateral trials were associated with reduced interhemispheric connectivity between the LMOG-RMOG and between the LVWFA-RVWFA (Figure 4.9). Thus, there is a general reduction in neural responses and interhemispheric connectivity for bilateral vs unilateral trials, regardless of target visual field. These results suggest that bilateral displays lead to mutual interference from both hemispheres.
One important methodological point about this finding bears mentioning. One limitation of beamforming analysis of EEG/MEG data is that when two sources of brain signal are highly correlated with each other, the algorithm can suppress signal from both sources, leading to an underestimation of signal strength. In conditions of bilateral visual stimulation, there is likely to be correlated activity in the two hemispheres, which may lead to suppression of the reconstructed signals. However, this limitation does not confound our finding of reduced ERFs and connectivity for bilateral trials. The suppression of correlated sources happens in the computation of beamformer weights. In the present study, one common set of beamformer weights was computed across all 12 conditions. The inclusion of unilateral trials reduces the overall correlation between sources in the two hemispheres, and furthermore, since the signals from all trials were spatially filtered with the same set of weights, comparisons between unilateral and bilateral conditions are valid. Thus, we are confident that the issue of suppression of correlated sources does not invalidate our finding that bilateral trials lead to reduced response magnitude and connectivity in both hemispheres.

Mutual interhemispheric interference can result from two possible accounts of callosal functioning, mutual inhibition and mutual excitation (Chiarello & Maxfield, 1996; van der Knaap & van der Ham, 2011). The inhibitory model suggests that both hemispheres participate in mutual inhibition of the contralateral hemisphere; laterality results from stronger inhibition originating from the dominant left hemisphere. In the context of the current results, neural responses for bilateral trials are reduced because of mutual inhibition from each hemisphere. The excitatory model suggests that corpus callosum acts to mediate mutual excitation between hemispheres and facilitate integration and information transfer. Under bilateral viewing
conditions, this mutual excitation results in interference, whereby excitatory information impedes concurrent processing of visual stimuli.

While both models predict reduced neural responses and interhemispheric connectivity under bilateral trials, the excitation model can better account for the results from the unilateral trials. LVF-rh trials evoked responses in both hemispheres, and were associated with increased wPLI at the LMOG-RMOG pairs, supporting the idea of excitatory right-to-left connectivity between the MOGs. The inhibitory model can not account for this interhemispheric transfer. Interestingly, early RVF-lh responses were exclusive to the left hemisphere and were associated with reduced LMOG-RMOG connectivity, suggesting that the excitatory connectivity is asymmetrical from right-to-left hemisphere. However, we did observe a later wave of connectivity in LMOG-RMOG (interhemispheric) and RMOG-RVWFA (intrahemispheric), specific to unilateral RVF-lh trials. This connectivity was present despite the lack of a distinct ERF response in right hemisphere regions to RVF-lh stimuli. The nature of this later wave of connectivity remains to be elucidated in further research, but it may represent an inhibitory process suppressing RH activity, which is asymmetrically present under the "ideal" conditions of RVF-lh stimulation, but counteracted by independent stimulation of RH visual areas under the bilateral conditions.

While to our knowledge no other studies have examined interhemispheric connectivity using bilateral word presentations, there is evidence from DCM-fMRI studies that both forms of interhemispheric interaction exist during language processing. Stephan et al., (2007) measured connectivity between four regions of interest located along the ventral visual word recognition stream, the bilateral lingual gyri (LG) and bilateral fusiform gyri (FG), during a lateralized letter decision task. The task induced interhemispheric connections that were conditional on visual
field; RVF-lh stimuli led to left-to-right excitation at both homotopic pairs, while LVF-rh stimuli led to right-to-left excitation at both homotopic pairs. Interestingly, there was a clear asymmetry in the strength of the connections with stronger right-to-left connectivity. Furthermore, there were no cases of inter or intrahemispheric inhibition.

Other DCM-fMRI studies have used central displays or auditory stimuli. Carreiras et al., (2009) found mutual excitatory connectivity along bilateral angular gyri, as well as negative feedback connectivity to visual VOIs when comparing single word reading vs object naming. More recently, Seghier et al., (2011) looked at interhemispheric connectivity of bilateral dorsal and ventral frontal VOIs during semantic decision tasks for words and pictures. They reported that semantic decisions on words lead to negative coupling from the left-to-right dorsal VOIs. Interestingly, Kawabata-Ducan et al., (2014) found support for both excitation and inhibition when studying readers of Kana and Kanji. Specifically, they reported bilateral excitation between left and right vOTs and asymmetrical right-to-left inhibition at the IFGs.

While all the above studies used visual presentations, Bitan et al., (2010) studied interhemispheric connectivity in children, ages 9-15, using a rhyme judgment task. They looked at connectivity between the LIFG, bilateral A1s, bilateral STG and left fusiform gyrus. Once again, there was support for both excitation and inhibition. The results for intrinsic connectivity showed negative right-to-left connectivity at the A1s and reciprocal positive connectivity at the STGs. In summary, the limited DCM studies to show evidence for interhemispheric inhibition along frontal regions (Seghier et al., 2011; Kawabata-Duncan et al., 2014) and mutual excitation along posterior regions (Stephan et al., 2007; Carreiras et al., 2008; Kawabata-Duncan et al., 2014; Bitan et al., 2010). Thus, in line with the current results, these studies suggest that
interhemispheric interactions along the ventral posterior language regions are primarily excitatory.

While excitatory connections are ostensibly necessary for transcallosal transfer in unilateral trials, the results also suggest that bilateral trials result in mutual interhemispheric interference. Interestingly, the behavioral consequences of this interference are asymmetrical, as accuracy for RVF-lh targets remain consistently high across all conditions. This likely reflects the specialization of the left hemisphere for processing verbal stimuli (Banich, 2003; Bourne, 2006; Bradshaw & Nettleton, 1983; Hellige, 1993). There are two ways that an unspecialized right hemisphere for language can result in an enhanced RVF-lh advantage with bilateral display: 1) bilateral displays interfere with transcallosal transfer causing further stimulus degradation during transfer or 2) bilateral displays completely block transcallosal transfer forcing the unspecialized RH to process the target in a direct access manner (Iacoboni & Zaidel, 1996; Weems & Zaidel, 2004). It is also possible that the true asymmetry in neural responses occur further downstream. Interference in this paradigm is largely mediated by the semantic and lexical properties of the distractor (Fernandino et al., 2007; Perrone-Bertolotti et al., 2013), and interhemispheric inhibition may play role in those later stages. More research is needed to delineate the interhemispheric interactions that mediate semantic and lexical interference.
Chapter 5
Interhemispheric interactions in semantic processing

5.1. Introduction

Semantic processing of verbal information involves a widespread bilateral network (Vigneau et al., 2011), with the two cerebral hemispheres specialized to process different types of semantic relationships (e.g., Beeman, 1993; Deacon et al., 2004; Federmeier, 2007). However, the role of interhemispheric communication in semantic processing is uncertain. There are two competing sets of theories regarding general interhemispheric interactions. Some theories suggest that these interactions are primarily inhibitory and serve to facilitate lateralization and hemispheric isolation (David B. Boles, 1987; Cook, 1986; Kinsbourne, 1970; Moscovitch, 1976; Eran Zaidel & Schweiger, 1984), while others suggest that these interactions are excitatory and serve to facilitate sensory and conceptual integration (Abernethy & Coney, 1990a; Beeman, 1993; Collins & Coney, 1998). Several reviews of this very broad topic have concluded that both mechanisms are likely present and the specific case of excitation or inhibition depends on the task and cortical areas involved (Bloom & Hynd, 2005; Nowicka & Tacikowski, 2011b; Schulte & Müller-Oehring, 2010; van der Knaap & van der Ham, 2011). Language processing is a complex multi-step process and perhaps not surprisingly, the evidence shows that it can involve both kinds of interactions; inhibition has been observed with more lateralized aspects of language production and response selection (e.g., Seghier, Josse, Leff, & Price, 2011; Thiel et al., 2006), and excitation has been observed with bilateral processes of perceptual and semantic integration (e.g., Abernethy & Coney, 1990a; Perrone-Bertolotti, Lemonnier, & Baciu, 2013; Stephan, Marshall, Penny, Friston, & Fink, 2007).
5.1.1. Interhemispheric Inhibition

Many theories of inhibition posit that interhemispheric inhibition is dependent on hemispheric activation for a particular task (Kinsbourne, 1970; Moscovitch, 1976; Eran Zaidel & Schweiger, 1984). In the case of language processing, the typical left hemisphere dominance results in asymmetrical left-to-right inhibition. This concept is supported by demonstrations of "unmasked" right hemisphere language activation in patients with aphasia following ischemic damage to the left hemisphere (e.g., Musso et al., 1999; Thulborn, Carpenter, & Just, 1999; Tillema et al., 2008). Recent studies have reported correlations between right hemisphere activation and the magnitude of left hemisphere tissue damage and dysfunction (Chu, Braun, & Meltzer, 2015; Sebastian & Kiran, 2011; Sims et al., 2016; Vitali et al., 2007), suggesting that the right hemisphere is disinhibited following left hemisphere damage. As support for the disinhibition hypothesis, some studies have shown that right hemisphere activation is aphasia is maladaptive: reactivation of surviving left hemisphere perilesional regions has been associated with better outcome (D. Saur et al., 2006), and inhibitory TMS to the right hemisphere has been associated with improved naming in patients (M. A. Naeser et al., 2010; Margaret A. Naeser et al., 2012; Otal et al., 2015) and verbal fluency in healthy controls (Thiel, Schumacher, et al., 2006b). However, several studies have also demonstrated adaptive right hemisphere activation in aphasia (Abo et al., 2004; Blasi et al., 2002; Cappa et al., 1997; Jenny Crinion & Price, 2005; W.-D. Heiss et al., 2003; Jed A. Meltzer, Wagage, Ryder, Solomon, & Braun, 2013; Ohyama et al., 1996; Perani et al., 2003; Thulborn, Carpenter, & Just, 1999a).

The studies cited above use tasks such as word generation, naming, and sentence comprehension which involve semantic, phonological and syntactic processing. As such, they do not provide direct evidence for disinhibition of semantic processing per se. Dual-task studies that
combine a lateralized word recognition task with a concurrent verbal working memory task provide more direct evidence for semantic disinhibition. These studies use a divided visual field (DVF) technique, in which words are presented on one side of the visual field, and are therefore projected to the opposite brain hemisphere due to the crossed connections of the visual system (Bourne, 2006). Thus, they allow for testing of the differential capacity of the two hemispheres to process visual-lexical information. These studies show that the right hemisphere’s capacity to process semantic information is improved when left hemisphere resources are preoccupied with maintaining items in verbal working memory (Faure & Blanc-Garin, 1994; Hutner & Liederman, 1991; Querné, Eustache, & Faure, 2000; Smith-Conway, Chenery, Angwin, & Copland, 2012). Presumably, the concurrent working memory task overloads the left hemisphere’s capacity to inhibit right hemisphere semantic processing.

