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Neural Mechanisms of Lexical Semantics: Investigating the Roles of Hubs and Distributed Action-Perception Systems

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NEURAL MECHANISMS OF LEXICAL SEMANTICS: INVESTIGATING THE ROLES OF HUBS AND DISTRIBUTED ACTION-PERCEPTION SYSTEMS

by

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ABSTRACT

Understanding the meaning of words and concepts is vital for communication, forming relationships, and navigating everyday life. Loss of this knowledge through brain damage can have drastic consequences for one’s health and well-being. It is therefore important to learn how this information is organized anatomically in the brain. In this dissertation, I report a series of structural and functional neuroimaging studies in healthy adults and survivors of stroke seeking to understand how lexical semantics are represented. Specifically, I used a variety of tasks to examine the contributions of putative ‘hubs’ and distributed action-perception systems. Results indicated that damage or disruption of the anterior temporal lobe was associated with impaired lexical access, but not necessarily nonverbal semantic difficulties. Damage to temporoparietal regions, on the other hand, was associated with impaired semantic access or tasks requiring percept-concept linkages. Disconnection of the left inferior frontal cortex from the lexical semantic network was related to worse canonical sentence comprehension, and its role in executively or semantically demanding tasks was supported. Further, damage and disruption of DAPS was shown to be related to impairments in action-related conceptual understanding for both nouns and verbs. Finally, a novel neuroimaging training paradigm in healthy adults revealed a likely role for the ATL in memory and identification of unique entities, independent from semantic demands. Together, these findings provide valuable insight about the anatomical organization of the lexical semantic system in the brain.

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CHAPTER 1

INTRODUCTION

Semantic memory includes one’s knowledge of concepts, objects, relations, facts, and the meanings of words and phrases. Retrieval and manipulation of this knowledge is vital for nearly all aspects of daily life, from simple object use and recognition to maintaining complex interpersonal relationships. A main goal of communication is to convey meaning, and hence semantic memory forms a critical component of language and communication. A variety of neurological conditions, such as stroke and dementias, can lead to severe lexical semantic impairments that prevent effective production or comprehension of language. Investigating the neuroanatomical organization of this system is imperative for the development of better rehabilitation and treatment approaches for a variety of disorders, including aphasia.

Decades of research using complementary methods such as neuroimaging, brain stimulation, and lesion-deficit association has revealed a complex and anatomically distributed lexical semantic system. It has been proposed that this system can be broadly separated into two categories (Binder & Desai, 2011; Desai & Riccardi, 2021; Ralph et al., 2017): putative ‘hub’ regions and distributed action-perception systems (DAPS). Hubs are implicated in semantic processing across many types of conceptual and input modalities, and may include the anterior temporal lobe (ATL), temporoparietal junction (TPJ), and inferior frontal cortex (IFC). DAPS, on the other hand, consist of primary and secondary sensory-motor areas and have been implicated in the representation of specific, corresponding conceptual modalities (e.g., manipulable nouns being partially represented by brain areas involved in tool use). However, the nature and level of contribution of hubs and DAPS to the representation of lexical semantic information remains controversial. This dissertation aims to clarify the specific functions of areas implicated in lexical semantic processing by using lesion-deficit and functional neuroimaging approaches.

Putative Lexical Semantic Hubs: Anterior Temporal Lobe, Temporoparietal Junction, and Inferior Frontal Cortex

Anterior Temporal Lobe

The functions served by the ATL and its subregions are controversial, and separate lines of research have generated theories that are somewhat incongruent. For example, the semantic 'hub and spoke' model proposes that the bilateral ATL stores coherent concepts for all semantic knowledge (Lambon Ralph et al., 2010b; Patterson et al., 2007; Ralph et al., 2017). In contrast to this, the 'dual route' model predicts a strong dissociation between left and right ATL function, with left ATL being involved specifically in lexical access and retrieval (e.g., object naming) and right ATL being involved in access to concepts via pictures (e.g., pyramids and palm trees task) and nonverbal semantics (e.g., thematic picture-picture matching; (Hurley et al., 2018; Mesulam et al., 2013)). Social processing theories, on the other hand, state that the ATL is specifically involved in processing social concepts and linking perceptual information of persons to relevant biographical information such as name or occupation (Olson et al., 2013; Olson et al., 2007; Wang et al., 2017). The ‘unique entities hypothesis’ argues that the ATL is involved in processing unique, one-of-a-kind entities such as famous people or places, with its specific role being name retrieval (Tranel, 2009). Finally, an additional line of evidence that is comparatively underrepresented in the neuroimaging literature demonstrates that portions of the ATL serve more general memory processes (Bowles et al., 2007b; Jackson & Schacter, 2004a; Titiz et al., 2017), introducing the need to experimentally dissociate these memory processes from semantic, social, or name-retrieval confounds. Lines of research produced by these theories have provided results that are challenging to reconcile with each other, making it difficult to parse the roles served by the ATL within the semantic system. Multiple chapters (especially 2, 3, and 6) of the current dissertation probe the functions of the ATL using structural and functional neuroimaging in healthy and clinical populations, and a more comprehensive literature review can be found therein.

