Semantics and Phonology in the Brains of Older Adults With and Without Aphasia

Dissertation

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By

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Abstract

Two essential components of language are semantics, or the meaning of language, and phonology, or the sounds that make up our words. Researchers have long sought to investigate the neural correlates of semantics and phonology; however, questions remain related to the specific brain regions comprising each network as well as the degree to which these networks coincide. Moreover, patterns of reorganization following injury to these networks in populations such as those with post-stroke aphasia remain unclear. Across three manuscripts, this dissertation addresses these questions, emphasizing the influence of aging on the language networks in the brain as well as reorganization during the process of recovery from post-stroke aphasia. Recent work examining the semantic and phonological networks in the brain has focused on neurologically intact younger adults. Considering many people who experience acquired language impairments are older adults, the first manuscript in this dissertation presents the results of a scoping review addressing the regions comprising the semantic and phonological brain networks in this aging population. The review finds that these brain networks are consistent with the networks of younger adults but may have subtle differences that should be further explored in a full systematic review or meta-analysis. The second manuscript in this dissertation specifically examines the resting-state functional connectivity of the inferior frontal gyrus, a region that has been implicated in both semantic and phonological brain networks and is often damaged in cases

of post-stroke aphasia. Compared with younger adults, we again found subtle differences that may be accounted for in part by theories of age-related de-lateralization of the dominant left hemisphere. We next correlated significant resting-state functional connectivity with behavioral tasks targeting semantics and phonology, which did not support theories of semantic specialization at the anterior inferior frontal gyrus and phonological specialization at the posterior inferior frontal gyrus; however, our sample size was small (n = 10). We further presented a case series exploring the resting-state connectivity in participants with post-stroke aphasia between regions that correlated with behavior in our neurologically intact sample. Few patterns were observed, but future directions are described. Finally, in the third manuscript, we report the results of several multiple linear regression analyses in a larger sample (n = 101) of people with chronic, post-stroke aphasia. The interaction between anterior left inferior front gyrus lesion load and resting-state connectivity between right pMTG and AG was an inconsistently significant predictor of semantic skills across the series of analyses. Future work is necessary to validate whether right pMTG and AG may serve as sites of compensatory reorganization for injury to anterior left inferior front gyrus. In conclusion, our results support the possibility of age-related differences in the semantic and phonological networks of older adults that may influence reorganization in post-stroke aphasia, though further research is needed to verify these findings and clarify the underlying mechanisms.

Dedication

This dissertation is dedicated to everyone who has experienced aphasia and to the friends, family, and loved ones who care for them.

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Fields of Study

Major Field: Speech and Hearing Science

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Chapter 1: Introduction

The idea for the research presented in this dissertation was inspired by recent work from Hallam et al. (2018) and the group led by Hartwigsen (Hartwigsen et al., 2016, 2020; Klaus & Hartwigsen, 2019). These research studies, among others, have highlighted potential methods of exploring reorganization in the brain following injury, such as in post-stroke aphasia. Aphasia is a language impairment that occurs in approximately one-third of stroke survivors (Flowers et al., 2016), causing various linguistic deficits. Two components of language that are often impacted in post-stroke aphasia and studied in the research literature are semantics and phonology, the meaning and sounds that make up language, respectively. The purpose of this body of work is to 1) better understand the semantic and phonological brain networks of older adults, 2) examine the role of the inferior frontal gyrus (an area often damaged in people with post-stroke aphasia) in these networks, and 3) identify potential sites of reorganization that could be targeted in future studies of non-invasive brain stimulation. The contents of this dissertation include three manuscripts that address these objectives in various ways.

The first manuscript, "Semantic and Phonological Brain Networks in Older Adults: A Systematic Scoping Review," reports the results of an a priori, systematic search of the literature using various participant populations and methods to examine semantics and phonology in the brains of older adults. In addition to describing the nature of the evidence

addressing the topic, we report brain regions with the potential for semantic or phonological specialization, as well as those with the potential to play a role in both language domains. We also discuss the similarities and differences between our findings and a recent meta-analysis conducted on research with younger adults. We conclude with future directions, such as how our findings can aid in conducting a similar meta-analysis or full systematic review of the semantic and phonological networks in older adults. This scoping review serves as a foundation for the following two empirical studies specifically exploring the role of the inferior frontal gyrus in semantics and phonology, as well as determining recovery from aphasia.

The next manuscript, "The Resting-State Functional Connectivity of the Inferior Frontal Gyrus in Older Adults and its Application to a Post-stroke Aphasia Case Series," contains two parts. In the first part, we examine the resting-state functional connectivity of the three subregions of the left and right inferior frontal gyrus, pars opercularis, triangularis, and orbitalis (corresponding to Brodmann areas 44, 45, and 47, respectively). Resting-state functional connectivity analyses measure the level of synchronization between two or more brain regions via correlations of their activity during wakeful rest (Biswal et al., 1995; Fox et al., 2005). The inferior frontal gyrus contains Broca's area (pars opercularis and triangularis) and is often damaged in people with post-stroke aphasia, disrupting their language functioning. The anterior-most segment of the inferior frontal gyrus (pars orbitalis) has been implicated in semantic processing (Devlin et al., 2003) and the posterior-most segment (pars opercularis), in phonological processing (Lorca-Puls et al., 2017). Moreover, a functional connectivity analysis of the three subregions in the

inferior frontal gyrus revealed that pars orbitalis has more connections with regions thought to be involved in semantics, while pars opercularis has more connections with regions thought to be involved in phonology (Xiang et al., 2010). Due to theories of age-related de-lateralization of the left hemisphere for language (Berlingeri et al., 2013; Cabeza, 2001, 2002), we expected that the right hemisphere inferior frontal gyrus might show more functional connectivity in our older participants than in the younger participants previously studied (Xiang et al., 2010). We also correlated functional connectivity with scores on tests of semantics and phonology to determine whether the results were meaningfully related to behavior.

The second part of the second manuscript involves a case series exploring patterns of functional connectivity in participants with aphasia. We specifically explored functional connectivity between regions that had correlated with the semantic and phonological tasks in our neurologically intact sample. Although most of these regions were in the left hemisphere, we examined them in the right hemisphere of our participants with aphasia, considering their large left hemisphere lesions. We describe possible patterns among these participants, in relation to their inferior frontal gyrus lesions and performance on behavioral tasks, as well as future directions.

In the final manuscript, "Semantics, Phonology, and the Right Hemisphere Resting-State Functional Connectivity of Stroke Survivors with Aphasia," we further explored the relationship between left inferior frontal gyrus lesions, right hemisphere resting-state functional connectivity, and behavior regarding semantics and phonology. This study involved a retrospective analysis in a much larger sample of participants with aphasia than

in the second manuscript. We expected that participants with larger lesions to the left inferior frontal gyrus who perform better on behavioral tasks might be benefiting from a compensatory mechanism in the right hemisphere. Therefore, we specifically hypothesized that interactions between lesion load to anterior or posterior inferior frontal gyrus and resting-state functional connectivity between right hemisphere homologues of semantic or phonological regions would predict semantic and phonological performance, respectively.

Together, these three manuscripts will improve our understanding of the semantic and phonological brain networks of older adults, examine the role of the inferior frontal gyrus in these networks, and speculate as to potential sites of reorganization that could be targeted in future studies of non-invasive brain stimulation, based on our results. Ultimately, this dissertation demonstrates that continued work is warranted to definitively determine the impact of aging on the semantic and phonological networks in the brain and how these networks can optimally be reorganized to promote recovery for people with aphasia.

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Chapter 2: Manuscript 1

Semantic and Phonological Brain Networks in Older Adults:

A Systematic Scoping Review

Victoria A. Diedrichs, Erin L. Meier, & Stacy M. Harnish

Abstract

The neural correlates of semantics and phonology have been studied extensively. However, reviews have largely focused on neurologically healthy young adults, emphasizing semantic or phonological networks, without consideration for their overlap. This scoping review specifically explores the interplay between the semantic and phonological neural networks in older adults to better understand the extent to which they may be distinct or overlapping. Following the PRISMA extension guidelines for scoping reviews, we carried out a systematic search strategy to identify relevant primary research journal articles. Thirty-eight studies were included in the scoping review, representing a range of populations (i.e., neurologically intact older adults, post-stroke aphasia, primary progressive aphasia, dementia, mild cognitive impairment, and Parkinson's disease) and methodologies (e.g., task-based functional magnetic-resonance imaging, lesion-symptom-mapping), with sample sizes ranging from 11 to 1,231 participants. Based on the number of studies identifying relationships with a given region, we report that the unique semantic network of older adults may include the left orbitofrontal cortex, temporal pole, inferior temporal gyrus, fusiform gyrus, precuneus, lateral occipital cortex, parahippocampal gyrus, and thalamus, as well as the right middle frontal gyrus and left uncinate fasciculus. The unique phonological network may include the left Heschl's gyrus, primary auditory cortex, superior temporal gyrus and sulcus, planum temporale, and the supramarginal and angular gyri in addition to the left arcuate fasciculus. Finally, parts of these networks that may overlap include left middle temporal gyrus and four white matter association tracts: the left inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal

fasciculus, and internal capsule. These regions largely overlap with regions implicated in the semantic and phonological networks of younger adults, but we highlight potential differences. The results of this scoping review are not conclusive due to the absence of a statistical analysis of our findings. However, we conclude that a meta-analysis addressing this topic is a potentially valuable future direction and make recommendations for ensuring the robustness of such an analysis.

Introduction

This scoping review will explore the interplay between semantic and phonological neural networks in older adults. The purpose of the review is four-fold, to 1) explore the extent to which the semantic and phonological brain networks in older adults appear to be distinct or overlapping, 2) summarize the nature of the evidence regarding these networks in the brain, 3) draw comparisons with the evidence related to the semantic and phonological networks in younger adults, and finally, 4) to gauge the potential value in conducting a systematic review or meta-analysis to address this topic. These goals align with the suggested rationale for a scoping review as outlined by Tricco and colleagues (2018).

Based on the purposes outlined above, the results of the scoping review will describe brain regions implicated in semantics, phonology, or both and the number of studies that support the role of each brain region. After describing the nature of the included studies (e.g., sample populations, methods used), we compare our results with the findings of a recent meta-analytic study examining a similar question about semantic and phonological functional organization in exclusively neurologically intact younger adults (Hodgson et al., 2021). Finally, we describe the future directions for this work, with specific attention to the potential for conducting a similar meta-analysis in older adults. Although we know a great deal about language organization in the brain, many questions remain.

To begin, we provide background on a common model of language in the brain: the dual-stream model (Hickok & Poeppel, 2004, 2007). Notably, similar models (Friederici

& Gierhan, 2013; Rauschecker & Scott, 2009) have been developed since the work of Hickok and Poeppel. Models unique to semantics (Binder & Desai, 2011; Huth et al., 2016; Lambon Ralph et al., 2017; Mahon & Caramazza, 2011; Mirman et al., 2017; Xu et al., 2016, 2017) and phonology (Ghaleh et al., 2018; Graves et al., 2008; Ripamonti et al., 2018) also exist, which will be explored further in the discussion.

The Dual Steam Model

Hickok and Poeppel first proposed a model for speech processing including a dorsal stream, that maps sound onto articulatory-based representations, and a ventral stream, which maps sound onto meaning (2004). This model evolved somewhat and later became referred to as the dual-stream model (Hickok & Poeppel, 2007). In this model, the authors propose that phonological processing involves the middle to posterior portions of the superior temporal sulcus bilaterally, with a potential weak left-hemisphere bias. The dorsal pathway then maps sensory or phonological representations onto articulatory motor representations in the left hemisphere, via the temporoparietal junction that caps the Sylvian fissure, the posterior inferior frontal gyrus, premotor cortex, and anterior insula. Meanwhile, the ventral pathway maps sensory or phonological representations onto lexical conceptual representations via the posterior middle temporal gyrus and posterior inferior temporal sulcus, bilaterally (though with a weak left-hemisphere bias), and the left-hemisphere anterior middle temporal gyrus and anterior inferior temporal sulcus.

In the dual-stream model, semantic processing occurs primarily in the anterior and poster regions of the temporal lobe and phonological-articulatory processing progresses

from the posterior temporal lobe to the temporoparietal junction and the posterior frontal lobe. This model has been substantiated in human subjects using functional MRI (fMRI) and diffusion tensor imaging (DTI) based tractography (Saur et al., 2008). Saur and colleagues found evidence for a dorsal pathway primarily via the arcuate and superior longitudinal fasciculi, connecting regions supporting nonword repetition, including anterior and posterior superior temporal gyrus, the pars opercularis of the inferior frontal gyrus, dorsal premotor cortex, and ventrolateral prefrontal cortex. They also found evidence for a ventral pathway consisting primarily of the extreme capsule, connecting regions supporting passive, sentence-level language comprehension, including anterior and posterior middle temporal gyrus, fusiform gyrus, and pars orbitalis and triangularis of the inferior frontal gyrus.

Importantly, the contrasts used by Saur et al. to identify regions involved in the ventral and dorsal streams prevent the likelihood of overlap in these two systems. In identifying the regions involved in the dorsal pathway, the authors contrasted repetition of nonwords with real words and in identifying regions involved in the ventral pathway, they contrasted listening to meaningful sentences (in German, for a German-speaking sample of participants) with listening to meaningless pseudosentences filled with nonwords. A more recent investigation into the neural correlates of the dorsal and ventral streams (Fridriksson, den Ouden, et al., 2018) utilized both region and connectome-based lesion-symptom mapping to reveal both cortical brain regions and the subcortical tracts connecting them that were associated with performance on a variety of speech and language measures. Their analysis found that damage to dorsal regions and the white matter

tracts connecting them largely informed speech production, articulation, and apraxia, whereas damage to ventral regions and the tracts connecting them was more likely to influence speech comprehension, but they did identify some overlap between the regions and connections involved. For example, the supramarginal gyrus and middle frontal gyrus were identified in region-wise lesion-symptom maps of both a composite of speech production assessments and a composite of primarily speech perception/comprehension assessments, using univariate and multivariate analyses, respectively.

Although the dual-stream model demonstrates neural correlates for semantics and phonology, it emphasizes the pathways for complete communication processes, that is, speech perception and production. This means that semantics and phonology may inherently play a role in both the dorsal and ventral streams. Both dorsal and ventral streams involve mapping sound onto other representations (i.e., articulatory and meaning-based representations, respectively), which indicates that processing the sounds of language, or phonology, is at least likely to be involved in both pathways. Moreover, there are many activities besides speech production and perception that engage semantic and phonological systems. In addition to auditory processing, semantic and phonological systems can be engaged via visual processing of images and/or orthography. Different regions may be engaged for nonverbal compared to lexical semantics, as well as for word-level compared to sentence or discourse-level semantic and phonological processes. Therefore, more information from a variety of semantic and phonological tasks is needed to address the question of overlap between semantic and phonological networks.

Semantic and Phonological Networks in Healthy Younger Adults

A recent study including a series of activation likelihood estimation meta-analyses (Hodgson et al., 2021) directly addresses the question of how dissociable the semantic and phonological brain networks are, detailing the extent of their overlap and distinction in neurologically intact younger adults (i.e., sample age < 40 in all included primary research articles).

Activity uniquely contributing to phonology, identified by contrasting with the semantic results, was found broadly in the left hemisphere at the superior posterior temporal lobe, posterior portions of the frontal lobe, and the inferior parietal lobule. Specific clusters were identified in left precentral gyrus, extending into pars opercularis of the inferior frontal gyrus, posterior superior temporal gyrus, supramarginal gyrus, extending into part of the angular gyrus, precuneus, and a small segment of fusiform gyrus. A smaller cluster was also identified in the posterior inferior temporal gyrus. Activity unique to semantics, contrasted with the phonological results, was found broadly in the left hemisphere at anterior and inferior portions of the temporal lobe, fusiform gyrus, and ventral inferior parietal lobule. Specific clusters were identified in left parahippocampal cortex, anterior middle and superior temporal gyri, ventral angular gyrus, dorsal posterior middle temporal gyrus, superior frontal gyrus, and pars orbitalis of the inferior frontal gyrus.

On the other hand, overlap was identified between the semantic and phonological activation likelihood maps most notably in the left inferior frontal and inferior temporal gyri. However, the authors revealed through additional analyses of working memory and

the multiple demand network (Fedorenko et al., 2013) that each of these regions also plays a role in domain-general cognitive control. Therefore, they propose that the left inferior frontal and inferior temporal gyri are not part of the core representational language network. Instead, they are domain-general cognitive control regions that are co-activated by semantic and phonological processing. However, the anterior-most part of the inferior frontal gyrus (i.e., pars orbitalis), as well as posterior middle temporal gyrus, appear to be specialized for semantic-specific control. Thus, no regions of overlap were identified between the semantic and phonological representational networks, suggesting that these representational networks are highly specialized. The overlap between the broader semantic and phonological networks all takes place at sites of overlap with domain-general cognition.

A limitation of this work in its application to populations with language disorders resulting from stroke or neurodegenerative disease, such as post-stroke and primary progressive aphasia, is that it does not address changes that may occur as a result of aging. People who experience post-stroke or neurodegenerative language disorders are often over the age of 40. By excluding studies focusing on samples over the age of 40, it is unclear how these networks apply to studies examining the neural correlates of semantics and phonology in clinical populations of older adults.

The Impact of Aging on Brain Networks

It has been reported that the most salient difference between the functional brain activity of older and younger adults related to cognition is that older adults are less

lateralized than their younger counterparts in the prefrontal cortex (Cabeza, 2001). This has been termed the hemispheric asymmetry reduction in older adults (HAROLD) model (Cabeza, 2002) and encompasses the domains of episodic memory, semantic memory, working memory, perception, and inhibitory control. Cabeza cites two different perspectives on why this de-lateralization takes place: a compensation hypothesis, speculating that bilateral activation helps counteract age-reclined neurocognitive decline, and a de-differentiation hypothesis, speculating that older adults struggle to activate highly specialized, lateralized cognitive regions.

Berlingeri et al. (2013) investigated these effects using picture naming, sentence judgment, picture recognition, and sentence recognition tasks, in addition to episodic long-term memory tasks. The authors concluded that while HAROLD-like effects can be observed outside frontal cortex (i.e., in temporal, parietal, occipital, and insular cortex), there may be other explanations for the differences between older and younger adults, namely a simple reduction in activation for the older participants. They also noted that activation for older adults was still prominently left-lateralized overall for their language tasks. Nevertheless, their results supported some degree of de-lateralization (i.e., bilateral activation in older adults) in several brain regions related to language, including the inferior frontal gyrus (pars triangularis and orbitalis), superior temporal pole, superior temporal gyrus, middle frontal gyrus, angular gyrus, inferior parietal lobule, calcarine fissure, and middle temporal gyrus.

In sum, our scoping review is warranted due to the evidence of differences between the neural organization of older and younger adults pertaining to language and cognition

(Berlingeri et al., 2013; Cabeza, 2001, 2002). Moreover, given that younger adults show specialization in their semantic and phonological networks, with some degree of overlap in domain-general cognitive regions, it is worth exploring this pattern in older adults.

Methods

Reporting guidelines from the PRISMA extension for scoping reviews (PRISMA-ScR; (Tricco et al., 2018) as well as recommendations from Arksey and O'Malley (2005) were used for the present study. A librarian at the first author's institution was consulted to assist with search strategy development. The systematic search strategy agreed upon by all authors and the librarian was carried out in July of 2022 by the first author. Three databases were searched for research articles addressing regions or networks of the brain involved in semantics and phonology: PubMed, Web of Science, and EBSCOhost. Search terms for each database are shown in Table 2.1.

The following a priori criteria determined whether studies were included: 1) the study consisted of an empirical analysis published in a peer-reviewed journal, 2) the article was written in English, 3) participants had a mean age of 60 or greater, 4) the study included behavioral tasks assessing both semantics and phonology (e.g., category and letter fluency), 5) the analyses included magnetic resonance imaging (MRI) data (e.g., task-based or resting state functional MRI, lesion-symptom mapping, diffusion-weighted or diffusion-tensor imaging) or intraoperative cortical stimulation data, and 6) the relationship between MRI or cortical stimulation data and behavioral performance was statistically analyzed.

Table 2.1 Search Strategy for Pubmed, Web of Science, and EBSCOhost Databases

Database	Terms	Refined By
Pubmed	((language[Title/Abstract] OR linguistic*[Title/Abstract] OR "language"[MeSH Terms]) AND (semantic*[Title/Abstract] OR "semantics"[MeSH Terms]) AND (phon*[Title/Abstract]) AND (mri[Title/Abstract] OR magnetic resonance imaging[Title/Abstract] OR neuroimaging[Title/Abstract] OR brain imaging[Title/Abstract] OR "neuroimaging"[MeSH Terms]))	language: English
Web of Science	TS=(language OR linguistic*) AND TS=(semantic*) AND TS=(phon*) AND TS=(mri OR magnetic resonance imaging OR neuroimaging OR brain imaging)	language: English
EBSCOhost	(language OR linguistic*) AND semantic* AND phon* AND (mri OR magnetic resonance imaging OR neuroimaging OR brain imaging)	language: English

Importantly, studies including clinical populations were included except when the analysis consisted only of fMRI activation, considering such activation may be influenced by lesions, atrophy, reorganization, and/or recovery. Reviews, comments, and book chapters that did not present new data were excluded; however, these were reviewed to identify additional studies that may have been missing from our search results. Foreign language articles were excluded due to constraints on time and translation costs. The mean

age of 60 was utilized as a cut-off based on prior reviews that used this age to distinguish older adults (Hoffman & Morcom, 2018). We did not specify the type of linguistic tasks to be used, other than that they must target semantics and phonology. As such, we accepted studies utilizing tasks engaging receptive, expressive, auditory, and visual systems at a variety of linguistic levels (e.g., single word-picture matching, sentence comprehension). Studies addressing only semantics or phonology (i.e., rather than both) were excluded due to the limitations of exploring these brain networks in separate samples. Only studies utilizing MRI or intraoperative data were included due to the inherent spatial advantage of these methods over others (e.g., EEG). Finally, any studies that did not statistically analyze the relationship between brain-based data and behavioral task performance were excluded due to limitations on interpreting the brain-behavior relationship.

Results from the database searches were exported to Mendeley and duplicates were removed. The first author screened all titles and abstracts. Undergraduate student research assistants identified and recorded the mean age of participants in the articles that passed the title and abstract screening process. The first author then reviewed articles including participants with a mean age of 60 or greater for the remaining eligibility criteria. Once final eligibility decisions were made on the full text of the articles reviewed, the following details from each included study were aggregated in a spreadsheet: 1) article citation, 2) atlas or parcellation used, 3) behavioral tasks used, 4) contrasts and analyses used, 5) regions associated with semantics only and coordinates, if provided, 6) regions associated with phonology only and coordinates, if provided, 7) regions associated with both semantics and phonology and coordinates, if provided, 8) multiple comparisons correction

technique, if used, and 9) population (e.g., healthy neurotypical adults, post-stroke aphasia, dementia).

Results

The screening and review process, with the number of articles examined and excluded at each stage, is depicted in Figure 2.1, as recommended by the PRISMA extension guidelines (Tricco et al., 2018). The three database searches produced a total of 2,561 results. Duplicates within each database were removed, yielding a total of 2,093 results. Next duplicates across databases were removed, yielding 1,212 unique articles. The titles and abstracts of these articles were screened by the first author. Articles that passed the title and abstract screening (n = 436) were screened for the mean age of participants by undergraduate research assistants. The full text of articles including participants with a mean age of 60 or greater (n = 92) were reviewed by the first author for other eligibility criteria. Of these, 54 were excluded, leaving 38 papers included in the scoping review. One additional paper that met all other inclusion criteria was excluded (Xing et al., 2018) because their study design and results could not be aggregated with the other included studies. Xing et al. (2018) used probabilistic tractography to reconstruct white matter tracts between cortical nodes activated by a naming task. Their results consisted of relating phonological or nonverbal semantic processing with direct pathways between two regions (e.g., left aSTG to left orbital inferior frontal gyrus). This differed from all other studies included in the scoping review, which identified discrete cortical regions or white matter association tracts.

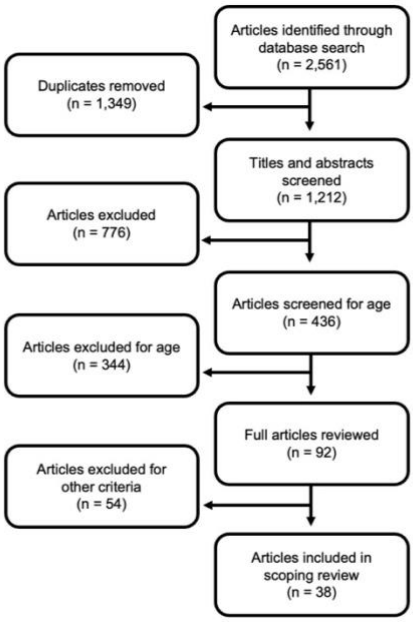


Figure 2.1 PRISMA Diagram of Screening and Review Processes

Publication years for the included articles ranged from 1999 to 2022. Fifteen studies were conducted in the United States, eleven in the United Kingdom, two each in Australia, Canada, and Germany, and one each in Finland, Norway, South Korea, Spain, Switzerland, and Taiwan. To answer the questions of interest, related to localizing the semantic and phonological networks in the brain, several different methodologies were employed by the included studies and some studies utilized more than one approach. Most studies used either a lesion-based approach (n = 16; e.g., voxel-based lesion-symptom mapping or voxel-based correlational methodology) or task-based functional MRI activation (n = 11). Additional methodological approaches included analysis of white matter measures (n = 2;

e.g., diffusion-weighted imaging), gray matter density/volume (n = 8), and cortical thickness (n = 1).

Table 2.2 Participant Demographics

Study	*N*	Age (years)	Sex[a]	Sample	Hand[b]
Alyahya et al. (2018)	48	63.31 (41-87)	14 F 34 M	Chronic post-stroke aphasia (12 m)	48 R
Alyahya et al. (2020A)	46	63.21 (44-87)	14 F 32 M	Chronic post-stroke aphasia (12 m)	46 R
Alyahya et al. (2020B)	42	63.11 (44-87)	14 F 28 M	Chronic post-stroke aphasia (12 m)	42 R
Baldo et al. (2006)	48	62.9 (43-80; SD = 9.6)	14 F 34 M	Chronic post-stroke aphasia (9 m)	48 R
Biesbroek et al. (2021)	1,231	66.6 (21-94; SD = 11.6)	464 F 767 M	Acute stroke	1179 R 12 L 21 A
Boukrina et al. (2015)	11	62.9 (46-83; SD = 8.7)	7 F 4 M	Subacute stroke (5 w)	11 R
Brambati et al. (2009)	10 56	61.7 (+/- 8)	36 F 30 M	NI controls Neurodegenerative disease	NR
Butler et al. (2014)	19 31	68.21 (59-80; SD = 5.99)	8 F, 11 M 5 F, 26 M	NI controls Chronic post-stroke aphasia (12 m)	19 R 31 R
Chang et al. (2020)	36 24 26	71.11 (SD = 5.97) 70.12 (SD = 7.79) 74.15 (SD = 8.49)	22 F, 14 M 16 F, 8 M 12 F, 14 M	NI controls S-MCI M-MCI	36 R 24 R 26 R
Chouiter et al. (2016)	191	62.2 (SD = 14.9)	71 F 120 M	Subacute stroke or tumor	191 R
Clark et al. (2014)	25 23 10	70.1 (SD = 6.9) 70.7 (SD = 7.4) 74.7 (SD = 7.8)	12 F, 13 M 5 F, 18 M 3 F, 7 M	NI controls MCI AD	25 R 23 R 10 R
Ellfolk et al. (2014)	28 28	61.3 (SD = 7.2) 60.3 (SD = 8.1)	13 F, 15 M 14 F, 14 M	NI controls PD	NR
Froehlich et al. (2018)	58 25	70.4 (63-79, SD = 3.4) 25 (21-35, SD = 3.67)	27 F, 31 M 18 F, 7 M	Older NI Younger NIc	58 R 25 R
Halai et al. (2017)	31	64.32 (45-84)	5 F, 26 M	Chronic post-stroke aphasia (12 m)	31 R

Continued

Table 2.2 continued

Halai et al. (2018)	46	65.46 (SD = 11.49)	13 F, 33 M	Chronic post-stroke aphasia (12 m)	46 R
Henry et al. (2012)	15	67.8 (SD = 8.5)	7 F, 8 M	NI controls	14 R, 1 L
	15	71.6 (SD = 7.7)	6 F, 9 M	PPA	14 R, 1 L
Martins et al. (2014)	14	63 (+/- 8)	6 F, 8 M	Older NI	14 R
	14	26 (+/- 5)	8 F, 6 M	Younger NI[c]	14 R
Meinzer et al. (2012)	14	69.2 (61-80, +/- 5.8)	7 F, 7 M	Older NI	14 R
	14	24.6 (19-32, +/- 4.4)	7 F, 7 M	Younger NI[c]	14 R
Pereira et al. (2009)	32	73.1 (SD = 5.9)	20 F, 12 M	PD	NR
Riello et al. (2022)	35	67.74 (51-82, SD = 7.6)	16 F, 19 M	PPA	NR
Rizio et al. (2017)	20	67.25	15 F, 5 M	Older NI	20 R
	20	23.7	10 F, 10 M	Younger NI[c]	20 R
Rochon et al. (2010)	10	61	3 F, 7 M	NI controls	10 R
	4	67.25 (50-83)	1 F, 3 M	Aphasia[c]	4 R
Rodriguez-Aranda et al. (2016)	24	66.21 (SD = 8.96)	9 F, 15 M	NI controls	NR
	18	64.94 (SD = 9.57)	9 F, 9 M	AD	
Saykin et al. (1999)	6	71 (SD = 4)	4 F, 2 M	NI controls	13 R
	9	79 (SD = 5)	3 F, 6 M	AD	2 L
Schmidt et al. (2019)	85	63.97 (22.4-85.8)	23 F, 62 M	Chronic post-stroke aphasia (5m)	NR
Schumacher et al. (2019)	38	64 (45-88)	11 F, 27 M	Chronic post-stroke aphasia (12 m)	38 R
Shafto et al. (2012)	16	75.75 (SD = 4.99)	NR	Older NI	NR
	14	23.86 (SD = 4.14)		Younger NIc	
Sonty et al. (2003)	11	66.5 (+/- 6.7)	6 F, 5 M	NI controls	11 R
	11	63.4 (+/- 4.6)	6 F, 5 M	PPA	11 R
Stark et al. (2019)	57	61.68 (+/- 12.02)	25 F, 32 M	Chronic aphasiad (6 m)	57 R
van Hees et al. (2014)	14	61.71 (49-81, SD = 10.07)	8 F, 7 M	NI controls	14 R
	8	56.38 (41-69, SD = 9.15)	5 F, 3 M	Aphasiac	8 R
Vonk et al. (2019)	505	74.1 (62-96)	281 F, 224 M	NI	461 R 32 L 11 A
Wilson et al. (2009)	9	65.7	7 F, 2 M	NI controls	7 R, 2 L
	5	61.4	4 F, 1 M	SD (PPA)	4 R, 1 L
Wilson et al. (2010)	10	68.5 (SD = 5.9)	5 F, 5 M	NI controls	9 R, 1 L
	60	65.85e	34 F, 26 M	PPA + dementia	44 R, 6 L

Continued

Table 2.2 continued

Woollams et al. (2018)	43	64.27 (44-87)	NR	Chronic post-stroke aphasia (12 m)	43 R
Zhang et al. (2013)	344	78.3 (SD = 4.8, 70-90)	187 F, 157 M	NI	321 R, 11 L, 12 A
Zhao et al. (2020)	70	65.21 (44-87)	17 F, 53 M	Chronic post-stroke aphasia (12 m)	70 R
Zhao et al. (2018)	35	63.8 (44-86)	12 F, 23 M	Chronic post-stroke aphasia (12 m)	35 R
Zhuang et al. (2016)	20	66.6 (60-78)	12 F, 8 M	Older NI	20 R
	20	23.7 (19-34)	10 F, 10 M	Younger NIc	20 R

Note. [a]Sex was only reported as male or female in the included studies, therefore no non-binary sexes are reported here. [b]For post-stroke participants, pre-morbid handedness is reported. [c]These groups of participants were not analyzed for the scoping review, due to mean age or the methods used (e.g., task-based fMRI activation in clinical sample). [d]In the study by Stark et al. (2019), only the Philadelphia Naming Test group was used, due to the mean age of the other group being below our minimum. [e]A weighted average was taken of the ages provided for all PPA and dementia groups. A = ambidextrous or other, AD = Alzheimer's dementia, F = female, L = left, M = male, MCI = mild cognitive impairment, M-MCI = multi-domain MCI, NI = neurologically intact, NR = not reported, PD = Parkinson's disease, PPA = Primary progressive aphasia, R = right, S-MCI = single-domain MCI.