5.1.2. Interhemispheric Excitation

The excitation account suggests that the corpus callosum acts to integrate information between hemispheres and mediates transcallosal transfer of perceptual and semantic information (Abernethy & Coney, 1990a; Beeman, 1993; Collins & Coney, 1998). In language processing, left hemisphere lateralization results from an asymmetrical excitatory transfer from the nondominant to dominant hemisphere (reviewed in, Nowicka & Tacikowski, 2011; Weems & Reggia, 2004). This account is supported by observations of interhemispheric semantic priming, in which primes presented to one visual field facilitate responses to the contralateral visual field. Abernethy and Coney (1990) used a lateralized lexical decision task with phonemic and semantic primes presented to the same or opposite visual field as the target. They found phonemic priming only when both prime and target were presented to the right visual field (RVF-lh), suggesting that the left hemisphere is uniquely responsible for processing phonemic information. Semantic
priming was found when both prime and target were projected to the left hemisphere, but also when the prime and target were projected to opposite hemispheres. This suggests, that unlike the left lateralized phonemic processes, semantic processing is bilateral and shared between hemispheres. Collins and Coney have since replicated interhemispheric priming under different presentation conditions and for different types of semantic relationships (Abernethy & Coney, 1993, 1996; Collins, 2002; Collins & Coney, 1998). These findings led them to propose a direct connections model wherein each hemisphere can process verbal stimuli independently, and semantic information is shared interhemispherically via spread of activation (Collins & Coney, 1998). More recent studies have also demonstrated interhemispheric priming under different tasks and languages (Dal Molin, Marzi, Banich, & Girelli, 2013; Kato & Okita, 2008; Korsnes & Magnussen, 2007).

5.1.3. Bilateral presentations

Studies using simultaneous bilateral displays have demonstrated that the presence of inhibition and excitation is contingent on task demands. Compared to unilateral presentations, bilateral presentations can facilitate responses for relatedness judgments (reviewed in, Leblanc-Sirois & Braun, 2014) and hinder responses during lateralized lexical decisions (Fernandino et al., 2007; Iacoboni & Zaidel, 1996; Olk & Hartje, 2001; Perrone-Bertolotti et al., 2013; Weems & Zaidel, 2004; Wey et al., 1993). The Dimond paradigm has been used extensively to study interhemispheric interaction. It requires a participant to compare two stimuli that are simultaneously presented to a single visual field, or to both (Dimond, 1969). A recent meta-analysis of seventy-five datasets from studies using the Dimond paradigm have shown that the key determinants of the (dis)advantage for bilateral presentations are task complexity and stimuli similarity. Bilateral presentations are disadvantageous when participants must match according
to simple low-level features (e.g., physical similarity) and are advantageous when participants must match according to complex features (e.g., semantic relatedness) (Leblanc-Sirois & Braun, 2014). These findings support the idea of two ‘bottlenecks’ for hemispheric processing: the interhemispheric bottleneck exists for simple tasks that can be processed by a single hemisphere and thus are punished by interhemispheric transfer, while the intrahemispheric bottle exist for complex tasks that overwhelm the processing capacities of a single hemisphere and as such override the costs of interhemispheric transfer.

Most relevant to current topic, bilateral advantage has been observed with semantic processing of Chinese synonyms (Zhang & Feng, 1999) and semantically related pictures (Kovisto, 2000, Koivisto & Revonsuo, 2003) and word pairs (Koivisto & Revonsuo, 2003; Davis et al., 2012; 2015). Recently, Davis et al., (2015) demonstrated that the bilateral processing advantage for visual and verbal stimuli was mediated by specific subsections of the corpus callosum; word matching was mediated by the genu and splenium-parietal regions while face matching was mediated by the splenium-occipital regions. fMRI functional connectivity was also domain specific; bilateral processing was associated with increased connectivity between the homologous temporal poles for words and between the fusiform gyri for pictures. In these domain-specific regions, interhemispheric connectivity decreased as difficulty increased. Together, the results suggest that domain specific homotopic regions that co-operate during semantic processing also decouple with increased task difficulty.

Bilateral presentations are not always beneficial: several studies have demonstrated that bilateral displays asymmetrically impair processing of LVF-rh targets, further enhancing the RVF-lh advantage in lateralized lexical decision (Fernandino et al., 2007; Iacoboni & Zaidel, 1996; Olk & Hartje, 2001; Perrone-Bertolotti et al., 2013; Weems & Zaidel, 2004; Wey et al.,
The magnitude of this bilateral effect depends on the feature overlap between the distractor and target (Fernandino et al., 2007; Perrone-Bertolotti et al., 2013). Perrone-Bertolotti et al., (2013) tested a number of distractor types and found the most interference with lexically incongruent distractors (e.g. a word distractor with a nonword target). Interestingly, semantically related distractors mitigated the RVF-lh advantage and distractors that were identical to the target abolished the effect entirely, suggesting that the interhemispheric transfer of semantic information can facilitate processing in this task.

The conflicting effects of bilateral displays suggest that interhemispheric interactions can be either interfering or facilitative depending on the task. In the case of the Dimond paradigm, the task requires the integration of stimuli from both visual fields, while with the bilateral effect, one visual field is attended to, and the other must be ignored. The current study extends this body of research on bilateral displays using a bilateral word recognition task, in which participants are asked to identify (by typing) two words that are briefly presented in the two visual fields. This design is in a way a middle ground between the two sets of studies, participants must process stimuli from both visual fields, but are not required to integrate the information to make a final response.

Given that the present study required participants to identify words presented to both visual fields, we explicitly controlled the visual field that participants responded to first (e.g., LVF-rh first, RVF-lh second or RVF-lh first, LVF-rh second). This was controlled for two reasons: 1) the effect of semantic relatedness on the first response will reflect a cleaner measure of automatic interhemispheric semantic transfer, while the effect of relatedness on the second response may be contaminated by top-down strategic processes (e.g., by responding with a word that is related to the first response); 2) attention was effectively biased towards the visual field of
first response. Indeed, the results show that accuracy was consistently higher for the first
response, regardless of visual field. More importantly, the typical RVF-lh advantage in
lateralized word recognition was present only when comparing responses to the second
(unattended) visual field; accuracy was equally high at both attended visual fields. The
mitigation of the RVF-lh advantage by directing attention has been demonstrated previously
(Ducrot & Grainger, 2007; Lindell & Nicholls, 2003; Mondor & Bryden, 1992; Nicholls &
Wood, 1998), and relationship between attention and the RVF-lh advantage is still debated (e.g.,
Barca et al., 2011; Hunter & Brysbaert, 2008; Lindell & Nicholls, 2003; McCarthy & Nobre,
1993; Nazir, 2000; Perez & Cohen, 2009; Simola, Holmqvist, & Lindgren, 2009). The current
study was not designed to address this debate, but instead was interested in the degree that
unattended stimuli are processed semantically, and the interhemispheric transfer of that semantic
information.

The two accounts of interhemispheric interactions make opposing predictions regarding
the effect of presenting semantically related word pairs across the visual fields. According to the
inhibition theory, related pairs should be no easier to identify, and possibly even harder to
identify than unrelated pairs. According to the excitation theory, related pairs should be easier to
identify. This form of semantic facilitation is analogous to semantic priming, with the exception
that in the current paradigm, both prime and target are presented simultaneously, and responses
to both words are required. It has been long established that semantic priming can result from
both automatic (unconscious) spread of activation and controlled (conscious) strategic processing
(e.g., Chiarello, 1985; M. Koivisto, 1998b). Automatic priming is encouraged through conditions
that prevent participants from consciously using the prime to facilitate target processing while
controlled priming occurs when participants are aware that the prime and target are likely
related. As such, short and long prime-target intervals encourage automatic and controlled priming, respectively (Chiarello, 1985).

The attentional manipulation in the current study encourages both automatic and controlled priming to occur. Priming of the attended visual field, which is always queried first, reflects automatic spread of activation, as both stimuli are presented simultaneously, effectively providing the shortest possible prime-target interval of 0ms. Priming of unattended visual field however, will reflect both automatic and controlled processes as the response submitted for the attended visual will influence the response submitted for the unattended visual field. In the current study, we were more interested in automatic interhemispheric interactions, in the absence of controlled processes. As such, priming at the attended visual field is the most relevant to the current research question. It is also important to note that the simultaneous presentation used in the current paradigm muddies the distinction between prime and target; for the remainder of the manuscript, priming is referring to the facilitation of word identification when a related word is presented to the contralateral visual field, irrespective of visual field and attention. Figure 5.1a outlines the four types of priming can occur: 1) priming of attended LVF-rh, 2) priming of attended RVF-lh, 3) priming of unattended LVF-rh, and 4) priming of unattended RVF-lh.

Priming in this study was tested with word pairs that were related by association. Related pairs were symmetrical (e.g., SHOE-FOOT) or asymmetrical (e.g., ATOM-BOMB) associates. Symmetrical word pairs are equally likely to prime each other, while with asymmetrical word pairs, the cue (ATOM) primes the target (BOMB), but not vice versa. In typical asymmetrical priming studies, pairs are presented in forwards and backwards conditions by manipulating the temporal order of stimulus presentation; forwards priming is found when the cue (ATOM) precedes the target (BOMB), and backwards priming is found when the target (BOMB) precedes...
the cue (ATOM) (e.g., Hutchison, Heap, Neely, & Thomas, 2014; Kandhadai & Federmeier, 2010; M. Koivisto, 1998a). The distinction of forwards and backwards association is less clear in a paradigm with simultaneous bilateral presentations. Instead, the relevant factor is the congruency between visual field and cue-target orientation. Specifically, a response is congruent if the visual field being read contains the target word (e.g. BOMB), as it should be facilitated by priming from the cue word (e.g. ATOM). In contrast, the response is incongruent if the visual field being read contains the cue word (ATOM), as it would be unlikely to benefit from priming from the target word (BOMB), due to the asymmetrical nature of the priming relationship (ATOM primes BOMB but not vice-versa). Figure 5.1b outlines the four types of asymmetrical priming that can occur 1) congruent LVF-rh priming, 2) congruent RVF-lh priming, 3) incongruent LVF-rh priming and 4) incongruent RVF-lh priming.

Figure 5.1 - **Priming effects under bilateral displays.** The left panel (A) outlines the interactions between attention and priming. The question mark highlights the visual field of response, and the star highlights the attended visual field. When the attended visual field is primed (1 and 2), attention is oriented towards the field of response, and priming is from the
unattended visual field, reflecting automatic priming processes (dashed line). When the unattended visual field is primed (3 and 4), attention is directed away from the visual field of response, and priming is from the attended visual field, reflecting controlled and automatic priming (solid line). The right panel (B) outlines the interaction between prime congruency and visual field. Priming is congruent (1 and 2) if the visual field of response contains the target (e.g., BOMB), and priming is incongruent (3 and 4) if the visual field of response contains the prime (e.g., ATOM). Congruent priming can result from automatic priming processes alone (dashed line), while incongruent priming requires controlled priming processes (solid line).

Asymmetrical word pairs were included for two reasons: 1) to more strictly test the hypothesis of the automatic interhemispheric spread of activation; automatic priming should only be present at congruent attended visual fields. 2) To test the possibility for an asymmetrical transfer of semantic information; given the left hemisphere dominance for language, it is possible that semantic information is spread asymmetrically from the right-to-left hemispheres. As such, priming should be greater when the target word is presented to the LVF-rh (e.g., BOMB) and the prime word is presented to the RVF-lh (e.g., ATOM), leading to the counterintuitive prediction that priming will be greater with presentations in the reverse order of reading direction (e.g., BOMB-ATOM). Some studies have indeed demonstrated an asymmetry in the transfer of visual information in word and letter processing (Barca et al., 2011; Doron et al., 2012; Selpien et al., 2015; Klaas E. Stephan et al., 2007), and greater interhemispheric priming was observed with targets presented to the LVH-rh and primes to the RVF-lh (Abernethy & Coney, 1993).

5.2. Methods

5.2.1. Participants

Sixty-four right-handed native English speakers participated in this study (46 Females, Mean = 18.59, SD = 1.15 years). All participants were undergraduate students and were
compensated with course credit for their participation. All participants gave informed consent prior to the start of the experiment.