Temporoparietal Junction

Similar to the ATL, the TPJ has been identified as an important part of the lexical-semantic system (Binder & Desai, 2011; Binder et al., 2009). Neuroimaging studies demonstrate that the TPJ, specifically the angular gyrus (AG), supramarginal gyrus (SMG), and posterior middle temporal gyrus (pMTG), is activated in response to a wide variety of words and concepts, suggesting that it is involved in semantic processing and feature integration (Binder & Desai, 2011; Bonner et al., 2013; Fernandino et al., 2016). Causal evidence, coming from TMS and lesion studies, has also demonstrated that the TPJ is involved in semantic processing, regardless of the lexicality of the task. For example, Hoffman et al. (2012) administered rTMS to the pMTG of healthy adults and found that it reduced performance in both picture and word versions of a semantic association task. Additionally, TPJ damage has been associated with semantic deficits as measured by a variety of tasks involving picture-based stimuli (Kemmerer et al., 2012; Noonan et al., 2009).

Some parts of this region, specifically the SMG and pMTG, may be involved specifically in lexical and phonological processing, and not necessarily modality-invariant semantic knowledge retrieval (Binder et al., 2016; Hickok & Poeppel, 2004, 2007). Under this framework, phonological wordforms are linked to their meanings, which are stored elsewhere in the brain. Evidence that the TPJ plays a special role in lexical and phonological processes, but not necessarily nonverbal semantics, comes largely from patient studies. For example, Robson et al. (2012) found that word comprehension impairments in patients with TPJ damage are predicted by phonological processing abilities, but not nonverbal semantic skills as measured by the picture version of the Pyramids and Palm Trees test. Using the Boston Naming Test and voxel-based lesion-symptom mapping, Baldo et al. (2013) found that damage to pMTG and underlying white matter was the only region associated with naming deficits after controlling for a variety of motor speech and visual recognition deficits. Additionally, patients with conduction aphasia, characterized by generally intact comprehension but poor speech repetition, have the highest lesion overlap in the TPJ region (Baldo et al., 2008; Buchsbaum et al., 2011; Damasio & Damasio, 1980; Hickok & Poeppel, 2016).

These studies provide evidence that TPJ subregions may not be vital for nonverbal semantic comprehension, and instead may be related to either speech production, or to lexical or phonological processes related to linking wordforms to their meanings. In the current dissertation, Chapter 2 uses lesion-symptom mapping to probe how subdivisions of the TPJ contribute to a variety of lexical and/or semantic tasks, Chapter 3 investigates its role in auditory word comprehension and sentence processing, and Chapters 4 and 5 ask if regions within the TPJ are disproportionately involved in the representation of concepts that have high action-relatedness.

Left Inferior Frontal Cortex

Comprehending a spoken sentence is a complex process that requires coordination of multiple cognitive resources, such as phonological, executive, lexical, syntactic, and semantic operations. Reflecting this complexity, studies demonstrate that the ATL, TPJ, and IFC functionally contribute to sentence processing via a wide variety of cognitive operations (Dronkers et al., 2004; Friederici, 2012; Hagoort & Indefrey, 2014; Walenski et al., 2019). Of these areas, the contribution of the left IFC (LIFC) in sentence comprehension remains particularly controversial.

While the LIFC has traditionally been associated with language production, its role in comprehension is somewhat more controversial (Desai & Riccardi, 2021; Fadiga et al., 2009a; Rogalsky & Hickok, 2011). In regards to sentence processing specifically, results of neuroimaging studies of the LIFC, here defined as Brodmann Areas (BA) 44 and 45, have been inconsistent (for review see Kemmerer (2021)). A meta-analysis of 53 neuroimaging studies comparing sentence listening or reading to control conditions found that the inferior frontal gyrus pars opercularis (IFGoper) and pars triangularis (IFGtri) were only activated in 13 and 23 studies, respectively (Hagoort & Indefrey, 2014). Indeed, multiple neuroimaging studies have found that reading or listening to sentences passively does not activate the LIFC compared to word lists (Humphries et al., 2006; Mazoyer et al., 1993; Rogalsky & Hickok, 2009). However, multiple neuroimaging studies have found LIFC activation for simple phrases and canonical word orders during tasks such as semantic/syntactic violation detection or meaningfulness judgment (Graessner et al., 2021; Schell et al., 2017; Zaccarella & Friederici, 2015). These findings suggest that LIFC may be involved in the comprehension of simple phrases and canonical sentences when there are task-related demands requiring attention to meaning or form. This is compatible with results suggesting that portions of LIFC are language-specific while others are domain general, meaning that LIFC would be most involved in cognitively demanding tasks that involve the storage or manipulation of verbal stimuli (Fedorenko et al., 2011; Fedorenko et al., 2012, 2013). A prediction that follows is that damage to the LIFC should be associated with canonical/simple sentence comprehension impairments when measured by tasks that orient attention to semantic/syntactic error detection or meaningfulness. However, neuropsychological evidence supporting this prediction is relatively scarce. While studies have found involvement of LIFC in sentence production or complex sentence comprehension (den Ouden et al., 2012), negative or mixed results are often found in comprehension of simple or canonical sentences (Caramazza et al., 2005; Kinno et al., 2009; Kinno et al., 2014; Magnusdottir et al., 2013; Wilson et al., 2016).