Participants

The number of participants included in each study and the sample populations are shown in Table 2.2. There was a wide range of sample sizes, from 11 to 1,231 participants in a single study, though most studies included under 100 participants. Due to the age criterion, the mean age was similar across studies, but ranged from 60 to 79 years, excluding mean ages for younger control samples that were used in comparison with older participants within the same study. Eight studies included only neurologically intact participants. Of these, six included both older and younger adult samples in order to directly compare the two groups. Out of 18 studies with a post-stroke population, 15 specifically included participants with post-stroke aphasia. Four studies included

participants with primary progressive aphasia (PPA) or semantic dementia (equivalent to the semantic variant of PPA). Additional studies included participants with other neurodegenerative diagnoses (n = 7), including Alzheimer's dementia (n = 3) and Parkinson's disease (n = 2). Fewer studies (n = 2) specifically included participants with mild cognitive impairment (MCI).

Table 2.3 Gray Matter Regions Implicated in Semantics, Phonology, or Both

		Left Hemisphere			Right Hemisphere		
Region	BA	Sem.	Phon.	Both	Sem.	Phon.	Both
frontal pole	10	2	0	2	1	0	1
Sup. frontal gyrus	6, 8	2	0	3	2	0	1
middle.frontal gyrus	9, 10	3	2	3	5	0	0
dorsolateral prefrontal cortex	46	0	0	0	1	2	0
inf. frontal gyrus	44, 45, 47	1	2	0	1	2	0
pars opercularis	44	4	3	4	0	1	0
pars triangularis	45	4	3	3	0	0	0
pars orbitalis	47	2	3	0	0	1	0
orbitofrontal cortex	11	3	0	1	1	0	0
SMA	6	1	1	0	0	2	0
precentral gyrus	4	1	5	4	1	3	3
temporal pole	38	9	4	2	0	2	0
Heschl's gyrus	41, 42	1	6	1	0	0	0
primary auditory cortex	41, 42	1	3	0	0	1	0
sup. temporal gyrus	22	8	13	6	1	2	2
sup. temporal sulcus	21 22	1	1	0	1	0	0
planum polare	38	0	4	3	0	0	0
planum temporale	22	0	8	1	0	0	0
middle temporal gyrus	21	12	11	5	0	0	0
inf. temporal gyrus	20	10	4	3	1	1	0
inf. temporal sulcus	20	0	1	0	0	0	0
fusiform gyrus	37	15	4	2	0	0	2
postcentral gyrus	1, 2, 3	1	1	3	1	0	1
sup. parietal lobe	5, 7	2	1	1	0	0	0
intraparietal sulcus	7, 39, 40	1	1	2	0	0	0
supramarginal gyrus	40	2	13	4	0	1	1
angular gyrus	39	4	8	4	0	1	1
temporo-parietal junction	39	1	0	0	0	0	0
precuneus	7	5	1	0	3	1	1

Continued

Table 2.3 continued

lateral occipital cortex	18, 19	6	1	3	2	0	1
middle occipital gyrus	19	1	1	1	0	1	0
cuneus	17	2	0	0	1	1	0
lingual gyrus	17, 18, 19	1	0	0	2	1	0
frontal operculum	-	0	0	2	0	0	0
central operculum	-	0	2	2	0	0	0
parietal operculum	-	0	5	1	0	0	0
insula	16	2	7	6	1	0	0
anterior cingulate	24, 32, 33	0	1	1	1	0	0
posterior cingulate	23, 31	1	2	0	2	0	1
paracingulate gyrus	31, 32	1	0	0	0	0	0
parahippocampus	34	6	0	1	1	1	1
hippocampus	--	4	0	2	1	1	1
amygdala	--	1	0	1	1	0	0
basal ganglia	--	0	1	0	0	0	0
caudate	--	1	0	2	2	1	0
pallidum	--	1	0	2	0	0	0
putamen	--	0	1	3	1	0	0
thalamus	--	3	0	1	1	0	0
nucleus accumbens	--	1	0	0	0	0	0
substantia nigra	--	0	0	0	0	1	0
left cerebellum	--	3	2	2	2	4	0

Note. Medial gray matter regions are not shown here. BA = Brodmann area.

The primary results of the scoping review are the brain regions associated with semantics, phonology, or both in older adults, and are summarized in Table 2.3 and Table 2.4, in terms of the number of studies that identified such functional relationships. The left hemisphere regions are depicted in Figure 2.2. The aggregated results of the included studies informed the specificity of the labels selected for the table. For example, the cingulate is listed as either anterior or posterior cingulate because all studies used either the anterior or posterior marker in their results. Many other regions, such as the superior temporal gyrus, are listed without subdivisions because many studies did not specify whether the anterior, mid, or posterior portion was implicated. However, where appropriate, a summary of the findings related to subdivisions within a given region will

be provided in the results described below (e.g., please see Brain Regions Implicated in Phonology for a description of findings related to the superior temporal gyrus, including its anterior and posterior subdivisions). Of note, for regions with common subdivisions, like the superior temporal gyrus, studies may be included in multiple categories if they found different relationships with the subdivisions (e.g., anterior superior temporal gyrus linked with phonology and posterior superior temporal gyrus linked with semantics).

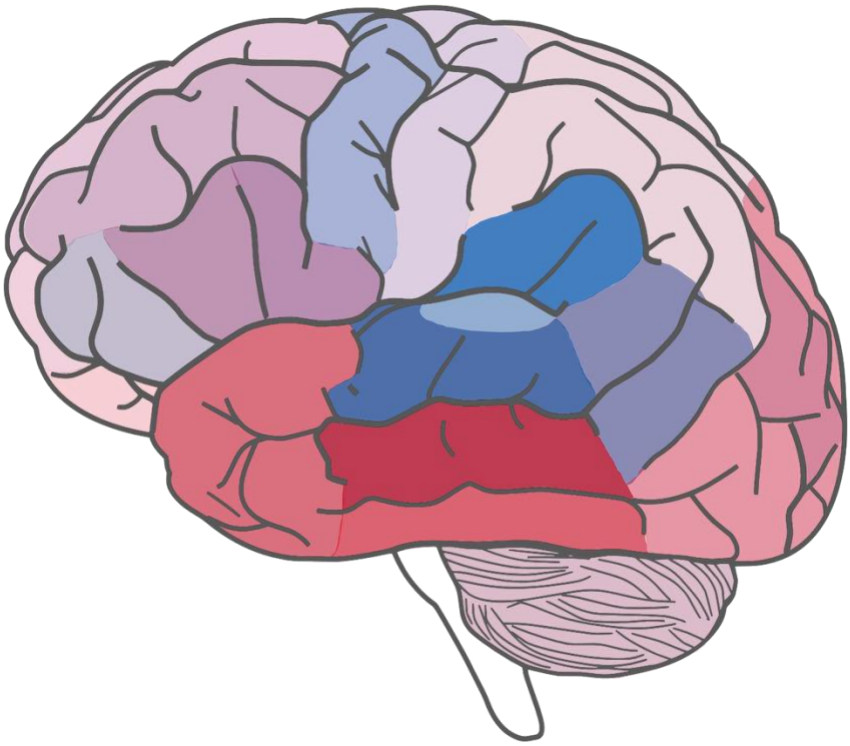
Table 2.4 White Matter Tracts Implicated in Semantics, Phonology, or Both

	Left Hemisphere			Right Hemisphere		
Tract	Sem.	Phon.	Both	Sem.	Phon.	Both
arcuate fasciculus	0	7	0	0	0	0
cingulum	2	0	0	1	0	0
anterior commissure	1	0	0	0	0	0
corona radiata	1	2	3	1	1	1
cortico-spinal tract	0	1	1	0	0	0
external capsule	0	1	3	1	1	1
fornix	1	0	3	1	0	1
frontal aslant tract	0	2	0	0	0	0
frontal striatal tract	0	1	0	0	1	0
inferior fronto-occipital fasciculus	5	1	4	2	1	1
inferior longitudinal fasciculus	4	1	4	0	0	0
internal capsule	3	3	3	2	1	1
medial lemniscus	0	1	0	0	1	0
optic radiations	0	0	1	0	0	0
sagittal stratum	0	1	2	0	1	1
superior longitudinal fasciculus	3	3	3	1	1	1
temporal stem	2	0	0	0	0	0
anterior thalamic radiation	1	2	0	0	1	0
posterior thalamic radiation	2	1	2	1	0	1
uncinate fasciculus	4	1	2	0	0	0
cerebral peduncle	0	1	1	0	1	0
cortico-ponto cerebellar tract	0	1	0	0	0	0

Note. Medial white matter association tracts are not shown here.

It was outside the scope of this review to definitively identify the language domain specificity (i.e., involvement in semantics *or* phonology) or universality (i.e., involvement in both semantics *and* phonology) of every brain region reported by the included studies. Instead, we highlight brain regions below with the potential for specificity or universality, based on the number of studies in each category. For example, if several studies found a relationship only with a semantic task and only a few identified a relationship with a phonological task or with both tasks, we report that region as having the potential for semantic specificity. This structure is not meant to imply conclusiveness of our results but rather to provide organization and draw attention to brain regions that should be investigated further.

Finally, if multiple analyses or experiments were run within a single study, we collapsed the results across all analyses within the study so that in the results, each study could appear only once as identifying a relationship with a given brain region (rather than being listed twice if two separate analyses supported a relationship between a brain region and phonology, for example). We chose to do this while aggregating the results for two reasons: first, to simplify the results, and second, because many of the studies that met inclusion criteria for the scoping review came out of the same laboratories and included overlapping participant samples. Collapsing results across all analyses within a single study prevented further potential inflation of the aggregated results.



Note. This figure was created by creating up to three layers for each region, representing semantics (red), phonology (blue), and both (purple). The transparency of each layer reflects the number of studies implicating that region in the given domain, where more papers is associated with a more opaque, darker color. The layer associated with the highest number of studies for a given region was placed on top so that color would appear most prominently.

Figure 2.2 Left Hemisphere Regions Implicated in Semantics, Phonology, or Both

Brain Regions with Potential Semantic Specialization

Based on the present scoping review, several regions demonstrate the potential to be specialized for semantics in older adults. These include the right middle frontal gyrus, and several left hemisphere regions, including the orbitofrontal cortex, temporal pole, inferior temporal gyrus, fusiform gyrus, precuneus, lateral occipital cortex, parahippocampal gyrus, and thalamus. In terms of white matter association tracts, the left

uncinate fasciculus was the only one to demonstrate the potential for semantic specialization.

Three studies identified a relationship between the left hemisphere middle frontal gyrus and semantics (Rizio et al., 2017; Saykin et al., 1999; Vonk et al., 2019), two identified such a relationship with phonology (Rodríguez-Aranda et al., 2016; Schmidt et al., 2019), and three implicated both language domains (Biesbroek et al., 2021; Froehlich et al., 2018; Woollams et al., 2018). However, six studies identified a relationship between the right hemisphere middle frontal gyrus and semantics (Froehlich et al., 2018; Meinzer et al., 2012; Pereira et al., 2009; Rochon et al., 2010; Rodríguez-Aranda et al., 2016), with none identifying a relationship with phonology or both language domains. While the left middle frontal gyrus may be more language-domain-general, the lack of studies implicating the right middle frontal gyrus in phonology makes a compelling case for its potential semantic specificity.

Interestingly, pars orbitalis does not appear to be strongly associated with semantics, given only two studies that found such a relationship with the left hemisphere region (Zhang et al., 2013; Zhuang et al., 2016), whereas three studies implicated the region in phonology (Rochon et al., 2010; Wilson et al., 2009; Woollams et al., 2018). However, the more ventral and medial orbitofrontal cortex may be implicated in semantics. Three studies implicated the left hemisphere region (Biesbroek et al., 2021; Pereira et al., 2009; Vonk et al., 2019), while one study indicated its role in both semantics and phonology (Woollams et al., 2018). Moreover, only one study reported findings related to the right orbitofrontal cortex, suggesting its involvement in semantics as well (Meinzer et al., 2012).

Nine studies indicated the left temporal pole in semantics (Baldo et al., 2006; Brambati et al., 2009; Henry et al., 2012; Pereira et al., 2009; Rodríguez-Aranda et al., 2016; Schumacher et al., 2019; Stark et al., 2019; Zhang et al., 2013; Zhao et al., 2018), four in phonology (Boukrina et al., 2015; Halai et al., 2018; Martins et al., 2014; Rochon et al., 2010), and two in both (Biesbroek et al., 2021; Woollams et al., 2018). The right temporal pole was only indicated in phonology, by two studies (Martins et al., 2014; Rochon et al., 2010).

Ten studies identified a relationship between semantics and the inferior temporal gyrus. Of these, four localized the relationship to the posterior portion (Baldo et al., 2006; Biesbroek et al., 2021; Halai et al., 2017; Stark et al., 2019), two to the dorsal portion (Butler et al., 2014; Halai et al., 2017), and the remainder did not specify (Henry et al., 2012; Pereira et al., 2009; Riello et al., 2022; Schmidt et al., 2019; Woollams et al., 2018). A fewer number of studies identified a relationship between phonology and the inferior temporal gyrus. Two reported involvement of the posterior portion (Alyahya et al., 2018; Schumacher et al., 2019), while one reported involvement of the anterior portion (Biesbroek et al., 2021), and the remaining study did not specify (Froehlich et al., 2018). Three studies identified a relationship with both semantics and phonology (Alyahya et al., 2020; Biesbroek et al., 2021; Schumacher et al., 2019). Only one study each found that the right inferior temporal gyrus had a relationship with semantics (Pereira et al., 2009) and phonology (Rodríguez-Aranda et al., 2016).

The left fusiform gyrus was reported to be involved in semantics by fifteen studies (Alyahya et al., 2018, 2020; Baldo et al., 2006; Biesbroek et al., 2021; Brambati et al.,

2009; Butler et al., 2014; Halai et al., 2017; Henry et al., 2012; Rizio et al., 2017; Rodríguez-Aranda et al., 2016; Stark et al., 2019; Van Hees et al., 2014; Woollams et al., 2018; Zhao et al., 2020; Zhuang et al., 2016), the largest consensus of any region reported. Only four studies reported involvement of the left fusiform in phonology (Boukrina et al., 2015; Brambati et al., 2009; Froehlich et al., 2018; Vonk et al., 2019) and two reported its involvement in both language domains (Schumacher et al., 2019; Wilson et al., 2009). The right fusiform was implicated in both semantics and phonology in two studies (Sonty et al., 2003; Wilson et al., 2009).

The left precuneus was indicated by five studies to be involved in semantics (Alyahya et al., 2018; Baldo et al., 2006; Ellfolk et al., 2014; Rizio et al., 2017; Rochon et al., 2010) and by only one to be involved in phonology (Martins et al., 2014). Three research groups indicated the right precuneus was involved in semantics (Meinzer et al., 2012; Rizio et al., 2017; Zhuang et al., 2016), while one each indicated its involvement in phonology (Martins et al., 2014) or both language domains (Vonk et al., 2019). One study implicated the medial precuneus in semantics (Rizio et al., 2017).

Six studies reported the lateral occipital cortex (Alyahya et al., 2018, 2020; Rochon et al., 2010; Stark et al., 2019; Vonk et al., 2019; Zhao et al., 2020) was related to semantics, while only one reported it was related to phonology (Martins et al., 2014) and three reported it was related to both domains (Alyahya et al., 2020; Biesbroek et al., 2021; Wilson et al., 2009). Studies reporting involvement of the right occipital were fairly evenly distributed across the three categories: two for semantics (Martins et al., 2014; Rochon et al., 2010), one for phonology (Froehlich et al., 2018), and one for both (Wilson et al., 2009).

Strikingly, six studies implicated the left parahippocampal gyrus in semantics (Biesbroek et al., 2021; Pereira et al., 2009; Saykin et al., 1999; Schumacher et al., 2019; Zhang et al., 2013; Zhuang et al., 2016), while only one implicated this region in both semantics and phonology (Rodríguez-Aranda et al., 2016). However, the functional implications for the right parahippocampus appear more mixed. One study each suggested it has a role in semantics (Pereira et al., 2009), phonology (Saykin et al., 1999), and both domains (Rodríguez-Aranda et al., 2016).

The left thalamus was associated with semantics in three studies (Pereira et al., 2009; Rodríguez-Aranda et al., 2016; Schumacher et al., 2019) and associated with both semantics and phonology in one (Biesbroek et al., 2021). One study found that the right thalamus was associated with semantics (Rodríguez-Aranda et al., 2016).

Finally, the left uncinate fasciculus was implicated in semantics by four studies (Alyahya et al., 2020; Butler et al., 2014; Halai et al., 2017; Zhao et al., 2020), while only one indicated its involvement in phonology (Boukrina et al., 2015) and two indicated it was involved in both domains (Chang et al., 2020; Woollams et al., 2018). On the other hand, no studies implicated the right uncinate fasciculus.

Brain Regions with Potential Phonological Specialization

Six gray matter regions were implicated in the phonological networks of older adults by the studies included in the scoping review: Heschl's gyrus, primary auditory cortex, superior temporal gyrus and sulcus, planum temporale, and the supramarginal and

angular gyri. Additionally, the left arcuate fasciculus demonstrated the potential for phonological specialization.

The left Heschl's gyrus and primary auditory cortex were together implicated by eight separate studies (Alyahya et al., 2018, 2020; Butler et al., 2014; Halai et al., 2017, 2018; Rochon et al., 2010; Woollams et al., 2018; Zhao et al., 2018). On the other hand, only two studies implicated left Heschl's gyrus (Vonk et al., 2019) and primary auditory cortex (Baldo et al., 2006) in semantics and one study indicated both language domains may be represented in left Heschl's gyrus (Biesbroek et al., 2021). The right hemisphere primary auditory cortex was only implicated in phonology by one of our included studies (Rochon et al., 2010).

Thirteen studies in total found a relationship between phonology and the left superior temporal gyrus, three of which localized this relationship to the anterior portion (Baldo et al., 2006; Chouiter et al., 2016; Zhao et al., 2020) and six localized it posteriorly (Alyahya et al., 2018, 2020; Brambati et al., 2009; Halai et al., 2017; Woollams et al., 2018; Zhao et al., 2020), though these localizations were not always mutually exclusive. The remaining studies did not specify a subdivision (Boukrina et al., 2015; Froehlich et al., 2018; Henry et al., 2012; Riello et al., 2022; Rochon et al., 2010). Two of the same studies identifying a relationship between the left superior temporal gyrus and phonology also found a relationship between a different subdivision and semantics, though the studies found the opposite pattern. Whereas Brambati et al. (2009) implicated the anterior superior temporal gyrus in semantics, Baldo and colleagues (2006) implicated the posterior subdivisions in semantics instead. One additional study implicated the posterior

subdivision in semantics (Stark et al., 2019), while the remaining five studies did not specify the subdivision involved in semantics (Martins et al., 2014; Pereira et al., 2009; Schmidt et al., 2019; Shafto et al., 2012; Vonk et al., 2019). Six studies found overlap between semantics and phonology in the left superior temporal gyrus (Chouiter et al., 2016; Saykin et al., 1999; Vonk et al., 2019; Wilson et al., 2009), including one citing the anterior subdivision (Woollams et al., 2018) and one citing both anterior and posterior subdivisions (Biesbroek et al., 2021). The right superior temporal gyrus was much less often implicated in semantics (Rodríguez-Aranda et al., 2016), phonology (Froehlich et al., 2018; Rochon et al., 2010), or both (Martins et al., 2014; Wilson et al., 2009), with no references to subdivisions.

The left planum temporale was found to be related to phonology by eight studies (Alyahya et al., 2018, 2020; Boukrina et al., 2015; Butler et al., 2014; Halai et al., 2017; Schumacher et al., 2019; Woollams et al., 2018; Zhao et al., 2020), whereas only one implicated this region in both semantics and phonology (Biesbroek et al., 2021). The right planum temporale was not reported to be involved in semantics or phonology by any of the included studies.

Two parietal regions, the left supramarginal and angular gyri have accumulated a great deal of evidence in support of their role in phonology, especially the former. Thirteen studies implicated the left supramarginal gyrus in phonology (Baldo et al., 2006; Boukrina et al., 2015; Brambati et al., 2009; Halai et al., 2018; Henry et al., 2012; Zhao et al., 2018), including seven localizing this relationship to the posterior portion (Alyahya et al., 2018, 2020; Chouiter et al., 2016; Halai et al., 2017; Schumacher et al., 2019; Woollams et al.,

2018; Zhao et al., 2020). Notably, Alyahya et al. (2020) specified that both anterior and posterior left supramarginal gyrus were involved in phonology, though the anterior portion was only involved for their measure of phonological production. Four studies suggested the left supramarginal gyrus plays a role in both semantics and phonology (Baldo et al., 2006; Biesbroek et al., 2021; Chouiter et al., 2016; Martins et al., 2014), while only two suggested it has a role specific to semantics (Rodríguez-Aranda et al., 2016; Vonk et al., 2019). The pattern was less striking for the left angular gyrus, but still notable in that eight studies suggested a relationship with phonology (Alyahya et al., 2018, 2020; Baldo et al., 2006; Brambati et al., 2009; Froehlich et al., 2018; Schumacher et al., 2019; Zhao et al., 2018, 2020), while four each suggested a relationship with semantics (Baldo et al., 2006; Henry et al., 2012; Stark et al., 2019; Vonk et al., 2019) or both language domains (Baldo et al., 2006; Biesbroek et al., 2021; Chouiter et al., 2016; Martins et al., 2014). Importantly, some studies again reported involvement of the left supramarginal and angular gyri in multiple categories (e.g., phonology and both semantics and phonology), either suggesting or explicitly stating that discrete subdivisions of these regions were involved in distinct functions.

As for white matter tracts, the left arcuate fasciculus was implicated in phonology by eight studies (Alyahya et al., 2018, 2020; Butler et al., 2014; Halai et al., 2017; Woollams et al., 2018; Zhao et al., 2018, 2020). Surprisingly, not a single study implicated the left arcuate fasciculus in semantics or in both semantics and phonology. Moreover, no studies reported involvement of the right arcuate fasciculus in either language domain.

Brain Regions with Potential Semantic-Phonological Generality

The totality of evidence aggregated for this scoping review suggests that there is not sufficient evidence in older adults to categorize most brain regions reported as being involved exclusively in semantics or phonology. Those described above have the most compelling evidence for specialization, but the remaining brain regions show more mixed evidence. At the same time, no brain regions demonstrate a greater number of studies implicating generality than specificity for either semantics or phonology. However, we will highlight one cortical region – the left middle temporal gyrus – and four white matter association tracts – the left inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus, and internal capsule – that may play a role in both language domains.

The left middle temporal gyrus was implicated in semantics and phonology by a similar number of studies, twelve and eleven, respectively. Pertaining to semantics, four studies implicated the anterior middle temporal gyrus (Brambati et al., 2009; Butler et al., 2014; Halai et al., 2017, 2018), while another four implicated the posterior middle temporal gyrus (Biesbroek et al., 2021; Chouiter et al., 2016; Stark et al., 2019; Zhao et al., 2018) and the remaining four did not specify a subdivision (Henry et al., 2012; Pereira et al., 2009; Schmidt et al., 2019; Shafto et al., 2012). Regarding phonology, the distribution more heavily favored the posterior segment (Alyahya et al., 2018; Boukrina et al., 2015; Brambati et al., 2009; Halai et al., 2017; Schumacher et al., 2019; Sonty et al., 2003; Zhang et al., 2013; Zhao et al., 2020), though two studies implicated the anterior subdivision (Biesbroek et al., 2021; Chouiter et al., 2016) and another did not specify (Froehlich et al.,

2018). Five studies implicated the left middle temporal gyrus in both semantics and phonology (Biesbroek et al., 2021; Chouiter et al., 2016), including two that indicated both the anterior and posterior subdivision were involved (Alyahya et al., 2020; Woollams et al., 2018) and another indicating only the anterior segment (Zhao et al., 2020). Only one study implicated the right middle temporal gyrus in phonology (Froehlich et al., 2018).

Four studies reported involvement of the left inferior fronto-occipital fasciculus in both semantics and phonology (Biesbroek et al., 2021; Chang et al., 2020; Rodríguez-Aranda et al., 2016; Zhao et al., 2020), whereas five suggested it was uniquely involved in the former (Alyahya et al., 2020; Butler et al., 2014; Halai et al., 2017; Stark et al., 2019; Woollams et al., 2018) and one suggested it was uniquely involved in the latter (Boukrina et al., 2015). Two studies also implicated the right inferior fronto-occipital fasciculus in semantics (Chang et al., 2020; Rodríguez-Aranda et al., 2016). Although most studies reporting a relationship with the inferior fronto-occipital fasciculi indicated they were involved in semantics, there were still a number of studies indicating involvement in phonology or both language domains.

The pattern of semantic and phonological involvement for the left inferior longitudinal fasciculus was similar to the pattern for the left inferior fronto-occipital fasciculus. Again, four studies implicated this association tract in both language domains (Alyahya et al., 2020; Schumacher et al., 2019; Woollams et al., 2018; Zhao et al., 2020) and one suggested its unique involvement in phonology (Alyahya et al., 2018), whereas four reported its unique involvement in semantics (Butler et al., 2014; Halai et al., 2017; Stark et al., 2019; Zhao et al., 2018). Unlike the inferior fronto-occipital fasciculus, no

studies reported a relationship between the right hemisphere inferior longitudinal fasciculus and either language domain.

The superior longitudinal fasciculus was reported by three studies apiece to be involved in semantics (Chouiter et al., 2016; Rodríguez-Aranda et al., 2016; Stark et al., 2019), phonology (Boukrina et al., 2015; Rodríguez-Aranda et al., 2016; Woollams et al., 2018), and both domains (Biesbroek et al., 2021; Chouiter et al., 2016; Rodríguez-Aranda et al., 2016). However, it is worth noting that the study by Rodríguez-Aranda et al. (2016) reported its involvement in all three categories, based on separate analyses, and also implicated right superior longitudinal fasciculus in all three categories. The study by Chouiter et al. (2016) reported the left superior longitudinal fasciculus was involved in both semantics and phonology, but in semantics to a greater extent when formally contrasted with phonology.

Finally, the left internal capsule was also reported by three studies apiece to be involved in semantics (Chang et al., 2020; Chouiter et al., 2016; Rodríguez-Aranda et al., 2016), phonology (Rodríguez-Aranda et al., 2016; Woollams et al., 2018; Zhao et al., 2020), and both language domains (Biesbroek et al., 2021; Chouiter et al., 2016; Rodríguez-Aranda et al., 2016). As above with the superior longitudinal fasciculus, the study by Chouiter et al. (2016) reported the left internal capsule was involved in both semantics and phonology, but in semantics to a greater extent when formally contrasted and Rodríguez-Aranda et al. (2016) reported involvement of the left and right internal capsule in all three categories based on separate analyses. Chang et al. (2020) also implicated the right internal capsule in semantics.