5.2.2. Stimuli

200 word pairs were selected from the University of South Florida Free Association Norms database (Nelson, McEvoy, & Schreiber, 2004). Briefly, these norms were developed through more than 6,000 participants conducting a discrete association task. Associative norms ranging from 0-1 were then created to represent the probability that a cue would generate a specific target. These normative values were used in the current experiment to select stimuli pairs that were symmetrically related, asymmetrically related, and unrelated. Fifty symmetrically associated word pairs (e.g., SHOE-FOOT) were selected based on the following conditions: cue-target association in both directions (e.g., SHOE-FOOT and FOOT-SHOE) were greater than 0.1, and the difference between the directional associations were less than 0.1. Fifty asymmetrically associated word pairs (e.g., ATOM-BOMB) were selected based on the following conditions: cue-target associations in the forward direction (e.g., ATOM-BOMB) was greater than 0.1 and cue-target associations in the backwards direction (e.g., BOMB-ATOM) was zero. Within each pair, stimuli were matched according to word length, number of phonemes, orthographic neighborhood, and CELEX word frequency. All variables were provided by the N-Watch program for psycholinguistic statistics (C. J. Davis, 2005). An additional set of 100 unrelated word pairs (e.g., GRIND-BOBE) were selected under the condition that the both forwards and backwards associations were equal to zero. Each unrelated pair was further matched to a specific related word pair in word length, number of phonemes, orthographic neighborhood, and CELEX word frequency (Table 5.1). Note that symmetrical and asymmetrical primes were analyzed in separate comparisons, rather than a full factorial design, because
symmetrical primes (M = 0.305, SD = 0.18) tended to be more highly associated than asymmetrical primes (M = 0.19, SD = 0.11).

<table>
<thead>
<tr>
<th>Symmetrically Related</th>
<th>Word 1</th>
<th>Word 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forwards Association</td>
<td>0.31 (0.19)</td>
<td>0.30 (0.17)</td>
</tr>
<tr>
<td>Backwards Association</td>
<td>0.34 (0.74)</td>
<td>3.42 (0.78)</td>
</tr>
<tr>
<td>Number of Phonemes</td>
<td>4.18 (0.72)</td>
<td>4.22 (0.76)</td>
</tr>
<tr>
<td>Length</td>
<td>1.65 (0.72)</td>
<td>1.59 (0.76)</td>
</tr>
<tr>
<td>Orthographic Neighbourhood</td>
<td>7.44 (5.84)</td>
<td>7.70 (6.02)</td>
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<table>
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<tr>
<th>Matched Unrelated</th>
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</thead>
<tbody>
<tr>
<td>Number of Phonemes</td>
<td>3.48 (0.74)</td>
<td>3.42 (0.78)</td>
</tr>
<tr>
<td>Length</td>
<td>4.18 (0.72)</td>
<td>4.22 (0.76)</td>
</tr>
<tr>
<td>Frequency</td>
<td>1.65 (0.76)</td>
<td>1.54 (0.73)</td>
</tr>
<tr>
<td>Orthographic Neighbourhood</td>
<td>7.86 (5.38)</td>
<td>6.78 (5.31)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Asymmetrically Related</th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Forwards Association</td>
<td>0.19 (0.11)</td>
<td>0.19 (0.17)</td>
</tr>
<tr>
<td>Backwards Association</td>
<td>0.34 (0.91)</td>
<td>3.58 (0.73)</td>
</tr>
<tr>
<td>Number of Phonemes</td>
<td>4.40 (0.70)</td>
<td>4.38 (0.75)</td>
</tr>
<tr>
<td>Length</td>
<td>1.46 (0.63)</td>
<td>1.45 (0.59)</td>
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<tr>
<td>Orthographic Neighbourhood</td>
<td>6.54 (5.90)</td>
<td>6.50 (5.17)</td>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Phonemes</td>
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<td>3.42 (0.78)</td>
</tr>
<tr>
<td>Length</td>
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</tr>
<tr>
<td>Frequency</td>
<td>1.65 (0.76)</td>
<td>1.54 (0.73)</td>
</tr>
<tr>
<td>Orthographic Neighbourhood</td>
<td>7.86 (5.38)</td>
<td>6.78 (5.31)</td>
</tr>
</tbody>
</table>

Table 5.1 – *Psycholinguistic statistics* – Mean (SD in parentheses) normative forwards and backwards association values are presented for related pairs. Mean (SD in parentheses) number of phonemes, length, word frequency and orthographic neighbourhood are all word pairs.

5.2.3. **Apparatus**

The experiments were conducted on a desktop computer using an Intel Core 2 Duo processor. Stimulus presentation and data collection were conducted using E-Prime software (Psychology Software Tools, Pittsburgh, PA). Participants were seated 66cm from a 56cm Asus LCD monitor with a screen refresh rate of 60Hz and responses were collected with a keyboard.
5.2.4. Design

The experiment consisted of both within and between-subject manipulations. All stimuli-related variables were manipulated within subjects and consisted of relatedness (related vs unrelated), associative symmetry (symmetrical vs asymmetrical), and associative directionality (forwards vs. backwards). Each participant completed 200 experimental trials comprised of 100 trials with related pairs and 100 trials with unrelated pairs. The related trials were further divided into 50 trials with symmetrically related pairs and 50 trials with asymmetrically related pairs. Finally, the asymmetrically related trials were further divided into 25 trials in the forward condition, wherein the cue was presented to the LVF-rh and target to the RVF-lh (e.g., ATOM-BOMB) and 25 trials in the backwards condition, wherein the target was presented to the LVF-rh and cue to the RVF-lh (e.g., BOMB-ATOM). The visual field positioning of each stimulus pair was counterbalanced across two experimental lists.

The experiment also included two additional between-subject manipulations: attended field (left or right) and visual angle. Attention was directed towards a specific visual field by asking each participant to identify the word from a specific visual field first; half of the participants identified the LVF-rh word first, half identified the RVF-lh word first. The visual angle manipulation was included to test the possible interaction between visual angle and hemispheric transfer, and involved presenting the stimuli pair 0.5 degrees or 2.5 degrees from fixation. Thus, participants were divided into four separate groups that independently manipulated attention and visual angle (Table 5.2).

5.2.5. Procedure

Figure 5.2 presents presentation sequence of a typical trial. Each trial began with a 1000ms central fixation cross, immediately followed by a 200ms presentation of the target
stimuli screen. The target screen presented a random digit from 0-9 at the center of the screen along with the target words in the two visual fields, presented with their inner edges subtending either 0.5 or 2.5 degrees from fixation, depending on the subject group. This screen was immediately followed by a response box that asked participants to identify the word on the LVF-rh (or RVF-lh), then the word on the RVF-lh (or LVF-rh), and finally the central digit. Digit identification was used to reject trials that likely involved eye movements (Bourne, 2006). Trials with correct and incorrect digit identification were analyzed separately.

Figure 5.2 - Example of an attend-left trial. A fixation cross is presented for 1000ms. This is followed by the stimulus screen for 200ms, containing the two targets and central fixation digit. Participants are then immediately prompted to type in the word on the left, then the word on the right, and the central digit.

5.3. Results

5.3.1. Analyses of Trials with Correct Digit Identification

Participants with less than five trials with correct digit identification in each condition were excluded from the analysis. Eight participants were excluded for this reason, resulting in a
total of fifty-six participants (38 females, Mean = 18.48 years, SD = 1.06 years) in the following analyses. Table 5.2 presents the number of participants in each of the four experimental groups.

Three analyses were conducted to address the three main questions of the study: 1) How does attention mediate visual field differences in word recognition and semantic processing? 2) Can semantic processing from the unattended visual field/hemisphere facilitate processing of the contralateral visual field/hemisphere? 3) Is there a directionality in interhemispheric transfer of semantic information? The full set of effects from each analysis are presented in Appendix 5.1, the following sections outline the results that are relevant to the current research questions.

### Table 5.2 - Digit identification sample size

<table>
<thead>
<tr>
<th>First Response Visual Field</th>
<th>Visual Angle</th>
<th>Digit Accuracy</th>
<th>Total Participated</th>
<th>Digit Correct Analysis</th>
<th>Digit Incorrect Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVF-rh</td>
<td>0.5</td>
<td>0.633 (0.056)</td>
<td>18</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>RVF-lh</td>
<td>0.5</td>
<td>0.634 (0.049)</td>
<td>15</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>LVF-rh</td>
<td>2.5</td>
<td>0.590 (0.0495)</td>
<td>15</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>RVF-lh</td>
<td>2.5</td>
<td>0.620 (0.0423)</td>
<td>16</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.620 (0.003)</td>
<td>64</td>
<td>56</td>
<td>32</td>
</tr>
</tbody>
</table>

Table 5.2 - **Digit identification sample size** – Mean (SEM in parentheses) digit identification accuracy and total sample size across the four participant groups. Total number of subjects in the digit-correct and digit-incorrect analyses are presented separately.

#### 5.3.1.1. Analysis 1 - Unrelated trials

The first question was addressed by analyzing unrelated trials only, in a 2x2x2 ANOVA, with all three factors treated as between-subjects variables. The three factors were: attention (attended side vs unattended side), visual field (left vs right), and visual angle: (0.5 vs 2.5 degrees). Even though subjects responded to words in both visual fields, treating the first two factors as between-subjects was necessary because of the way the experiment was counterbalanced, with some subjects instructed to respond first to the right visual field (and thereby attending to it more strongly) and others instructed to respond first to the left. Between-subjects ANOVA revealed significant main effects of visual field \( F(1.52) = 5.418, p <0.05, \)
partial $\eta^2 = 0.0944$, reflecting higher accuracy for RVF-lh, attention [$F(1,52) = 43.144, p < 0.001$, partial $\eta^2 = 0.453$], reflecting higher accuracy for the attended visual field, and visual angle [$F(1,52) = 8.505, p<0.01$, partial $\eta^2 = 0.141$], reflecting higher accuracy for 0.5 degrees. Critically, there was also a significant interaction between visual field and attention [$F(1,52) = 6.314, p<0.05$, partial $\eta^2 = 0.108$]. Follow-up independent samples t-tests comparing visual fields showed a significant RVF-lh advantage for the unattended side [$t(52) = 3.179, p<0.005$, corrected], but not for the attended side [$t(52) = -0.443, p>0.05$, uncorrected] (Figure 5.3a). All remaining interactions were not significant.

All analyses in this experiment showed an accuracy advantage for subjects viewing the two words at the smaller visual angle of 0.5 degrees, except for those analyses restricted to the attended visual field. However, the factor of visual angle did not significantly interact with any of the other experimental variables. Therefore, we collapsed across it in the figures. Hence, all accuracy graphs contain data from participants viewing the words at both angles, 0.5 and 2.5 degrees.

A) Digit Correct

B) Digit Incorrect

Figure 5.3 - Analysis 1: Unrelated trials. Plots presents word identification accuracy at each unattended (left) and attended visual field (right). Results from digit-correct (left) and digit-incorrect (right) trials are plotted separately. Significant visual field differences marked and thresholded as follows: *$p<0.05$, **$p<0.005$, ***$p<0.005$
5.3.1.2. Analysis 2 - Symmetrically Related

The results from the first analysis showed that attention facilitated word identification and interacted with visual field; the typical RVF-lh advantage disappeared for the attended side but persisted for the unattended side. The second research question investigated whether semantic information can be automatically shared between the two cerebral hemispheres. Sharing of such information would be indicated by priming, in the form of increased recognition accuracy when the word in the opposite visual field is related. As described in the introduction, the attentional manipulation is likely to result in two forms of semantic priming with potentially additive effects; priming of the unattended visual field (field of second response) may reflect both automatic and top-down processes. For example, when attending to "SHOE," the participant may be able to consciously guess that the other word is "FOOT," being aware that some of the word pairs are related. In contrast, priming of the attended visual field (field of first response) should yield a cleaner indicator of only automatic processes. As such, the subsequent analyses assessed unattended and attended trials separately. We report the results of both, but priming of the attended visual field (from the unattended one) is of greater experimental interest, as a measure of the automatic transfer of semantic information between the two hemispheres.