In Chapter 3, we argue that some of these negative/mixed results regarding canonical sentence comprehension may be due to the types of tasks used to probe sentence processing abilities, as well as methodological limitations such as relying on traditional lesion-symptom mapping techniques without examining more widespread cortical disconnection. Specifically, we investigated the involvement of the LIFC in a novel sentence sensibility judgment task, while controlling for tasks that measure processes involved in sentence comprehension such as auditory single-word comprehension and lexical semantics. We also used connectome-lesion symptom-mapping alongside traditional VLSM. This allowed for the identification of regions/connections that likely contribute to sentence comprehension via lexical semantic processes (i.e., impair all or multiple tasks when damaged), or contribute to sentence comprehension more specifically (i.e., only impairs the sentence comprehension task when damaged).

Distributed Action-Perception Systems: Causal Evidence for Conceptual Representation

As described above, putative ‘hub’ regions are commonly found to contribute to processing a wide variety of concepts (Binder & Desai, 2011; Binder et al., 2009). At the same time, a number of modality-specific areas also appear to contribute to concepts that load heavily on that modality (Kiefer &

Pulvermuller, 2012; Meteyard et al., 2012). This is consistent with the view that DAPS play an important role in representing conceptual knowledge (Barsalou, 2008b). However, causal evidence directly linking disruption of DAPS to specific conceptual deficits has been somewhat limited, especially in post-stroke patient populations (Meteyard et al., 2012). This gap in the literature has led some to argue that DAPS do not directly contribute to conceptual processing, and that they instead play an auxiliary or epiphenomenal role (Caramazza et al., 2014; Mahon, 2015).

In Chapters 4 and 5, we address this gap by investigating the post-stroke neural correlates of semantic impairments for action-related concepts compared to their non-action related counterparts. We used a carefully controlled set of stimuli that matched action and non-action conditions in a variety of possible psycholinguistic confounds that had not been controlled for in previous similar studies. Further, we used multiple methods, including lesion-symptom mapping and resting-state functional connectivity analysis to probe possible contributions of DAPS homologues in the undamaged hemisphere.

Dissertation Aims

Previous studies have revealed the complex and anatomically distributed lexical semantic system, but debate persists regarding the specific functions of the implicated areas. Particularly, the roles of ATL, IFC, and TPJ, three putative ‘hub’ regions that are consistently involved in a wide variety of tasks, require delineation. Outside of these hub areas, another controversy pertains to whether DAPS functionally contribute to the representation of corresponding conceptual modalities. Specifically, this dissertation uses multiple methods to address four main questions.

Aim 1: Delineate the lexical and semantic contributions of ATL and TPJ

What are the lexical and semantic contributions of the left ATL and TPJ? Do both areas serve as modality-invariant semantic hubs, or does their involvement depend on varying lexical and semantic demands? I present data in Chapter 2 from a lesion-symptom mapping investigation using four tasks that vary in their lexical and semantic demands indicated that damage to the left TPJ was associated with impairments to nonverbal semantics (PPT), as well as tasks that require linking words and their associated meanings (two lexical tasks with a semantic component). Damage to ATL impaired tasks with high lexical demands, even if semantic demands are relatively low (e.g., a simple lexical decision task). At the same time, left ATL damage or disconnection was not associated with a nonverbal semantic task (Pyramids and Palm Trees). This finding is difficult to reconcile under the ‘hub and spoke’ theory, as that would predict damage to left ATL should impair all tasks with a semantic component. Instead, this aligns with theories suggesting that the left ATL is vital for lexical access, while left TPJ may play an important role in tasks that require semantic access, regardless of if there is a lexical component.

Aim 2: Investigate the role of putative hubs in sentence comprehension

What are the roles of the IFC, ATL, and TPJ in canonical sentence comprehension? Of these regions, the IFC is especially controversial. Damage to left IFC has inconsistent effects on canonical sentence comprehension, and IFC has traditionally been implicated specifically in production or for complex (as opposed to simple) syntactic structures. However, past neuropsychological studies of simple canonical sentence comprehension have been subject to limitations that must be considered. First, the majority of patient studies measure comprehension by using sentence-picture matching, where incompatible pictures for canonical sentences are created either by switching the positions of the agent and the patient (for reversible sentences) or changing the entity that is the direct object (for nonreversible). This manipulation captures thematic role assignment or single word comprehension, respectively, but does not necessarily capture other aspects of comprehension, especially those related to verb comprehension or the grammatical and semantic coherence of the verb with the noun phrases in the sentence. Using alternative comprehension tasks in patients may provide additional information about the neuroanatomical substrates of sentence processing.

A second limitation is that most patient studies of canonical sentence comprehension have used traditional lesion-deficit association methods, such as region- or voxel-based lesion-symptom mapping (R/VLSM), as opposed to connectome-based lesion-symptom mapping (CLSM). R/VLSM can only detect areas of overlapping necrosis/gliosis. In contrast, CLSM can complement traditional R/VLSM methods by detecting effects of disrupted white matter connectivity resulting from damage anywhere along white matter tracts that connect two grey matter regions. To address these limitations, Chapter 3 (Riccardi et al., 2022a) presents findings using R/VLSM as well as CLSM in chronic stroke survivors to investigate how damage or disconnection of left ATL, TPJ, and IFC was associated with canonical sentence comprehension in a novel auditory sentence sensibility judgment task. We also used four control tasks that measured phonological, lexical semantic, executive, and short-term memory processes to determine whether ATL, TPJ, and IFC were overlapping neural substrates for these processes and sentence comprehension.