In reporting the results of the scoping review, it is important to note that one study (Wilson et al., 2010) reported no significant findings connecting any brain regions with semantics, phonology, or both language domains. As a result, this study is not otherwise listed in the results above. Additionally, the study by Clark et al. (2014) included large ROIs with many brain regions (e.g., the inferior parietal/superior temporal ROI included the superior temporal gyrus, the transverse temporal region, inferior parietal lobule, and the supramarginal gyrus). Because gray matter volumes were not localized to specific regions within these large ROIs, it was impossible to know which of the regions included in our classification scheme (Table 2.3) were or were not activated within the ROIs. Therefore, we left these large, multi-region ROIs out of our results. However, we did not exclude the study because one of their ROIs consisted of the inferior frontal gyrus, including pars opercularis, triangularis, and orbitalis. Considering several other studies reported relationships between semantics or phonology and the inferior frontal gyrus without specifying a subregion (i.e., pars opercularis, triangularis, and orbitalis), we classified these results by Clark et al. (2014) in the same way, as *inferior frontal gyrus (unspecified)*.

Older and Younger Adult Comparisons

Six of the studies in our scoping review (Froehlich et al., 2018; Martins et al., 2014; Meinzer et al., 2012; Rizio et al., 2017; Shafto et al., 2012; Zhuang et al., 2016) included and directly compared older and younger participants. Only the results from the older participants (in some cases, after contrasting with younger participants) were included in

our aggregate results above, given the focus of the scoping review. Therefore, here we describe the results of younger participants from these six studies, in comparison with their older counterparts. Among these six studies it was common for older adults to demonstrate positive activity that exceeded younger adults for some of the targeted tasks, in a variety of brain regions (Froehlich et al., 2018; Martins et al., 2014; Meinzer et al., 2012; Rizio et al., 2017). It was rarer for younger adults to have positive activity exceeding that of older adults, and this occurred when the comparison between younger and older adults consisted of contrasts reflective of greater demands (e.g., hard over easy; Shafto et al., 2012), rather than when comparing activity during a single task condition.

In the studies by Froehlich et al. (2018) and Meinzer et al. (2012), younger adults had no significant activity remaining when contrasted with that of older adults. Similarly, Rizio and colleagues (2017) found no significant activity in younger adults contrasted with older adults for their semantic condition (when contrasted with either their unrelated or phonological conditions). However, when the phonological was contrasted with the unrelated condition, they did find greater activity in right postcentral gyrus, right supramarginal gyrus, and bilateral middle temporal gyrus in younger adults. When the phonological was contrasted with the semantic condition, they found greater activity in bilateral central opercular cortex, right insula, left putamen, bilateral precentral gyrus, bilateral postcentral gyrus, right supramarginal gyrus, right lingual gyrus, bilateral precuneus, and bilateral cuneus in the younger group. The opposite pattern was shown by Martins et al. (2014). When contrasting either of their two phonological conditions (rhyme and onset) with their semantic conditions, Martins and colleagues (2014) found that

younger adults had no remaining significant positive activity above and beyond that of older adults. However, when they contrasted their semantic condition with their onset condition, they found greater activity for younger adults in occipital cortex (Brodmann areas (BA) 17 and 18) and when contrasting their semantic condition with their rhyme condition, they found greater activity for younger adults in ventrolateral prefrontal cortex (area 47/12), posterior cingulate cortex (BA 23), inferior temporal cortex (BA 20), inferior parietal cortex (BA 40), precuneus (BA 7), and occipital cortex (BA 17).

In Shafto et al., (2012), older adults had increased activity for low (compared to high) imageability words in the left middle/superior temporal gyrus. That said, a direct contrast did not reveal any regions with a stronger effect of imageability in older than younger adults, even though younger adults did not demonstrate any regions with a significant main effect of imageability. On the other hand, the younger group did demonstrate an effect of phonological cohort competition in the left inferior frontal gyrus, with greater activity when competition was higher. This effect was greater than the older adults, who demonstrated no main effects of cohort competition. Younger adults also demonstrated a greater effect of imageability for high compared with low competition words in the left inferior frontal gyrus, bilateral cerebellum, and left supplementary motor area. Comparatively, older adults' imageability effect did not differ based on cohort competition.

Finally, Zhuang et al. (2016) found no significant age differences on their rhyme task, but did find differences in their semantic task. The semantic task elicited significantly greater activation in older than younger adults in the left inferior frontal gyrus (BA 44, 45,

and 47), extending into the rolandic operculum, insula, and superior temporal pole (BA 38), the left fusiform gyrus, left parahippocampus (BA 37), and bilateral posterior cingulate (BA 23), extending into the right precuneus and hippocampus. However, a significant positive correlation between left inferior frontal gyrus activity and performance on the semantic task was actually driven by the younger group. The authors suggest that the lack of a significant correlation among the older adults may reflect limited power of their sample size (n = 20) or increased variability of behavior and brain activity in older adults, concluding that their results still support the notion of age-related preservation and enhancement of semantic abilities.

Discussion

The first purpose of our scoping review was to explore the extent to which the semantic and phonological networks in older adults appear to be distinct or overlapping. The results of our scoping review suggest that there is overlap within the semantic and phonological brain networks of older adults, but that there is also specialization. We identified a number of regions that may be specialized for semantics or phonology based on a relatively greater number of studies implicating a relationship with one or the other.

Semantic Specialization

A relatively larger number of studies implicated several left hemisphere regions in semantics, including the orbitofrontal cortex, temporal pole, inferior temporal gyrus, fusiform gyrus, precuneus, lateral occipital cortex, parahippocampal gyrus, and thalamus.

All of these regions have been repeatedly implicated in semantics. For example, several appear in the hub-and-spoke model of controlled semantic cognition proposed by Lambon Ralph et al. (2017). The anterior temporal lobe, which encompasses the temporal pole, as well as the anterior superior, middle, and inferior temporal gyri, serves as the multi-modal hub in this model. This region is often atrophied in those with semantic dementia, or the semantic variant of PPA (Hodges & Patterson, 2007; Lambon Ralph & Patterson, 2008), causing a multi-modal impairment of semantic knowledge. The anterior temporal lobe is also connected to the orbitofrontal cortex and pars orbitalis by the uncinate fasciculus (Lambon Ralph et al., 2017). This association tract has been implicated as part of the ventral pathway (Friederici & Gierhan, 2013) that maps sound onto meaning according to the dual-stream model put forth by Hickok & Poeppel (2004, 2007).

The right middle frontal gyrus was also implicated in semantics, which is more unusual. However, this was the right hemisphere region identified by our scoping review to have the most support for a role in language. Based on the HAROLD hypothesis (Cabeza, 2001, 2002), we anticipated that the right hemisphere may be more involved in the language networks of our older adults than in younger adults (Hodgson et al., 2021). Notably, the role of the right middle frontal gyrus was also implicated in a picture naming task for older adults by Berlingeri et al. (2013), who were explicitly testing the HAROLD hypothesis.

Phonological Specialization

Left primary auditory cortex and Heschl's gyrus were implicated in phonology based on the studies included in our review. A recent voxel-based lesion-symptom-mapping study (VLSM) found that damage to Heschl's gyrus was associated with impairments in repetition and phonological abilities in spontaneous speech, but not in impairments of articulation and prosody (Ripamonti et al., 2018). Likewise, a larger number of studies implicated the superior temporal and supramarginal gyri in phonology than in semantics or both domains. The supramarginal gyrus was highlighted for its involvement in phonology in a meta-analysis of parietal cortex functionality (Humphreys & Lambon Ralph, 2015) and the posterior superior temporal gyrus has been shown to selectively respond to lexical phonological processes (Graves et al., 2008).

The arcuate fasciculus has been studied in relation to language since the 19th century, when pioneers of neuropsychology such as Paul Broca, Karl Wernicke, and the lesser known Constantin Von Monakow developed models of the language network in the brain (Catani & Mesulam, 2008). The more recent neurocognitive model of language put forth by Hickok & Poeppel (2004, 2007) includes a dorsal stream that maps sound onto articulatory-based representations, essential for phonological processing. The arcuate fasciculus has repeatedly been implicated in this dorsal stream (Friederici & Gierhan, 2013; Saur et al., 2008).

Semantic and Phonological Generality

Although there were no regions with a comparatively prominent number of studies indicating involvement in both domains than in either semantics or phonology alone, it was

also common for at least a couple of studies to suggest a region was involved in both domains. In other words, it was rare among the included studies to identify a relationship in only the semantic or phonological category (i.e., a "0" in the "both" column and in either the semantic or phonological column of Table 2.3). When this did happen, there were often only one or two studies indicating a relationship with the identified domain, suggesting a paucity of evidence overall.

A relatively equal number of studies implicated the middle temporal gyrus in semantics and phonology, while several also implicated this region in both domains. It is possible that regions such as the middle temporal gyrus, which are large, may have subdivisions functionally organized for semantics and phonology. Not all of the included studies specified whether the anterior or posterior portion of a region was involved. Among the studies that did provide this information, it appeared that the posterior segment may be specialized for phonology, which would align with the results of a recent cortico-cortical evoked potentials study (Nakae et al., 2020), but a definitive pattern did not emerge.

Most of the white matter tracts that appear to be involved in both language domains in the present scoping review have been found to be specialized for either semantics or phonology in previous work. For example, the superior longitudinal fasciculus has been implicated in the dorsal tract (Friederici & Gierhan, 2013; Saur et al., 2008) of the dual stream model (Hickok & Poeppel, 2004, 2007), which is involved in mapping sound to articulatory representations – an important process in phonological decoding. Similarly, the inferior fronto-occipital fasciculus (Friederici & Gierhan, 2013) and inferior longitudinal fasciculus (Saur et al., 2008) have both been implicated as neural correlates of

the ventral stream (Hickok & Poeppel, 2004, 2007). However, the internal capsule has less often been implicated in language and is not typically included in the neural correlates of the dual stream model.

The Nature of the Evidence

The second purpose of the present scoping review was to explore the nature of the evidence examining semantic and phonological brain networks in older adults. Importantly, we narrowed our search to studies utilizing MRI or cortical stimulation (i.e., during awake surgery) methodologies, thus eliminating studies utilizing EEG, PET, or other potentially informative techniques. There were relatively fewer cortical stimulation studies included in our search results and none met eligibility criteria after screening, typically due to a lack of clarity in the description of the behavioral tasks or a lack of statistical analysis. Within the MRI literature that met inclusion criteria, we found a variety of methodologies used, including primarily lesion-symptom-mapping studies in post-stroke aphasia, gray matter volume mapping for PPA, and task-based fMRI in neurologically intact older adults. Among these, there was further variability in the analyses used, which dictate the extent to which we can draw conclusions related to the degree of distinction and overlap between the semantic and phonological networks. Some studies specifically completed conjunction or subtraction analyses that provide more specific information respectively addressing which brain regions are involved in both semantic and phonological tasks and which regions are involved in one task more than the other.

Comparison with Younger Adults

Our third purpose was to compare our findings with the results of a meta-analysis examining the semantic and phonological networks of neurologically intact younger adults (Hodgson et al., 2021). Compared with the networks of younger adults, our review of the literature including older adults largely demonstrates a similar pattern in their semantic and phonological networks. We found a larger number of studies implicating the left orbitofrontal cortex, temporal pole, inferior temporal gyrus, fusiform gyrus, precuneus, lateral occipital cortex, parahippocampus, and thalamus in semantics than in phonology or both domains. In younger adults, Hodgson et al. (2021) similarly found support for pars orbitalis (in close proximity to orbitofrontal cortex), the anterior temporal lobe (including the temporal pole), fusiform gyrus, inferior temporal lobe, and parahippocampal cortex playing a unique role in semantics.

The results of Hodgson et al. (2021) did not support a unique role for the left precuneus, lateral occipital cortex, or the thalamus in semantics, but did additionally identify left ventral angular gyrus, dorsal posterior middle temporal gyrus, and superior frontal gyrus. While these differences may be the product of age-related changes in the brain, there are other potential explanations. For example, it is possible that we did not capture some of the additional regions they identified due to a number of our included studies not describing the location of activation, lesion, etc. within a region (e.g., *ventral* angular gyrus, *dorsal posterior* middle temporal gyrus). As for the left precuneus, lateral

occipital cortex, and thalamus identified by our study, these regions may not survive a direct contrast with regions involved in phonology.

We also found a larger number of studies implicating left primary auditory cortex, Heschl's gyrus, superior temporal gyrus, and supramarginal gyrus in phonology than in semantics or both domains. Hodgson et al. (2021) similarly identified left posterior superior temporal gyrus and supramarginal gyrus (extending into part of the angular gyrus) as uniquely contributing to phonology. As identified in Hodgson et al. (2021), the posterior superior temporal gyrus may include primary auditory cortex and Heschl's gyrus. However, the authors also identified left precentral gyrus, pars opercularis of the inferior frontal gyrus, and precuneus as phonological regions. Perhaps these regions become less specialized for phonology as a result of aging and are later recruited for semantic tasks as well. This idea would be supported by the number of studies in our review that implicated the precentral gyrus, pars opercularis, and precuneus in either semantics or both domains.

One difference that we anticipated was a potentially larger number of right hemisphere regions being involved in semantics, phonology, or both, based on accounts of de-lateralization in the prefrontal cortex and language network that accompanies aging (Berlingeri et al., 2013; Cabeza, 2001, 2002). We did not see prominent involvement of the right hemisphere in older adults; however, one right hemisphere region was identified by our review: the right middle frontal gyrus, implicated in semantics. When contrasting the results of their full semantic and phonological analyses, Hodgson et al. (2021) did not identify any right hemisphere regions uniquely contributing to either language domain. On the other hand, they did identify the right dorsomedial prefrontal cortex as involved in

semantics using a limited data set and identified two more right hemisphere regions in their semantic activation likelihood analysis with the full data set: right superior/middle temporal gyrus and right inferior frontal gyrus/insula. The right middle frontal gyrus was not specifically identified by any of these analyses as being involved in semantics or phonology, suggesting a non-linguistic role in younger adults. Its involvement in semantics for older adults may provide evidence that recruitment of domain-general cognitive regions alters the structure of the semantic network as a result of aging. Whether the involvement of the right middle frontal gyrus is maladaptive (Meinzer et al., 2012) – a failed attempt at overcoming the age-related changes in the semantic network – or compensatory (Berlingeri et al., 2013; Reuter-Lorenz & Cappell, 2008; Vergallito et al., 2018) – a successful adaptation that approximates the younger semantic network – remains unclear.

Hodgson and colleagues (2021) do not specifically discuss the language domain-general regions they identified through their analyses (i.e., active for both semantics and phonology), but their figure demonstrates overlap at the left superior frontal, inferior frontal, superior to middle temporal, inferior temporal, and supramarginal gyri, as well as the right inferior frontal and superior temporal gyri. Our review only identified the left middle temporal gyrus with potentially convincing evidence of its involvement in both domains, although we also described the possibility of functionally distinct subdivisions. This may suggest increasing specialization of the semantic and phonological networks with age, but more likely demonstrates an insufficient number of studies to identify such overlap, especially in the context of studies that explicitly contrasted the two domains and may not have performed a conjunction analysis to explore their common correlates.

Although Hodgson and colleagues' study (2021) did not address white matter association tracts involved in semantics and phonology, evidence suggests it is unclear whether our results are related to age. Many studies examining the white matter association tracts involved in speech and language processes are patient studies with clinical samples (Friederici & Gierhan, 2013). Studies supporting involvement of the inferior fronto-occipital fasciculus in the ventral route (i.e., mapping sound to meaning), come from patient populations consisting of both older (mean age: 57.5 years; Rolheiser et al., 2011) and younger (mean ages: 33 and 38 years; Duffau et al., 2005, 2009) adults. Likewise, involvement of the inferior longitudinal fasciculus is supported by a study with a younger neurologically intact sample (mean age: 34 years; Saur et al., 2008). Involvement of the uncinate fasciculus in the ventral route was questioned by a study with a younger patient sample (mean age: 38 years; Duffau et al., 2009) that reported it was likely a redundant or compensatory pathway for semantics, but supported by a study with an older post-stroke aphasia sample, (mean age: 63; Harvey et al., 2013).

Regarding the dorsal route (i.e., mapping sound to articulatory representations), both the arcuate and superior longitudinal fasciculi were supported by Saur et al. (2008) as being involved in speech repetition in their younger sample. Damage to both tracts was also related to repetition deficits in an older post-stroke sample (mean age: 58 years; (Breier et al., 2008). Troutman and Diaz (2020) found main effects for diffusion metrics (fractional anisotropy and radial diffusivity) in dorsal tracts (arcuate and superior longitudinal fasciculi) on a picture-word interference task with phonological distractors, but also found main effects for radial diffusivity in ventral tracts (middle and inferior longitudinal

fasciculus), and the fronto-striatal comparison tract. These effects were no longer significant when covarying for age, but they did not find any significant interaction effects between age and white matter. Taken together, these findings complicate the question of whether the potential language domain-general role for the superior and inferior longitudinal fasciculi and inferior fronto-occipital fasciculus in our scoping review is due to age-related differences. To these authors' knowledge, a recent comprehensive review of white matter tractography studies examining pathways involved in semantics and/or phonology focusing on either younger or older adults has not been published. This could be an appropriate next step and complement to the present work, though it may be more beneficial further in the future after more empirical studies have been conducted.

Future Directions

Finally, our fourth purpose was to determine the potential value of a subsequent systematic review to address the topic of semantic and phonological network specialization. Our scoping review demonstrates that there is a large accumulation of evidence addressing the semantic and phonological neural correlates in older adults, which could be used to conduct a meta-analysis or full systematic review. Such a project would provide a compelling complement to existing work addressing this topic in the healthy, younger adult population (Hodgson et al., 2021). Moreover, a meta-analysis or full systematic review would yield stronger, more reliable conclusions related to the topic than what we were able to aggregate in the present scoping review. However, given the variety of methods, tasks, and populations (e.g., post-stroke aphasia, PPA, MCI, neurologically

intact) included in this literature, it will be important to establish eligibility criteria to reduce confounds and maximize the interpretability of the results.

The activation likelihood estimation meta-analyses conducted by Hodgson et al. (2021) did not include participants from clinical populations, only neurologically intact younger adults. Based on the results of our review, 21 of our included studies included a neurologically intact sample (either as the primary sample or a control for a clinical sample). However, only 11 of these included task-based fMRI activation methods, which may not be sufficient to conduct a meta-analysis. As a result, it may be worth adding studies targeting only semantics or phonology in a meta-analysis. In the present review, we excluded such studies in favor of those that examined both domains in the same sample. However, the meta-analyses conducted by Hodgson et al. (2021) did include activation studies that only examined one domain or the other. Therefore, this could be an option to increase the sample size in a meta-analysis specifically targeting older adults. Additionally, Hodgson et al. (2021) included PET studies, which is another option to improve the robustness of a potential meta-analysis.

Finally, it was outside the scope of the present review to statistically analyze the relationship between regions implicated in semantics and phonology, such as with formal contrasts, but a future meta-analysis or full systematic review could fill this gap. Although a given region may be involved in both semantics and phonology, it may have a stronger role in or preference for one language domain over the other. In the present scoping review, we speculated as to the preference of certain regions for one domain over the other based on the number of studies that identified a relationship between each region and language

domain. However, using this method, it was not possible to discern any potential statistical differences between a region's involvement in each domain. A meta-analysis could provide further information related to regional involvement in and preference for semantics or phonology through conducting formal contrasts as in Hodgson et al. (2021).

Limitations

The present scoping review was limited by several factors. First among them is the issue of repeated participants. There were overlapping groups of participants in some study samples that were explicitly reported (e.g., Butler et al., 2014; Halai et al., 2017). Additional participant samples likely overlapped in other studies that did not explicitly report it due to work being conducted within the same laboratories or recruiting from the same area. Therefore, results from these studies may have effectively weighted the results of our scoping review in favor of findings that may be unique to the overlapping sample of participants included, rather than reflecting generalizable trends in the broader population.

Additional limitations of our scoping review primarily concern the different methodologies used by the included studies. For example, a main objective of our scoping review was to determine the extent to which semantic and phonological networks in older adults are distinct or overlapping. Yet, not all studies formally contrasted semantic and phonological tasks, in order to statistically determine areas uniquely contributing to each function. Moreover, not all studies used methods to combine semantic and phonological outcomes (e.g., conjunction analysis) to determine areas contributing to both functions.

The presence of lesions in studies with post-stroke participants also contributed to methodological differences. For one, lesion size was inconsistently controlled for across the included studies. However, Alyahya et al. (2018) report different findings for regions associated with their semantic factor before and after controlling for lesion size, suggesting that this inconsistency may have contributed to differences in outcomes across studies. Another concern related to lesion studies is that these studies were limited in their ability to demonstrate hemispheric differences in older adults. Researchers that conducted lesion-symptom-mapping on patients with damage isolated to the left hemisphere (e.g., due to stroke) could only reveal left hemisphere brain regions associated with semantic and phonological skills. Out of 38 studies included in the review, 16 reported lesion-behavior relationships based on participant samples and 10 of these included participants with lesions only in the left hemisphere. Of the remaining six studies, four did not explicitly exclude participants with right hemisphere lesions, but the presence of aphasia was an inclusion requirement, effectively limiting their sample to primarily participants with left hemisphere lesions (Halai et al., 2017, 2018; Woollams et al., 2018; Zhao et al., 2018). The other two studies report including participants with both left and right hemisphere lesions (Biesbroek et al., 2021; Chouiter et al., 2016). Studies including lesion-symptom mapping on the left hemisphere alone were included in the review because we felt they could provide important insight as to the shared or specialized nature of the semantic and phonological networks in older adults, as well as the nature of the left hemisphere's changing role in language as a result of aging. However, the absence of right hemisphere involvement in these studies remains a limitation.

A broader limitation relates to the general inclusion of studies with clinical populations in this review, as opposed to analyzing only studies conducted on neurologically intact older adults. Our goal is to better understand the semantic and phonological networks in non-brain-injured older adults as a foundation for research examining the neural correlates of aphasia and its recovery. Given that part of the purpose of the scoping review was to gauge the nature of the evidence and the types of research studies that could begin to answer our questions, we chose to include samples of participants with neurological damage (e.g., post-stroke aphasia, Alzheimer's dementia). We excluded studies examining fMRI activations in clinical populations to prevent the influence of their lesion, atrophy, reorganization, and/or recovery from impacting our exploration of intact semantic and phonological networks in older adults. However, including studies with clinical populations is not without problems. Most studies examining language in clinical populations cannot take into account any recovery that may have taken place when considering the relationship between the affected site (e.g., stroke lesion or location of reduced gray matter density in PPA) and behavior, unless they collected and included data from the acute phase or onset in their analysis, which is often not the case. Particularly in participants with chronic post-stroke aphasia, reorganization and recovery during the time since their stroke may have led to improvements in behavioral performance. Therefore, a damaged region may not appear to be as associated with a given function if the behavioral performance is not as severely impaired as it was shortly after the cerebrovascular accident.

There were additional limitations regarding our question of differences between the language networks of older and younger adults. Many studies included in the present review only examined older adults. We included these studies to address our question related to the degree of overlap and distinction between semantic and phonological brain networks in older adults. However, some studies explicitly contrasted older and younger participant brain activations, allowing for a direct comparison of brain regions involved in particular tasks, as discussed above. Moreover, we compared our overall findings with the results of Hodgson et al. (2021) in younger adults. Studies directly comparing older and younger participants provided unique insights and methodological considerations.

Some studies explicitly comparing older and younger adults' brain activity related this differential activity in older adults with their behavioral performance (Meinzer et al., 2012). In such cases, it is helpful in determining whether differential activity is perhaps a maladaptive part of the aging process or compensatory in nature. For example, Meinzer et al. (2012) found that activity in some areas was negatively correlated with accuracy on their in-scanner semantic task (i.e., postcentral gyrus/precuneus BA 3/7; medial/middle frontal gyrus, BA 6 and 9; middle/inferior frontal gyrus, BA 11), suggesting maladaptation. Similarly, Riello and colleagues (2022) found that greater superior temporal gyrus volumes were associated with poorer letter fluency performance. However, many studies did not report such analyses exploring the relationship between brain activation and behavioral accuracy. As a result, it is not possible to disentangle which components of the semantic and phonological networks of older adults may facilitate linguistic abilities and which may contribute to their decline. Moreover, the study by Meinzer and colleagues (2012) also

reported differential negative activity in older adults (compared with the younger group) and its relationship to behavioral performance, which not all studies explored. They found that *more negative* activity in postcentral/inferior parietal gyrus (BA 3/40) and the precuneus/cingulate gyrus (BA 7/31) was related to *better* performance on the in-scanner semantic task.

Finally, we consider the types of behavioral tasks used in the included studies. Many of the included studies utilized verbal fluency tasks, which are commonly recognized to require not only semantic or phonological linguistic ability but other cognitive elements, such as executive functioning, attention, initiation, and processing speed (Parmera et al., 2021). Moreover, semantic processing is involved in both semantic and phonemic fluency tasks, due to the use of real words with meaning and the organization of word-retrieval processes in which semantically-related items are more likely to be activated (Schwartz et al., 2003). The same could be said for phonology influencing both tasks, given that phonological encoding is necessary to produce a given target word. Therefore, regions commonly activated by these two tasks may not reflect an overlap in semantic and phonological processing so much as an overlap in common executive processes or the common semantic or phonological requirements of the task.

Other task concerns include the use of data reduction methods (e.g., principal components analysis) to isolate semantic and phonological processes (e.g., Halai et al., 2017, 2018). Although these methods do successfully produce participant scores related to their performance on all tasks loading onto a given component, the resulting components are limited by the assessments entered into the analysis. If these assessments are not

balanced in terms of task demands outside of semantics and phonology (e.g., working memory, attention, inhibition), the resulting factors may be imbalanced as well (e.g., a phonological component may also reflect working memory ability, while a semantic component may also reflect inhibition). However, there are also inherent limitations in creating completely balanced tasks used to isolate semantic and phonological abilities.

Task difficulty also impacts performance and activation. Tasks that do not sufficiently challenge a participant may not yield expected activations, for example in the right hemisphere of older adults (Zhuang et al., 2016). Alternatively, tasks that are too challenging may also preclude expected activations. One solution to this problem of task difficulty is to use adaptive paradigms, such as those developed by Wilson et al. (2017, 2018, 2019; Yen et al., 2019). These studies were not included in the present scoping review due to the fact that the semantic and phonological tasks were not conducted within the same sample of participants, but the paradigms provide promise for improving out understanding of the degree of specialization and overlap within the semantic and phonological systems.

Conclusion

The present scoping review explored the semantic and phonological networks in the brains of older adults, the degree to which they were unique versus overlapping, and how they compared to the same networks in younger adults. We found evidence to support some brain regions being specialized for semantics or phonology, despite many brain regions likely subserving both domains. We also found evidence for subtle differences in

the networks of older compared with younger adults. Our findings should be verified in future studies, such as a full systematic review or meta-analysis addressing the topic. We discuss considerations related to optimizing the robustness and interpretability of such an endeavor; for example, whether to include clinical populations and studies that investigated only semantics or phonology.

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Chapter 3: Manuscript 2

The Resting-State Functional Connectivity of the Inferior Frontal Gyrus in Older Adults and its Application to a Post-stroke Aphasia Case Series

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Abstract

The subregions of the left inferior frontal gyrus are suspected of having distinct functional specializations. For example, the anterior-most subregion, pars orbitalis, is thought to be involved in semantics, and the posterior-most subregion, pars opercularis, is thought to be involved in phonology. Studies have also found distinct patterns of functional connectivity for each of the subregions in young, neurologically intact adults. The first part of the present study explores patterns of functional connectivity among pars orbitalis, triangularis, and opercularis of the left and right inferior frontal gyri in a group of neurologically intact older adults. We next correlated the resting-state functional connectivity between seeds and significant clusters with scores on tasks targeting semantics and phonology to gauge the functional specialization of these subregions. In the second part of the present study, we examined patterns of resting-state functional connectivity, between regions identified via the correlation analysis, in the right hemisphere of participants with chronic post-stroke aphasia and report our findings as a case series. We hypothesized that the functional connectivity of our older adults would be similar to that of the younger adults previously reported, but expected to find more robust connectivity with and within the right hemisphere, due to theories of age-related hemispheric de-lateralization for cognitive functioning, including language. We expected participants with aphasia who had large lesions to pars opercularis and better phonological skills to have greater functional connectivity between regions correlated with phonological test scores in our neurologically intact sample. Likewise, we expected participants with large lesions to pars orbitalis and better semantic skills to have greater functional connectivity between

regions correlated with semantic test scores in the neurologically intact sample. The results of the first part of the study were largely consistent with our hypotheses in that the right pars triangularis and orbitalis in our older participants had relatively more widespread patterns of connectivity than the younger adults in previous work. We identified four pairs of regions that had significant correlations with semantic (i.e., pars opercularis and supramarginal gyrus; pars orbitalis and middle temporal gyrus; and pars orbitalis and middle frontal gyrus) and phonological tasks (i.e., pars triangularis and middle frontal gyrus; and pars orbitalis and middle temporal gyrus) and were also significantly functionally connected in the right hemisphere. (Note that one pair of regions correlated with both a semantic and phonological task.) Patterns of resting-state functional connectivity between these regions, left hemisphere lesion load, and behavior are discussed for each participant with aphasia.

Introduction

Researchers have long sought to map functional specialization for cognitive abilities, including language, onto discrete brain regions. Understanding the functional organization of the brain is especially important in clinical scenarios, such as avoiding eloquent areas during neurosurgery or targeting specific regions with technologies like non-invasive or deep-brain stimulation. One anatomical region whose functional specialization has been frequently investigated and often debated is the left hemisphere inferior frontal gyrus (LIFG), which contains Broca's area. The present study examines the resting-state functional connectivity of the LIFG in neurologically intact older adults, as well as its relationship with behavioral performance on semantic and phonological tasks in an effort to better understand the cortical networks serving language. Additionally, we explore the resting-state functional connectivity between regions identified in our neurologically intact sample in individuals with chronic post-stroke aphasia. We relate the connectivity in our participants with aphasia to descriptions of their behavioral task performance and lesion load to the subregions of the LIFG. The goal of this study is to establish hypotheses regarding functional reorganization that can be used in future studies exploring reorganization and effects of treatment (e.g., non-invasive brain stimulation) in the post-stroke aphasia population.