The second analysis included symmetrically related and unrelated trials in a mixed 2x2x2 design, with visual field (left vs right) and visual angle (0.5 vs 2.5 degrees) treated as between-subjects factors, as explained in Analysis 1. Relatedness (related vs. unrelated) was treated as a within-subjects factor.

5.3.1.2.1 Unattended Visual Field

Mixed-design ANOVA for words presented in the unattended visual field (field of second response) revealed significant main effects of visual field \( [F(1,52) = 9.626, p < 0.005, \text{partial } \eta^2 = \)
0.1562], reflecting higher accuracy for RVF-lh, relatedness [F(1,52) = 139.947, p <0.001, partial \( \eta^2 = 0.729 \)], reflecting higher accuracy for related words, and visual angle [F(1,52) = 5.757, p < 0.05, partial \( \eta^2 = 0.098 \)], reflecting higher accuracy for the smaller angle. No interactions were significant. These results show that both left and right visual fields, when unattended (second response), receive priming from the attended contralateral visual field, and that priming does not mitigate the RVF-lh advantage (Figure 5.4a). As explained in the introduction, priming in the unattended field may reflect both automatic and controlled processes. As such, priming in the attended field offers a cleaner measure of the automatic spread of semantic information between hemispheres.

5.3.1.2.1. Attended Visual Field

Mixed-design ANOVA on recognition accuracy for words in the attended field revealed a significant main effect of relatedness [F(1,52) = 38.369, p < 0.005, partial \( \eta^2 = 0.425 \)], reflecting higher accuracy for related trials. All remaining effects were not significant. These results show that both visual fields received priming from the unattended contralateral visual field (Figure 5.4a). Furthermore, the lack of a main effect of visual field confirms the finding of the earlier analysis of unrelated trials only (Figure 5.3a), that accuracy in the attended field is uniformly high regardless of whether it is the left or right field. Nonetheless, the effect of semantic relatedness appears to be additive to the benefits of attention.

In summary, the analyses of symmetrical priming illustrate that semantic information is shared between hemispheres regardless of which side is attended, and this effect is independent and additive of the RVF-lh advantage for the unattended visual field. The presence of the effect in the unattended visual field could be accounted for by either automatic, interhemispheric sharing of semantic information, or by strategic, top-down processes. However, the persistence
of the priming effect in the attended visual field confirms that automatic interhemispheric spreading of semantic information occurs.

Figure 5.4 - **Analysis 2: Symmetrically related trials.** Plots presents word identification accuracy for unrelated (grey) and related (white) words at the LVF (left) and RVF (right). Unattended (top) and attended (bottom) visual fields are plotted separately. Digit-correct (left) and digit-incorrect (right) trials are also plotted separately. Significant visual field differences marked and thresholded as follows: *p<0.05, **p<0.005, ***p<0.005

5.3.1.3. **Analysis 3 - Asymmetrically Related**

The results from the second analysis showed priming at both unattended and attended visual fields. The demonstration of priming at the attended visual field is suggestive of an automatic interhemispheric transfer of semantic information. To further investigate the claim of automatic transfer, a third analysis with asymmetrical word pairs (e.g., ATOM-BOMB) was conducted. As described in the introduction, the critical factor with regards to asymmetrical priming is whether or not the visual field in question contains the target (BOMB), and thus can benefit from the presence of prime (ATOM) presented to the contralateral visual field. As such, evidence for automatic transfer priming will be assessed by the interaction between relatedness
and priming congruency; priming should only occur when the prime-target orientation is congruent with the visual field of interest. Furthermore, the possibility for an asymmetrical directionality in interhemispheric transfer was tested by assessing the magnitude of priming at each visual field.

The third research question was addressed by including only asymmetrically related and unrelated trials a mixed 2x2x2x2 design, with visual field (left vs right) and visual angle (0.5 vs 2.5 degrees) treated as between-subjects factors, and relatedness (related vs. unrelated) and prime congruency as a within-subjects factors. Again, note that although participants responded to words in both visual fields, one field (left or right) was responded to first, and thus "attended," making visual field a between-subjects factor for these analyses.

5.3.1.3.1. Unattended Visual Field

Mixed-design ANOVA of unattended trials revealed significant main effects of visual field \[F(1,52) = 11.587, p<0.005, \text{partial } \eta^2 = 0.182\], reflecting higher accuracy for RVF-lh, relatedness \[F(1,52) = 35.251, p<0.001, \text{partial } \eta^2 = 0.404\], reflecting higher accuracy for related words, and visual angle \[F(1,52) = 5.99, p<0.05, \text{partial } \eta^2 = 0.1033\], reflecting higher accuracy for 0.5 degrees. Finally, there was a marginally significant interaction between prime congruency and relatedness \[F(1,52) = 4.021, p=0.0502, \text{partial } \eta^2 = 0.0717\]. Follow-up t-tests showed significant effects of relatedness at congruent \[t(55) = 5.762, p<0.001, \text{corrected}\] and incongruent \[t(55) = 2.341, p<0.05, \text{corrected}\] visual fields; the interaction reflected stronger priming at the congruent visual fields. All remaining effects were not significant.

The hypothesis of asymmetrical directional transfer was tested with planned paired t-tests comparing related and unrelated trials at each visual field. T-tests within congruent visual fields (e.g., BOMB) showed significant effects of relatedness at the LVF-rh \[t(27) = 3.799, p<0.005, \text{corrected}\].
and RVF-lh [t(27) = 4.287, p<0.001, corrected], while t-tests within incongruent visual fields (e.g., ATOM) showed a significant effect at the LVF-rh [t(27) = 3.112, p<0.05, corrected] and not effect at the RVF-lh [t(27) = 0.773, p>0.05, uncorrected]. These results, shown in Figure 5.5a, demonstrate that that priming of the unattended visual field depended on the directionality of the word pair. As expected, priming in the congruent condition occurred for both visual fields, but in the incongruent condition, priming was present for LVF-rh targets only. This may reflect sharing of semantic information preferentially from the left to the right hemisphere, but as discussed above, priming in the unattended field can involve a mix of automatic and controlled processing. The best test of automatic spreading of semantic information is congruent priming in the attended field, addressed below.

Figure 5.5 - Analysis 3: Asymmetrically related trials, unattended visual fields (2nd word). Plots present word identification accuracy for unrelated (grey) and related (white) words at the LVF (left) and RVF (right). Congruent (top) and incongruent (bottom) visual fields are plotted separately. Digit-correct (left) and digit-incorrect (right) trials are also plotted separately. Significant visual field differences marked and thresholded as follows: *p<0.05, **p<0.005, ***p<0.005
5.3.1.3.2. Attended Visual Field

Mixed-design ANOVA of attended trials revealed a main effect of relatedness \[F(1,52) = 12.639, p < 0.001, \text{ partial } \eta^2 = 0.1956\], reflecting higher accuracy for related trials, and a marginally significant interaction between prime congruency and relatedness \[F(1,52) = 3.379, p=0.0717, \text{ partial } \eta^2 = 0.061\]. Follow-up t-tests showed that relatedness was significant at congruent visual fields \[t(55) = 3.416, p<0.005, \text{ corrected}\] and insignificant at incongruent visual fields \[t(55) = 1.3216, p>0.05, \text{ uncorrected}\]. All remaining effects were not significant. Thus, the congruency manipulation appears to have worked: priming occurred only in the predicted direction according to the asymmetric associative relationship between the prime and target words.

The hypothesis of directional transfer was tested with planned paired t-tests comparing related and unrelated trials at each visual field. Planned paired t-tests within congruent visual fields showed a significant effect of relatedness at the LVF-rh \[t(27) = 2.841, p<0.05, \text{ corrected}\] and a marginally significant effect at the RVF-lh \[t(27) = 2.035, p<0.1, \text{ uncorrected}\]. Within incongruent visual fields, the effects of relatedness were insignificant at the LVF-rh \[t(27) = 0, p =1, \text{ uncorrected}\] and marginally significant at the RVF-lh \[t(27) = 2.001, p<0.1, \text{ uncorrected}\]. Overall, these results, as shown in Figure 5.6a, indicate that the strongest priming seems to occur for directional transfer of semantic information from the left to the right hemisphere, i.e. congruent priming in the attended visual field for LVF-rh targets. However, given that marginally significant priming also occurred for congruent attended RVF-lh targets, semantic transfer is likely to occur bidirectionally between the two hemispheres, although it may be slightly stronger from the dominant left hemisphere to the subordinate right hemisphere.
Figure 5.6 - **Analysis 3: Asymmetrically related trials, attended visual fields (1st word).** Plots present word identification accuracy for unrelated (grey) and related (white) words at the LVF (left) and RVF (right). Congruent (top) and incongruent (bottom) visual fields are plotted separately. Digit-correct (left) and digit-incorrect (right) trials are also plotted separately. Significant visual field differences marked and thresholded as follows: *p<0.05, **p<0.005, ***p<0.005

### 5.3.2. Analyses of Trials with Incorrect Digit Identification

The present experiment required participants to report the identity of a centrally-positioned digit in addition to the two words presented at the two sides. This manipulation was intended to enforce central fixation. However, this resulted in a challenging task. Digit accuracy was around 60% across the four participant groups (Table 5.2), giving us the opportunity to analyze trials with correct and incorrect digit identification separately. Thus, a second set of analyses was conducted of trials with incorrect digit identification. These trials are likely to have involved broken fixation. If the observed experimental effects are attributable to patterns of saccades rather than genuine transcortical interactions, one would expect the effects to be enhanced on these trials. If instead the effects are attributable to patterns of information transfer in the brain following on peripheral visual stimulation, the effects should be attenuated instead.
As with the first set of analyses, participants with less than five trials with incorrect digit identification in each condition were excluded from the analyses. Thirty-two participants were excluded for this reason, resulting in a total of thirty-two participants (24 females, Mean = 18.72 years, SD = 1.08 years) included in the final analysis. Table 2 presents the number of participants in each of the four between-subjects group for this analysis and the full set of effects from each analysis are presented in Appendix 5.2. The following sections outline the effects that were relevant to the analysis of trials with correct digit identification.

5.3.2.1. **Analysis 1 - Unrelated Trials**

Between-subjects ANOVA revealed a significant main effect of attention \[ F(1,28) = 63.478, \ p < 0.001, \ \eta^2 = 0.634 \], and a marginally significant interaction between visual field and attention \[ F(1,28) = 3.568, \ p < 0.1, \ \eta^2 = 0.113 \]. Follow-up t-tests showed an insignificant RVF-lh advantage at unattended visual fields \[ t(30) = 1.414, \ p > 0.05, \ \text{uncorrected} \] and an insignificant LVR-rh advantage at the attended visual fields \[ t(30) = -1.5447, \ p > 0.05, \ \text{uncorrected} \]. These results suggest that the RVF-lh advantage for the unattended visual fields is no longer present in these trials (Figure 5.3b).

5.3.2.2. **Analysis 2 - Symmetrically related trials**

5.3.2.2.1. **Unattended Visual Field**

Mixed-model ANOVA revealed a significant main effect of relatedness \[ F(1,28) = 66.175, \ p < 0.001, \ \eta^2 = 0.703 \], reflecting higher accuracy for related trials. All other effects were not significant. These results show that both unattended visual fields receive priming (Figure 5.4b).
5.3.2.2. Attended Visual Field

Mixed-model ANOVA revealed a significant main effect of relatedness \[F(1,28) = 29.138, p<0.001, \text{partial } \eta^2 = 0.506\], reflecting higher accuracy for related trials. These results show there is priming for both attended visual fields (Figure 5.4b).

5.3.2.3. Analysis 3 - Asymmetrically related pairs

5.3.2.3.1. Unattended Visual Field

Mixed-model ANOVA revealed no significant main effects or interactions (Figure 5.5b).