Aim 3: Examine the causal contributions of DAPS to conceptual representation

Do DAPS functionally contribute to the representation of corresponding conceptual modalities? Embodied cognitive accounts predict that damage or disruption of DAPS should be associated with greater relative impairments to semantic knowledge pertaining to specific, corresponding conceptual types. This hypothesis has received limited or mixed support in investigations of post-stroke populations, and some limitations must be considered. First, multiple patient studies have directly compared verbs to nouns, introducing confounds that are unrelated to conceptual modality. Comparing within grammatical class (e.g., manipulable vs. non-manipulable nouns or action vs. non-action verbs) while controlling for psycholinguistic variables is important to better understand the role of DAPS in conceptual representation. Second, some studies have used tasks such as picture naming, which do not necessarily require retrieval of deep semantic knowledge related to features such as manipulability or action-relatedness. Using a task that requires deeper semantic analysis of concepts may reveal functional contributions of DAPS. Finally, and as addressed above, prior studies have largely used traditional VLSM methods. Complementary CLSM may reveal associations between the disconnection of DAPS that are not directly damaged by the lesion and impairments in conceptual knowledge.

Presented in Chapters 4 and 5 are two studies (Riccardi et al., 2020; Riccardi et al., 2019) that use V- and CLSM in chronic stroke survivors to investigate whether damage/disruption of DAPS was associated with greater relative impairments to corresponding conceptual modalities, as measured by a semantic similarity judgment task. We compared within grammatical class (e.g., manipulable vs. nonmanipulable nouns and action vs. non-action verbs) and controlled for a variety of psycholinguistic variables. Taken together, these studies found evidence that damage and disruption of primary and secondary DAPS resulted in greater relative impairments for manipulable/action categories compared to the control conditions, providing causal support for theories of embodied cognition.

Aim 4: Investigate the ATL in the identification of unique entities

Although the above studies shed light on the contributions of hubs and DAPS within the lexical semantic system, the specific role of the ATL requires further investigation due to the sheer number of hypotheses that surround the ATL's function. Prior studies have shown that the ATL is associated with name retrieval for unique entities such as famous faces and landmarks (Tranel, 2009), as well as retrieving social information about familiar people (Olson et al., 2013; Olson et al., 2007). However, these findings can be partially accommodated under the semantic hub account because these entities are often part and parcel with rich semantic information (i.e., people tend to know a lot about famous or familiar people and places). As such, the factors of familiarity and semantic knowledge must be dissociated in order to clarify the function of the ATL. Prior studies that have used famous or personally familiar faces and landmarks have not been able to properly distinguish these two factors. Similarly, the ATL has been implicated in training studies wherein participants are trained to associate additional information with visual stimuli, but again it can be unclear if the ATL is involved specifically in the retrieval of associated information or in the identification of specific, familiar entities. These questions establish the need for an fMRI investigation that properly dissociates simple familiarity effects from associated information retrieval. Thus, in a novel training study, participants were exposed to six different categories (persons, objects, buildings, words, non-words, and numbers) of non-famous visual stimuli prior to fMRI scanning, making those stimuli 'familiar'. No additional semantic information was given about the items. These 'familiar' items were then presented to participants in the scanner along with 'unfamiliar' items (i.e., previously unseen stimuli) from the same categories. We addressed two main questions using traditional univariate analysis, as well as multi-voxel pattern analysis (MVPA) which provides increased sensitivity by taking into account patterns of voxel activation. First, is the ATL involved in the identification of familiar compared to novel entities, even when controlling for associated semantic content? Second, what is the scope of the effect of familiarity? That is, will familiarity-related activation in the ATL be restricted to more socially salient stimuli such as persons, as predicted by the social processing account? Or will the effect be seen for any type of entity, including more non-semantic stimuli such as non-words and numbers?

This thesis includes five empirical chapters (Chapters 2-6), which address the aims described above. Three of these chapters (Chapters 3-5) are already published (Riccardi et al., 2022a; Riccardi et al., 2020; Riccardi et al., 2019), with one chapter (Chapter 2) under review.

CHAPTER 2

LEXICAL AND SEMANTIC IMPAIRMENTS AFTER ANTERIOR TEMPORAL AND TEMPOROPARIETAL LESIONS

Introduction

The anterior temporal lobe (ATL[1]) and temporo-parietal junction (TPJ[2]) are putative lexical-semantic 'hubs' (Ralph et al., 2017; Seghier, 2013). Damage to ATL and TPJ in stroke or dementias can cause severe language impairments. However, their specific roles are controversial (Bonner et al., 2013; Bonner & Price, 2013; Persichetti et al., 2021; Simmons & Martin, 2009). One question pertains to their relative contributions to tasks that vary in lexical or semantic demands. The 'hub and spoke' account proposes the ATL integrates and stores all concepts (Ralph et al., 2017). Under this framework, left and right ATL are vital for semantic processing regardless of lexical demands, with a slight preference of left ATL for lexical stimuli (Rice et al. (2015b)). Evidence for this comes from transcranial magnetic stimulation (TMS) and semantic dementia (SD). SD is associated with ATL atrophy (Hodges & Patterson, 2007b), and patients can display semantic impairments for both word- and picture-based semantic tasks (Lambon Ralph et al., 2010b). TMS in healthy adults has found