The left inferior frontal gyrus

Numerous studies have reported a distinction between the activity of the subregions of the LIFG using a variety of research methods, including task-based fMRI and inhibitory

neuromodulation, such that the anterior portion (aLIFG), including pars orbitalis, is associated with semantics and the posterior portion (pLIFG), including pars opercularis, is associated with phonology (Bokde et al., 2001; Burton et al., 2003; Cannestra et al., 2000; Devlin et al., 2003; Fiez, 1997; Gough et al., 2005; Hartwigsen et al., 2017; Lorca-Puls et al., 2017; Poldrack et al., 1999; Sakreida et al., 2019). Other studies have further supported this characterization by demonstrating unique patterns of structural and functional connectivity, showing that the aLIFG is more connected with regions thought to be involved in semantics, whereas the pLIFG is more connected with regions thought to be involved in phonology (Battistella et al., 2019; Nakae et al., 2020; Xiang et al., 2010). Pars triangularis, in the center of the LIFG, may contribute to both phonology and semantics, as well as lexical retrieval and syntax, more broadly (Heim et al., 2008; Heim, Eickhoff, & Amunts, 2009).

However, the view of the LIFG as representing a functional gradient from semantics at the anterior end to phonology at the posterior end is not without objection (Gold et al., 2005; Gold & Buckner, 2002; Heim, Eickhoff, Friederici, et al., 2009). For example, Gold and Buckner (2002) found that anterior LIFG (pars orbitalis and triangularis) was significantly activated during a pseudoword phonological decision task and that this activation was significantly greater than in their phonological decision task with word stimuli. Although, the authors also noted that the anterior LIFG demonstrated greater activation for the semantic task than either phonological task. Similarly, the posterior LIFG (pars opercularis) responded significantly for both semantic and phonological decision tasks, but to the phonological version with pseudowords to a greater

extent (Gold & Buckner, 2002). In another study, Gold and colleagues (Gold et al., 2005) found similar results and advocated for a domain-preferentiality model rather than a domain-specific one, suggesting that the LIFG is globally responsive to both semantic and phonological processing tasks, but that the anterior and posterior portions are more strongly activated by semantics and phonology, respectively.

Likewise, Heim, Eickhoff, Friederici, et al. (2009) argue that Brodmann Area 44 (BA 44; corresponding to pars opercularis) responds similarly to semantic, syntactic, and phonological demands. Their study revealed a positive effect for semantic and syntactic priming in posterior LIFG via greater activity during a naming task on heterogenous blocks of trials with greater task demands than homogenous blocks that primed selection of the correct category (semantics) or gender (syntax). On the other hand, they found a negative effect for phonological priming, such that the posterior LIFG demonstrated greater activity during naming of homogenous blocks, where all words started with the same initial phoneme, than heterogenous blocks where all words started with different initial phonemes. The authors propose that because homogenous phonological trials (where words began with the same initial phoneme) may have created greater competition, the posterior LIFG may have been more active to accommodate these greater task demands, complementing its greater activation to the greater demands of the heterogeneous semantic and syntactic trials. However, participants responded with faster latencies to the heterogeneous trials across all three conditions (semantics, syntax, and phonology), complicating their results and suggesting that the increased activity during the heterogeneous semantic and syntactic blocks may not represent heightened difficulty.

Uddén and Bahlmann (2012) suggested that the LIFG follows a rostro-caudal abstraction gradient during cognitive control processes that organizes the broader lateral pre-frontal cortex. Cognitive control refers to the ability to flexibly adapt behavior to achieve a given intention (Miller & Cohen, 2001) and it contributes to many cognitive activities, including language. The hypothesis by Uddén and Bahlmann (2012) is consistent with evidence of greater semantic involvement at aLIFG, due to semantics being a more abstract and generalizable aspect of language, and greater phonological involvement at pLIFG, due to phonology being more concrete and specific to language. However, this suggested distribution of language-specific and domain-general functions is in direct contrast with other findings.

While Snyder et al. (2007) did find greater activation for their nonword phonological condition (contrasted with semantic-specific activation) in the rear-most segment of pars opercularis, this effect was only marginally significant and was not present in the rest of pars opercularis. Due to its pattern of activations, the authors suggest that the pLIFG is involved in cognitive control generally, not specific to phonology, and that other studies have found phonology-specific preferences in this region due to task conditions. For example, including unfamiliar nonwords that are phonologically similar to real words may elicit activation related to novelty and the semantics of phonological neighbors (e.g., "gat" may trigger semantics related to "cat"). Similarly, Wagner et al. (2000) found that the pLIFG demonstrated across-task priming effects, unlike the aLIFG, which demonstrated only semantic-specific priming effects. Although, phonology was not addressed in this study, only semantic decisions (i.e., abstract vs. concrete) and non-

semantic decisions (i.e., uppercase vs. lowercase). The findings by Snyder et al. (2007) and Wagner et al. (2000) are supported by a recent study implicating that domain-specific cognitive control regions exist for semantics, including the aLIFG, but that regions involved in controlling phonological processes, such as pLIFG, may have a more domain-general role in cognitive control (Hodgson et al., 2021).

Importantly, the majority of studies addressing the topic of LIFG functional specialization, including those described above, include neurologically intact young adult participants. Further work may reveal greater clarity in the role of the LIFG in this population, but evidence is also needed to address the functionality of the LIFG in older adults since it has been suggested that cognitive and language networks may change as a result of aging (Berlingeri et al., 2013; Cabeza, 2001, 2002). This is of particular importance to developing theories of neural reorganization following stroke, which most often affects older adults. A better understanding of post-stroke reorganization and recovery can lead to advances in diagnosis and treatment. For example, theories of reorganization may inform target site selection in treatments utilizing both inhibitory and excitatory non-invasive brain stimulation.

Reorganization during recovery

Less than a quarter of individuals with aphasia make a full recovery by 18 months post-stroke (Laska et al., 2001). Most frequently, aphasia, which results from damage to the brain's language network, is treated with behavioral speech therapy by a speech-language pathologist. However, even the most effective behavioral treatments have

limitations. Recent studies have investigated non-invasive brain stimulation as an adjuvant to speech therapy to improve recovery (Fridriksson et al., 2018; Saxena & Hillis, 2017; for a review, see Crosson et al., 2019). Non-invasive brain stimulation involves applying a device to the scalp to modulate cortical excitability. To do so, repetitive transcranial magnetic stimulation, one variety of non-invasive brain stimulation, emits pulses that create a shifting magnetic field (Saxena & Hillis, 2017). While non-invasive brain stimulation is shown to be effective overall, studies demonstrate vast heterogeneity in terms of who benefits most. This may be due to a variety of factors, including a genetic predisposition (Fridriksson, Elm, et al., 2018), the timing of stimulation (Ashaie et al., 2022), or the location of stimulation and montage placement (Cherney et al., 2021; Datta et al., 2011; Galletta et al., 2015). As such, it remains unclear where therapeutic stimulation should be applied to achieve the best outcomes for various language skills and how the effectiveness of a given stimulation site may differ across participants with variable lesions and deficits. According to Saxena and Hillis (2017), more studies are needed to determine appropriate sites of stimulation.

Neuroimaging can help identify candidate sites for therapeutic stimulation by revealing compensatory changes in activity in people with aphasia who demonstrate behavioral recovery. Resting-state functional connectivity data is an encouraging neuroimaging method to use due to the ability to correlate synchronized functional connectivity between intact regions with out-of-scanner tasks, ensuring the ease of testing those with aphasia (Klingbeil et al., 2019). There is now consensus in the field that complex cognitive processes such as language are the product of distributed interactive brain

systems (Crosson et al., 2019; Hickok & Poeppel, 2004; Ulm et al., 2018), which functional connectivity analyses allow us to evaluate. Unlike task-based fMRI, which measures the magnitude of change in brain activity and can be obscured by effort or inefficiency, especially in clinical populations (Kiran & Thompson, 2019), connectivity analyses measure the level of synchronization between two or more brain regions via correlations of their activity over the time course of scanning (Biswal et al., 1995; Fox et al., 2005). This technique has previously been used in studies of language (Hampson et al., 2002) and in participants with post-stroke aphasia(Guo et al., 2019; for a review, see Meier, 2022). Despite concerns about cognitive processing during wakeful rest (Crosson et al., 2019), evidence suggests overlap between language network connectivity during resting and task-active states (Jackson et al., 2016). In fact, one study has already examined the potential of resting-state functional connectivity patterns to predict behavioral performance of individuals with aphasia (Ramage et al., 2020), finding that connectivity between multiple pairs of brain regions predicted performance on subtests from a common language battery.

Therefore, in the present study, we will first examine the functionality of the LIFG in a group of neurologically intact older adults through the use of resting-state functional connectivity, correlated with behavioral performance on tasks targeting semantics and phonology. We will then explore these patterns of functional connectivity in a group of stroke-survivors with aphasia in conjunction with their performance on semantic and phonological assessments.

Seed-based Connectivity Analysis in Neurotypical Participants

In our first experiment, we aimed to identify cortical connectivity in the language network of neurologically intact older adults, specifically using pars orbitalis, triangularis, and opercularis as seeds for a resting state functional connectivity analysis. Based on previous findings (Xiang et al., 2010), we hypothesize that pars orbitalis and opercularis of our participants will demonstrate different patterns of connectivity, including increased connectivity with the angular and supramarginal gyrus, respectively. However, we expect that there may be increased right hemisphere connectivity in our sample, due to theories of age-related de-lateralization (Berlingeri et al., 2013; Cabeza, 2001, 2002). Finally, we also predict that some of the patterns of connectivity with pars orbitalis and opercularis will positively correlate with semantic and phonological assessment scores, respectively (e.g., connectivity between pars orbitalis and angular gyrus correlating with semantic scores). These findings will build on the existing literature to elucidate potentially unique patterns of LIFG connectivity in older adults.

Reorganization-Focused Case Series in Participants with Aphasia

In our second experiment, we aimed to identify the relationships between lesion load to LIFG subregions (pars orbitalis, triangularis, and opercularis), resting-state functional connectivity patterns identified in the above analysis with neurologically intact participants, and performance on semantic and phonological assessments. We will specifically explore the resting-state functional connectivity between regions that correlated with semantic and phonological performance in the neurologically intact participants. If these regions are located in the left hemisphere, we will examine right

hemisphere homologues in our participants with aphasia, considering the loss of viable tissue throughout much of the left hemisphere for many of our participants. We expect that higher connectivity between regions correlated with semantic or phonological performance in our neurologically intact participants will correspond to better performance in our participants with aphasia as well, especially in the face of damage to pars orbitalis or pars opercularis, respectively. This descriptive case series analysis will lay the groundwork for larger statistical analyses in the future.

Methods

Participants

Ten adults with aphasia were recruited from the The Ohio State University Aphasia Initiative and Wexner Medical Center as part of an ongoing research study (NIH R01DC017711). Inclusion criteria for the parent study consisted of a diagnosis of chronic aphasia (i.e., 6+ months post-stroke), age from 18 to 85 years old, status as a native English speaker, no history of neurological disease or disorder except for a single left hemisphere stroke, and no MRI contraindications (e.g., cardiac pacemaker, pregnancy). Participants also had functional vision and hearing, evidenced by screening. Vision screening involved identifying symbols on 20/100 line on the Lea Symbols Line test (Hyvärinen et al., 1980) at a distance of 16 inches with any necessary vision correction, to verify that participants could see the words and pictures presented during testing. To account for typical, age-related hearing loss, pure tone hearing screening was conducted at 40 dB HL at the speech frequencies of 500, 1000, and 2000 Hz (similar to Rochon et al., 2010). Participants were

able to hear all tones presented in at least one ear, verifying their ability to hear auditory stimuli presented during testing. Participants with hearing aids were excluded due to the contraindication for MRI.

An age-matched neurologically intact control group was recruited (n = 10) to conduct the resting-state functional connectivity analysis with the left and right hemisphere LIFG seeds as well as to establish comparisons with the participants with aphasia. Demographic comparisons for both participant groups are provided in Table 3.1.

Table 3.1 Comparison of neurologically intact and aphasia group demographics

Demographics	Aphasia	Neurologically intact	*t*
Gender (female, male)[a]	4, 6	5, 5	
Race (white, African American)[b]	7, 3	9, 1	
Age (years), mean (range, SD)	56.3 (39-78, 12.11)	59.7 (39-71, 8.87)	-0.72 (p = 0.48)
Education (years)[c], mean (range, SD)	14.8 (12-16, 1.93)	15.4 (12-16, 1.35)	-0.80 (p = 0.43)

Note. [a]The demographics questionnaire included an "other" gender option; however no participants reported a gender other than female or male. Therefore, only female and male genders are reported. [b]The demographics questionnaire included a variety of race and ethnicity options; however, only white and African American are reported because these were the only options selected by participants. [c]Education was reported as 1-16+ years, where 16+ years includes education beyond 16 years.

MRI Scanning and Preprocessing

All scanning took place at the Center for Cognitive and Behavioral Brain Imaging at OSU in a Siemens Prisma 3 Tesla MRI scanner, using a 32-channel headcoil. Neuroimaging entailed structural imaging, including a high-resolution T1-weighted

MPRAGE (TR = 2400ms; TE = 2.24ms; voxel resolution = 0.8x0.8x0.8mm; flip angle = 8°), as well as functional imaging, including task-independent resting-state EPI scans (TR = 2000ms; TE = 28.4ms; voxel resolution = 2x2x2mm; flip angle = 76°; multi-band acceleration = 3). During each of two 5-min. resting-state scans, participants maintained a wakeful resting state, lying still with their eyes open, maintaining fixation on a white cross on a black background (as in Hallam et al., 2018; Jackson et al., 2016). Participants were instructed not to do or think about anything in particular. Two scans were used, rather than one 10-min. scan, due to early participants having difficulty lying still and staying awake.

The cortical surface of each hemisphere was then computationally reconstructed from the T1-weighted anatomical volume using Freesurfer (Dale et al., 1999; Fischl, 2012), after reconstructing the lesioned tissue using the intact right hemisphere (VBG software; Radwan et al., 2021). Preprocessing of the resting state fMRI data entailed a standard pipeline. Resting state data were motion corrected, surface-registered to the fsaverage (MNI305) template space and smoothed on the surface (3mm FWHM). We performed nuisance signal regression of head-motion (6 motion parameters and their 6 temporal derivatives), and ventricular and white matter signals (CompCorr, see Behzadi et al., 2007). We then calculated framewise displacement by taking the sum of the absolute derivatives of the 6 motion parameters for each time point, and censored all timepoints above 1mm framewise displacement. Lesion masks were derived from a consensus between two lesion masks manually-drawn on the T1-weighted image by the first author and a trained research assistant using ITK-SNAP (Yushkevich et al., 2006). Resting state data were then further preprocessed in MATLAB (2018) using custom scripts.

Language and Cognitive Testing

Outside the scanner, all participants completed the category coordinates (semantic) and a nonword identity (phonological) probe span tasks from the Temple Assessment of Language and Short-term memory in Aphasia (TALSA; Martin et al., 2018). In these tasks, participants are required to indicate whether the probe item, presented after a list of one to seven items, is related to any of the previous items in a specific way, namely whether they are category coordinates (e.g., piano & guitar) or matching nonwords (e.g., sorbel & sorbel). These were delivered using E-Prime 3.0 software (2019). All participants also completed category (i.e., animals) and letter (i.e., "S") verbal fluency tasks as well as nonverbal tests of access to semantic knowledge and recognition memory from the Comprehensive Aphasia Test (CAT; Swinburn et al., 2004). The latter two, along with a nonverbal working memory test (Spatial Span; Wechsler, 1997), were used to account for participants' nonverbal semantic and memory skills. For participants with aphasia, the remainder of the CAT was completed in addition to the Boston Naming Test (BNT; Kaplan et al., 2001), and an in-house auditory word-picture verification task (WPVT) using images from the BNT, to obtain a comprehensive picture of each participant's language abilities.

Analysis

Seed-based Connectivity Analysis in Neurologically Intact Participants

We first identified patterns of functional connectivity for three seeds, subregions of the LIFG corresponding to pars opercularis (BA 44), pars triangularis (BA 45), and pars

orbitalis (BA 47), in our sample of neurologically intact older adults (n = 10). Seed regions of interest (ROIs) were defined in the left and right hemispheres using the corresponding parcels from the atlas by Glasser et al. (2016; i.e., parcel 44 for pars opercularis, 45 for pars triangularis, and both 47l and 47s for pars orbitalis). Functional connectivity was computed for both hemispheres with seeds from both hemispheres (e.g., left hemisphere pars opercularis, triangularis, and orbitalis to the whole left and right hemispheres), and a group analysis was subsequently computed using the general linear model in FreeSurfer (Fischl, 2012), for each seed region. Multiple comparison correction was completed using 1,000 permutations with a vertex-wise cluster forming threshold of $p < .0001$ and a cluster-wise threshold of $p < .05$.

Next, to characterize functional relationships with these measures of connectivity and explore the possibility of a semantic-to-phonological anterior-to-posterior organization in the LIFG, we conducted a series of Pearson's correlation analyses between functional connectivity and behavior. We obtained measures of the functional connectivity between each seed and its significant clusters within the same hemisphere (Tables 3.2-3.4). Pearson's correlations were calculated between the mean activation across voxels over the time-course of the resting-state scan in each ROI (e.g., left pars opercularis and one of the clusters identified as having significant functional connectivity with left pars opercularis) using custom scripts in MATLAB (2018). Despite knowing that each of these clusters had already demonstrated functional connectivity with one of the seeds from the GLM analysis above, calculating the functional connectivity between seeds and clusters allowed us to quantify their synchronization within each participant and correlate it with behavior. This

was completed for each run of resting-state scanning. Each Pearson's *r* was Fisher's Z-transformed in order to take the mean across the two resting-state runs for each participant. We next calculated Pearson's correlations between participants' mean Fisher's Z-transformed resting state functional connectivity and their performance on the TALSA and fluency tasks using the stats package in R (R Core Team, 2022). Pearson's correlations between .10 and .29 were considered small; .30 and .49, medium; .50 or greater, large (Cohen, 1992).

For the category and letter verbal fluency measures we were able to correct for age, education, and race (as in Gladsjo et al., 1999), yielding a standardized T-score. Whereas Gladsjo et al. (1999) completed three trials of letter fluency, given the prompts "F," "A," and "S," as in the Controlled Oral Word Association subtest of the Multilingual Aphasia Examination (Benton et al., 1994), we completed only one trial of letter fluency using the letter "S," as in the CAT. Therefore, in order to arrive at an appropriate T-score, we tripled participants' scores in the correction calculation. For the TALSA, no such correction formula or T-score conversion was available, given that the assessment is still under research and development.

Considering language is typically lateralized to the left hemisphere, we first examined the relationship with behavior using resting state connectivity between left hemisphere seeds and clusters. However, we also examined connectivity between right hemisphere seeds and clusters given that our intention was to explore patterns of resting-state connectivity in our participants with aphasia, who have large left hemisphere lesions, preventing examination of left hemisphere clusters.

Reorganization-Focused Case Series in Participants with Aphasia

We chose to explore resting-state connectivity in participants with aphasia, at the single subject level, between seeds and clusters identified from the correlation analyses in our neurologically intact participants, above. We selected seeds and clusters with significant ($p < .10$), uncorrected, positive correlations with the TALSA or fluency tasks. Considering our small sample of neurologically intact participants (n = 10), these methods were used to maximize our likelihood of identifying regions with resting-state connectivity that could be explored in our case series.

Functional connectivity was computed for the participants with aphasia in the same way as it was computed for neurologically intact participants, above. The Fisher's Z-transformed Pearson correlation was calculated between the mean signal across all voxels in each pair of ROIs. Pairs consisted of one of the three right hemisphere seed ROIs and one of its right hemisphere clusters identified to have functional connectivity with that seed in the neurologically intact participants. Participants' behavioral performance, lesions, and resting-state connectivity will be described as a case series.

Results

Seed-based Connectivity Analysis in Neurologically Intact Participants

Results of the seed-based connectivity analyses are shown in Figures 3.1 and 3.2. As can be seen in Table 3.2, left pars opercularis was functionally connected to seven

clusters in the left hemisphere and three clusters in the right. Other than being functionally connected to itself, the clusters were somewhat different in left and right hemispheres. Two left hemisphere clusters were located in the supramarginal gyrus and others included frontal regions, like superior frontal gyrus, precentral gyrus, and pars triangularis. Right hemisphere clusters included the superior parietal lobe and the calcarine fissure. The latter, as well as the lingual gyrus cluster in the left hemisphere, are likely the result of the task conditions in which participants had their eyes open during rest. Right pars opercularis was overall less functionally connected than the left. Clusters included the supramarginal gyrus and rostral middle frontal cortex in both hemispheres, as well as left lateral orbitofrontal cortex and right superior frontal gyrus.

Left pars triangularis is prominently functionally connected to the frontal lobe, with multiple clusters in superior frontal cortex in both the left and right hemisphere and left caudal middle frontal gyrus (Table 3.3). It is additionally functionally connected to left superior temporal sulcus and the insula. Right pars triangularis is functionally connected to more clusters overall (in both hemispheres) than left pars triangularis. Clusters are located through the frontal, temporal, and parietal lobes, as well as the insula and occipital lobe.

Finally, left pars orbitalis is functionally connected to the greatest number of clusters of any of our seeds (Table 3.4). The pattern is relatively similar in both hemispheres, with clusters in the superior frontal lobe, middle temporal gyrus, and the medial occipital lobe (again, likely due to the eyes-open task condition). Right pars orbitalis also has functional connections in the superior frontal lobe, middle temporal gyrus, and

inferior parietal lobe (left supramarginal gyrus) bilaterally, as well as in left inferior temporal lobe, right anterior and posterior cingulate, and right superior temporal lobe.

Table 3.2 Clusters functionally connected to left and right pars opercularis

	Left pars opercularis			Right pars opercularis		
Cluster	Region[a]	Size[b]	Peak MNI coordinates x, y, z	Region[a]	Size[b]	Peak MNI coordinates x, y, z
Left hemisphere						
1	pars opercularis	1148.15	-46.1, 10.0, 16.4	pars opercularis	146.91	-47.1, 15.8, 9.5
2	supramarginal	386.64	-59.0, -46.8, 30.8	lateral orbitofrontal	114.22	-41.2, 26.6, -12.0
3	superior frontal	343.83	-9.9, 0.6, 67.6	rostral middle frontal	86.47	-35.6, 44.3, 19.9
4	precentral	209.34	-45.1, -1.7, 45.2	supramarginal	61.61	-55.8, -47.1, 36.4
5	lingual	206.81	-5.8, -88.0, -2.8			
6	pars triangularis	168.81	-44.7, 37.3, -0.6			
7	supramarginal	118.62	-50.4, -50.2, 44.4			
Right hemisphere						
1	pars opercularis	299.03	49.4, 11.6, 13.7	pars opercularis	1465.08	54.8, 16.5, 13.8
2	superior parietal	39.08	27.5, -60.9, 30.6	supramarginal	614.55	57.6, -43.6, 22.4
3	pericalcarine	36.08	15.2, -85.9, 5.5	rostral middle frontal	133.62	23.3, 45.8, 21.2
4				superior frontal	59.50	8.8, 37.3, 34.0

Note. Cluster-wise threshold of $p < .05$. [a]Labels from the Desikan-Killiany atlas in FreeSurfer. [b]In mm^2.

Table 3.3 Clusters functionally connected to left and right pars triangularis

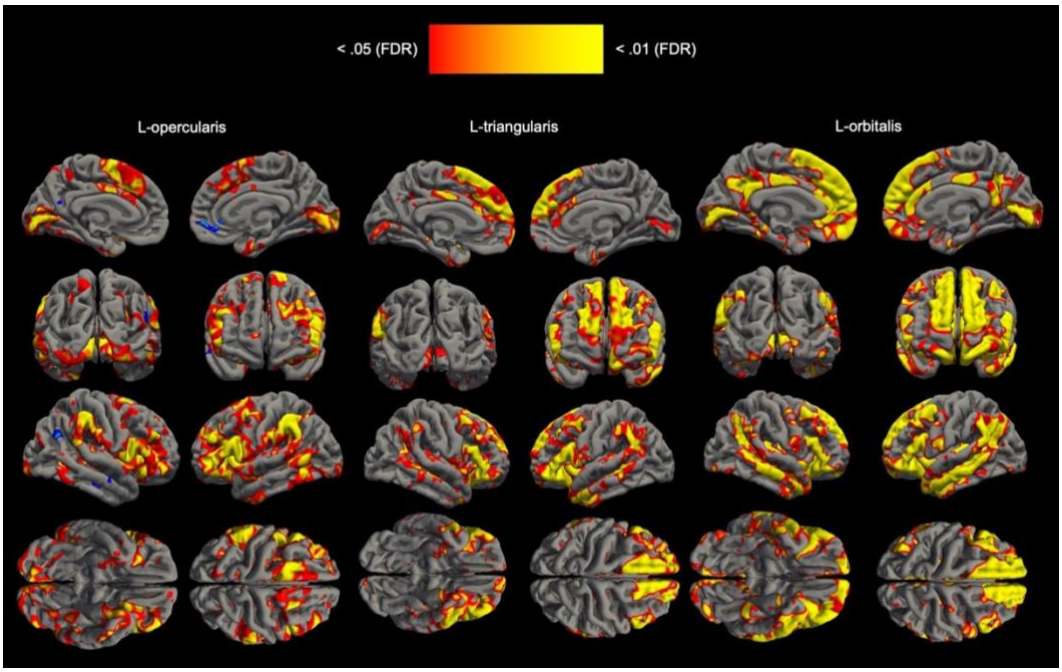
	Left pars triangularis			Right pars triangularis		
Cluster	Region[a]	Size[b]	Peak MNI coordinates x, y, z	Region[a]	Size[b]	Peak MNI coordinates x, y, z
Left hemisphere						
1	pars opercularis	1614.78	-53.5, 23.6, 9.9	pars triangularis	825.55	-39.5, 26.5, 6.2
2	superior frontal	664.30	-6.9, 24.8, 54.4	superior frontal	161.16	-7.5, 24.3, 51.7
3	superior frontal	372.33	-14.2, 56.0, 21.1	inferior parietal	96.68	-41.8, -51.3, 13.8
4	supramarginal	190.61	-49.6, -51.6, 19.0	precuneus	74.77	-7.6, -46.1, 46.3
5	middle temporal	173.17	-54.0, 0.9, -29.6	superior temporal	72.84	-45.5, -18.7, -7.3
6	superior frontal	139.48	-7.6, 35.8, 29.5	insula	67.91	-35.3, 11.8, -5.2
7	banks superior temporal sulcus	99.94	-50.4, -43.4, -1.2	lateral orbitofrontal	67.22	-35.3, 25.5, -12.3
8	caudal middle frontal	70.13	-39.4, 7.0, 47.3	lateral occipital	64.12	-32.4, -83.6, -15.4
9	insula	59.22	-34.6, 15.7, -3.9	transverse temporal	57.07	-39.2, -28.3, 10.9
Right hemisphere						
1	pars triangularis	600.78	48.2, 35.4, 0.1	pars triangularis	2209.92	46.3, 28.1, 2.9
2	superior frontal	221.02	9.1, 20.2, 59.9	rostral middle frontal	620.26	23.9, 50.1, 12.6
3	superior frontal	101.09	18.0, 43.3, 34.9	superior frontal	501.74	6.7, 41.3, 44.6
4				supramarginal	447.82	54.4, -41.5, 37.1
5				middle temporal	150.72	61.2, -35.8, -7.3
6				superior frontal	96.28	8.4, 16.3, 57.0
7				caudal anterior cingulate	92.39	8.7, 26.4, 25.7
8				inferior parietal	87.23	51.4, -53.9, 38.0
9				caudal middle frontal	83.88	37.7, 6.5, 42.0
10				lateral orbitofrontal	75.08	26.7, 20.7, -20.9
11				lingual	69.70	4.6, -84.6, -5.5

Note. Cluster-wise threshold of $p < .05$. [a]Labels from the Desikan-Killiany atlas in FreeSurfer. [b]In mm^2.