5.3.2.3.1. Attended Visual Field

Mixed-model ANOVA revealed a significant main effect of visual field \[F(1,31) = 4.325, p<0.05, \text{partial } \eta^2 = 0.1304\], reflecting higher accuracy at the LVF-rh, and a significant three-way interaction between prime congruency, relatedness and visual angle \[F(1,28) = 6.45, p<0.05, \text{partial } \eta^2 = 0.187\]. All other effects are not significant (Figure 5.6b).

5.4. Discussion

The current study assessed interhemispheric transfer of semantic information using a bilateral word recognition task; participants tried to report the words seen in both visual fields, along with a centrally presented digit to enforce central fixation. As participants are likely to pay more attention to the side that they will report first, we counterbalanced the side of first report across subjects, thus directing attention to opposite sides in different subject groups to control for the attentional bias. Additional manipulations included visual angle, and relatedness between words, which was symmetrical on some trials and asymmetrical on others. The results from unrelated trials showed that directing attention improved overall accuracy for both visual fields.
Furthermore, while accuracy was comparable between the attended left and right visual fields, there was an RVF-lh advantage for the unattended visual fields.

A key concern in the design of this study was the possibility that participants might make eye movements to one or both of the words, thus foveating them and defeating the goal of presenting them to opposite hemispheres. Furthermore, participants might decide to focus on the field of first response, instead of the center. To prevent this, we also required participants to report the identity of a centrally presented digit in addition to the two words (Bourne, 2006). The digit report makes central fixation the optimal strategy for performance on the task, so that the subject can keep both words within their overall field of vision while also reading the digit correctly. Not only does this design yield an ideal range of performance in word recognition (approximately 30-70% correct across the various conditions), it also allowed us to separately analyze trials with correct and incorrect digit identification. Trials with incorrect digit identification are more likely to involve eye movements. If the observed differences between conditions are attributable to selective fixation of one word, then these trials should exhibit enhanced effects rather than attenuated ones. In analysis 1, the interaction between visual field and attention was no longer significant for these trials, and the visual field advantage for the attended visual field was biased towards the LVF-rh (Figure 5.3b). These results suggest that the observed effects of attention and visual field are genuinely attributable to hemispheric lateralization. Finally, the visual angle manipulation showed a general pattern of higher accuracy with the smaller visual angle, but did not interact with any other effect of interest. The finding that smaller visual angles did not reduce the effects of visual field or attention is consistent with split-fovea theory (reviewed in, Ellis & Brysbaert, 2010), which posits that the hemispheric division of the human visual fields extends all the way to the very center of the retina, while
other studies suggest that the fovea may be represented in both hemispheres. However, this was not the focus of the study and will not be discussed further. The most likely explanation for better word recognition performance at the smaller visual angle is simply the well-known decline in visual acuity occurring at increasing distances from the fovea (Strasburger, Rentschler, & Jüttner, 2011).

5.4.1. The RVF-lh Advantage

Two competing accounts of the RVF-lh advantage in word recognition are based on structural asymmetries in language lateralization, and on attentional asymmetries across visual fields, (reviewed in, Ducrot & Grainger, 2007). Evidence for both accounts can be found in eye tracking studies that assessed within-word fixation positions across different languages. In left-to-right languages, readers tend to fix towards the left of a word, leaving a majority of the word in the RVF-lh. This visual position asymmetry is strongly correlated with the visual field asymmetry in lateralized word recognition, suggesting that they reflect the same mechanisms (Brysbaert, Vitu, & Schroyens, 1996). Importantly, within-word fixations in right-to-left languages show a more symmetrical visual position advantage that is not completely reversed towards an actual LVF-rh advantage (Deutsch & Rayner, 1999; Farid & Grainger, 1996; Nazir, 2000), suggesting that reading direction plays a role in the RVF-lh advantage, but is not the only contributing factor.

Direct evidence for the cerebral asymmetry hypothesis was recently demonstrated in studies showing a positive correlation between the magnitude of the RVF-lh advantage and the lateralization of brain activation in fMRI (Hunter & Brysbaert, 2008; Van der Haegen, Cai, Seurinck, & Brysbaert, 2011). However, several attentional cueing studies have also demonstrated that validly cuing attention towards the target visual field leads to improved
identification accuracy (McCann, Folk, & Johnston, 1992; Mondor & Bryden, 1992; Sieroff & Posner, 1988), and critically, mitigates the RVF-lh advantage (Ducrot & Grainger, 2007; Lindell & Nicholls, 2003; Mondor & Bryden, 1992; Nicholls & Wood, 1998). Researchers cite these findings to suggest that both cerebral asymmetries and attentional biases contribute to the RVF-lh advantage (Ducrot & Grainger, 2007; Vergilino Perez et al., 2012).

In the current study, attention mitigated the RVF-lh advantage, primarily by enhancing LVF-rh processing, but post-hoc analyses show that both visual fields benefit from attention [LVF-rh: t(54) = 5.5704, p<0.001, corrected; RVF-lh: t(54) = 2.633, p<0.05, corrected] (Figure 5.3a). These results clearly demonstrate that attentional mechanisms are involved in the RVF-lh advantage. Interestingly, results from the symmetrically related word pairs suggest that semantic processing is independent of the attentional mechanisms that contribute to the RVF-lh advantage.

5.4.2. Symmetrical Priming

Results from symmetrically related pairs showed priming at both unattended visual fields. However, priming at the unattended visual fields alone is not sufficient evidence for interhemispheric transfer of semantic information. Responses to the unattended visual field were always made following responses to the attended visual field. As such, top-down mechanisms related to making the first response likely contributed to the priming effect. While participants were not notified of the relatedness manipulation, many eventually noticed that some pairs were related, and reported adopting a strategy of guessing a related word for the second (unattended) response. However, these results do suggest that unattended words are processed semantically, irrespective of visual field. Interestingly, priming was comparable across the two unattended visual fields, and the RVF-lh advantage persisted with related trials (Figure 5.3a), suggesting that RVF-lh advantage is not due to an asymmetry in semantic processing.
Priming at the attended visual fields provides more convincing evidence for the automatic interhemispheric transfer of semantic information. Since participants always responded to the attended visual field first, priming is likely uncontaminated by top-down processes. This is further evidenced by the analysis of asymmetrical pairs, showing that neither attended visual fields received priming in the incongruent condition, when the visual field contained the prime word instead of the target word. (Figure 5.6a). Interestingly, symmetrical priming was present at both attended visual fields, suggesting that 1) words at both unattended visual fields are processed semantically, and 2) this semantic information is transferred between hemispheres.

These findings add to the current literature showing that interhemispheric semantic transfer can facilitate responses both in tasks that require integration of multiple stimuli (S. W. Davis & Cabeza, 2015; S. W. Davis, Kragel, Madden, & Cabeza, 2012; Mika Koivisto, 2000; Mika Koivisto & Revonsuo, 2003; Zhang & Feng, 1999), and in tasks that require responses to one specific visual field (Abernethy & Coney, 1990b, 1993, 1996; Collins, 2002; Collins & Coney, 1998; Dal Molin et al., 2013; Kato & Okita, 2008; Korsnes & Magnussen, 2007; Perrone-Bertolotti et al., 2013). The current findings demonstrate that automatic interhemispheric spread of semantic information can facilitate the identification of words in both visual fields. As such, these results, further support the theory of interhemispheric excitation with regards to semantic processing in word recognition.

5.4.3. Asymmetrical Priming

Word recognition studies have demonstrated an asymmetrical transfer of information between hemispheres. Transfer of perceptual information has been seen in a preferential right-to-left direction (Barca et al., 2011; Selpien et al., 2015; Klaas E. Stephan et al., 2007), and semantic information has also been shown to be transferred asymmetrically, with greater priming
for targets in the LVF-rh and primes in the RVF-lh (Abernethy & Coney, 1990). Asymmetrically related word pairs were included to further assess directionality of semantic transfer. As with symmetrical pairs, priming was found at both unattended visual fields, likely reflecting post-hoc strategic guessing. Interestingly, priming at the attended visual field, which reflects automatic semantic transfer, was significant only when the target was presented to the attended LVF-rh (e.g., BOMB-ATOM). This finding, which is consistent with that of Abernethy and Coney (1993), suggests that the automatic transfer of semantic information may be asymmetrical; the semantic content from the RVF-lh asymmetrically primed processing of LVF-rh stimuli. Furthermore, while attended priming is significant at both visual fields with symmetrical pairs, priming at the LVF-rh is numerically larger and more statistically significant (Figure 5.4a).

This pattern may reflect a bias in the direction of information flow between the two hemispheres, but the preferred direction is uncertain, and depends on one’s model of how word recognition in the subordinate right hemisphere occurs. There are two models of interhemispheric interactions in word recognition that can account for the observed asymmetries in priming, the interhemispheric transfer model and the direct access model (Iacoboni & Zaidel, 1996; Olk & Hartje, 2001; Weems & Reggia, 2004). The interhemispheric transfer model suggests that while the right hemisphere can process some aspects of verbal stimuli, words presented to the LVF-rh are eventually transferred to the dominant left hemisphere via the corpus callosum. In contrast, the direct access model suggests that each hemisphere processes verbal stimuli independently, and lexicosemantic information is shared between hemispheres.

Before considering how these models can account for the findings, it is important to recapitulate the theoretical mechanism that allows for semantic priming. Specifically, priming occurs because a target word was immediately preceded by a semantically related prime that
activated semantic representations that overlap with the representation of the target, and thereby facilitated subsequent recognition of the target. In our experiment, the two words were presented simultaneously. Therefore, considerations of temporal order depend critically on information flow between the two hemispheres. With asymmetrical pairs, the priming relationship necessitates that the prime is processed before the target, at least in cases with automatic priming; post-lexical processes can contribute to backwards asymmetrical priming (e.g., Koivisto, 1998), but we have argued above that priming at the attended visual field reflects the automatic spread of activation.

The current results showed that asymmetrical attended priming was significant in only one condition, when participants are attending to a target presented to the LVF-rh (e.g., BOMB-ATOM) (Figure 5.6a). Figure 5.7 presents schematic diagrams outlining how each model can account for this pattern of results. While both models can account for these results, we propose that the interhemispheric transfer model is more parsimonious with the current findings. Under the transfer models, the cue (e.g., ATOM) is projected directly to the left hemisphere, thus activating the semantic network related to ATOM, which leads to activation of representations underlying the primed target BOMB. Subsequent processing of the target BOMB is then facilitated when it is transferred from the right-to-left hemispheres (Figure 5.7a). According to the direct access models, both hemispheres process the two words in parallel and priming occurs through the interhemispheric spread of semantic activation. To account for these findings, left hemisphere processing of the cue (e.g., ATOM) must be sufficiently faster than right hemisphere processing of the target (e.g., BOMB) to overcome the temporal cost of transcallosal transfer (Figure 5.7b). While there is indeed evidence that the left hemisphere is specialized for automatic
whole-word reading (Ellis, 2004; Lindell, 2006), whether or not this provides the necessary processing advantage to accommodate the cost of transcallosal transfer is harder to determine.