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[1] Here, we use 'ATL' to refer to approximately the anterior third of the temporal lobe. This definition is consistent with the original hub-and-spoke model in Patterson et al. (2007) and Ralph et al. (2017)

[2] We use the term TPJ to refer to the cluster of areas consisting of angular gyrus, pMTG, pSTG, and supramarginal gyrus. We adopt this term here while keeping in mind that its various sub-regions have differing functionality, and we examine each of its sub-regions individually.

that disruption of left or right ATL impairs semantic processing of both words and pictures (Lambon Ralph et al., 2009; Pobric et al., 2010).

However, evidence also suggests that left ATL is vital for lexical access/retrieval, but not nonverbal semantics. Left ATL resection patients do not usually display semantic impairments (Simmons & Martin, 2009), yet can show impairments on lexical tasks (Warren et al., 2016). SD patients with predominant left ATL atrophy perform abnormally on lexical association tasks, while performance is spared for nonverbal semantic tasks such as picture-picture matching (Mesulam et al., 2013). Left ATL damage impairs naming, but spares access to conceptual information (Tranel, 2009). Impaired conceptual retrieval occurs only after the atrophy spreads into posterior temporal areas or right ATL (Snowden et al., 2018), suggesting that left ATL is necessary for lexical access but not semantics.

Like the ATL, TPJ is an important part of the lexical-semantic system (Binder & Desai, 2011). Angular gyrus (AG) and posterior middle temporal gyrus (pMTG) are activated by many words and concepts, suggesting a role in semantic feature integration (Bonner et al., 2013; Fernandino et al., 2016). TMS to pMTG of healthy adults reduced performance in picture and word versions of a semantic association task (Hoffman et al., 2012). Patients with TPJ damage display comprehension deficits, as measured by multiple picture-based tasks (Kemmerer et al., 2012).

However, some areas in TPJ may be involved specifically in lexical access/retrieval (Hickok & Poeppel, 2007), wherein pMTG maps phonological wordforms to their meanings. Evidence for this comes from studies showing that word comprehension impairments in patients with posterior temporal damage is predicted by phonemic processing abilities, but not nonverbal semantics (Robson et al., 2012). pMTG is highly connected with areas involved in language comprehension (Turken & Dronkers, 2011), suggesting that comprehension deficits may be due to disrupted connectivity between the TPJ and distributed areas involved in deeper semantic processing (Bonilha et al., 2017).

In sum, the contributions of putative hubs to lexical, as opposed to semantic, processing are controversial. Here, we used three complementary lesion-symptom mapping (LSM) methods in left-hemisphere stroke survivors, namely lesion, resting-state connectivity, and fractional anisotropy. Participants performed four tasks that vary in their lexical and semantic demands in a retrospective analysis. We directly compared the neural correlates of performance in these tasks to identify areas important for lexical access and/or nonverbal semantics. Importantly, we included analyses of microstructural integrity and functional connectivity, allowing us to probe potential contributions of unlesioned areas in the right hemisphere.

Materials and Methods

Participants

Neuroimaging data were available for 120 participants (41 female) with unilateral left hemisphere stroke. Past power analysis has demonstrated that samples of ~50 or greater afford sufficient power to detect medium-to-large effects in stroke survivors in most brain areas (Kimberg et al., 2007a).

Participants were at least 6 months post-stroke (M = 39.4 m, years, range=6-237 m) with a mean age at the time of testing of 58.5 years (range = 29-81 y) and mean Western Aphasia Battery (WAB) Aphasia Quotient of 71.3 (SD = 27.1). All participants signed an informed consent, and the University of South Carolina Institutional Review Board approved the research. The data for behavioral tasks were available for between 120 and 59 participants. Differing number of participants in the tasks was due to time constraints during testing or changes in testing protocol over approximately 5 years of data collection.

Materials and Procedure

Four tasks were selected based on their reliance on lexical (L) and/or semantic (S) demands (Table 2.1). Object Naming (ON; number of participants n=120) and Auditory Word Recognition (AWR; n=120) contain both lexical and semantic components (L+S) in that they require processing of a lexical item (either for comprehension or for production), and require object identification. The picture version of Pyramids and Palm Trees (PPT; n=102) task requires judging associations between object pictures, and hence is a primarily semantic task (S). Finally, lexical decision (LD; n=59) is primarily a lexical task (L). Although semantic information is activated implicitly when a word is processed, lexical decision does not strictly require understanding of concept features, and hence can be considered a low-semantic-demand task. By contrasting L, S, and L+S tasks, we can assess the relative contribution of brain regions, especially ATL and TPJ. These tasks are described in more detail below.

Table 2.1 Lexical and semantic demands of the four tasks.