Table 3.4 Clusters functionally connected to left and right pars orbitalis

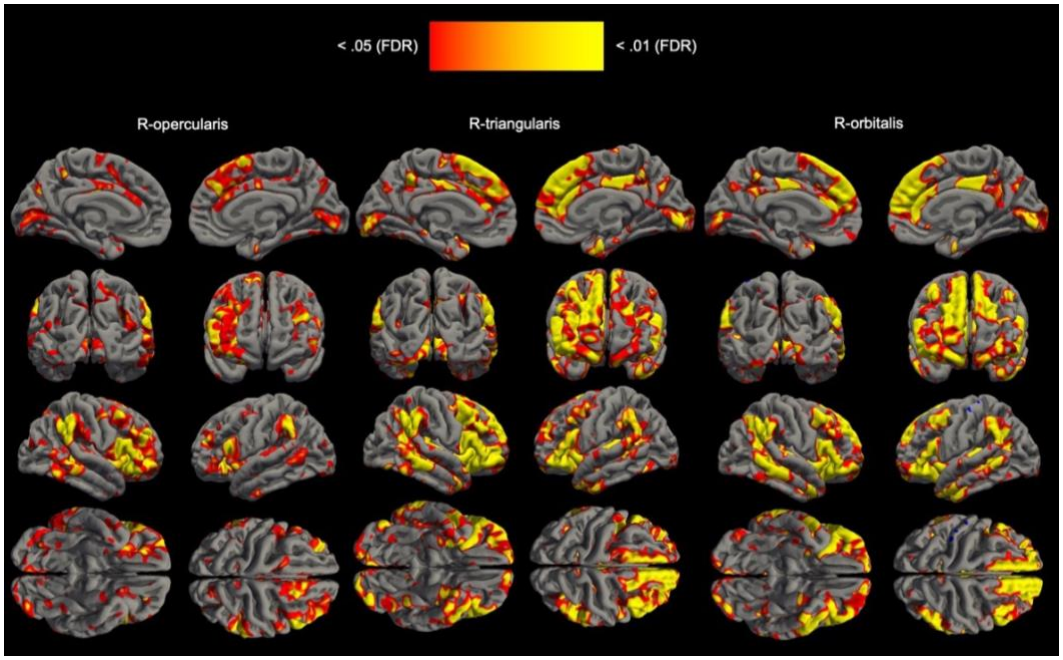
	Left pars orbitalis			Right pars orbitalis		
			Peak MNI coordinates			Peak MNI coordinates
Cluster	Region[a]	Size[b]	x, y, z	Region[a]	Size[b]	x, y, z
Left hemisphere						
1	superior frontal	2574.43	-8.5, 46.2, 24.9	pars triangularis	1184.68	-41.6, 33.5, -4.7
2	lateral orbitofrontal	1107.54	-38.5, 24.9, -14.1	rostral middle frontal	268.92	-20.6, 48.4, 30.9
3	inferior parietal	829.76	-46.7, -62.6, 35.8	supramarginal	232.06	-56.8, -51.7, 26.9
4	middle temporal	626.38	-53.2, -28.9, -11.7	superior frontal	153.26	-9.1, 45.1, 29.0
5	pars opercularis	466.11	-53.1, 23.6, 14.3	inferior temporal	100.43	-47.9, -11.1, -34.2
6	caudal middle frontal	393.85	-35.7, 24.4, 44.5	middle temporal	87.12	-60.9, -48.0, -0.3
7	isthmus cingulate	337.85	-8.5, -49.2, 29.3	middle temporal	82.28	-53.7, -30.8, -11.3
8	middle temporal	327.27	-57.6, -4.6, -27.5			
9	frontal pole	183.56	-7.0, 61.8, -11.5			
10	transverse temporal	127.97	-37.6, -29.8, 12.0			
11	middle temporal	100.15	-60.5, -12.7, -20.8			
12	lingual	99.52	-4.1, -87.9, -4.4			
13	insula	80.49	-35.5, 10.0, -5.4			
Right hemisphere						
1	superior frontal	1383.84	8.4, 55.3, 21.9	lateral orbitofrontal	1967.48	37.9, 25.6, -16.7
2	lateral orbitofrontal	676.97	42.8, 27.2, -13.7	superior frontal	899.87	20.0, 45.2, 32.6
3	inferior parietal	351.28	44.3, -55.5, 26.4	inferior parietal	631.58	50.6, -53.9, 37.0
4	pars opercularis	269.27	54.7, 22.6, 16.4	banks superior temporal sulcus	559.35	59.8, -44.8, -1.2
5	banks superior temporal sulcus	203.61	58.2, -44.9, -0.8	superior frontal	439.42	8.7, 45.4, 35.1
6	superior temporal	191.45	50.7, -27.7, 7.2	posterior cingulate	209.57	4.4, -17.6, 38.3
7	middle temporal	145.83	53.3, 4.8, -31.7	rostral anterior cingulate	105.98	8.3, 39.8, 1.9
8	precuneus	118.61	12.0, -53.0, 30.0	caudal middle frontal	103.86	42.0, 17.8, 45.4
9	pars triangularis	87.51	45.1, 28.4, 2.4	middle temporal	97.57	54.0, 3.9, -31.3
10	middle temporal	75.90	62.3, -17.0, -19.9	superior temporal	90.87	48.8, -25.3, 5.1

Note. Cluster-wise threshold of $p < .05$. [a]Labels from the Desikan-Killiany atlas in FreeSurfer. [b]In mm^2.



Note. n = 10. Patterns of connectivity from all three left hemisphere seeds are relatively symmetrical in both hemispheres, but appear to be slightly left lateralized. All three seeds are functionally connected to inferior frontal and parietal cortex, with more variability in their superior frontal and temporal connections. Pars opercularis has the weakest connectivity of the three seeds with medial and lateral superior frontal cortex; its temporal lobe connectivity is primarily in the posterior region with lesser connectivity at the anterior superior and inferior temporal lobe (left > right hemisphere). Pars triangularis has the weakest connectivity of the three seeds with inferior parietal cortex; its temporal lobe connectivity consists of the inferior temporal pole and posterior middle temporal gyrus (left > right hemisphere). Pars orbitalis appears to have the strongest overall connectivity of the three seeds, prominent throughout the superior frontal and middle temporal lobes, with more right temporal connectivity than the other seeds.

Figure 3.1 Resting-State Functional Connectivity from Left IFG Seeds



Note. n = 10. Patterns of connectivity from the three right hemisphere seeds are somewhat symmetrical in both hemispheres, but appear to be more ipsilaterally lateralized (to right hemisphere) than the left hemisphere seeds. All three seeds are again functionally connected to inferior frontal and parietal cortex, with more variability in their superior frontal and temporal connections. Pars opercularis appears to have the least functional connectivity overall, but notable sites are in the posterior temporal lobe and dorsolateral frontal cortex (right > left hemisphere). Pars triangularis appears to have the greatest functional connectivity overall, including prominent connectivity throughout prefrontal cortex and at in posterior middle temporal gyrus (right > left hemisphere). Pars orbitalis appears to have the most symmetrical pattern across hemispheres, with notable connectivity throughout much of prefrontal cortex and at both anterior inferior and posterior middle temporal gyri.

Figure 3.2 Resting-State Functional Connectivity from Right IFG Seeds

The correlation analyses between resting-state connectivity and the behavioral tasks are depicted in Tables 3.5 and 3.6. We identified eight significant ($p < .10$) positive correlations between behavior and resting-state functional connectivity in the left or right hemisphere. In the left hemisphere, functional connectivity between pars opercularis and three of its clusters correlated with the semantic tasks, although there were two negative

correlations with the letter fluency task as well. None of the functional connectivity with left pars triangularis was significantly correlated with any of the behavioral tasks. On the other hand, functional connectivity between left pars orbitalis and three of its clusters correlated with semantic tasks and one of these also correlated with letter fluency.

Of these, there were three left hemisphere clusters that had also been identified as significant clusters in the right hemisphere resting-state connectivity analysis: supramarginal gyrus (connected with pars opercularis, correlated with the semantic TALSA probe span), middle temporal gyrus (connected with pars orbitalis, correlated with the semantic TALSA probe span and letter fluency), and the caudal middle frontal gyrus (connected with pars orbitalis, correlated with category fluency). These were selected as the best candidates to explore in our participants with aphasia considering the foundation of functional connectivity between the right hemisphere homologues of these regions may already exist. Additionally, one of the eight positive correlations involved resting-state connectivity between a right hemisphere seed and cluster: pars triangularis and caudal middle frontal gyrus (correlated with the phonological TALSA probe span). This pair of regions was also selected to explore in our participants with aphasia, yielding a total of four seed and cluster pairs.

Table 3.5 Behavior and LH Resting-state Connectivity Correlations

Seed	Cluster	Category Fluency	TALSA CC	Letter Fluency	TALSA NI
Opercularis	pars opercularis	0.27	0.24	-0.17	0.08
Opercularis	supramarginal	0.41	0.80*	0.38	0.32
Opercularis	Superior frontal	-0.37	0.28	-0.62*	0.39
Opercularis	precentral	-0.27	0.14	-0.02	0.14
Opercularis	Lingual	0.18	0.68*	-0.32	0.49
Opercularis	Pars triangularis	0.65*	0.35	0.17	0.27
Opercularis	supramarginal	0.01	-0.30	-0.59*	0.00
Triangularis	pars opercularis	-0.11	0.21	-0.20	-0.06
Triangularis	superior frontal	-0.20	-0.44	-0.29	-0.52
Triangularis	superior frontal	0.10	0.09	-0.31	0.52
Triangularis	supramarginal	0.31	0.08	0.27	0.08
Triangularis	Middle temporal	-0.30	-0.14	-0.26	-0.38
Triangularis	Superior frontal	0.42	0.20	0.39	-0.10
Triangularis	Banks superior temporal sulcus	-0.07	0.35	-0.13	0.31
Triangularis	Caudal middle frontal	-0.46	0.19	0.19	-0.33
Triangularis	insula	0.52	0.44	0.25	0.14
Orbitalis	superior frontal	0.45	0.44	-0.07	0.06
Orbitalis	Lateral orbitofrontal	-0.51	0.05	-0.60*	0.29
Orbitalis	Inferior parietal	0.11	0.05	-0.17	0.29
Orbitalis	Middle temporal	0.17	0.62*	0.57*	0.34
Orbitalis	Pars opercularis	-0.37	0.18	-0.07	0.07
Orbitalis	Caudal middle frontal	0.56*	0.31	0.14	-0.01
Orbitalis	Isthmus cingulate	-0.06	0.14	-0.34	0.02
Orbitalis	Middle temporal	0.23	0.25	-0.05	-0.25
Orbitalis	frontal pole	-0.15	-0.02	-0.35	-0.07
Orbitalis	Transverse temporal	0.61*	0.34	0.19	-0.01
Orbitalis	Middle temporal	0.41	0.21	-0.08	0.16
Orbitalis	lingual	-0.13	0.21	-0.06	0.17
Orbitalis	insula	-0.21	-0.08	-0.53	0.14

Note. CC = Category Coordinates. NI = Nonword Identity. TALSA = Temple Assessment of Language and Short-term Memory in Aphasia.

*$p < .10$, uncorrected

Table 3.6 Behavior and RH Resting-state Connectivity Correlations

Seed	Cluster	Category Fluency	TALSA CC	Letter Fluency	TALSA NI
Opercularis	Pars opercularis	-0.69*	-0.28	-0.24	0.21
Opercularis	supramarginal	-0.48	0.41	-0.12	0.25
Opercularis	Rostral middle frontal	-0.21	0.14	0.13	-0.36
Opercularis	Superior frontal	0.05	0.24	-0.21	-0.23
Triangularis	Pars triangularis	0.31	0.30	0.22	0.51
Triangularis	Rostral middle frontal	0.23	0.18	-0.04	0.40
Triangularis	Superior frontal	0.14	0.21	-0.13	0.32
Triangularis	supramarginal	0.38	0.13	-0.29	0.32
Triangularis	Middle temporal	0.04	0.09	-0.30	0.24
Triangularis	Superior frontal	-0.61*	0.06	-0.41	0.39
Triangularis	Caudal anterior cingulate	0.10	0.54	-0.29	0.41
Triangularis	Inferior parietal	0.13	-0.10	0.01	0.22
Triangularis	Caudal middle frontal	0.28	0.21	-0.15	0.62*
Triangularis	Lateral orbitofrontal	-0.03	0.13	-0.04	0.29
Triangularis	lingual	0.16	0.16	-0.56*	0.31
Orbitalis	Lateral orbitofrontal	0.16	-0.01	-0.16	0.03
Orbitalis	Superior frontal	0.00	0.17	-0.04	0.10
Orbitalis	Inferior parietal	0.41	0.13	-0.11	0.30
Orbitalis	Banks superior temporal sulcus	0.42	0.15	-0.13	-0.10
Orbitalis	Superior frontal	0.30	0.07	-0.18	-0.14
Orbitalis	Posterior cingulate	-0.28	-0.36	-0.28	-0.07
Orbitalis	Rostral anterior cingulate	0.04	-0.11	-0.29	-0.24
Orbitalis	Caudal middle frontal	-0.41	-0.42	-0.13	-0.33
Orbitalis	Middle temporal	0.21	0.31	-0.59*	0.15
Orbitalis	Superior temporal	0.37	0.30	0.08	0.31

Note. CC = Category Coordinates. NI = Nonword Identity. TALSA = Temple Assessment of Language and Short-term Memory in Aphasia.

*$p < .10$, uncorrected

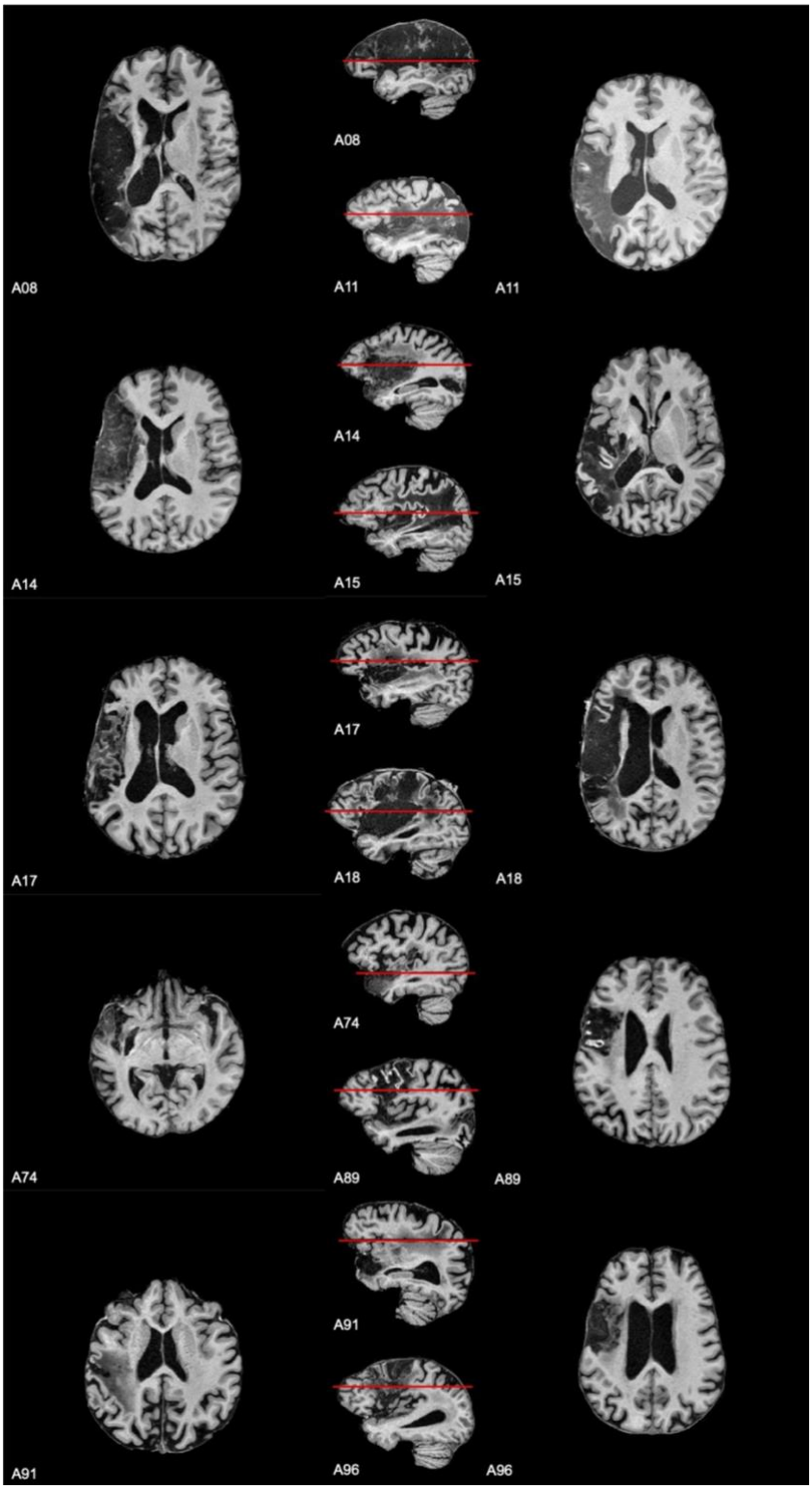


Figure 3.3 Lesions of Participants with Aphasia

Reorganization-Focused Case Series in Participants with Aphasia

Demographic information and broad language measures for participants with aphasia are presented in Table 3.7. Details specifically pertaining to the participants' lesions, semantic and phonological performance, and resting-state functional connectivity are presented in Table 3.8.

Participant A08

A08's lesion, the largest in our sample, accounts for approximately 198.02 cc (198,022mm^3) of the left hemisphere. Anteriorly, the lesion begins within pars triangularis of the IFG, sparing pars orbitals, yet severely impacting pars opercularis. A08 demonstrated comparable receptive and expressive language skills on the CAT, with slightly greater receptive than expressive difficulty. Moderate to severe word-finding impairment was apparent on the BNT for this participant. His semantic and recognition memory appeared largely intact, though spatial memory was impaired. A08 performed well on the TALSA-Nonword Identity task, though experienced considerably greater difficulty with the Category Coordinates version. His scores on the WPVT were near ceiling for trials including both semantic and phonological foils. Functional connectivity was low for both right hemisphere pairs involving pars orbitalis, but moderate for the remaining two (i.e., pars opercularis and supramarginal gyrus; pars triangularis and middle frontal gyrus).

Participant A11

A11's lesion is approximately 116.37 cc (116,368 mm^3). Virtually none of the LIFG is affected by A11's lesion, damaging just 2% of pars opercularis. A11 has a mild-moderate language impairment, evidenced by comparatively high scores on the BNT and CAT modality mean. Receptive and expressive abilities seem to be relatively equally affected. His performance on the spatial span suggests a memory deficit, though his superior performance on the backward spatial span suggests better working than short-term memory. A11 performed better on the semantic version of the TALSA probe span than the phonological version, but had relatively low scores on both, perhaps due to memory deficits. His category fluency was far superior to his letter fluency. However, his WPVT scores are equal, showing no difference between semantic and phonological foils, having performed nearly perfectly in both conditions. Between pars orbitalis and middle frontal gyrus, A11's connectivity was low, but connectivity was moderate to high between the remaining right hemisphere pairs.

Participant A14

A14's stroke affected the majority of the LIFG, damaging over 70% of each subregion and encompassing 135.63 cc (135,625 mm^3) in total. A14's language is severely affected, based on her BNT score of 10 and her relatively low performance for our sample, across receptive and expressive language domains. Her memory seems to also be affected, which may have contributed to lower performance on both TALSA probe spans, as with A11. Although her category and letter fluency are equal, she performed better on the phonological version of both the TALSA probe span and the WPVT, suggesting a greater

deficit in semantic access. A14's resting state connectivity between pars orbitalis and middle temporal gyrus was virtually absent. However, connectivity between the three remaining pairs of right ROIs was high.

Participant A15

In A15, the LIFG is entirely intact, spared of any damage, despite her 86.39 cc (86,394 mm^3) lesion. Scores on the BNT and CAT suggest a severe language impairment overall, similar to A14, except with relatively spared repetition. A short-term and working memory deficit is clearly present, based on her low scores for the spatial span and TALSA probe span tasks. A15 shows perhaps a slight receptive advantage for phonology, but she produced more items in the category fluency task (3) than in letter fluency (0). Moderate resting-state connectivity was present between three of the four right hemisphere pairs (i.e., not pars triangularis and middle frontal gyrus).

Participant A17

Despite having a smaller lesion of 73.31 cc (73,314 mm^3), A17 has extensive damage to pars opercularis and over half of pars triangularis. Though, pars orbitalis is relatively spared. A17 has a relatively severe language impairment, affecting repetition and word-finding most of all. His writing is comparatively more preserved. Memory does not appear to be affected as severely as the other participants in the sample, though he demonstrates better working (backward span) than short-term (forward span) memory and difficulty with the TALSA probe span tasks. He performed better on the semantic version

(category coordinates) of the TALSA probe span but showed a greater semantic access impairment on the fluency and WPVT tasks. Resting-state functional connectivity was moderate to high across all right hemisphere region pairs, but strongest between right pars opercularis and supramarginal gyrus.

Participant A18

A18's lesion consists of approximately 160.94 cc (160,944 mm^3) of left hemisphere and is quite expansive, severely impacting pars opercularis, approximately half of pars triangularis, and roughly a third of pars orbitalis. Language and cognitive testing revealed a similar pattern in A18 as in A08. Receptive and expressive language skills via the CAT appeared comparable. His BNT performance was identical to A08, revealing moderate to severe word-finding impairment. His semantic and recognition memory appeared similarly intact. However, A18 appears to have a milder spatial memory deficit and demonstrated greater difficulty on both TALSA probe span tasks. A18 performed better on the Nonword Identity version than Category Coordinates, like A08, but demonstrated greater difficulty on trials of the WPVT with semantic foils than those with phonological foils. A18 had moderate to high functional connectivity between all four pairs of right hemisphere ROIs. Connectivity was strongest between right pars orbitalis and the middle frontal and temporal gyri.

Participant A74

At 35.81 cc (35,810 mm^3) in size, A74's lesion is the smallest in our sample. Her lesion does not impact the LIFG, evidenced by less than 1% damage to pars orbitalis and no damage to the other subregions. A74 has a relatively mild impairment, affecting spoken language more severely than written language and expressive language more than receptive. Her spatial memory is only mildly impaired, considering her age. She also demonstrates a slight, but consistent semantic impairment. She performed better on the semantic version of the TALSA probe span, WPVT, and fluency tasks. Functional connectivity was moderate to high for three of A74's right hemisphere pairs, but weakest of all between pars orbitalis and middle temporal gyrus.

Participant A89

Pars opercularis is most affected by A89's lesion, 54.18 cc (54,175 mm^3) in size, followed by partial damage to pars triangularis and none to pars orbitalis. A89's moderate to severe language impairment is characterized by more severe deficits in reading and writing. She has a relatively severe impairment of short-term and working memory as well. Semantic access appears to be more severely impacted than phonology, based on her performance on the WPVT and TALSA probe spans. She performed identically on the fluency tasks; however, people without language impairments tend to perform better in category fluency than letter fluency. A89 had relatively low to moderate resting-state connectivity across the right hemisphere region pairs.

Participant A91

The LIFG was only minorly impacted by A91's 63.30 cc (63,301 mm^3) lesion, at pars opercularis. Based on his CAT scores, A91 has the mildest language impairment of our participants. Although, his short-term and working memory do seem to be affected slightly, taking his age into account. A91 demonstrates a relatively mild impairment to both semantic access and phonology as well. He performed slightly better on the phonological versions of the TALSA and WPVT than the semantic versions and did reasonably well in letter fluency. Resting-state functional connectivity was high across three of the four right region pairs, but low between pars orbitalis and middle temporal gyrus.

Participant A96

A96's 53.07 cc (53,065 mm^3) lesion impacts the majority of pars opercularis, but leaves pars triangularis relatively spared and pars orbitalis unaffected. A96 has a moderate to severe language impairment, characterized by stronger performance on confrontation naming and poorer comprehension. Spatial short-term and working memory are impaired as well. A91 performed better on the phonological versions of the fluency and WPVT tasks but scored identically on both the semantic and phonological version of the TALSA probe span. His resting-state connectivity was low between two of the right hemisphere pairs, but moderate to high in the remaining two (i.e., pars triangularis and middle frontal gyrus; pars orbitalis and middle frontal gyrus).

Table 3.7 Demographics and Cognitive-Linguistics for Participants with Aphasia

	A08	A11	A14	A15	A17	A18	A74	A89	A91	A96
Age	55	41	53	56	60	39	73	54	78	54
Months post-CVA	33	97	13	116	13	84	6	11	57	19
Sex	M	M	F	F	M	M	F	F	M	M
Race	B	W	W	B	W	W	W	W	W	B
BNT	27	41	10	12	4	27	36	13	41	44
Spatial Span For.	4	5	6	5	5	6	6	4	5	4
Spatial Span Back.	4	6	4	4	6	5	6	4	4	4
CAT *T-score (raw score)*										
Mod. Mean	49.66	51.67	45.83	46.00	46.33	48.83	57.16	51.17	65.67	48.67
Comp. Spoken Lang.	49 (41)	51 (44)	47 (38)	40 (27)	47 (37)	50 (42)	53 (48)	50 (43)	64 (59)	47 (38)
Comp. Written Lang.	48 (39)	51 (44)	46 (35)	46 (34)	49 (41)	48 (38)	62 (56)	48 (37)	65 (58)	44 (29)
Rep.	50 (47)	52 (52)	42 (12)	54 (56)	40 (4)	52 (50)	58 (65)	58 (64)	60 (68)	50 (46)
Naming	54 (46)	57 (58)	47 (18)	47 (20)	45 (10)	48 (25)	52 (42)	51 (37)	69 (83)	56 (53)
Reading	45 (8)	50 (40)	45 (8)	45 (10)	45 (9)	46 (15)	63 (65)	48 (29)	71 (70)	47 (26)
Writing	52 (54)	49 (40)	45 (10)	44 (22)	52 (54)	49 (40)	55 (62)	52 (55)	65 (75)	48 (39)
Sem. Memory	(9)	(10)	(10)	(10)	(10)	(8)	(10)	(8)	(10)	(9)
Rec. Memory	(10)	(10)	(9)	(10)	(10)	(10)	(10)	(10)	(10)	(10)

Note. BNT is out of 60. Spatial Span reported as maximum span length. Semantic and Recognition Memory tasks are out of 10. BNT = Boston Naming Test. CAT = Comprehensive Aphasia Test. CVA = cerebrovascular accident.

Table 3.8 Lesion Load, Semantics, Phonology, and Functional Connectivity for Participants with Aphasia

		% damage			Behavioral assessments						Resting-state functional connectivity			
		P	S		Semantic			Phonological			S	P	S & P	S
ID	Les. Vol. (cc)	BA 44	BA 45	BA 47	Cat. Flu.	TALSA CC	WPVT sem. foils	Let. Flu.	TALSA NI	WPVT phon. foils	BA 44 & SMG	BA 45 & MFG	BA 47 & MTG	BA 47 & MFG
A15	86.39	0%	0%	0%	3	0.00	41	0	2.88	49	0.44	0.08	0.49	0.54
A74	35.81	0%	0%	< 1%	1	1.80	54	7	2.97	59	0.48	0.58	0.13	0.62
A11	116.36	2%	0%	0%	12	1.93	59	2	0.80	59	0.51	0.63	0.63	0.36
A91	63.30	16%	0%	0%	16	3.80	55	9	4.69	59	0.80	0.61	0.13	0.75
A96	53.07	82%	16%	0%	9	0.80	50	2	0.80	58	0.24	0.47	0.24	0.54
A89	54.18	98%	31%	0%	2	2.88	47	2	2.97	60	0.34	0.43	-0.08	0.30
A08	198.02	96%	45%	1%	6	2.80	56	3	5.97	57	0.44	0.42	0.26	0.27
A17	73.31	95%	60%	15%	1	2.88	39	3	0.80	52	0.79	0.60	0.40	0.58
A18	160.94	96%	46%	36%	3	1.67	50	1	4.91	58	0.60	0.42	0.72	0.69
A14	135.62	91%	87%	72%	2	0.53	29	2	2.61	55	0.69	0.53	-0.03	0.59
NI	--	--	--	--	20.3	5.93	--	15.4	5.84	--	0.77	0.39	0.47	0.46

Note. Participants are ordered based on lesion load. Participants at the top of the table have the most intact left inferior frontal gyrus. Moving down the table, damage progresses from pars opercularis (BA 44) to pars orbitalis (BA 47). Therefore, participants at the bottom of the table have the most damage to left inferior frontal gyrus. Mean scores and resting-state functional connectivity is shown for the neurologically intact group (n = 10) in the last row (these participants were not administered the WPVT). Lesion volume is reported in native space. Resting-state functional connectivity for right hemisphere regions is reported as Pearson's *r* (transformed back from Fisher's Z after taking the mean of resting-state scans). BA = Brodmann's area. Cat. Flu. = category fluency. Let. Flu. = letter fluency. MFG = middle frontal gyrus. MTG = middle temporal gyrus. NI = neurologically intact. P = phonological. S = semantic. SMG = supramarginal gyrus. TALSA = Temple Assessment of Language and Short-term Memory in Aphasia. WPVT = Word Picture Verification Task (auditory).

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Discussion

The purpose of the present study was to examine the patterns of resting-state functional connectivity between three seed regions in the IFG of each hemisphere, correlate these patterns of functional connectivity with performance on tasks targeting semantics and phonology, and explore how the involved brain regions may inform functional reorganization in stroke-survivors with aphasia.

Seed-based Connectivity Analysis in Neurologically Intact Participants

Compared with the results of Xiang et al. (2010), the seed-based connectivity patterns in our sample of neurologically intact older adults broadly differ in multiple ways. First, our older participants demonstrated greater connectivity with occipital regions, likely due to the nature of the scanning conditions, in which our participants had their eyes open during resting-state scanning, whereas younger participants had their eyes closed (Xiang et al., 2010). Additionally, right homologues of IFG subregions appear to be functionally connected to larger clusters within the left hemisphere IFG subregions in the older participants. Some of the differences observed between our older adults and the younger adults from Xiang et al. (2010) may be attributable to the fact that the scanning time was longer for the latter group, potentially yielding more consistent and robust connectivity results. However, differences may also be due to the effects of age-related reduction in hemispheric lateralization (and increased bilaterality) for cognitive-linguistic functions throughout prefrontal cortex and beyond (Berlingeri et al., 2013; Cabeza, 2001, 2002). To some extent, this extends beyond the IFG. Although the right pars opercularis in younger

adults (Xiang et al., 2010) shows strong, roughly symmetrical connectivity patterns in the left and right hemispheres, the connectivity patterns of right pars triangularis and orbitalis are weaker globally, whereas the right pars triangularis and orbitalis in our older participants have relatively widespread patterns of connectivity. Each of the seed regions will be addressed, in turn.

In our older adults, the left pars opercularis was not connected to the left temporal pole, insula, putamen, and superior parietal lobule, or right precentral gyrus, postcentral gyrus, posterior temporal lobe, insula, and putamen to the same extent as in the younger adults in Xiang et al. (2010). There were additional sites that, despite having apparent connectivity with left pars opercularis in Figure 3.1, did not survive cluster correction (e.g., left posterior middle temporal gyrus). As for right pars opercularis (Figure 3.2), connectivity to left temporal pole, insula, putamen, posterior temporal lobe, and precentral gyrus, as well as right pre- and postcentral gyrus, superior parietal lobule, anterior superior temporal gyrus, insula, and putamen was comparatively lacking.