Figure 5.7 – Priming under models of transcallosal transfer. Schematic diagram outlining information transfer under the callosal relay (left) and direct access (right) models that can account for priming of attended LVF-rh targets (BOMB) with asymmetrical word pairs. Superscripted values highlight the transfer steps for each word. Under the callosal relay model, both words arrive at the contralateral hemisphere at step 1. ATOM is then transfer intrahemispherically to the left hemisphere language processor (step 2), while BOMB is transferred to the right hemisphere homologue (step 2). Step 3 involves the transfer of BOMB towards the LH, which has already processed ATOM (step

It is important to note that these two models are not mutually exclusive, and recent imaging studies provide evidence for both right-to-left interhemispheric transfer and parallel right hemisphere processing. In an MEG study of lateralized lexical decisions, Barca et al., (2011) assessed source localized responses to words presented to each visual field. The results showed that LVF-rh stimuli resulted in an asymmetrical transfer of visual information from the right-to-left occipital gyri. However, the results also showed an LVF-rh response at the right hemisphere homologue of the visual word form area, suggesting that words presented to the LVF-rh are both transferred to the left hemisphere and processed within the right hemisphere.
Dal Molin et al., (2013) recently presented evidence for different channels of callosal transfer in an ERP study using a lateralized odd-even discrimination task. Participants were tasked discriminating odd and even numbers presented to the left and right visual fields. Semantically congruent and incongruent primes (e.g., E- for even and O- for odd) were presented contralaterally and ipsilaterally to the target. The ERP results show a dissociation in the transfer of spatial information, pertaining to the spatial location of the target and prime, and the transfer of semantic information pertaining to the semantic content of the prime and target. Analyses if the P1 and N2 components showed an effect of spatial congruity, but not semantic congruity, while analyses of N400 showed effects of semantic congruity but not spatial congruity. These results provide evidence for multiple stages of interhemispheric interactions.

5.5. Conclusion

The current study adds to the body of literature regarding transcallosal interaction in language processing. The results show that the semantic content of words presented to one visual field can facilitate the identification of words presented to the contralateral visual field. This suggests that lateralized semantic processing leads to excitatory communication between hemispheres, and there is some evidence that transcallosal interactions are asymmetrical, with a bias for right-to-left transfer. Further research with neuroimaging and effective connectivity is necessary to delineate the precise location and directionality for interhemispheric semantic transfer.
Chapter 6
General Discussion

The goal of this dissertation was to delineate the interhemispheric interactions involved in sentence comprehension (Chapters 2 and 3) and visual word recognition (Chapters 4 and 5). Specifically, the studies were designed to outline when and where interhemispheric interactions are inhibitory and excitatory. The literature in aphasia and word recognition address the inhibition/excitation distinction in different ways. In the aphasia literature, this debate is couched in the two possible mechanisms for right hemisphere activation following left hemisphere damage: right hemisphere disinhibition (Jenny Crinion & Price, 2005; Margaret A. Naeser et al., 2005b; Dorothee Saur et al., 2006) and right hemisphere recruitment (Raboyeau et al., 2008). In the visual word recognition, the debate is based on two models of lateralized word recognition (reviewed in, Weems & Reggia, 2004): the callosal relay model, which suggests asymmetrical excitatory transcallosal transfer (Olk & Hartje, 2001), and the direct access model, which suggests independent hemispheric processing (Iacoboni & Zaidel, 1996), resulting in interhemispheric inhibition (Cook, 1986). The four studies in this dissertation provide strong evidence for excitatory interactions in both sentence comprehension and visual word recognition. The following discussion will review the results in the current context of the inhibition/exhibition debate.

6.1. Sentence Comprehension in Aphasia

In Chapters 2 and 3, I presented neuroimaging data collected from both aphasia patients and healthy controls during a sentence comprehension task. Aphasia patients commonly exhibit atypical right hemisphere activation in language tasks (e.g., Cao, Vikingstad, George, Johnson,
& Welch, 1999; Crinion & Price, 2005; Leff et al., 2002; Musso et al., 1999; Perani et al., 2003; Rosen et al., 2000; Sharp, Scott, & Wise, 2004; Weiller et al., 1995), although the adaptive nature of this activation is debated (Jenny Crinion & Price, 2005; Margaret A. Naeser et al., 2005b; Dorothee Saur et al., 2006). Recent studies have reported correlations between right hemisphere activation and left hemisphere tissue damage (Sebastian & Kiran, 2011; Sims et al., 2016; Skipper-Kallal et al., 2017; Vitali et al., 2007), suggesting that right hemisphere homologues are compensating for damaged tissue.

Chapter 2 extended this line of research by assessing the relationship between perilesional tissue dysfunction and right hemisphere activation. The results showed that spontaneous signals emitted from perilesional tissue exhibited characteristic markers of tissue dysfunction: the preponderance of high-amplitude low-frequency oscillations (Butz et al., 2004b; Harmony, Fernández-Bouzas, et al., 1995; Calixto Machado et al., 2004; Marcus Meinzer et al., 2004; Filippo Zappasodi, Tombrei, Milazzo, Rossini, & Tecchio, 2007), and reduced signal complexity (Hornero, Escudero, Fernández, Poza, & Gómez, 2008; Jeong-Hyeon Park, Kim, Kim, Cichocki, & Kim, 2007; Anjali Raja Beharelle, Kovačević, McIntosh, & Levine, 2012). Critically, the magnitude of perilesional tissue dysfunction was correlated with task-activation in right hemisphere homologues. These findings suggest that right hemisphere activation is not only compensating for lesioned tissue, but also for dysfunctional perilesional tissue.

The two competing theories of interhemispheric interactions have different accounts as to why the right hemisphere will activate in response to left hemisphere tissue dysfunction. The inhibition theory suggests that right hemisphere activation results from the disinhibition of the right hemisphere (Jenny Crinion & Price, 2005; Margaret A. Naeser et al., 2004; Dorothee Saur et al., 2006). The excitation account suggests that right hemisphere activation may result from
uncontrolled left hemisphere excitation originating from the perilesional rim; this form of excitation disrupts processing by providing irrelevant and interfering information (Chiarello & Maxfield, 1996). Indeed, unlike lesioned tissue, perilesional tissue is not silent, but emits persistent low-frequency oscillations (Butz et al., 2004b; Harmony, Fernández-Bouzas, et al., 1995; Calixto Machado et al., 2004; Marcus Meinzer et al., 2004; Filippo Zappasodi et al., 2007). The results from Chapter 2 demonstrated a positive correlation between perilesional low-frequency oscillations and right hemisphere language activation. It should be noted that both accounts consider right hemisphere homologous activation as maladaptive. This is in agreement with a previous analysis of the same dataset demonstrating that successful sentence comprehension in patients was associated with adaptive recruitment of non-homologous extrasylvian areas in the right hemisphere (Jed A. Meltzer et al., 2013).

The analyses in Chapter 2 were not designed to discriminate between excitative and inhibitory interactions. In Chapter 3, I directly explored this distinction using Dynamic Causal Modelling (DCM) analysis of fMRI data collected from the same participants doing the same task. DCM is advantageous in that it allows for both the characterization of directional connectivity, as well as positive and negative coupling (K.E. Stephan et al., 2010). The results from controls suggest that auditory sentence comprehension involved excitative transfer from right-to-left auditory cortices (A1), and inhibitory feedback regulation from the left inferior frontal gyrus (LIFG). Importantly, we failed to find any evidence for homotopic inhibition, as predicted by the interhemispheric inhibition account.

The results from controls are further supported by the pattern of correlations between behavioral outcomes and connectivity in patients; the best performing patients showed connectivity patterns that mirrored controls, whereas the worst performing patients showed
connectivity in the opposite direction. For example, controls and well-performing patients both exhibited asymmetrical positive coupling from the RA1-to-LA1, while poor-performing patients exhibited negative coupling from the RA1-to-LA1. These results suggest that impaired comprehension does not result from a release of homotopic inhibition, but instead a disruption in excitatory auditory transfer. These findings are in line with a recent study of speech perception, demonstrating right-to-left coupling between auditory cortices in controls, and a reduction in that coupling in aphasia patients (Schofield et al., 2012). Interestingly, the results from Chapter 3 also demonstrated a negative correlation between comprehension and LA1-to-RA1 coupling, with the worst performing patients exhibiting positive left-to-right coupling (Figure 3.6). Similarly, in Chapter 2, I reported a correlation between perilesional low-frequency oscillatory power and right hemisphere task activation (Figure 2.4). While the studies in Chapters 2 and 3 used different regions of interest, we see in both cases, right hemisphere homologues are activated by a dysfunctional left hemisphere. In a follow-up analysis, I repeated the correlational analysis of perilesional dysfunction and right hemisphere homologue activity from Chapter 2, using the A1 ROIs from Chapter 3. The results show that RA1 task activation is correlated with the magnitude LA1 low-frequency oscillatory power \( r(16) = 0.490, p<0.05 \), but not with LA1 multiscale entropy \( r(16) = -0.152, p>0.05 \) (Figure 6.1). Taken together, these findings suggest that the right hemisphere activation in this patient group did not result from disinhibition, but instead, maladaptive recruitment from a dysfunctional left hemisphere.
Figure 6.1 - **The magnitude of MEG task activation (8-30Hz ERD) at the RA1 plotted as a function of LA1 relative delta, and MSE (B).** ROIs are taken from the DCM analysis in Chapter 3, and MEG data are taken from Chapter 2. Pearson’s correlations are presented with each figure. Significant at *p<0.05.

### 6.2. Lateralized word recognition

One of the more surprising results from Chapter 3 was the importance of the asymmetrical homotopic connectivity from RA1-to-LA1. This suggests that language lateralization results not from asymmetric homotopic inhibition, but instead asymmetrical excitatory transfer of perceptual information. The topic of perceptual transfer in language was further explored in Chapters 4 and 5 using lateralized word recognition tasks. The strictly lateralized projections of the visual system allowed for more direct assessments of interhemispheric transfer under conditions where stimuli were projected to a single hemisphere (M. S. Gazzaniga, 2000).

As mentioned several times throughout this dissertation, lateralized word recognition is typically associated with an RVF-lh advantage, and this advantage is enhanced with simultaneous bilateral displays (David B. Boles, 1987; D.B. Boles, 1995; Fernandino et al., 2007; Iacoboni & Zaidel, 1996; Olk & Hartje, 2001; Perrone-Bertolotti et al., 2013; Seitz & McKeever, 1984; Weems & Zaidel, 2004, 2005; Wey et al., 1993). There are two competing models of lateralized word recognition that can account for this effect (reviewed in Weems &
Reggia, 2004), and they disagree on linguistic capabilities of the right hemisphere. The callosal relay model assumes that the language processing is exclusive to the left hemisphere, as such all verbal stimuli from the LVF-rh must be relayed through the corpus callosum, resulting in stimulus degradation. The RVF-lh advantage is enhanced with bilateral displays due to intrahemispheric competition between the LVF-rh word that must be transferred and the RVF-lh word that was directly projected to the left hemisphere (Olk & Hartje, 2001). Alternatively, the direct access model assumes that both hemispheres have the capacity for linguistic processing and lateralized words are processed independently in each hemisphere. The RVF-lh advantage arises from the innate left hemisphere specialization for language, and bilateral displays result in an enhanced RVF-lh advantage due to asymmetrical inhibition of the right hemisphere from the dominant left hemisphere (Cook, 1986; Olk & Hartje, 2001).

Recent models of lateralized word recognition combine aspects from both accounts; some processing occurs independently within each hemisphere, but there is eventual interhemispheric transfer (McCandliss et al., 2003; Rauschecker et al., 2012). However, the precise stage for this transfer is unclear. A great deal of recent research in visual word recognition was focused on the Visual Word Form Area (VWFA), an area located at the posterior ventral occipitotemporal cortex that is consistently activated in response to visual word forms (L. Cohen et al., 2000; McCandliss et al., 2003). While the specificity of VWFA activation to just word forms is debated (Price & Devlin, 2003, 2011), there is general agreement, that this region is a critical node in the visual word recognition network. Recent models suggest that the VWFA acts as a gateway from the visual system to the left hemisphere language network (McCandliss et al., 2003; Rauschecker et al., 2012). Critically, this suggests that the first possible step for interhemispheric transfer in
visual word recognition happens between the VFWA and its right hemisphere homologue (RVWFA).