Task	Type
Lexical Decision	L
Object Naming	L+S
Auditory Word Comprehension	L+S
Pyramids and Palm Trees	S

Object Naming

Object naming (ON) and auditory word recognition (AWR) were administered by a licensed speech pathologist as part of the WAB (Kertesz, 2007). Object naming (ON) consists of 20 real objects which the participant must name one-by-one. The patient must orally produce the name of objects that are indicated by the tester. This task requires nonverbal object recognition first, then linking that visual form to the appropriate lexical item, and finally production. ON has moderate semantic demands (i.e., requiring recognition but not deeper conceptual retrieval) and has both lexical and nonverbal requirements.

Auditory Word Recognition

Auditory word recognition (AWR) consists of 60 real objects and pictures. The speech pathologist speaks aloud the name of one of the pictures/objects, and the participant must point to the correct item. In AWR, a word is said aloud to the patient, who must then point to the appropriate picture or object. Similar to ON, AWR also requires linking a wordform to a visual object, but here the visual semantic information is being retrieved after hearing the wordform first.

Lexical Decision

Lexical decision (LD) consisted of 80 verbs, 80 nouns, and 160 phonologically plausible pseudowords presented visually and used in previous studies (Desai et al., 2015; Riccardi et al., 2022b). Participants were instructed to indicate as quickly and as accurately as possible whether the presented word was real or not by pressing one of two buttons. LD is a binary decision about whether the presented word is real, meaning that it is a lexical task with low semantic demands (i.e., retrieval of word meaning is not required for successful completion of the task).

The LD task included presentation of a fixation cross (500 ms), a mask (‘########’, 100 ms), a prime (50 ms), mask (100 ms), followed by the target. The stimuli were presented on a laptop PC running E-prime software (version 1.2, Psychology Software Tools, Inc.) Participants had five seconds to respond. The prime was the same as the target word/pseudoword in capital letters for half of the stimuli, and a consonant string also in capital letters for the other half. Primed and unprimed accuracies were averaged together. There were 160 trials, divided equally between words and pseudowords, in both the verb and noun versions of the LD task. Pseudowords were selected from the English Lexicon Project (ELP) database (http://elexicon.wustl.edu; (Balota et al., 2007)) such that words and pseudowords were matched in number of letters, bigram frequency, orthographic neighborhood size, and LD accuracy.

Picture Pyramids and Palm Trees

The picture pyramids and palm trees (PPT) consists of 52 picture triplets where, for each triplet, the target picture is associated more to one of the two choices (Howard & Patterson, 1992). Participants are instructed to choose which of the bottom two pictures is most associated with the one at the top. PPT has the lowest lexical demands, but highest semantic demands of the tasks used here. Patients must determine which two pictures out of three are the most conceptually related, meaning that in addition to nonverbal object recognition, they must also be able to link objects conceptually while ignoring a distractor item.

MRI Data Acquisition

MRI data were attained with a Siemens 3T Trio System with a 12-channel head coil and a Siemens 3T Prisma System with a 20-channel coil. Participants underwent two anatomical MRI sequences: (i) T1-weighted imaging sequence with an MP-RAGE (magnetization-prepared rapid-gradient echo) [TFE (turbo field echo)] sequence with voxel size = 1 mm3, FOV (field of view) = 256 × 256 mm, 192 sagittal slices, 9° flip angle, TR (repetition time) = 2,250 msec, TI (inversion time) = 925 msec, TE (echo time) = 4.15 msec, GRAPPA (generalized autocalibrating partial parallel acquisition) = 2, and 80 reference lines; and (ii) T2-weighted MRI with a 3D sampling perfection with application optimized contrasts by using different flip angle evolutions (SPACE) protocol with the following parameters: voxel size = 1 mm3, FOV = 256 × 256 mm, 160 sagittal slices, variable flip angle, TR = 3,200 msec, TE = 212 msec, and no slice acceleration. The same slice center and angulation were used as in the T1 sequence.

Functional connectivity was measured using resting-state fMRI imaging. Images were acquired with an EPI sequence with FOV = 208 x 208 mm, 64 x 64 matrix size of 3.25 mm voxels, 75 degree flip angle, 34 axial slices (3 mm thick with 20% gap yielding 3.6 mm between slice centers), TR = 1850 msec, TE = 30 msec, GRAPPA = 2, 32 reference lines, sequential descending acquisition, 196 volumes acquired.

Fractional anisotropy to measure microstructural neural integrity was computed using diffusion tensor imaging (DTI). We used a monopolar sequence with 82 isotropic (2.3 mm) volumes (x10 B = 0, x72 B = 1000), TR = 4987 msec, TE = 79.2 msec, 90 x 90 matrix, with parallel imaging GRAPPA = 2, and 50 contiguous slices. The sequence was acquired in two series (41 and 43 volumes in each series) with opposite phase encoding allowing us to spatially undistort the images with TOPUP.

MRI Preprocessing

Lesions

Lesions were defined in native space by a neurologist (L. Bonilha) in MRIcron (Rorden et al., 2012) on individual T2-weighted images. Preprocessing started with coregistration of the T2-weighted images to match the T-weighted images, allowing the lesions to be aligned to native T1 space. Images were warped to standard space using enantiomorphic (Nachev et al., 2008) segmentation-normalization (Ashburner & Friston, 2005) custom Matlab script (https://github.com/rordenlab/spmScripts/blob/master/nii_enat_norm.m) to warp images to an age-appropriate template image found in the Clinical Toolbox. The normalization parameters were used to reslice the lesion into standard space using linear interpolation, with subsequent lesion maps stored at 1 × 1 x 1-mm resolution and binarized using a 50% threshold (because interpolation can lead to fractional probabilities, this step confirms that each voxel is categorically either lesioned or unlesioned without biasing overall lesion volume). Normalized images were visually inspected to verify quality.