Compared with the younger participants (Xiang et al., 2010), the left pars triangularis (Figure 3.1) of our older participants was not connected to the left supplementary motor area, superior parietal lobule, postcentral gyrus, or putamen. However, it was connected to some clusters not identified in the younger participants, such as the left posterior banks of the superior temporal sulcus, temporal pole, and superior frontal lobe. Right pars triangularis (Figure 3.2) was not as functionally connected to left putamen, right pre- or postcentral gyrus, right caudate, or right putamen; it was instead

connected to left insula and superior temporal gyrus (including Heschl's gyrus), as well as right superior frontal lobe, middle frontal gyrus, and anterior cingulate.

Finally, the left pars orbitalis (Figure 3.1) in our older adults was not as connected to left caudate and putaman, right caudate and putamen in the younger adults participants in Xiang et al. (2010). Instead, left pars orbitalis was more connected to the left frontal pole, transverse temporal (Heschl's) gyrus, and insula, as well as right posterior superior temporal sulcus. In these participants, the right pars orbitalis (Figure 3.2) was not as connected to the right caudate and putamen as in their younger counterparts. That said, right pars orbitalis was more connected to a variety of other regions, including left middle frontal cortex, supramarginal gyrus, superior frontal lobe, middle to inferior temporal gyrus, and right inferior parietal lobe, superior temporal sulcus to middle temporal gyrus, and cingulate.

The results of our correlation analyses between resting-state functional connectivity and behavioral tasks targeting semantics and phonology do not support the notion of an anterior-to-posterior semantic-to-phonological functional organization in the LIFG. Instead, the correlations in our small sample of neurologically intact participants (n = 10) would suggest that the LIFG in these older adults is potentially more specialized for semantics throughout the region. However, resting-state functional connectivity between pars orbitalis and one of its clusters also correlated with letter fluency, suggesting potential involvement in phonology as well.

Reorganization-Focused Case Series in Participants with Aphasia

In our sample, no participants had damage to pars orbitalis without damage to both other LIFG subregions. As shown in Table 3.8, lesions seemed to progress anteriorly, from pars opercularis to pars orbitalis, such that damage to the more posterior subregions always exceeded that of more anterior subregions (i.e., damage to pars opercularis > pars triangularis > pars orbitalis). Perhaps this is due to the structure of the middle cerebral artery, which supplies this region of the brain. For people with aphasia resulting from stroke etiology, the middle cerebral artery is often the source of the infarct or hemorrhage, given that it broadly supplies the lateral surface of the brain surrounding the Sylvian fissure. Although this same parent artery and primary branch (i.e., superior trunk) typically supplies the entire LIFG (Gibo et al., 1981), the pattern of damage seen in our participants may be due to differences in the secondary branches supplying LIFG subregions.

A91 had the highest level of resting-state functional connectivity in two of the four right hemisphere ROI pairs (i.e., pars opercularis and supramarginal gyrus; pars orbitalis and middle frontal gyrus) and the second highest in a third (i.e., pars triangularis and middle frontal gyrus). Notably, A91 is also the oldest participant in our sample. It is possible that this level of functional connectivity reflects his age, in line with the hemispheric asymmetry reduction in older adults (HAROLD) hypothesis (Cabeza, 2001, 2002). This theory originally suggested that aging contributed to a de-lateralization of specialized cognitive regions in prefrontal cortex. However, research has also provided evidence of de-lateralization in temporal, parietal, occipital, and insular cortex in older adults compared with their younger counterparts, in response to language tasks (Berlingeri et al., 2013). Indeed, A91's resting-state connectivity exceeds the mean of our neurologically intact

participants in three out of four pairs of right hemisphere regions. The mean age of our neurologically intact participants (59.7 years) was almost 20 years younger than A91 (78 years).

A08, A17, and A18 all had lesions prominently affecting pars opercularis, but largely sparing pars orbitalis. Despite the damage to pars opercularis, A08 and A18 demonstrated relatively high performance on the phonological version of tasks, especially the TALSA and WPVT. A18 demonstrated strong functional connectivity between pars orbitalis and middle temporal gyrus (0.72), but A08 did not (0.26). Both demonstrated moderate connectivity between pars triangularis and middle frontal gyrus (0.42), which was slightly higher than the control mean (0.39). A17 did not perform as well on the phonological tasks, despite having higher resting-state connectivity between pars triangularis and middle frontal gyrus (0.60). However, A17 was five years older than A08 and 21 years older than A18. He also experienced his stroke considerably later in life than A08 or A18. Perhaps A17's age at the time of his stroke may account for the heightened functional connectivity seen in the right hemisphere, whereas connectivity between pars triangularis and middle frontal gyrus for A08 and A18 may serve a more compensatory function. However, A14's lesion also prominently affected pars opercularis (in addition to pars triangularis and orbitalis), and despite poor performance on the phonological tasks, she had higher resting-state functional connectivity between right pars triangularis and middle frontal gyrus than A08 or A18 (0.53). She was also younger than A08 by two years and experienced her stroke relatively recently prior to participation (at approximately the same age as A08).

Ultimately, there are many factors that may influence resting-state functional connectivity and it appears that factors we did not or could not consider in the present case series (e.g., lesion load to other left hemisphere regions and pre-morbid levels of resting-state functional connectivity, respectively) likely influenced our participants' connectivity.

Limitations

It is important to consider several limitations in interpreting the findings of the present study. First, there are limitations to using task-free, resting-state functional connectivity to test hypotheses about behavior, particularly language-related behavior. Jackson et al. (2016) demonstrated overlap in the task-active and task-free (resting-state) connectivity of the anterior temporal lobe, an area known to be involved in semantics (Lambon Ralph et al., 2017). The authors suggest that this demonstrates semantic cognition is necessary for the internal processes that occur during rest. While it may also be intuitive that subvocal, inner speech occurring during rest would activate a network overlapping with that involved in phonological processing, this has not explicitly been demonstrated, to the best of the authors' knowledge. Therefore, resting-state functional connectivity between regions suspected to be specialized for phonology may exhibit greater differences from a task-active phonological network.

Next, there are methodological differences between the resting-state functional connectivity analysis we conducted in our sample of neurologically intact older adults and the analysis conducted by Xiang et al. (2010) in a younger cohort. For example, our scanning conditions included participants keeping their eyes open during wakeful rest, we

used a different atlas and procedure to identify the seed regions in the LIFG, and we also used different software (i.e., FreeSurfer) to conduct pre-processing. Although our seeds are likely quite similar to those of Xiang et al. (2010), considering the subregions of the LIFG are defined in relatively similar ways across common atlases, the overall analysis was not identical. Therefore, the differences we identified between our older group and the younger group of Xiang et al. (2010) may, in part, be explained by the differences in our methodologies.

The correlations we conducted between resting-state functional connectivity and behavioral scores on tests of semantics and phonology produced a limited number of significant, positive results. This may be due to our correlation analysis being underpowered by our small sample of neurologically intact older adults (n = 10). Moreover, we did not correct the results of our correlation analysis for multiple comparisons. Therefore, the potential utility of the regions correlated with semantic or phonological scores in neural reorganization during recovery from aphasia should be interpreted with caution.

It was beyond the scope of the present study to explore the patterns of lesion load and resting-state functional connectivity in subcortical structures. However, it has been suggested that the integrity of subcortical structures, such as the dominant (e.g., left) basal ganglia, may be a necessary precursor for reorganization and re-lateralization to the right hemisphere (Crosson et al., 2005). The extent to which lesions in our participants involve subcortical structures may provide insight as to the degree to which these participants were

able to re-lateralize and the effectiveness of this re-lateralization, as compared with potentially maladaptive age-related changes.

Finally, due to the small sample of participants with aphasia (n = 10) and their heterogeneous lesion characteristics, we were not able to statistically analyze the relationship between LIFG lesion load, semantic and phonological performance, and resting-state connectivity. We instead opted for a case series approach to explore these relationships. Although this work produced interesting insights, future work should statistically analyze these relationships in larger samples of people with and without aphasia, including subgroup analyses of individuals with similar lesion profiles.

Future Directions

In order to better understand the differences in functional connectivity of the inferior frontal gyrus in older adults compared with their younger counterparts, it is warranted to conduct a direct comparison with more stringent controls. For example, such a comparison should include equal sized and education-matched samples, identical scanning conditions (e.g., eyes open vs. closed), identical scanning parameters (e.g., scanner, scanning time), the same atlas, and identical pre-processing methods (e.g., motion correction, smoothing). A better understanding of age-related differences in the functional connectivity of the inferior frontal gyrus would clarify the applicability of the HAROLD hypothesis (Cabeza, 2001, 2002) in this region. Larger sample sizes would also allow for more power to detect significant correlations with behavioral tasks.

Another possible direction is to utilize functional ROIs (fROIs) for the subregions of the IFG and/or significant clusters. There are inherent limitations to identifying ROIs with an atlas. Individual differences in functional brain organization may contribute to a proportion of participants showing either no or spurious activation in a given parcel that is defined by an atlas. Moreover, even when activation roughly aligns with the parcellation of an atlas, there can still be problems of reduced activation (i.e., only a portion of the ROI is activated) or missed activation (i.e., activation bleeds over the boundaries of the ROI). These problems can be addressed with the use of fROIs, defined on an individualized basis (Fedorenko et al., 2010). Using functional ROIs entails first defining a relatively large parcel based on activation during task-based fMRI, which is used as a search space in individual subjects. Then, activation within the search-space parcel for each individual participant is defined as their unique fROI. Using this method would allow for more accurate measures of individualized functional connectivity as well as observations related to the size and specific location of individual fROIs across participants.

Finally, as mentioned above, future work should also statistically analyze the relationships between LIFG lesion load, semantic and phonological performance, and resting-state connectivity in larger samples of people with aphasia, including subgroup analyses of individuals with similar lesion profiles. This will provide further insight related to sites of either compensatory or maladaptive reorganization that could be targeted with excitatory or inhibitory non-invasive brain stimulation, respectively. After determining candidate sites, a natural next step would be to test candidate sites in a clinical trial utilizing sham-controlled non-invasive brain stimulation as an adjuvant to semantic and/or

phonological behavioral treatment for individuals with aphasia who have damage to the LIFG. Additional directions include comparing non-invasive brain stimulation target sites determined from these methods with sites chosen for showing greater task-based fMRI activity (Fridriksson, Rorden, et al., 2018), as well as identifying reorganized network connectivity in the setting of damage to regions other than the LIFG.

Conclusions

There are potentially age-related differences in the resting-state functional connectivity of the LIFG in younger and older adults. Additionally, exploring the relationships between lesion-load, functional connectivity, and behavior provides a promising direction for understanding reorganization in post-stroke aphasia. However, age-related right hemisphere activity and functional connectivity should be considered when exploring these potential mechanisms of reorganization involving the right hemisphere in stroke-survivors with aphasia.

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Chapter 4: Manuscript 3

Semantics, Phonology, and the Right Hemisphere Resting-State Functional Connectivity of Stroke Survivors with Aphasia

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Abstract

Numerous studies have suggested functional specialization of the left inferior frontal gyrus, such that the anterior portion (including pars orbitalis) is associated with semantics and the posterior portion (including pars opercularis) is associated with phonology. Given that the left inferior frontal gyrus is often damaged in people with post-stroke aphasia and that recent studies have investigated reorganization in response to short-term, virtual lesions created with transcranial magnetic stimulation, we investigated potential long-term reorganizational mechanisms in chronic aphasia. To do so, we conducted a series of multiple linear regression analyses, predicting semantic and phonological behavior with lesion load to anterior or posterior left inferior frontal gyrus, resting-state functional connectivity between right hemisphere homologues of language regions, and interactions between the two. We included resting-state functional connectivity between three pairs of homologues to reported semantic regions (i.e., anterior inferior frontal gyrus, angular gyrus, and posterior middle temporal gyrus) and between three pairs of homologues to reported phonological regions (i.e., posterior inferior frontal gyrus, anterior superior temporal gyrus, and supramarginal gyrus). We hypothesized that the interactions between lesion load to anterior or posterior left inferior frontal gyrus and resting-state functional connectivity between semantic or phonological homologues, respectively, would be significant predictors of semantic and phonological skills. Our results indicated that the interaction between left anterior inferior frontal gyrus lesion load and right posterior middle temporal gyrus and angular gyrus functional connectivity significantly predicted semantic skills. However, the results were inconsistent across a

variety of subsequent robustness analyses, calling their validity into question. Neither lesion load to posterior inferior frontal gyrus, resting-state connectivity between phonological homologues, or interactions between the two significantly predicted phonological skills. Future studies should clarify the role of right posterior middle temporal gyrus and angular gyrus in reorganization following damage to the left anterior inferior frontal gyrus to determine their potential to serve as target sites for investigations of non-invasive brain stimulation treatment for semantic. Examining the relationship between lesion load to discrete regions, functional neuroimaging, and behavior is a promising direction for improving our understanding of neural reorganization in post-stroke aphasia.

Introduction

It has been suggested by numerous studies utilizing a variety of neuroimaging methods that the subregions of the left inferior frontal gyrus (LIFG) are functionally organized, such that the anterior portion (aLIFG), including pars orbitalis, is associated with semantics and the posterior portion (pLIFG), including pars opercularis, is associated with phonology (Bokde et al., 2001; Burton et al., 2003; Cannestra et al., 2000; Devlin et al., 2003; Gough et al., 2005; Hartwigsen et al., 2017; Lorca-Puls et al., 2017). Considering the LIFG is often damaged in individuals with post-stroke aphasia, the functionality of this region is relevant for diagnosis and treatment. Moreover, the LIFG provides an opportunity to better understand reorganization during recovery from post-stroke aphasia.

Functional changes in response to LIFG disturbance have been explored in both post-stroke aphasia and neurologically intact populations. Hartwigsen and colleagues have completed several studies implementing inhibitory repetitive transcranial magnetic stimulation (rTMS) to create temporary, virtual lesions, followed by task-based functional magnetic resonance imaging (fMRI) to determine the brain's response to the perturbation of aLIFG vs pLIFG. In one recent study, they found a double dissociation showing that inhibiting aLIFG delayed reaction times on a semantic task, while inhibiting pLIFG delayed reaction times on a phonological task in neurologically intact adults (Klaus & Hartwigsen, 2019). A study by Hallam et al. (2018) explored activation and connectivity in people with post-stroke aphasia involving executive-semantic deficits as a result of damage to the LIFG. When post-stroke aphasia participants listened to meaningful sentences, the authors found greater activity in the ventral anterior temporal lobe and

posterior middle temporal gyrus (pMTG) than in controls. They also found that stronger connectivity between pMTG and anterior superior temporal gyrus (aSTG) in the patients predicted better performance on the Camel and Cactus Test of verbal semantic associations (presented as words). This suggests connectivity between the two regions may play a role in preservation or recovery of semantic cognition in the setting of LIFG injury. Notably, Hallam et al. included participants with damage to both pLIFG and aLIFG in their sample. Therefore, while highlighting the potential compensatory activity of aSTG and pMTG, the authors' findings are complicated by the heterogeneous LIFG lesions in the sample.

Other studies have specifically explored the involvement of additional brain regions in response to aLIFG and pLIFG perturbation. For example, Hartwigsen's group (2016) found evidence that the angular gyrus (AG) was able to compensate for the temporarily impaired aLIFG in the short-term based on the fact that semantic decisions were delayed to a greater extent when AG was inhibited immediately prior to inhibition of aLIFG than when only aLIFG was inhibited. The pMTG was not targeted or examined in this study, but a follow-up study investigated its role.

Wawrzyniak et al. (2017) demonstrated a correlation between the connectivity from aLIFG (but not pLIFG) to pMTG and faster response times on a semantically demanding task conducted outside the scanner. They found that this relationship was weaker after inhibitory stimulation (continuous theta burst) virtually lesioned the aLIFG, again demonstrating the consequences of aLIFG damage on semantic performance. Crucially, performance on the semantically demanding task was unchanged when the inhibitory stimulation targeted the pMTG instead. This suggests that the aLIFG was able to

immediately modulate its activity to account for the impaired pMTG, but that the pMTG was not able to do the same in response to aLIFG inhibition. This may contradict the findings of Hallam et al. (2018), but considering the study by Hallam and colleagues involved stroke-survivors with chronic aphasia, it is unclear whether the pMTG may take on a compensatory role in the face of long-term (as opposed to temporary, short-term) damage.

Recalling that the study by Hallam et al. (2018) found that the degree of connectivity between pMTG and aSTG predicted better performance on the Camel and Cactus Test of verbal semantic associations in their participants, the role of the aSTG comes into question. Although the aSTG has been implicated in semantic activity (Visser & Lambon Ralph, 2011), its role consistently reflects sensitivity to auditory stimuli and some results suggest that this is independent of whether input is meaningful (Murphy et al., 2017), calling into question its role in semantics. Functional connectivity has been demonstrated between the aSTG and a distinct set of brain regions that are specialized for auditory-based language, including the supramarginal gyrus (SMG; Jackson et al., 2016). Importantly, the SMG has previously been implicated in phonological processing (Lorca-Puls et al., 2017), specifically in conjunction with the pLIFG (Hartwigsen et al., 2016). Thus, in the study by Hallam et al. (2018) it is unclear whether the aSTG is compensating for semantic or phonological processing that both may have been involved in the verbal (written) version of the Camel and Cactus Test.

Taken together, these studies suggest functional specialization of the aLIFG and pLIFG for semantics and phonology, respectively, and implicate several brain regions in

reorganization following damage to these areas. The AG may play a role in short-term semantic network compensation following aLIFG damage and although the pMTG may not have an impact in the short-term, it may be involved in longer-term recovery. The SMG has demonstrated functional relevance for phonological decisions, in combination with the pLIFG, and is functionally connected to aSTG, a region implicated in auditory linguistic processing.

The present study aims to explore the roles of each of these regions further, specifically in their ability to compensate for lesions to aLIFG and pLIFG. Our goal is to identify potential sites of reorganization that could potentially be targeted with transcranial electrical stimulation stimulation treatments to facilitate recovery. To do so, we have used resting-state functional connectivity data. Resting-state functional connectivity measures the synchronization between the activity in two regions at rest. There are potential confounds to fMRI, such as the question of whether activation reflects effort vs. efficiency (Kiran & Thompson, 2019). Although functional connectivity can be impacted by this issue as well, (e.g., two regions are considered highly functionally connected because they both increased in activity as a result of increasing neurological effort, or a lack of efficiency), relating functional connectivity to behavior strengthens the case for its use in investigations of neural reorganization.

Recent studies have begun to explore the utility of resting-state functional connectivity to reveal mechanisms of reorganization in stroke-survivors with aphasia. In addition to the study mentioned above by Hallam et al. (2018) that related functional connectivity to performance on behavioral assessments, a recent study by Ramage et al.

(2020) used functional connectivity between various regions of interest (ROIs) as predictors for performance on several subtests of the Western Aphasia Battery (WAB; Kertesz, 2006). The authors identified left hemisphere intrahemispheric and bilateral interhemispheric connections that were predictive of language performance on several WAB subtests. Notably, they identified one right hemisphere intrahemispheric connection that was predictive of overall language severity, but this relationship was negative. That is, greater functional connectivity between the right inferior frontal gyrus and right pMTG predicted worse overall aphasia severity. This is reinforced by the ideas that right hemisphere activity in pre-morbidly left-lateralized patients with aphasia may be maladaptive and that increased activity in the right hemisphere seems to be linked with an age-related decline in language skills of neurologically intact older adults (Meinzer et al., 2012).

However, the difficulty remains that in people with post-stroke aphasia, left hemisphere lesions vary in size and are often large, encompassing considerable territory within the language network. Moreover, there is still considerable debate over the potential role of the right hemisphere in recovery from post-stroke language impairment, with research supporting both maladaptive and facilitatory roles for the right hemisphere (Meier, 2022; Turkeltaub, 2015). Therefore, in this preliminary investigation of the potential compensatory mechanisms underlying recovery from post-stroke aphasia caused by lesions affecting the LIFG, we chose to examine resting-state functional connectivity in the right hemisphere, between three pairs of suspected semantic homologues (i.e., right aIFG, pMTG, and AG) and three pairs of suspected phonological homologues (i.e., right pIFG,

aSTG, and SMG). We specifically hypothesized that the interactions between lesion load to aLIFG or pLIFG and resting-state functional connectivity would be significant predictors of semantic and phonological skills. Right hemisphere regions with functional connectivity that significantly predicts language performance, or interactions with lesion load to predict language performance, can be investigated further in future experiments and potentially targeted in non-invasive brain stimulation treatment studies.

Methods

Participants and Behavioral Data Acquisition

We retrospectively analyzed data collected from participants recruited at the Center for the Study of Aphasia Recovery (C-STAR) at the University of South Carolina (UofSC) and the Medical University of South Carolina (MUSC). Participants all met the following eligibility criteria: 1) experiencing a left-hemisphere ischemic or hemorrhagic stroke (without right hemisphere involvement), 2) having chronic aphasia ($\geq$ 12 months post stroke), 3) being between 21 and 80 years old, 4) speaking English as their primary language for $\geq$ 20 years, 5) being able to provide written or verbal consent, 6) having adequate verbal output and auditory comprehension (i.e., a Western Aphasia Battery-Revised Spontaneous Speech or Auditory Comprehension rating scale scores of > 1), and 7) having no contraindications for magnetic resonance imaging (MRI). Individuals with multiple left hemisphere strokes were included if all structural lesions were confined to the supratentorial region.

Table 4.1 Behavioral Assessments

Assessment	Domain	Description
KDT	Semantics	Semantic association of action pictures – The participant points to one of two action pictures best matching the target action picture. 52 points possible.
PPTT	Semantics	Semantic association of object pictures – The participant points to one of two object pictures best matching the target object picture. 52 points possible.
TALSA: Rhyme Judgment, 5-sec unfilled delay (nonwords)	Phonology	Phonological judgments with short-term memory demand – The participant listens to two nonwords and, after a 5-second, unfilled delay, indicates whether they rhymed. 20 points possible.
TALSA: Rhyme Judgment, 5-sec filled delay (nonwords)	Phonology	Phonological judgments with working memory demand – The participant listens to two nonwords and, after a 5-second delay (filled by reading numbers) indicates whether they rhymed. 20 points possible.
PALPA 16: Phonological Segmentation of Initial Sounds (nonwords)	Phonology	Segmentation of initial phonemes of nonwords – The participant listens to a nonword and is asked to point to the initial phoneme from an array of five letters, representing phonemes. 15 points possible.
PALPA 17: Phonological Segmentation of Final Sounds (nonwords)	Phonology	Segmentation of final phonemes of nonwords – The participant listens to a nonword and is asked to point to the final phoneme from an array of five letters, representing phonemes. 15 points possible.

Note. KDT = Kissing and Dancing Test. PALPA = Psycholinguistic Assessment of Language Processing Abilities. PPTT = Pyramids and Palm Trees Test. TALSA = Temple Assessment of Language and Short-term Memory in Aphasia.

Behavioral testing took place at research laboratories at UofSC and MUSC. The Institutional Review Boards at both universities approved the data collection for the respective studies. All participants completed written informed consent prior to participation. All assessments were administered or supervised by American Speech-Language and Hearing Association (ASHA) certified speech-language pathologists with experience working with individuals with aphasia. We identified 101 participants who underwent structural MRI, resting-state functional MRI, and had been administered a

majority of the target assessments of semantic and phonological skills (Table 4.1). Participant demographics are presented in Table 4.2.

Table 4.2 Demographics and Behavioral Assessment Scores

Demographics/Assessment	*N* (%)	
Sex		
Female	38 (38%)	
Male	63 (62%)	
Other	0 (0%)	
Race		
Asian/Pacific Islander	1 (1%)	
Black/African American	26 (26%)	
White	74 (73%)	
Other	0 (0%)	
	M (*SD*)	Range
Age (*years*)	60.24 (10.86)	29-80
Time post-CVA (*months*)	55.16 (53.51)	11-241
PPTT	44.97 (6.55)	14-52
KDT	45.91 (6.10)	12-52
TALSA Rhyme (*filled*)	13.91 (3.06)	7-20
TALSA Rhyme (*unfilled*)	14.78 (2.98)	5-20
PALPA 16	8.56 (3.62)	0-15
PALPA 17	7.35 (4.18)	0-15

Note. *n* = 101. CVA = cerebrovascular accident. KDT = Kissing and Dancing Test. PALPA = Psycholinguistic Assessment of Language Processing Abilities. PPTT = Pyramids and Palm Trees Test. TALSA = Temple Assessment of Language and Short-term Memory in Aphasia.

MRI Data Acquisition and Preprocessing

Participants underwent high-resolution T1- and T2-weighted neuroimaging acquired with a Siemens Trio 3T scanner fitted with a 12-channel head coil. T1-weighted imaging utilized an MP-RAGE sequence with 1 mm isotropic voxels, a 256 x 256 matrix

size, a 9° flip angle, and a 92-slice sequence with repetition time (TR) = 2250 ms, inversion time (TI) = 925 ms, and echo time (TE) = 4.11 ms. T2-weighted scans were acquired using a 3-dimensional T2-weighted SPACE sequence covering the whole head and with a resolution of 1 mm^3 with a field of view = 256 x 256 mm, 160 sagittal slices, variable degree flip angle, TR = 3200 ms, TE = 212 ms. Lesion masks were manually drawn on T2-weighted images by an expert neurologist or trained study staff member, both blinded to the behavioral data. T2-weighted images were also co-registered to participants' T1-weighted images, and the lesions were then spatially transformed to native T1 space using the resulting function.

The cortical surface of each hemisphere was then computationally reconstructed from the T1-weighted anatomical volume using Freesurfer (Dale et al., 1999; Fischl, 2012), after reconstructing the lesioned tissue using the intact right hemisphere (VBG software; Radwan et al., 2021). Preprocessing of the magnetic resonance and fMRI data entailed a standard pipeline. Resting state data were motion corrected, surface-registered to the fsaverage (MNI305) template space, and smoothed on the surface (3mm FWHM). We performed nuisance signal regression of head-motion (6 motion parameters and their 6 temporal derivatives), and ventricular and white matter signals (CompCorr, see Behzadi et al., 2007). We then calculated framewise displacement by taking the sum of the absolute derivatives of the 6 motion parameters for each time point, and censored all timepoints above 1mm framewise displacement. Resting state data were then further preprocessed in MATLAB (2018) using custom scripts. Resting state functional connectivity was

calculated as the Fisher's Z-transformed Pearson's correlation between the mean activation across voxels over the time-course of the resting-state scan in each ROI.

Statistical Analysis

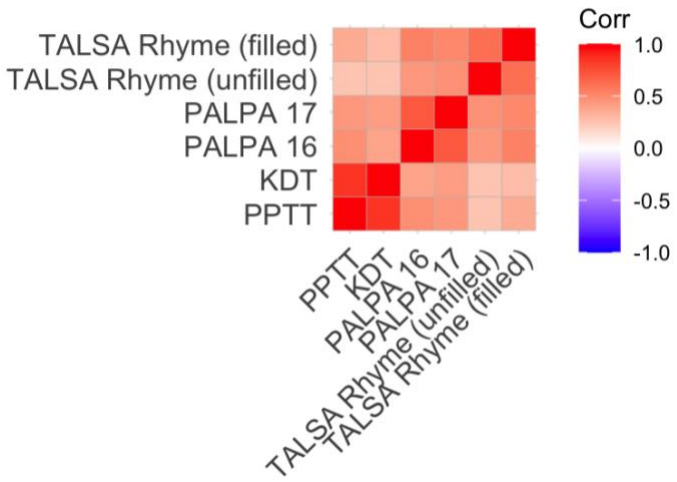
All analyses were performed using R statistical software (R Core Team, 2022). Using the lavaan package in R (Rosseel, 2012), we first conducted a confirmatory factor analysis (CFA), as a data reduction technique, on the behavioral assessments that serve as our outcome measures of interest (Table 4.1). CFA is a statistical technique used to verify the factor structure of a set of observed variables. In this case, we used CFA to confirm the presence of two factors representative of the underlying latent constructs of interest: semantics and phonology. Individual participant scores on these two factors represent a value similar to a composite score. Prior to the CFA, we imputed the median value of eight missing scores (i.e., approximately 1% of total behavioral data) from five unique participants for four different assessments (i.e., Psycholinguistic Assessment of Language Processing Abilities (PALPA) 16, PALPA 17, Temple Assessment of Language and Short-term Memory in Aphasia (TALSA) Rhyme Judgment - filled, and TALSA Rhyme Judgment - unfilled). Given that we selected behavioral tasks that are commonly accepted as involving either semantics or phonology, we chose to use a correlated, two-factor solution for the CFA, where the two semantic assessments loaded onto one factor and the four phonological assessments loaded onto the other (see Table 4.1 for assessments, Figure 4.1 for a correlation matrix of all assessments, and Table 4.3 for the factor loadings of the

CFA). Although the overall chi-square test was significant (χ^2 = 24.26, *df* = 8, *p* = .002), other indices suggest a fair model fit (CFI = .95, RMSEA = .142).

Table 4.3 Confirmatory Factor Analysis Loadings

Observed Variables (Assessments)	Latent Variables (Factors)	
	Phonological Factor Standardized Loadings	Semantic Factor Standardized Loadings
PPTT	0	0.98
KDT	0	0.86
TALSA Rhyme (filled)	0.68	0
TALSA Rhyme (unfilled)	0.60	0
PALPA 16	0.84	0
PALPA 17	0.82	0

Note. *n* = 101. CFA results obtained using maximum likelihood estimation. Interfactor correlation = .55. Factor loadings are standardized by the latent predictor variables and by the outcome variables. Values equal to 0 are fixed rather than freely estimated loadings. CFA = confirmatory factor analysis. KDT = Kissing and Dancing Test. PALPA = Psycholinguistic Assessment of Language Processing Abilities. PPTT = Pyramids and Palm Trees Test. TALSA = Temple Assessment of Language and Short-term Memory in Aphasia.



Note. n = 101. KDT = Kissing and Dancing Test. PALPA = Psycholinguistic Assessment of Language Processing Abilities. PPTT = Pyramids and Palm Trees Test. TALSA = Temple Assessment of Language and Short-term Memory in Aphasia.