This model conflicts with recent studies demonstrating hemispheric transfer between early visual areas (Barca et al., 2011; Selpien et al., 2015; Klaas E. Stephan et al., 2007). The study in Chapter 4 was designed to explore these conflicting accounts, and measured connectivity between bilateral VWFAs and bilateral middle occipital gyri (MOG) during a lexical decision task incorporating both unilateral and bilateral trials. The results from unilateral trials showed evidence for multiple stages of interhemispheric transfer between bilateral middle occipital gyri (MOG) and between bilateral VWFA. Interestingly, LMOG-RMOG connectivity was significantly greater for LVF-rh trials, while LVWFA-RVWFA connectivity was comparable for both LVF-rh and RVF-lh targets (Figure 4.7). The results from unilateral trials support the assumption of early right-to-left callosal relay between perceptual regions, but also demonstrate symmetrical synchronization between bilateral VWFAs.

Researchers have suggested that bilateral displays block interhemispheric transfer and force direct-access processing of RH targets (Fernandino et al., 2007; Perrone-Bertolotti et al., 2013; Weems & Zaidel, 2005). Indeed, the results from Chapter 4 clearly demonstrate that interhemispheric connectivity is reduced with bilateral trials (Figure 4.9). However, even with bilateral trials, there was some evidence for callosal relay. First, interhemispheric connectivity in bilateral trials was still above pre-stimulus baseline levels. Second, the main effect of visual field for LMOG-RMOG connectivity shows that both unilateral and bilateral trials are associated with an asymmetrical transfer of LVF-rh targets. Together, the results suggest that under bilateral displays conditions, callosal relay is impeded but not completely blocked.
The results from Chapter 4 support previous findings that interhemispheric interactions between posterior perceptual areas are predominantly excitatory (Carreiras et al., 2009; Kawabata Duncan et al., 2014; Klaas E. Stephan et al., 2007). However, interhemispheric inhibition has been demonstrated for down-stream processes like semantic and response competition (Kawabata Duncan et al., 2014; Seghier, Josse, Leff, & Price, 2011). The study in Chapter 5 was designed to assess interhemispheric interactions in semantic processing using a bilateral word recognition task. The results from Chapter 5 demonstrate that word identification from both visual fields was facilitated by semantic information from the contralateral visual field. Furthermore, there was some evidence that this benefit was asymmetrical, with LVF-rh targets receiving more priming. This was particularly evident in the analysis of asymmetrically related word pairs (e.g., ATOM-BOMB), which showed greater priming when the target (BOMB) was presented to the LVF-rh (Figure 5.6).

This pattern of asymmetrical priming is again more parsimonious with the callosal relay model, as outlined in Figure 5.7. Specifically, the BOMB-ATOM pair leads to priming because the target (BOMB) is projected to the right hemisphere while the cue (ATOM) is projected to the left hemisphere. Thus, priming occurs because the dominant left hemisphere is already primed by the cue and thus facilitates processing of BOMB when it arrives. This asymmetrical facilitation of LVF-rh targets is in agreement with a recent demonstration that the typical enhancement of the RVF-lh advantage by bilateral displays is mitigated with semantically related word pairs (Perrone-Bertolotti et al., 2013).

The results from the studies in this dissertation suggest that transcallosal interactions in both sentence comprehension and word recognition are primarily excitatory. Interestingly, evidence for inhibition was found only in Chapter 3, and involved feedback inhibition from the
LIFG and bilateral A1s. However, it is important to note that language processing comprises a complex set of abilities, and while sentence comprehension and word recognition cover the two extreme ends of receptive language processing, there is more evidence that language production, which is typically left-lateralized, necessitates interhemispheric inhibition (e.g., Margaret A. Naeser et al., 2010; Vigneau et al., 2006).

6.3. Limitations and Future Directions

The four studies in this dissertation have outlined the importance of excitatory interhemispheric connectivity in both sentence comprehension and visual word recognition. The results from Chapters 2 and 3 are particularly relevant to the literature in stroke rehabilitation. Chapter 2 demonstrated a novel technique to identify dysfunctional perilesional tissue that was correlated with compensatory right hemisphere activation. This technique provides a promising biomarker for rehabilitation through non-invasive brain stimulation. Techniques such as TMS and tDCS have been demonstrated to facilitate language recovery in stroke; however, a majority of the studies have targeted regions based on anatomical landmarks (Margaret A. Naeser et al., 2005b, 2010) and task activation (Griffis et al., 2016; Jerzy P. Szafarski et al., 2011). The localization technique from Chapter 2 is currently being used in our lab to target underactive perilesional tissue for non-invasive brain stimulation.

In Chapter 3, I demonstrated the behavioral importance of directional connectivity between the left and right auditory cortices. Regions associated with disrupted interhemispheric connectivity may make ideal targets for non-invasive stimulation. For example, the results showed that inhibitory RA1-to-LA1 and excitatory LA1-to-RA1 coupling were both associated with poor performance. As such, patients may benefit from excitatory RA1 stimulation to encourage positive RA1-to-LA1 coupling and inhibitory LA1 stimulation to discourage LA1-to-
RAI coupling. This line of research will test the potential of connectivity-based stimulation protocols and further delineate the effects of brain stimulation on interhemispheric connectivity.

One major limitation of Chapter 3 was that many patients were excluded due to the strict requirements regarding ROI location and activation associated with DCM analyses (K. Friston, Moran, & Seth, 2013). Directed functional connectivity measures, like Granger Causality on the other hand, are more flexible with regards to both ROI location and activation. Both DCM and GC allow for the measurement of directed connectivity between brain regions, however DCM is concerned with explicit models of casual interactions, while GC is defined in terms of statistical dependences. As such, DCM and GC have been labelled as confirmatory and exploratory techniques, respectively (K. Friston, 2011; Roebroeck, Formisano, & Goebel, 2011). DCM was chosen in Chapter 3 for two reasons: 1) to specifically to test models of interhemispheric interactions between the left and right IFGs, and 2) GC analysis of fMRI data can be problematic due to slow temporal dynamics and regional variability of haemodynamic responses. However, given the inherent variability in both lesion location and residual language activation, exploratory studies using less stringent directed functional connectivity measures like GC are necessary to better characterize interhemispheric interactions in aphasia.

Chapters 4 and 5 were focused on lateralized word recognition, and like Chapters 2 and 3, demonstrated the importance of excitatory interhemispheric connectivity. Chapter 4 looked at the very early stages of visual word recognition and demonstrated interhemispheric transfer between occipital regions. This initial transfer was unique to trials with LVF-rh targets, suggesting that interhemispheric transfer is asymmetrical from the right-to-left hemispheres. However, weighted phase lag index (wPLI), the connectivity measure used in Chapter 4, is an undirected measure of functional connectivity. As such, the conclusion regarding asymmetrical
transfer is not supported by the measure itself, but rather by its enhancement under an experimental manipulation that explicitly stimulated a single hemisphere. Future studies that employ directed measures such as GC and DCM are necessary to confirm that hemispheric transfer is indeed asymmetrical, and to examine the role of asymmetrical transfer under more ecologically valid conditions, such as typical reading with foveal fixation.

The focus of Chapter 4 on very early perceptual regions precluded the analysis of lexicosemantic inhibition. This was partly addressed by Chapter 5, which demonstrated that semantic information from the contralateral hemisphere can indeed facilitate lateralized word recognition. The obvious next step in this line of research will involve neuroimaging and directed connectivity to identify the neural correlates of this interhemispheric priming. Furthermore, the study in Chapter 5 included only bilateral trials; it is possible that unrelated trials were associated with interhemispheric inhibition, but the experiment lacked the appropriate contrast to demonstrate this inhibition. As such, the ideal follow-up would include both bilateral and unilateral trials to assess the possibility for both semantic facilitation and semantic competition.

6.4. Conclusions

The studies in this dissertation add to the overall literature regarding hemispheric interactions by highlighting the importance of interhemispheric cooperation in both sentence comprehension and word recognition. However, more lateralized language tasks such as speech production and phonological processing are more likely to involve inhibition, and the interhemispheric interactions in these tasks need further exploration. Many of the neuroimaging techniques applied and discussed in this dissertation can be applied to better characterize language processes that involve inhibition. This dissertation is simply a small contribution to
decades of research regarding the corpus callosum. Advances in brain imaging technology give scientists remarkable power to elucidate the function of this massive fiber bundle. Yet, given the incredible complexity of language comprehension, language production, and hemispheric coordination, it is likely that the mystery of interhemispheric communication in language will remain unsolved for many decades to come.
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## Appends

### Analysis 1 - Unrelated

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### Analysis 2 - Symmetrical Unattended

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<tr>
<td>VA</td>
<td>$F(1,52) = 5.575$</td>
<td>0.020 *</td>
<td>0.0982</td>
</tr>
<tr>
<td>VF</td>
<td>$F(1,52) = 9.626$</td>
<td>0.003 **</td>
<td>0.1562</td>
</tr>
<tr>
<td>Relatedness x VA</td>
<td>$F(1,52) = 1.642$</td>
<td>0.206</td>
<td>0.0206</td>
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<tr>
<td>Relatedness x VF</td>
<td>$F(1,52) = 0.265$</td>
<td>0.609</td>
<td>0.0051</td>
</tr>
<tr>
<td>VA x VF</td>
<td>$F(1,52) = 0.001$</td>
<td>0.981</td>
<td>0.0001</td>
</tr>
<tr>
<td>Relatedness x VA x VF</td>
<td>$F(1,52) = 0.001$</td>
<td>0.982</td>
<td>0</td>
</tr>
</tbody>
</table>

### Analysis 3 - Asymmetrical Unattended

<table>
<thead>
<tr>
<th>Effect</th>
<th>F-Value</th>
<th>P-Value</th>
<th>Partial Eta-Squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congruency</td>
<td>$F(1,52) = 2.003$</td>
<td>0.163</td>
<td>0.0371</td>
</tr>
<tr>
<td>Relatedness</td>
<td>$F(1,52) = 35.251$</td>
<td>$1E-04 ***$</td>
<td>0.404</td>
</tr>
<tr>
<td>VA</td>
<td>$F(1,52) = 5.990$</td>
<td>0.018 *</td>
<td>0.1033</td>
</tr>
<tr>
<td>VF</td>
<td>$F(1,52) = 11.587$</td>
<td>0.001 **</td>
<td>0.1822</td>
</tr>
<tr>
<td>Congruency x Relatedness</td>
<td>$F(1,52) = 4.021$</td>
<td>0.05</td>
<td>0.0717</td>
</tr>
<tr>
<td>Congruency x VA</td>
<td>$F(1,52) = 1.376$</td>
<td>0.246</td>
<td>0.0258</td>
</tr>
<tr>
<td>Congruency x VF</td>
<td>$F(1,52) = 0.509$</td>
<td>0.479</td>
<td>0.0097</td>
</tr>
<tr>
<td>Relatedness x VA</td>
<td>$F(1,52) = 0.014$</td>
<td>0.905</td>
<td>0.0003</td>
</tr>
<tr>
<td>Relatedness x VF</td>
<td>$F(1,52) = 0.493$</td>
<td>0.486</td>
<td>0.0094</td>
</tr>
<tr>
<td>VA x VF</td>
<td>$F(1,52) = 0.346$</td>
<td>0.559</td>
<td>0.0066</td>
</tr>
<tr>
<td>Congruency x Relatedness x VA</td>
<td>$F(1,52) = 0.107$</td>
<td>0.745</td>
<td>0.0021</td>
</tr>
<tr>
<td>Congruency x Relatedness x VF</td>
<td>$F(1,52) = 0.995$</td>
<td>0.323</td>
<td>0.0187</td>
</tr>
<tr>
<td>Congruency x VA x VF</td>
<td>$F(1,52) = 1.882$</td>
<td>0.176</td>
<td>0.0349</td>
</tr>
<tr>
<td>Relatedness x VA x VF</td>
<td>$F(1,52) = 1.397$</td>
<td>0.243</td>
<td>0.0262</td>
</tr>
<tr>
<td>Congruency x Relatedness x VA x VF</td>
<td>$F(1,52) = 0.161$</td>
<td>0.69</td>
<td>0.0031</td>
</tr>
</tbody>
</table>