Resting-state functional connectivity

Motion correction for fMRI data was achieved via SPM12's 'relaign and unwarp' default procedure. Slice timing correction was achieved with SPM12. Brain extraction was performed with SPM12's default pm_brain_mask. The extracted mean fMRI volume for each subject was aligned to the extracted T2-weighted image to determine the spatial change between the fMRI data and lesion mask. The fMRI data were spatially smoothed with a 6 mm FWHM Gaussian kernel.

The process outlined in Yourganov et al. (2018b) was used to eliminate lesion artifacts. FSL MELODIC was used to decompose the data into independent components and calculate the Z-scored spatial maps for each component. The maps were then thresholded at $p < .05$ and compared with the lesion mask for that patient. If the overlap (measured via the Jaccard index) between the lesion and the thresholded IC map was greater than 5%, the corresponding component was considered as overlapping significantly with the lesion. These components were then regressed out of the fMRI data using fsl_refilt in the FSL package.

Fractional Anisotropy

The processing of diffusion-weighted images used the pipeline described by Peters et al. (2018). Specifically, diffusion images were undistorted using FSL's TOPUP and Eddy tools with excess scalp removed using the FSL BET tool. FSL's dtifit tool was used to compute an FA map. To improve registration between T1 and DTI spaces, the scalp-stripped (based on segmentation estimates) T1 image was nonlinearly normalized (using SPM12’s ‘old normalization’ function) to match the undistorted FA image. This leverages the similarity of the image intensity in the T1 scan and the FA map, with the high resolution and tissue contrast allowing the T1 scan to achieve superior normalization accuracy. The same transformation matrix was applied to the map of segmented cortical ROIs and the probabilistic white matter map (in T1 space) to transform these maps in DTI space (using nearest neighbor interpolation to preserve discrete regions).

Experimental design and statistical analysis

Our primary aim was to use lesion-symptom mapping (LSM) to directly compare the neural correlates of four tasks (LD, AWR, ON, PPT) requiring various levels of lexical and semantic retrieval. Percent of correct responses for each task was calculated, and these scores were used in subsequent analyses. All following analyses used the NiiStat software (www.nitrc.org/projects/niistat/).

We used three complementary LSM methods: voxel-, region-, and connectome-based (VLSM, RLSM, CLSM; each described in more detail below). In brief, VLSM identifies where damage is associated with behavior at the voxel level within the stroke territory. RLSM, here derived from fractional anisotropy (FA), identifies regions where microstructural integrity is related to behavioral scores. CLSM, derived from resting-state functional-connectivity (rsFC), reveals where disrupted connectivity between any two regions is associated with impairment.

A number of pairwise comparisons are possible using the four tasks, apart from an examination of each task individually. Given our goals for this study, we use the following strategy to identify regions and connections contributing selectively to lexical or semantic processing. First, we used the L task (LD) as a control for lexical processing and compare it against L+S and S tasks. This resulted in three comparisons: AWR vs. LD, ON vs. LD, and PPT vs. LD. Similarly, we used the S task as a baseline, contrasting it against L+S and L tasks. This resulted in two additional comparisons: AWR vs. PPT, and ON vs. PPT. This covers five out of the six possible pairwise comparisons between tasks. For each comparison, the maximum number of participants available for both tasks were used (e.g., n=102 for AWR vs. PPT, and n=59 for AWR vs. LD)

These comparisons were performed for VLSM, CLSM, and RLSM analyses described below. Performance in each task was regressed out from the other in a pairwise manner using the Freedman-Lane method (Freedman & Lane, 1983). This method is used in LSM studies when attempting to quantify relative impairments on different tasks in a single group of participants (Riccardi et al., 2022b; Riccardi et al., 2020; Riccardi et al., 2019), and results are similar to creating a difference score between two tasks or using the 'subtraction method'. In these analyses, lesion volume was included as a covariate and family-wise error was controlled for using permutation correction for multiple comparisons (1000 permutations, $p < .05$). Permutation correction is a nonparametric significance test comparing a test statistic to a null distribution that is derived by randomly permuting existing data. Permutation testing relies on minimal assumptions, approaches exact control of false positives, and is one of the most robust methods for conducting LSM (Baldo & Dronkers, 2018; Baldo et al., 2012).

To improve power and minimize spatial bias, only voxels (or regions) with non-zero values in at least 10% of the patients were considered in the statistical analyses, according to current LSM recommendations (Baldo & Dronkers, 2018; Karnath et al., 2018). All analyses were restricted to a set of 40 bilateral language-specific and domain-general brain regions in the Johns Hopkins University atlas (JHU; (Faria et al., 2012; Wakana et al., 2004)) that directly or indirectly support language production and comprehension (Fig. 2.1; lesion incidence shown in Fig. 2.2), based on work by Fedorenko and colleagues (Fedorenko, 2014; Fedorenko & Thompson-Schill, 2014) and used in previous work from our own group (Schwen Blackett et al., 2022). These regions covered large portions of frontal, parietal, and temporal lobes.