Figure 4.1 Behavioral Assessment Correlation Matrix

Next, we used a hypothesis-driven, hierarchical approach to determine whether our predictors of interest (i.e., lesion load to aLIFG or pLIFG, resting-state functional connectivity between right hemisphere homologues of language regions, and the interaction between these) would explain additional variance in language skills above and beyond variables shown to be predictive of language skills. See Table 4.4 for a summary of the outcome and explanatory variables used in all analyses. Our outcome variables consisted of estimated values, for each participant, for the latent phonological and semantic factors determined in the CFA above. These values were estimated using regression. Following our hierarchical analysis, we conducted a data-driven, backward stepwise linear regression analysis, which was used to compare with the results of our hypothesis-driven hierarchical analysis.

Table 4.4 Explanatory and Outcome Variable Summary

Explanatory Variables	*M* (*SD*)	Range
Age	60.24 (10.86)	29-80
LH lesion load	0.15 (0.11)	<0.00-0.55
LH aIFG lesion load	0.28 (0.32)	0.00-0.98
LH pIFG lesion load	0.41 (0.40)	0.00-1.00
RH aIFG-AG connectivity	2.08 (0.44)	0.95-3.40
RH aIFG-pMTG connectivity	1.89 (0.39)	0.84-2.66
RH pMTG-AG connectivity	2.15 (0.39)	1.05-3.91
RH pIFG-SMG connectivity	1.55 (0.43)	-0.88-2.50
RH pIFG-aSTG connectivity	1.15 (0.39)	-0.45-2.10
RH aSTG-SMG connectivity	1.42 (0.37)	0.54-2.21
Outcome Variables		
Phonological factor scores	0.00 (0.93)	-2.41-1.89
Semantic factor scores	0.00 (0.99)	-4.79-1.09

Note. n = 101. Lesion loads were calculated as a proportion of damaged out of total voxels in a given area. Connectivity was calculated as the Fisher's Z-transformed Pearson's correlation between the mean activation across voxels over the time-course of the resting-state scan in each region. Factor sores were estimated for the latent variables from the CFA using the regression method. These factor scores represent participants' performance across four phonological assessments and two semantic assessments. AG = angular gyrus. a/pIFG = anterior/posterior inferior frontal gyrus. aSTG = anterior superior temporal gyrus. CFA = confirmatory factor analysis. LH = left hemisphere. pMTG = posterior middle temporal gyrus. RH = right hemisphere. SMG = supramarginal gyrus.

Hierarchical Linear Regression

We began with two baseline multiple linear regression models (Models 0) including only left hemisphere lesion load (the proportion of lesion volume over the total left hemisphere size for each participant) and age as predictors for phonological and semantic factor scores. There is robust evidence that lesion volume contributes to linguistic behavior in people with aphasia (Johnson et al., 2022). Although age at the time of stroke has also been shown to significantly predict aphasia severity (Johnson et al., 2022), these data were

not available to us. Therefore, age at the time of participation was used as the second predictor. Age has also been associated with changes in the hemispheric lateralization of language (Berlingeri et al., 2013; Cabeza, 2001, 2002), which could impact the degree to which right hemisphere homologues are involved in language processing.

The next two models included our new variables of interest as predictors for phonological factor scores (Model 1) and semantic factor scores (Model 2). In both models, left hemisphere lesion load was used as the first predictor and age was used as the second predictor, in line with our hierarchical approach, to demonstrate whether lesion load to regions within the LIFG, resting-state functional connectivity between right hemisphere language homologues, or the interaction between these would significantly predict semantic or phonological behavior after accounting for the extent of the lesion and age.

In addition to left hemisphere lesion load and age, Model 1 included pLIFG and aLIFG lesion load as categorical variables (i.e., four levels representing 0-24.9%, 25-49.9%, 50-74.9%, and 75-100% damage), resting-state functional connectivity between three pairs of right hemisphere phonological homologues (i.e., pIFG and SMG, pIFG and aSTG, aSTG and SMG), and the interaction between pLIFG lesion load and resting-state functional connectivity between each pair of right hemisphere regions (e.g., pLIFG lesion load × pIFG-SMG functional connectivity), for a total of ten predictor variables. In Model 2, the resting-state functional connectivity predictors consisted of three pairs of right hemisphere semantic homologues (i.e., aIFG and AG, aIFG and pMTG, pMTG and AG) and the interactions included aLIFG lesion load and resting-state functional connectivity

between each pair of these right hemisphere regions (e.g., aLIFG lesion load × aIFG-AG functional connectivity).

In addition to these two models, the same models were run with the opposite outcome variables (i.e., Model 3: explanatory variables for Model 1 used to predict the semantic factor scores; Model 4: explanatory variables for Model 2 used to predict the phonological factor scores). This was done to determine the domain-specificity of our predictors. That is, we wanted to determine whether functional connectivity between the hypothesized semantic and phonological brain regions would predict language performance irrespective of the specific language domain, suggesting less functional specialization of aLIFG and pLIFG. Therefore, we included six planned multiple linear regression analyses in total.

Backward Stepwise Linear Regression

We also planned to complete a backward stepwise selection analysis (i.e., backward elimination) on the models with significant predictors aside from the covariates of left hemisphere lesion load and age. Using the MASS package in R (Venables & Ripley, 2003), variables were chosen at each step based on the model's Akaike information criterion (AIC) and AIC was used to determine the stopping point for the stepwise selection process. Variables were removed when they improved (i.e., reduced) the AIC and the backward elimination process stopped when removing a variable increased the AIC.

Results

Hierarchical Linear Regression Analyses

Baseline Models (0)

Both baseline models were statistically significantly, explaining approximately 24% of the variance in phonological factor scores (Adj. R^2 = .236, $F(2,98) = 16.44$, $p < .001$; Table 4.5) and 19% of the variance in semantic factor scores (Adj. R^2 = .189, $F(2,98) = 12.63$, $p < .0001$; Table 4.6). Individually, both left hemisphere overall lesion load ($p < .0001$) and age ($p < .05$) were significant predictors of phonological factor scores, but only left hemisphere overall lesion load ($p < .0001$) significantly predicted semantic factor scores.

Table 4.5 Model 0 (baseline) - Phonology

Variable name	*B*	*SE*	*t*	*P*	Fit
(Intercept)	1.55	0.49	3.17	.0020	
LH lesion load	-3.98	0.72	-5.57	< .0001	
Age	-0.02	0.01	-2.05	.0427	
					R^2 = 0.251
					Adj. R^2 = 0.236

Note. n = 101. Outcome variable: phonological factor scores. Lesion load was calculated as a proportion of damaged out of total voxels in the left hemisphere overall. Factor sores were estimated for the latent phonological variable from the CFA using the regression method. These factor scores represent participants' performance across four phonological assessments. CFA = confirmatory factor analysis. LH = left hemisphere.

Table 4.6 Model 0 (baseline) - Semantics

Variable name	*B*	*SE*	*t*	*P*	Fit
(Intercept)	0.69	0.53	1.30	.1970	
LH lesion load	-3.92	0.78	-5.01	< .0001	
Age	< 0.00	0.01	-0.18	.8570	
					R^2 = 0.205
					Adj. R^2 = 0.189

Note. *n* = 101. Outcome variable: semantic factor scores. Lesion load was calculated as a proportion of damaged out of total voxels in the left hemisphere overall. Factor sores were estimated for the latent semantic variable from the CFA using the regression method. These factor scores represent participants' performance across two semantic assessments. CFA = confirmatory factor analysis. LH = left hemisphere.

Primary Models (1 and 2)

In Model 1, left hemisphere lesion load, age, aLIFG and pLIFG lesion load, resting-state functional connectivity between three pairs of right hemisphere homologues of phonological regions, and the interactions between pLIFG lesion load and functional connectivity were used to predict participant scores on the phonological factor from our CFA (Table 4.7). We specifically expected the interactions to be significant predictors. The results of Model 1 indicated that although the model was statistically significant, explaining approximately 20% of the variance in phonological factor scores overall (Adj. R^2 = .198, $F(20,80) = 2.24$, $p < .01$), the only significant predictor was left hemisphere lesion load ($p < .001$). Moreover, this model explained less of the variance in phonological factor scores than our baseline model from above (Adj. R^2 = .236, $F(2,98) = 16.44$, $p < .001$).

Table 4.7 Model 1 - Phonology

Variable name	*B*	*SE*	*t*	*P*	Fit
(Intercept)	0.69	0.53	1.30	.1970	
LH lesion load	-3.92	0.78	-5.01	< .0001	
Age	< 0.00	0.01	-0.18	.8570	
LH pIFG load					
25-50%	-0.80	1.25	-0.64	.5244	
50-75%	-1.32	2.18	-0.61	.5461	
75-100%	0.55	1.11	0.50	.6207	
LH aIFG load					
25-50%	0.40	0.30	1.33	.1862	
50-75%	0.02	0.34	0.06	.9508	
75-100%	0.03	0.38	0.07	.9417	
RH connectivity					
pIFG-SMG	-0.28	0.65	-0.44	.6641	
pIFG-aSTG	1.02	0.98	1.04	.3017	
aSTG-SMG	-0.54	0.56	-0.97	.3337	
Interactions					
pIFG-SMG connect. X					
25-50% pIFG load	1.07	1.26	0.85	.3983	
50-75% pIFG load	0.12	2.40	0.05	.9602	
75-100% pIFG load	0.21	0.97	0.22	.8303	
pIFG-aSTG connect. X					
25-50% pIFG load	-1.31	1.66	-0.79	.4340	
50-75% pIFG load	1.21	3.84	0.31	.7543	
75-100% pIFG load	0.26	1.49	0.17	.8642	
aSTG-SMG connect. X					
25-50% pIFG load	0.25	1.30	0.19	.8468	
50-75% pIFG load	-0.46	2.28	-0.20	.8402	
75-100% pIFG load	-0.81	1.08	-0.75	.4579	
					R^2 = 0.359
					Adj. R^2 = 0.199

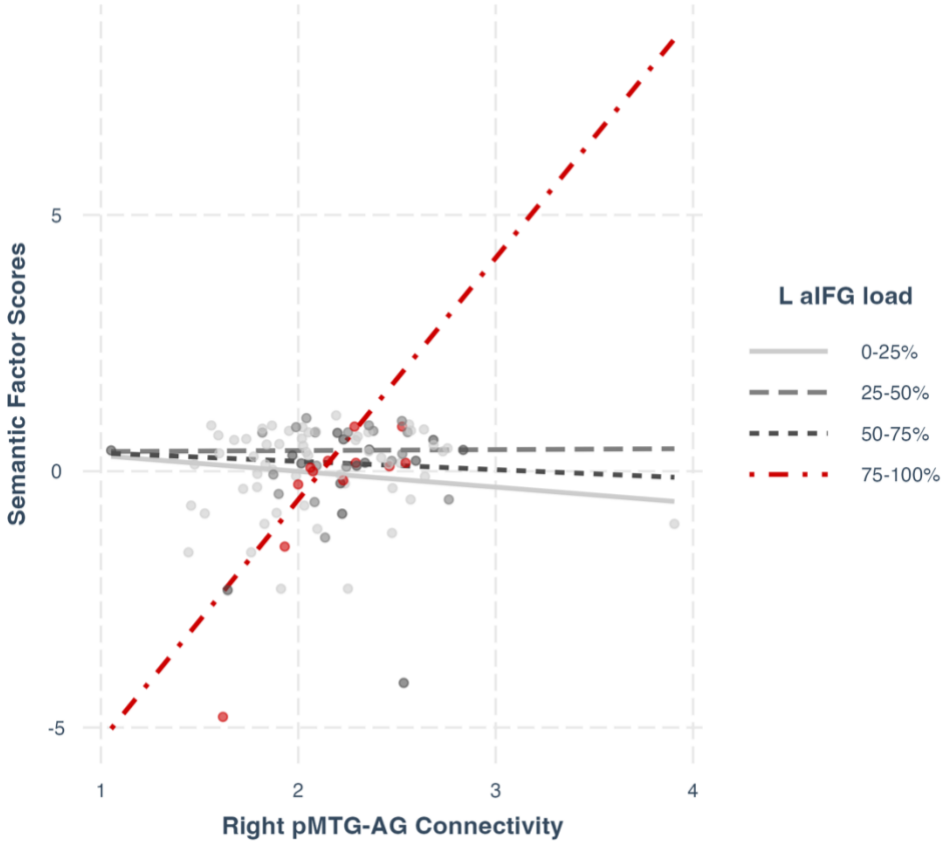
Note. n = 101. Outcome variable: phonological factor scores. Lesion load was calculated as a proportion of damaged out of total voxels. Connectivity was calculated as the Fisher's Z-transformed Pearson's correlation between the mean activation across voxels over the time-course of the resting-state scan in each region. Factor sores were estimated for the latent phonological variable from the CFA using the regression method. These factor scores represent participants' performance across four phonological assessments. a/pIFG = anterior/posterior inferior frontal gyrus. aSTG = anterior superior temporal gyrus. CFA = confirmatory factor analysis. LH = left hemisphere. RH = right hemisphere. SMG = supramarginal gyrus.

In Model 2, left hemisphere lesion load, age, aLIFG and pLIFG lesion load, resting-state functional connectivity between three pairs of right hemisphere homologues of semantic regions, and the interactions between aLIFG lesion load and functional connectivity were used to predict participant scores on the semantic factor from our CFA (Table 4.8). Model 2 was statistically significant, explaining 32% of the variance in semantic factor scores overall (Adj. R^2 = .323, $F(20,80) = 3.39$, $p < .0001$), and included three significant predictors: left hemisphere lesion load ($p < .001$), aLIFG lesion load (for the group with the largest lesions > 75%, $p < .01$), and the interaction between aLIFG lesion load (for the same group with the largest lesions > 75%) and right pMTG-AG functional connectivity ($p < .001$). Model 2 explained more of the variance in semantic factor scores than the baseline model from above (Adj. R^2 = .189, $F(2,98) = 12.63$, $p < .0001$). The relationship between semantic factor scores and the interaction between aLIFG lesion load and right pMTG-AG functional connectivity is shown in Figure 4.2. Figures 4.2-4.5 were constructed using the interactions package in R (Long, 2019).

Table 4.8 Model 2 - Semantics

Variable name	*B*	*SE*	*t*	*P*	Fit
(Intercept)	0.42	0.95	0.45	.6567	
LH lesion load	-4.05	1.01	-4.02	.0001	
Age	-0.01	0.01	-0.72	.4765	
LH aIFG load					
25-50%	0.77	1.84	0.42	.6760	
50-75%	1.16	1.31	0.88	.3798	
75-100%	-7.63	2.27	-3.35	.0012	
LH pIFG load					
25-50%	-0.57	0.31	-1.81	.0745	
50-75%	-0.21	0.35	-0.58	.5639	
75-100%	0.01	0.33	0.04	.9674	
RH connectivity					
aIFG-AG	0.25	0.41	0.62	.5401	
aIFG-pMTG	0.37	0.58	0.63	.5277	
pMTG-AG	-0.31	0.41	-0.74	.4588	
Interactions					
aIFG-AG connect. X					
25-50% aIFG load	0.21	1.37	0.16	.8761	
50-75% aIFG load	-2.56	1.52	-1.69	.0959	
75-100% aIFG load	-1.42	0.89	-1.58	.1174	
aIFG-pMTG connect. X					
25-50% aIFG load	-0.78	1.63	-0.48	.6345	
50-75% aIFG load	2.16	1.37	1.58	.1179	
75-100% aIFG load	-0.01	1.20	-0.01	.9921	
pMTG-AG connect. X					
25-50% aIFG load	0.33	1.37	0.24	.8124	
50-75% aIFG load	0.14	1.24	0.12	.9077	
75-100% aIFG load	5.02	1.30	3.87	.0002	
					R^2 = 0.459
					Adj. R^2 = 0.323

Note. *n* = 101. Outcome variable: semantic factor scores. Lesion load was calculated as a proportion of damaged out of total voxels. Connectivity was calculated as the Fisher's Z-transformed Pearson's correlation between the mean activation across voxels over the time-course of the resting-state scan in each region. Factor sores were estimated for the latent semantic variable from the CFA using the regression method. These factor scores represent participants' performance across two semantic assessments. a/pIFG = anterior/posterior inferior frontal gyrus. AG = angular gyrus. CFA = confirmatory factor analysis. LH = left hemisphere. pMTG = posterior middle temporal gyrus. RH = right hemisphere.



Note. n = 101. The regression line of the interaction is most pronounced for those with the largest lesions to aIFG (dashed red line). This interaction was a significant predictor of semantic factor scores in Model 2 ($p < .05$). AG = angular gyrus. L aIFG = left anterior inferior frontal gyrus. pMTG = posterior middle temporal gyrus.

Figure 4.2 The Interaction Between aLIFG Lesion Load and Right pMTG-AG Connectivity on Semantic Factor Scores

Cross-linguistic Models (3 and 4)

Model 3 consisted of identical predictor variables to Model 1; however, these predicted scores on the semantic factor instead of the phonological factor, to determine whether pLIFG lesion load and functional connectivity between right hemisphere

phonological region homologues would have an impact on language performance across domains (Table 4.9). Similar to Model 1, Model 3 was statistically significant and explained 21% of the variance in semantic factor scores overall (Adj. R^2 = .214, F(20,80) = 2.36, p < .01), but the only significant predictor was again left hemisphere lesion load (p < .0001). Compared to the baseline model predicting semantic factor scores (Adj. R^2 = .189, F(2,98) = 12.63, p < .0001), Model 3 explained additional variance; however, Model 3 explained less of the variance in semantic factor scores than Model 2 (Adj. R^2 = .323, F(20,80) = 3.39, p < .0001). Model 4 consisted of identical predictor variables to Model 2; however, these predicted scores on the phonological factor instead of the semantic factor, to determine whether aLIFG lesion load and functional connectivity between right hemisphere semantic region homologues would have an impact on language performance across domains (Table 4.10). The results followed a similar pattern to Model 3. Model 4 was statistically significant, explaining 19% of the variance in phonological factor scores (Adj. R^2 = .193, F(20,80) = 2.19, p < .01) and left hemisphere overall lesion load was the only significant predictor (p < .0001). Model 4 explained less of the variance in phonological factor scores than the baseline model (Adj. R^2 = .236, F(2,98) = 16.44, p < .001), but was comparable to Model 1 (Adj. R^2 = .198, F(20,80) = 2.24, p < .01).

Table 4.9 Model 3 (cross-linguistic) - Semantics

Variable name	*B*	*SE*	*t*	*P*	Fit
(Intercept)	-0.60	0.99	-0.61	.544	
LH lesion load	-4.61	1.11	-4.15	< .0001	
Age	0.01	0.01	0.79	.433	
LH pIFG load					
25-50%	0.46	1.31	0.35	.729	
50-75%	-1.66	2.29	-0.72	.472	
75-100%	0.55	1.16	0.47	.638	
LH aIFG load					
25-50%	0.42	0.32	1.31	.194	
50-75%	0.18	0.35	0.51	.612	
75-100%	0.39	0.40	0.97	.334	
RH connectivity					
pIFG-SMG	-0.40	0.68	-0.59	.559	
pIFG-aSTG	0.26	1.03	0.26	.798	
aSTG-SMG	0.76	0.59	1.29	.203	
Interactions					
pIFG-SMG connect. X					
25-50% pIFG load	0.11	1.33	0.08	.936	
50-75% pIFG load	0.16	2.53	0.07	.949	
75-100% pIFG load	0.82	1.02	0.80	.425	
pIFG-aSTG connect. X					
25-50% pIFG load	0.27	1.75	0.15	.878	
50-75% pIFG load	3.50	4.04	0.87	.389	
75-100% pIFG load	-1.26	1.57	-0.80	.425	
aSTG-SMG connect. X					
25-50% pIFG load	-0.96	1.36	-0.70	.484	
50-75% pIFG load	-1.91	2.40	-0.80	.428	
75-100% pIFG load	-0.14	1.14	-0.12	.902	
					R^2 = 0.371
					Adj. R^2 = 0.213

Note. n = 101. Outcome variable: semantic factor scores. This model used the same predictors as Model 1 (phonological) to determine their domain specificity. Lesion load was calculated as a proportion of damaged out of total voxels. Connectivity was calculated as the Fisher's Z-transformed Pearson's correlation between the mean activation across voxels over the time-course of the resting-state scan in each region. Factor sores were estimated for the latent semantic variable from the CFA using the regression method. These factor scores represent participants' performance across two semantic assessments. a/pIFG = anterior/posterior inferior frontal gyrus. aSTG = anterior superior temporal gyrus. CFA = confirmatory factor analysis. LH = left hemisphere. RH = right hemisphere. SMG = supramarginal gyrus.

Table 4.10 Model 4 (cross-linguistic) - Phonology

Variable name	*B*	*SE*	*t*	*P*	Fit
(Intercept)	0.93	0.97	0.95	.344	
LH lesion load	-4.27	1.04	-4.12	<.0001	
Age	-0.01	0.01	-1.14	.259	
LH aIFG load					
25-50%	-0.30	1.89	-0.16	.873	
50-75%	-0.87	1.35	-0.65	.519	
75-100%	0.10	2.34	0.04	.965	
LH pIFG load					
25-50%	-0.11	0.32	-0.34	.735	
50-75%	-0.43	0.37	-1.19	.239	
75-100%	-0.01	0.34	-0.03	.975	
RH connectivity					
aIFG-AG	-0.06	0.42	-0.14	.887	
aIFG-pMTG	0.46	0.60	0.77	.447	
pMTG-AG	-0.19	0.43	-0.45	.655	
Interactions					
aIFG-AG connect. X					
25-50% aIFG load	-1.19	1.41	-0.85	.401	
50-75% aIFG load	0.23	1.56	0.15	.885	
75-100% aIFG load	-0.77	0.92	-0.84	.405	
aIFG-pMTG connect. X					
25-50% aIFG load	-0.37	1.67	-0.22	.824	
50-75% aIFG load	-0.17	1.41	-0.12	.906	
75-100% aIFG load	-0.66	1.23	-0.53	.597	
pMTG-AG connect. X					
25-50% aIFG load	1.84	1.41	1.30	.196	
50-75% aIFG load	0.38	1.28	0.30	.768	
75-100% aIFG load	1.37	1.34	1.03	.308	
					R^2 = 0.354
					Adj. R^2 = 0.193

Note. *n* = 101. Outcome variable: phonological factor scores. This model used the same predictors as Model 2 (semantics) to determine their domain specificity. Lesion load was calculated as a proportion of damaged out of total voxels. Connectivity was calculated as the Fisher's Z-transformed Pearson's correlation between the mean activation across voxels over the time-course of the resting-state scan in each region. Factor sores were estimated for the latent phonological variable from the CFA using the regression method. These factor scores represent participants' performance across four phonological assessments. a/pIFG = anterior/posterior inferior frontal gyrus. AG = angular gyrus. CFA = confirmatory factor analysis. LH = left hemisphere. pMTG = posterior middle temporal gyrus. RH = right hemisphere.

Stepwise Backward Elimination Regression Analysis

As planned, we conducted a stepwise backward elimination analysis using the predictor and outcome variables from Model 2 (Table 4.11). This was the only backward elimination regression conducted because Model 2 was the only model from the above multiple linear regression analyses with a significant predictor other than one of the covariates expected to significantly contribute to the outcomes (i.e., left hemisphere lesion load and age) based on previous literature (Johnson et al., 2022). The results of the backward elimination regression included seven of the original ten predictors: left hemisphere lesion load, aLIFG lesion load, resting-state functional connectivity between all three pairs of right hemisphere semantic homologues (i.e., aLIFG, AG, and pMTG) and the interactions between aLIFG lesion load and functional connectivity for two pairs of semantic homologues: aIFG-AG and pMTG-AG. In other words, age, pLIFG lesion load, and the interaction between aLIFG lesion load and functional connectivity between aLIFG and pMTG were eliminated as predictors.

Table 4.11 Stepwise Backward Elimination (Model 2 - Semantics)

Variable name	*B*	*SE*	*t*	*P*	Fit
(Intercept)	-0.19	0.58	-0.32	.7486	
LH lesion load	-4.42	0.93	-4.76	< .0001	
LH aIFG load					
25-50%	0.68	1.79	0.38	.7068	
50-75%	0.76	1.26	0.60	.5471	
75-100%	-6.88	2.18	-3.17	.0021	
RH connectivity					
aIFG-AG	0.29	0.36	0.78	.4357	
aIFG-pMTG	0.66	0.44	1.49	.1390	
pMTG-AG	-0.52	0.37	-1.41	.1631	
Interactions					
aIFG-AG connect. X					
25-50% aIFG load	-0.64	1.04	-0.62	.5381	
50-75% aIFG load	-0.54	1.05	-0.51	.6114	
75-100% aIFG load	-1.59	0.70	-2.26	.0262	
pMTG-AG connect. X					
25-50% aIFG load	0.52	1.15	0.45	0.65	
50-75% aIFG load	0.27	1.09	0.24	.8086	
75-100% aIFG load	4.90	1.16	4.22	< .0001	
					R^2 = 0.413
					Adj. R^2 = 0.326

Note. n = 101. Outcome variable: semantic factor scores. Three of the original predictors from Model 2 were eliminated: age, pLIFG lesion load, and the interaction between aLIFG lesion load and functional connectivity between aLIFG and pMTG. Lesion load was calculated as a proportion of damaged out of total voxels. Connectivity was calculated as the Fisher's Z-transformed Pearson's correlation between the mean activation across voxels over the time-course of the resting-state scan in each region. Factor sores were estimated for the latent semantic variable from the CFA using the regression method. These factor scores represent participants' performance across two semantic assessments. a/pIFG = anterior/posterior inferior frontal gyrus. AG = angular gyrus. CFA = confirmatory factor analysis. LH = left hemisphere. pMTG = posterior middle temporal gyrus. RH = right hemisphere.

Robustness Analyses

Continuous LIFG Lesion Load Predictors

Additional analyses were completed to assess the robustness of Model 2. First, we conducted another multiple linear regression using the same predictors and outcomes

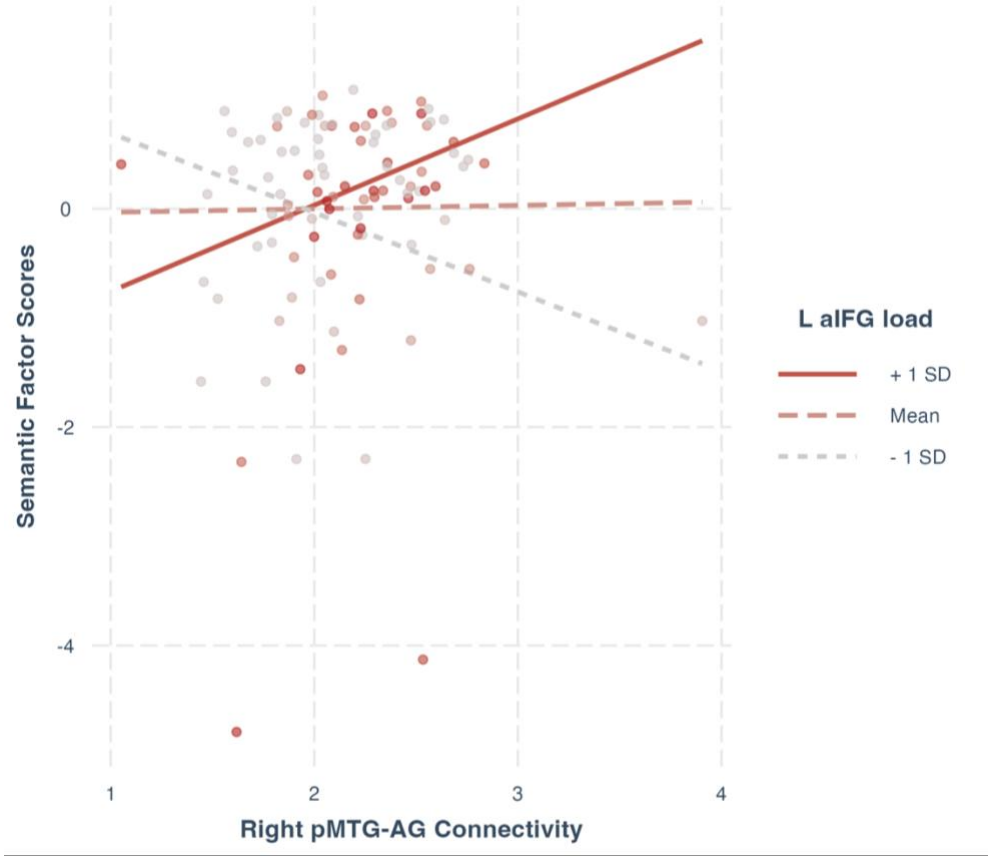
except that aLIFG and pLIFG lesion load were entered as continuous, rather than categorical, variables. In our next multiple linear regression model, we used a transformed version of the semantic factor outcome variable to correct for some observed heteroscedasticity between the fitted observations and residuals of the model. Finally, we removed four potential outliers from our original sample (n = 101) and ran the original Model 2 without them.

Lesion load to aLIFG and pLIFG were entered into our models above as categorical variables in order to promote interpretability and visualization (Fig 4.2). However, we conducted a secondary multiple linear regression using continuous versions of the aLIFG and pLIFG lesion load variables (i.e., percentage of damaged voxels; Table 4.12). The results of this analysis were similar to the original analysis in that the overall model was statistically significant, explaining approximately 25% of the variance in semantic factor scores (Adj. R^2 = .250, $F(10,90) = 4.329$, $p < .0001$); however, the interaction between aLIFG lesion load and right pMTG-AG connectivity was only marginally significant (p = .0543; Figure 4.3), as was the interaction between aLIFG lesion load and right aIFG-AG connectivity (p = .0682). Left hemisphere overall lesion load remained significant (p < .00001).