### Analysis 3 - Asymmetrical Attended

<table>
<thead>
<tr>
<th>Effect</th>
<th>F-Value</th>
<th>P-Value</th>
<th>Partial Eta-Squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congruency</td>
<td>$F(1,52) = 0.513$</td>
<td>0.477</td>
<td>0.0098</td>
</tr>
<tr>
<td>Relatedness</td>
<td>$F(1,52) = 12.639$</td>
<td>$1E-04 ***$</td>
<td>0.1955</td>
</tr>
<tr>
<td>VA</td>
<td>$F(1,52) = 3.676$</td>
<td>0.061</td>
<td>0.066</td>
</tr>
<tr>
<td>VF</td>
<td>$F(1,52) = 0.287$</td>
<td>0.594</td>
<td>0.0055</td>
</tr>
<tr>
<td>Congruency x Relatedness</td>
<td>$F(1,52) = 3.379$</td>
<td>0.072</td>
<td>0.061</td>
</tr>
<tr>
<td>Congruency x VA</td>
<td>$F(1,52) = 0.413$</td>
<td>0.523</td>
<td>0.0079</td>
</tr>
<tr>
<td>Congruency x VF</td>
<td>$F(1,52) = 1.775$</td>
<td>0.189</td>
<td>0.033</td>
</tr>
<tr>
<td>Relatedness x VA</td>
<td>$F(1,52) = 1.451$</td>
<td>0.234</td>
<td>0.0271</td>
</tr>
<tr>
<td>Relatedness x VF</td>
<td>$F(1,52) = 0.230$</td>
<td>0.633</td>
<td>0.0044</td>
</tr>
<tr>
<td>VA x VF</td>
<td>$F(1,52) = 0.194$</td>
<td>0.661</td>
<td>0.0037</td>
</tr>
<tr>
<td>Congruency x Relatedness x VA</td>
<td>$F(1,52) = 0.360$</td>
<td>0.551</td>
<td>0.0069</td>
</tr>
<tr>
<td>Congruency x Relatedness x VF</td>
<td>$F(1,52) = 1.250$</td>
<td>0.269</td>
<td>0.0235</td>
</tr>
<tr>
<td>Congruency x VA x VF</td>
<td>$F(1,52) = 1.653$</td>
<td>0.204</td>
<td>0.0308</td>
</tr>
<tr>
<td>Relatedness x VA x VF</td>
<td>$F(1,52) = 1.229$</td>
<td>0.273</td>
<td>0.0331</td>
</tr>
<tr>
<td>Congruency x Relatedness x VA x VF</td>
<td>$F(1,52) = 0.011$</td>
<td>0.916</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Appendix 5.1 – All main effects and interactions from analyses of trials with correct digit identification
### Appendix 5.2 – All main effects and interactions from analyses of trials with incorrect digit identification

<table>
<thead>
<tr>
<th>Analysis Design</th>
<th>Effect</th>
<th>F-Value</th>
<th>P-Value</th>
<th>Partial Eta-Squared</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analysis 1 - Unrelated</strong></td>
<td>Attention</td>
<td>F(1,28) = 63.478</td>
<td>1E-04 ***</td>
<td>0.6939</td>
</tr>
<tr>
<td></td>
<td>VA</td>
<td>F(1,28) = 0.050</td>
<td>0.825</td>
<td>0.0018</td>
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<tr>
<td></td>
<td>VF</td>
<td>F(1,28) = 1.950</td>
<td>0.174</td>
<td>0.0651</td>
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<tr>
<td></td>
<td>Attention x VA</td>
<td>F(1,28) = 0.577</td>
<td>0.454</td>
<td>0.0202</td>
</tr>
<tr>
<td></td>
<td>Attention x VF</td>
<td>F(1,28) = 3.568</td>
<td>0.069</td>
<td>0.113</td>
</tr>
<tr>
<td></td>
<td>VA x VF</td>
<td>F(1,28) = 0.035</td>
<td>0.854</td>
<td>0.0012</td>
</tr>
<tr>
<td></td>
<td>Attention x VA x VF</td>
<td>F(1,28) = 0.031</td>
<td>0.861</td>
<td>0.0011</td>
</tr>
<tr>
<td><strong>Analysis 2 - Symmetrical Unattended</strong></td>
<td>Relatedness</td>
<td>F(1,28) = 66.175</td>
<td>1E-04 ***</td>
<td>0.7027</td>
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<tr>
<td></td>
<td>VA</td>
<td>F(1,28) = 0.027</td>
<td>0.872</td>
<td>0.0009</td>
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<tr>
<td></td>
<td>VF</td>
<td>F(1,28) = 2.274</td>
<td>0.143</td>
<td>0.0751</td>
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<tr>
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<td>Relatedness x VA</td>
<td>F(1,28) = 1.259</td>
<td>0.271</td>
<td>0.043</td>
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<tr>
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<td>Relatedness x VF</td>
<td>F(1,28) = 0.145</td>
<td>0.707</td>
<td>0.0051</td>
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<tr>
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<td>VA x VF</td>
<td>F(1,28) = 0.285</td>
<td>0.598</td>
<td>0.0101</td>
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<td>Relatedness x VA x VF</td>
<td>F(1,28) = 0.093</td>
<td>0.762</td>
<td>0.0033</td>
</tr>
<tr>
<td><strong>Analysis 2 - Symmetrical Attended</strong></td>
<td>Relatedness</td>
<td>F(1,28) = 29.138</td>
<td>1E-04 ***</td>
<td>0.506</td>
</tr>
<tr>
<td></td>
<td>VA</td>
<td>F(1,28) = 0.752</td>
<td>0.393</td>
<td>0.0262</td>
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<tr>
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<td>VF</td>
<td>F(1,28) = 3.744</td>
<td>0.063</td>
<td>0.1179</td>
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<tr>
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<td>Relatedness x VA</td>
<td>F(1,28) = 3.364</td>
<td>0.077</td>
<td>0.1073</td>
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<td></td>
<td>Relatedness x VF</td>
<td>F(1,28) = 2.527</td>
<td>0.123</td>
<td>0.0827</td>
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<tr>
<td></td>
<td>VA x VF</td>
<td>F(1,28) = 0.098</td>
<td>0.756</td>
<td>0.0035</td>
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<tr>
<td></td>
<td>Relatedness x VA x VF</td>
<td>F(1,28) = 0.041</td>
<td>0.84</td>
<td>0.0015</td>
</tr>
<tr>
<td><strong>Analysis 3 - Asymmetrical Unattended</strong></td>
<td>Congruency x Relatedness</td>
<td>F(1,28) = 3.238</td>
<td>0.083</td>
<td>0.1037</td>
</tr>
<tr>
<td></td>
<td>Relatedness</td>
<td>F(1,28) = 3.595</td>
<td>0.068</td>
<td>0.1138</td>
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<tr>
<td></td>
<td>VA</td>
<td>F(1,28) = 0.128</td>
<td>0.723</td>
<td>0.0046</td>
</tr>
<tr>
<td></td>
<td>VF</td>
<td>F(1,28) = 1.494</td>
<td>0.232</td>
<td>0.0507</td>
</tr>
<tr>
<td></td>
<td>Congruency x Relatedness</td>
<td>F(1,28) = 4.046</td>
<td>0.054</td>
<td>0.1263</td>
</tr>
<tr>
<td></td>
<td>Congruency x VA</td>
<td>F(1,28) = 1.141</td>
<td>0.295</td>
<td>0.0392</td>
</tr>
<tr>
<td></td>
<td>Congruency x VF</td>
<td>F(1,28) = 0.001</td>
<td>0.972</td>
<td>0</td>
</tr>
<tr>
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<td>Relatedness x VA</td>
<td>F(1,28) = 1.111</td>
<td>0.301</td>
<td>0.0382</td>
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<tr>
<td></td>
<td>Relatedness x VF</td>
<td>F(1,28) = 0.007</td>
<td>0.934</td>
<td>0.0003</td>
</tr>
<tr>
<td></td>
<td>VA x VF</td>
<td>F(1,28) = 0.011</td>
<td>0.917</td>
<td>0.0004</td>
</tr>
<tr>
<td></td>
<td>Congruency x Relatedness x VA</td>
<td>F(1,28) = 1.313</td>
<td>0.262</td>
<td>0.0448</td>
</tr>
<tr>
<td></td>
<td>Congruency x Relatedness x VF</td>
<td>F(1,28) = 0.201</td>
<td>0.685</td>
<td>0.0071</td>
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<tr>
<td></td>
<td>Congruency x VA x VF</td>
<td>F(1,28) = 0.270</td>
<td>0.608</td>
<td>0.0095</td>
</tr>
<tr>
<td></td>
<td>Relatedness x VA x VF</td>
<td>F(1,28) = 0.005</td>
<td>0.942</td>
<td>0.0002</td>
</tr>
<tr>
<td></td>
<td>Congruency x Relatedness x VA x VF</td>
<td>F(1,28) = 0.095</td>
<td>0.76</td>
<td>0.0034</td>
</tr>
<tr>
<td><strong>Analysis 3 - Asymmetrical Attended</strong></td>
<td>Congruency x Relatedness</td>
<td>F(1,28) = 7.078</td>
<td>0.047</td>
<td>0.1872</td>
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<tr>
<td></td>
<td>Relatedness</td>
<td>F(1,28) = 6.448</td>
<td>0.046</td>
<td>0.0226</td>
</tr>
<tr>
<td></td>
<td>VA</td>
<td>F(1,28) = 0.949</td>
<td>0.338</td>
<td>0.0328</td>
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<tr>
<td></td>
<td>VF</td>
<td>F(1,28) = 4.200</td>
<td>0.05</td>
<td>0.1304</td>
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<tr>
<td></td>
<td>Congruency x Relatedness</td>
<td>F(1,28) = 0.021</td>
<td>0.885</td>
<td>0.0008</td>
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<tr>
<td></td>
<td>Congruency x VA</td>
<td>F(1,28) = 0.333</td>
<td>0.569</td>
<td>0.0117</td>
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<td>Congruency x VF</td>
<td>F(1,28) = 1.846</td>
<td>0.185</td>
<td>0.0619</td>
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<td>Relatedness x VA</td>
<td>F(1,28) = 3.039</td>
<td>0.092</td>
<td>0.0978</td>
</tr>
<tr>
<td></td>
<td>Relatedness x VF</td>
<td>F(1,28) = 0.065</td>
<td>0.801</td>
<td>0.0023</td>
</tr>
<tr>
<td></td>
<td>VA x VF</td>
<td>F(1,28) = 0.181</td>
<td>0.673</td>
<td>0.0064</td>
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<tr>
<td></td>
<td>Congruency x Relatedness x VA</td>
<td>F(1,28) = 6.448</td>
<td>0.017</td>
<td>0.1872</td>
</tr>
<tr>
<td></td>
<td>Congruency x Relatedness x VF</td>
<td>F(1,28) = 1.223</td>
<td>0.278</td>
<td>0.0419</td>
</tr>
<tr>
<td></td>
<td>Congruency x VA x VF</td>
<td>F(1,28) = 0.554</td>
<td>0.463</td>
<td>0.0194</td>
</tr>
<tr>
<td></td>
<td>Relatedness x VA x VF</td>
<td>F(1,28) = 0.005</td>
<td>0.946</td>
<td>0.0002</td>
</tr>
<tr>
<td></td>
<td>Congruency x Relatedness x VA x VF</td>
<td>F(1,28) = 0.137</td>
<td>0.714</td>
<td>0.0049</td>
</tr>
</tbody>
</table>