Table 4.12 Model 2 - Semantics (with continuous predictors)

Variable name	*B*	*SE*	*t*	*P*	Fit
(Intercept)	0.18	0.96	0.19	.8539	
LH lesion load	-5.15	0.98	-5.24	< .0001	
Age	< -0.01	0.01	-0.24	.8119	
LH aIFG load	-1.53	1.73	-0.88	.3806	
LH pIFG load	0.17	0.34	0.50	.6201	
RH connectivity					
aIFG-AG	0.40	0.42	0.95	.3453	
aIFG-pMTG	0.56	0.59	0.95	0.35	
pMTG-AG	-0.63	0.44	-1.42	0.1598	
Interactions					
aIFG-AG connect. X aIFG load	-1.81	0.98	-1.85	.0682	
aIFG-pMTG connect. X aIFG load	0.36	1.35	0.27	.7897	
pMTG-AG connect. X aIFG load	2.37	1.21	1.95	.0543	
					R^2 = 0.325
					Adj. R^2 = 0.250

Note. *n* = 101. Outcome variable: semantic factor scores. In this model, lesion loads were entered as continuous, rather than ordinal (i.e., 0-25%, 25-50%, 50-75%, 75-100%) predictors. Lesion load was calculated as a proportion of damaged out of total voxels. Connectivity was calculated as the Fisher's Z-transformed Pearson's correlation between the mean activation across voxels over the time-course of the resting-state scan in each region. Factor sores were estimated for the latent semantic variable from the CFA using the regression method. These factor scores represent participants' performance across two semantic assessments. a/pIFG = anterior/posterior inferior frontal gyrus. AG = angular gyrus. CFA = confirmatory factor analysis. LH = left hemisphere. pMTG = posterior middle temporal gyrus. RH = right hemisphere.



Note. n = 101. The significant interaction from Model 2 was a marginally significant predictor (p = .0543) of semantic factor scores when IFG lesion loads were entered as continuous variables instead of ordinal. However, the interaction still appears most pronounced for those with the largest aIFG lesions (solid red line). AG = angular gyrus. L aIFG = left anterior inferior frontal gyrus. pMTG = posterior middle temporal gyrus.

Figure 4.3 The Interaction Between Continuous aLIFG Lesion Load and Right pMTG-AG Connectivity on Semantic Factor Scores

Transformation of the Outcome Variable

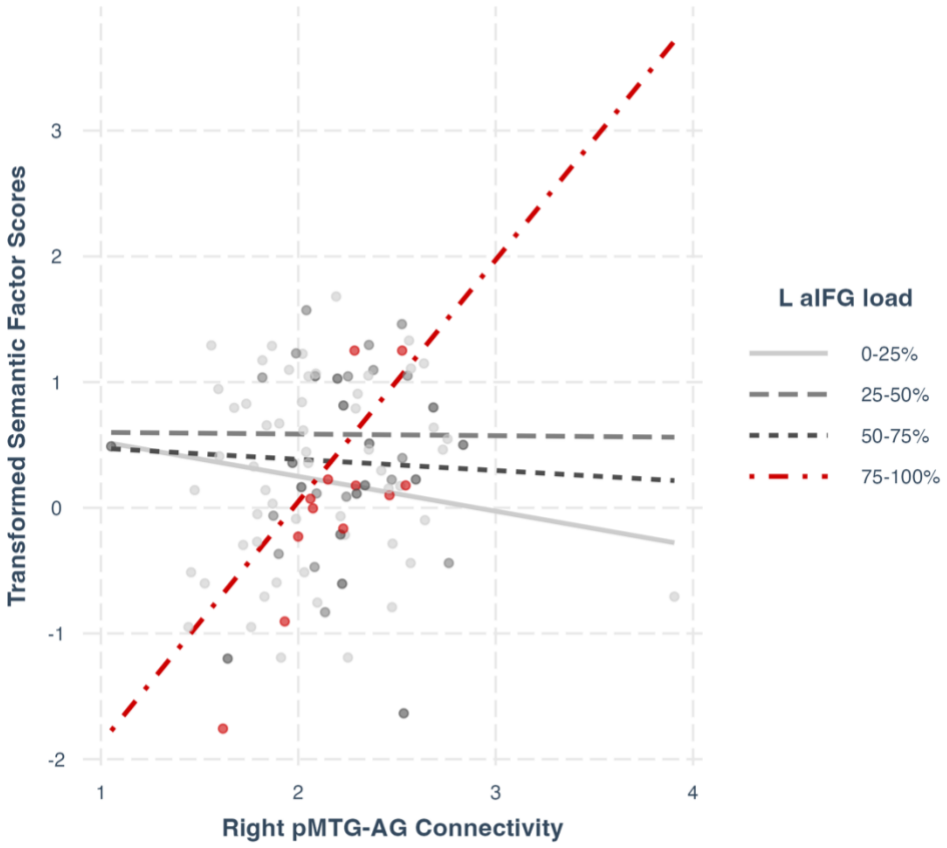
We transformed the semantic factor scores using a Yeo-Johnson power transformation (Yeo & Johnson, 2000), which was selected to preserve the sign of the scores, considering some values were negative. After transformation of the semantic factor scores, we conducted the same regression as the original Model 2 (Table 4.13). This model

was also statistically significant, explaining 26% of the variance in the transformed semantic factor scores (Adj. $R^2 = .259$, $F(20,80) = 2.751$, $p < .001$). The interaction between aLIFG lesion load and pMTG-AG functional connectivity remained significant for the group with the largest aLIFG lesions ($p < .05$), in addition to left hemisphere overall lesion load ($p < .001$). A new predictor was also significant: pLIFG lesion load for the group with 25-50% damage ($p < .05$). The relationship between the transformed semantic factor scores and the interaction between aLIFG lesion load and right pMTG-AG functional connectivity is shown in Figure 4.4.

Table 4.13 Model 2 - Semantics (with transformed outcome variable)

Variable name	*B*	*SE*	*t*	*P*	Fit
(Intercept)	0.24	0.76	0.31	.7557	
LH lesion load	-3.11	0.81	-3.86	.0002	
Age	< -0.01	0.01	-0.17	.8623	
LH aIFG load					
25-50%	0.63	1.47	0.43	.6695	
50-75%	0.84	1.05	0.80	.4242	
75-100%	-3.12	1.82	-1.71	.0905	
LH pIFG load					
25-50%	-0.51	0.25	-2.05	.0432	
50-75%	-0.25	0.28	-0.88	.3803	
75-100%	0.10	0.26	0.39	.6978	
RH connectivity					
aIFG-AG	0.25	0.32	0.77	.4434	
aIFG-pMTG	0.32	0.46	0.69	.4925	
pMTG-AG	-0.28	0.33	-0.84	.4049	
Interactions					
aIFG-AG connect. X					
25-50% aIFG load	0.17	1.10	0.15	.8790	
50-75% aIFG load	-1.81	1.21	-1.49	.1398	
75-100% aIFG load	-0.22	0.72	-0.30	.7640	
aIFG-pMTG connect. X					
25-50% aIFG load	-0.62	1.30	-0.48	0.64	
50-75% aIFG load	1.43	1.09	1.30	.1961	
75-100% aIFG load	-0.55	0.96	-0.57	0.57	
pMTG-AG connect. X					
25-50% aIFG load	0.26	1.10	0.24	.8104	
50-75% aIFG load	0.19	0.99	0.19	.8505	
75-100% aIFG load	2.20	1.04	2.12	.0374	
					R^2 = 0.408
					Adj. R^2 = 0.259

Note. *n* = 101. Outcome variable: semantic factor scores, transformed to reduce heteroscedasticity using a Yeo-Johnson power transformation (Yeo & Johnson, 2000). Lesion load was calculated as a proportion of damaged out of total voxels. Connectivity was calculated as the Fisher's Z-transformed Pearson's correlation between the mean activation across voxels over the time-course of the resting-state scan in each region. Prior to transformation, factor sores were estimated for the latent semantic variable from the CFA using the regression method. These factor scores represent participants' performance across two semantic assessments. a/pIFG = anterior/posterior inferior frontal gyrus. AG = angular gyrus. CFA = confirmatory factor analysis. LH = left hemisphere. pMTG = posterior middle temporal gyrus. RH = right hemisphere.



Note. n = 101. The significant interaction from Model 2 remained a significant predictor of semantic factor scores ($p < .05$) when semantic factor scores were transformed (Yeo-Johnson) to reduce heteroskedasticity. The interaction is still most pronounced for those with the largest lesions to aIFG (dashed red line). AG = angular gyrus. L aIFG = left anterior inferior frontal gyrus. pMTG = posterior middle temporal gyrus.

Figure 4.4 The Interaction Between aLIFG Lesion Load and Right pMTG-AG Connectivity on Transformed Semantic Factor Scores

Excluding Outliers

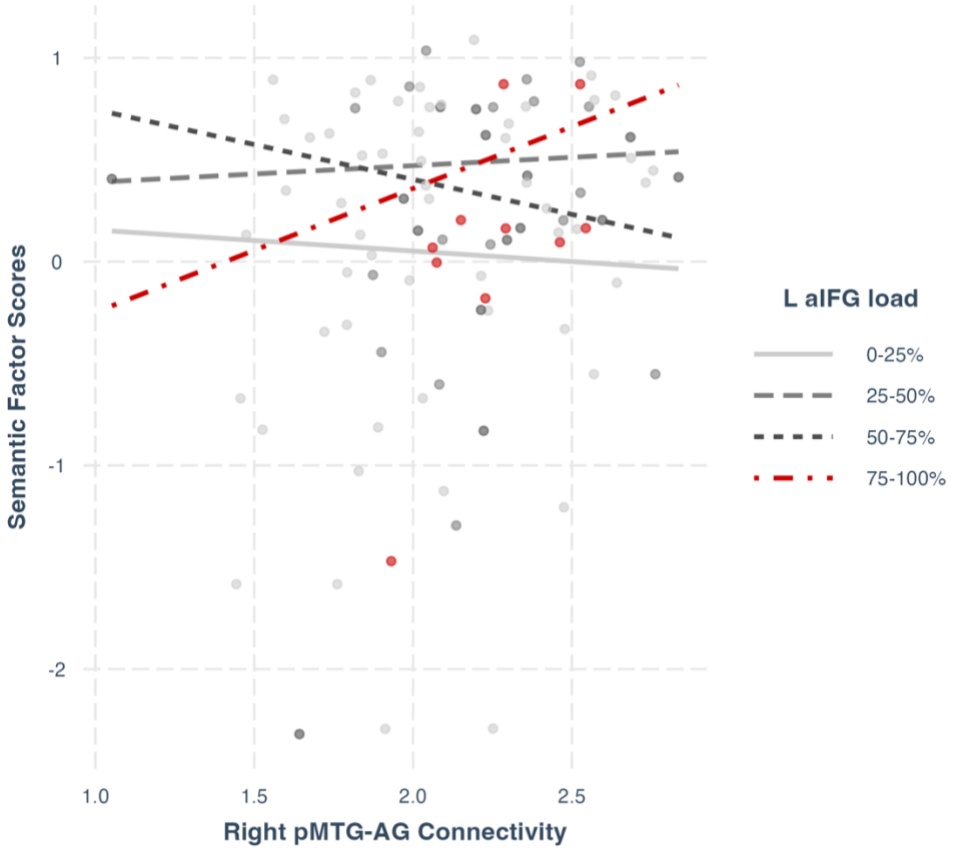
Finally, we excluded four outliers from our original sample (n = 101) for a sample size of 97. Participants removed from the original sample were outliers in terms of semantic factor scores, overall left hemisphere lesion load, and/or functional connectivity between

right pMTG-AG. One of these participants was an outlier on two variables. After removing the four outliers, the model remained significant, explaining 20% of the variance in semantic factor scores (Adj. R^2 = .198, $F(20,76) = 2.185$, $p < .01$; Table 4.14). However, the only significant predictors were left hemisphere overall lesion load ($p < .001$) and lesion load to pLIFG for the group with 25-50% damage ($p < .05$). The relationship between semantic factor scores and the interaction between aLIFG lesion load and right pMTG-AG functional connectivity in this sub-sample is shown in Figure 4.5.

Table 4.14 Model 2 - Semantics (excluding outliers)

Variable name	*B*	*SE*	*t*	*P*	Fit
(Intercept)	-0.53	0.82	-0.65	.5206	
LH lesion load	-3.36	0.94	-3.58	.0006	
Age	< 0.01	0.01	0.37	.7150	
LH aIFG load					
25-50%	1.06	1.56	0.68	.4986	
50-75%	0.55	1.14	0.48	.6297	
75-100%	0.08	2.87	0.03	.9778	
LH pIFG load					
25-50%	-0.54	0.27	-2.00	.0487	
50-75%	-0.42	0.31	-1.39	.1679	
75-100%	0.01	0.28	0.05	.9605	
RH connectivity					
aIFG-AG	0.27	0.34	0.79	.4299	
aIFG-pMTG	0.28	0.51	0.56	.5795	
pMTG-AG	-0.10	0.44	-0.24	.8146	
Interactions					
aIFG-AG connect. X					
25-50% aIFG load	0.23	1.15	0.20	.8440	
50-75% aIFG load	-0.79	1.33	-0.59	0.56	
75-100% aIFG load	0.50	0.85	0.59	.5553	
aIFG-pMTG connect. X					
25-50% aIFG load	-0.79	1.38	-0.57	.5712	
50-75% aIFG load	1.02	1.19	0.85	.3959	
75-100% aIFG load	-1.19	1.09	-1.09	.2786	
pMTG-AG connect. X					
25-50% aIFG load	0.19	1.18	0.16	.8760	
50-75% aIFG load	-0.24	1.06	-0.23	.8228	
75-100% aIFG load	0.71	1.42	0.50	.6190	
					R^2 = 0.365
					Adj. R^2 = 0.198

Note. n = 101. Outcome variable: semantic factor scores. This model was identical to Model 2, except four outliers were excluded. Lesion load was calculated as a proportion of damaged out of total voxels. Connectivity was calculated as the Fisher's Z-transformed Pearson's correlation between the mean activation across voxels over the time-course of the resting-state scan in each region. Factor sores were estimated for the latent semantic variable from the CFA using the regression method. These factor scores represent participants' performance across two semantic assessments. a/pIFG = anterior/posterior inferior frontal gyrus. AG = angular gyrus. CFA = confirmatory factor analysis. LH = left hemisphere. pMTG = posterior middle temporal gyrus. RH = right hemisphere.



Note. n = 97. The significant interaction from Model 2 was no longer a significant predictor of semantic factor scores (p = .6190) when four outliers were excluded. However, the interaction still appears most pronounced (in a positive direction) for those with the largest lesions to aIFG (dashed red line). AG = angular gyrus. L aIFG = left anterior inferior frontal gyrus. pMTG = posterior middle temporal gyrus.

Figure 4.5 The Interaction Between aLIFG Lesion Load and Right pMTG-AG Connectivity on Semantic Factor Scores Excluding Outliers

Discussion

The purpose of the present retrospective analysis was to identify potential sites of compensatory activity in the right hemispheres of stroke-survivors with aphasia. We used multiple linear regression to predict scores on two factors resulting from a CFA: a phonological and a semantic factor. Predictors included overall left hemisphere lesion load,

age, lesion load to aLIFG and pLIFG, as well as rsFC between right hemisphere homologues of suspected semantic and phonological regions. We hypothesized that the interactions between LIFG lesion load and right hemisphere rsFC would predict factor scores, suggesting that synchronization between right hemisphere regions facilitates linguistic performance for individuals with lesions to specific regions of the LIFG. Significant interactions would indicate the potential sites of compensatory activity.

Hierarchical Linear Regression Analyses

The results of our Model 1 did not support the notion of right hemisphere resting-state functional connectivity between homologues of suspected phonological regions facilitating phonological performance independently or based on interactions with pLIFG lesion load in our sample. On the other hand, Model 2 explained additional variance in semantic factor scores beyond that explained by the baseline Model 0. Moreover, the interaction between aLIFG lesion load and rsFC between right hemisphere pMTG and AG significantly predicted semantic factor scores. This interaction appeared to be a unique predictor of semantic performance based on the results of Model 4, where it was not a significant predictor of phonological factor scores. However, this result was not consistent across all robustness analyses.

Stepwise Backward Elimination Regression and Robustness Analyses

The interaction between aLIFG lesion load and pMTG-AG connectivity was selected by the backward stepwise elimination regression that we conducted, among other

predictor variables, but it was only marginally significant in the analysis using continuous versions of the aLIFG and pLIFG variables. After transforming the semantic factor scores to reduce heteroscedasticity, the aLIFG lesion load and pMTG-AG functional connectivity interaction remained significant for the group with the largest aLIFG lesions. However, when removing four participants with outlying factor scores, lesion loads, or connectivity, the results again differed. The interaction between aLIFG lesion load and pMTG-AG connectivity was not significant, but pLIFG lesion load for the group with 25-50% damage was a significant predictor.

It is difficult to interpret the role of pLIFG lesion load predicting semantic factor scores for participants with 25-50% damage in two of our robustness analyses: the final model, excluding outliers, and the model with the transformed semantic factor scores. First, the solution to our CFA produced two correlated factors, one for semantics and one for phonology. Although the correlated two-factor solution was the best solution to our CFA, having correlated factors introduces the potential problem, in our analyses, of increasing the likelihood that lesion loads to the LIFG subregions would predict unexpected behavioral outcomes (e.g., pLIFG lesion load predicting semantic factor scores), even if the subregions are indeed specialized for different functions. However, we attempted to control for this by including both aLIFG and pLIFG lesion loads as predictors in each model, as well as by performing the cross-linguistic analyses in Models 3 and 4. Ultimately, the *B* coefficients were relatively small in both cases (Tables 4.13 and 4.14) and only 12 participants had between 25 and 49.99% damage to the pLIFG. Given the inconsistency of these results, the small coefficients, and such a small group of participants, it is possible

that these results are spurious. If pLIFG lesion load was predictive of semantic factor scores on its own (i.e., without considering interactions with resting-state functional connectivity), we would expect to see the same pattern in participant groups with larger lesion loads. However, we did not see that pLIFG lesion load was predictive of semantic factor scores in the group of 33 participants with at least 75% damage.

As for the outliers, a clear pattern does not emerge related to our hypotheses. The first outlier had a moderately large left hemisphere lesion, with extensive damage to both aLIFG and pLIFG. This participant also had relatively strong functional connectivity between the three pairs of right hemisphere semantic homologues, especially the aIFG and AG. However, their performance on the semantic factor score was the lowest in the sample, hence the reason for their exclusion. The next outlier also had an extremely low semantic factor score and these two participants' scores were far lower than the rest of the sample. This second outlier had an even larger overall lesion – the second largest – that also significantly impacted both the aLIFG and pLIFG, causing them to be an outlier both in terms of their semantic factor score and left hemisphere lesion load. Despite a low semantic factor score, resting state connectivity between this participant's three pairs of semantic homologues was high.

The third outlier had the largest left hemisphere lesion overall, with near complete damage to both the aLIFG and pLIFG. For this participant, functional connectivity was moderate between the right hemisphere semantic homologues, but highest for pMTG and AG. However, their semantic factor score was somewhat low. The fourth and final outlier had, by far, the highest level of resting-state functional connectivity between right pMTG

and AG. Their connectivity was generally high across all right hemisphere region pairs, especially the semantic homologues. Their overall lesion was relatively small, impacting pLIFG more than aLIFG, and their semantic factor score was low. In sum, none of these outlier participants seem to exemplify our hypothesized pattern of having higher semantic factor scores in conjunction with higher right hemisphere functional connectivity between semantic homologues in the presence of prominent aLIFG damage.

Despite inconsistency in the outcomes of the regression models (Tables 4.8 and 4.11-4.14), Figures 4.2-4.5 consistently show that the relationship between semantic factor scores and right hemisphere pMTG-AG connectivity differs based on the degree of lesion load to the aLIFG, suggesting a potential underlying pattern. Future work can clarify the degree to which this pattern may be generalizable to the broader population of stroke-survivors with aphasia or sample-specific.

Pertaining to the functionality of the LIFG, our results tentatively support the notion of functional specialization for semantics in the aLIFG, based on findings that interactions between aLIFG lesion load and right hemisphere semantic homologue functional connectivity significantly predicted semantic factors scores in some of our analyses, but did not predict phonological factor scores in Model 4. Our results regarding the potential functional specialization for phonology in pLIFG are inconclusive. Neither the model predicting phonological factor scores (Model 1) nor the model predicting semantic factor scores (Model 3) included any significant predictors other than the covariate of left hemisphere overall lesion load, which we expected to strongly predict behavior based on

previous findings (Johnson et al., 2022). Ultimately, more work is necessary to confirm the functional specialization of aLIFG and further explore the functionality of the pLIFG.

Limitations

There are several limitations to the current study. First, the use of CFA to reduce the number of outcome variables came at the cost of being able to easily interpret the coefficients of our multiple linear regression analyses, as the change in factor scores is more abstract than change in raw test scores (i.e., via number of points). However, given the numerous predictor variables and interactions in our models, interpreting the resulting coefficients would have likely been a challenge with the use of raw test scores as the outcome variables as well.

Another limitation to the present study is a lack of correction for multiple comparisons. Due to the exploratory nature of the study, we reported the raw *p* values across analyses. With a total of eight analyses, the overall results of Model 2, as well as the models with the continuous predictor variable and transformed outcome variable would remain significant after Bonferroni correction of an α of .05 (i.e., $p < .006$). The model excluding outliers would not remain significant. However, a primary purpose of the present study was to identify whether functional connectivity between any of the pairs of right hemisphere homologues was predictive of behavior in individuals with damage to aLIFG or pLIFG. As such, we planned to interpret the significance of the coefficients to identify meaningful pairs of right hemisphere regions and interactions with lesion load. With correction at the level of individual coefficients, none of these would remain significant.

Conclusion

In conclusion, our results provide preliminary support for the specialization of aLIFG for semantics, as well as the potential role of right hemisphere regions (i.e., pMTG and AG) in compensating for aLIFG damage. The right pMTG and/or AG may serve as candidate sites for excitatory transcranial electrical stimulation, such as tDCS, to promote recovery of semantics in stroke-survivors with aphasia. Prior to moving forward with studies of non-invasive brain stimulation, it would be beneficial to conduct further research to confirm the potentially compensatory role of these brain regions. More work is also necessary to investigate the potential role of right hemisphere brain regions in recovery of phonological language abilities.

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Conflicts of Interest and Sources of Funding

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Chapter 5: General Summary and Discussion

The three manuscripts included in this dissertation have explored the semantic and phonological networks in older adults, the role of the inferior frontal gyrus in these networks, and the potential for right hemisphere resting-state connectivity to inform our understanding of reorganization in post-stroke aphasia following damage to the left inferior frontal gyrus. The first manuscript reported findings from our scoping review of the state of the literature addressing the neural correlates of semantics and phonology in aging adults. The second manuscript presented results of a resting-state functional connectivity seed-based analysis of the inferior frontal gyrus subregions in older adults, as well as a case series in participants with aphasia exploring patterns of connectivity in the right hemisphere. The third and final manuscript presented results of a series of multiple linear regression analyses using lesion load to the left inferior frontal gyrus and resting-state functional connectivity between right hemisphere homologues of language regions to predict semantic and phonological skills in people with chronic post-stroke aphasia.

Our scoping review identified 38 studies that met inclusion criteria. These studies included a variety of participant populations (e.g., neurologically intact older adults, post-stroke aphasia, primary progressive aphasia, Parkinson's disease, dementia, mild-cognitive impairment) and methods (e.g., fMRI, lesion-symptom-mapping, tractography). Most studies had samples of under 100 participants, though many studies came from the same laboratories and may have had overlapping samples. The results of our scoping review

included a distinct set of brain regions with the potential to be specialized for semantics (i.e., left orbitofrontal cortex, temporal pole, inferior temporal gyrus, fusiform gyrus, precuneus, lateral occipital cortex, parahippocampal gyrus, and thalamus, right middle frontal gyrus, and left uncinate fasciculus) and a set potentially specialized for phonology (i.e., left Heschl's gyrus, primary auditory cortex, superior temporal gyrus and sulcus, planum temporale, supramarginal and angular gyri, and arcuate fasciculus). These regions largely overlapped with regions identified in younger adults (Hodgson et al., 2021), with few exceptions (i.e., left precuneus, lateral occipital cortex, and thalamus; right middle frontal gyrus).

Although we anticipated higher levels of right hemisphere involvement, based on accounts of age-related de-lateralization in the prefrontal cortex and language network (Berlingeri et al., 2013; Cabeza, 2001, 2002), the only right hemisphere region identified by our review was the right middle frontal gyrus, implicated in semantics. This region was not identified in the study by Hodgson and colleagues (2021), suggesting a potentially non-linguistic role in younger adults and extra-linguistic recruitment in older adults. Despite many regions with evidence of involvement in both semantics and phonology, few had more evidence for generality than specificity (i.e., more studies found involvement in both a semantic and phonological task than in one or the other). However, we did identify one cortical region (i.e., left middle temporal gyrus) and four white matter association tracts (i.e., left inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus, and internal capsule) that may play a role in both language domains. Although Hodgson and colleagues (2021) do not specifically discuss the

language domain-general regions their meta-analyses identified, they do show that the superior to middle temporal gyrus is a site of overlap in one of their figures. We conclude our scoping review with considerations for a future meta-analysis of the semantic and phonological networks in older adults.

In the second manuscript, we reported results of our resting-state functional connectivity analysis of the inferior frontal gyrus of older adults. Compared with younger adults from Xiang et al. (2010), the right pars triangularis and orbitalis in our older participants have relatively wider-spread patterns of connectivity, potentially due to the effects of age-related de-lateralization (Berlingeri et al., 2013; Cabeza, 2001, 2002). Our correlation analysis revealed eight significant ($p < .10$) positive correlations between behavior and resting-state functional connectivity in the left or right hemisphere. These correlations did not support the notion of an anterior to posterior, semantic to phonological functional organization in the left inferior frontal gyrus (Poldrack et al., 1999; Sakreida et al., 2019). However, this may have been due to various limitations of our design.

Among the left hemisphere functional connectivity, we identified three pairs of regions that also had significant functional connectivity in the right hemisphere (even though it was not correlated with behavior). Therefore, we used these three pairs of regions in the right hemisphere and one additional pair of right hemisphere regions that was correlated with behavior in a case series exploring potential patterns of post-stroke neural reorganization. Interestingly, two of these four pairs of regions involved the middle frontal gyrus. Our case series highlighted some insights and considerations for future studies. Namely, that the potential for age-related de-lateralization, as well as the full extent of the

lesion in both cortical and subcortical territory should be taken into account in studies of neural reorganization that examine the right hemisphere.

Finally, the third manuscript reported our results from a series of multiple linear regression analyses using lesion load to the anterior and posterior left inferior frontal gyrus and right hemisphere resting-state functional connectivity between homologues of semantic and phonological regions, as well as the interactions between these, to predict semantic and phonological skills. We did not find support for right hemisphere resting-state connectivity or left hemisphere inferior frontal gyrus lesion load predicting phonological scores. In our first set of analyses, we did find that the interaction between anterior left inferior frontal gyrus lesion load and resting-state connectivity between right pMTG and AG predicted semantic scores. This was partially corroborated by significant results in one of our robustness analyses using a transformed outcome variable, marginally significant results in another where lesion load to anterior inferior frontal gyrus was entered as a continuous, rather than a categorical predictor, and non-significant results in the final analysis excluding four potential outliers. These results suggest that the right hemisphere posterior middle temporal and angular gyri hold promise as sites of reorganization in response to left anterior inferior frontal gyrus injury. However, further work is necessary to validate these findings and explore alternative mechanisms of reorganization.

Two patterns appear across these three manuscripts. First, the right hemisphere middle frontal gyrus may play a role in the language of older adults. Based on the studies included in our scoping review, this region may be relevant for semantics. However, this region appeared again as a significant cluster connected with pars triangularis in the

resting-state functional connectivity analysis of the neurologically intact older adults in our second manuscript. Moreover, the resting-state connectivity between these two regions was correlated with performance on a phonological task. One of our semantic tasks positively correlated with functional connectivity between pars orbitalis and its significant cluster in the middle frontal gyrus, but this was in the left hemisphere. Although it may be unclear what linguistic role the right middle frontal gyrus plays in older adults (e.g., semantics, phonology, or both), its repeated appearance in these accounts of older adults, in the absence of relevance for younger adults, suggests older adults may recruit this domain-general cognitive region for language. This recruitment may be either a maladaptive or compensatory mechanism related to aging and could be tested in future studies using a variety of methods (e.g., comparing performance before and after inhibiting the region with transcranial electrical stimulation, correlating performance with activity in the region during task-based fMRI).

The other pattern concerns the anterior inferior frontal gyrus, and by extension, orbitofrontal cortex. The results of our scoping review found a potential role for the left orbitofrontal cortex in semantics for older adults, based on the results of the included studies. Neither the posterior inferior frontal gyrus nor its neighboring precentral gyrus was implicated in phonology by the scoping review. Our final manuscript found that participants with lesions to left anterior inferior frontal gyrus may have developed increased functional connectivity between right pMTG and AG as a compensatory mechanism to facilitate semantics, based on the significant interaction in our results. No such results were observed for lesion load to left posterior inferior frontal gyrus. Perhaps

we observed this pattern in our final study due to left anterior inferior frontal gyrus and/or orbitofrontal cortex remaining specialized for semantics in older adults, whereas posterior inferior frontal gyrus does not.

In sum, many open questions remain related to the semantic and phonological networks of older adults, as well as the mechanisms and patterns of reorganization in stroke-survivors with aphasia. However, the three manuscripts included in this dissertation have yielded interesting findings and highlighted future directions. Future work should attempt to statistically analyze the literature related to the semantic and phonological networks of older adults through a meta-analysis, by including additional studies that only examined either semantics or phonology. Additionally, it would be valuable to conduct a controlled analysis to compare the resting-state connectivity of the inferior frontal gyrus in younger and older adults. Finally, future studies should use functional region of interest analyses to explore the resting-state functional connectivity of older adults with and without aphasia to capture individualized activity and connectivity more accurately.

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