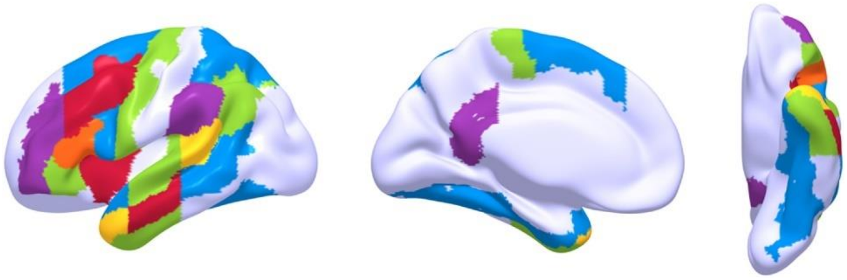

Figure 2.1 20 left-hemisphere language ROIs.

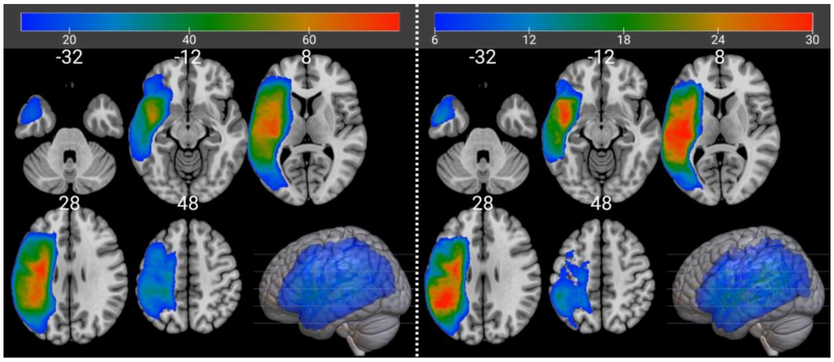

Figure 2.2 Lesion incidence map

Voxel-based lesion-symptom mapping

VLSM was used within the ROI mask for all tasks and task contrasts. Voxelwise lesion incidence map is shown in Fig. 2. VLSM binarily demarcates each voxel as either lesioned or unlesioned and tests the probability that damage to a voxel is associated with behavioral performance (Bates et al., 2003). A t-test is conducted at every voxel within the ROI mask, comparing the performance of the group with damage to that voxel to the group without damage. Results are then thresholded at $p < 0.001$ voxel-wise and cluster-corrected to $p < .05$ using 1000 permutations to robustly correct for familywise error.

VLSM is a powerful method for detecting brain-behavior relationships, but it has limitations that can be partially addressed using complementary CLSM and RLSM methods. First, VLSM can only detect effects within the confines of the stroke territory. In our current patient population, using it in isolation would restrict analysis to the left hemisphere. Resting-state CLSM and fractional anisotropy-derived RLSM can detect effects associated with connectivity or microstructural integrity in brain areas outside of the stroke territory, including in the right hemisphere. Second, due to VLSM's voxel-level spatial resolution it also requires a high degree of spatial overlap between patients to detect effects (i.e., many patients having damage in the same voxel(s)). However, C- and RLSM sacrifice this spatial specificity in favor of averaging values within a given pre-defined brain region, reducing the need for spatial overlap at the individual voxel level. Third, it is possible for two undamaged or only partially damaged brain areas (areas A and B) to display disrupted connectivity following direct damage to area C, and this disrupted connectivity may be behaviorally relevant. Using VLSM alone would only detect a behavioral association with area C, while it is possible for CLSM to detect the behavioral association with poor connectivity between A and B.

Connectivity-based lesion-symptom mapping

CLSM (Gleichgerrcht et al., 2017) was used to investigate whether rsFC between brain regions was predictive of task impairments. To conduct CLSM, a unique rsFC connectome was made for every participant with the following steps: (1) determination of the probabilistic grey matter map from T1-weighted images; (2) segmentation of the grey matter map into 189 ROIs according to the JHU atlas, (3) calculation of the ROI-specific time course of the BOLD signal by averaging across all voxels within each ROI; (4) creating a 189 x 189 correlation matrix for each participant, where positive values indicate greater time-locked activation of two regions; (5) restricting the original 189 x 189 correlation matrix to connections between the 40 bilateral ROIs used in the current study. In these analyses, rsFC strengths between each ROI in the connectome are used in mass univariate general linear models to find associations with task impairments. That is, it identifies where weaker connectivity is associated with worse performance. Using the 40 bilateral ROIs, all connections within the left and right hemispheres (190 connections each) and between hemispheres (400 connections) were considered, and FWE corrected to $p < .05$ using 1000 permutations.

Region-based lesion-symptom mapping

We used fractional anisotropy (FA)-derived RLSM to determine where microstructural integrity was related to behavioral impairment. For each participant, a single FA value was calculated for each of the 40 ROIs, representing that area's microstructural integrity. FA is a measure of directional water diffusion that assesses microscopic brain matter integrity, with intact neural material having more directional diffusion and therefore higher FA (Beaulieu, 2002). Grey matter FA has been used to study traumatic brain injury, Alzheimer's disease, and post-stroke language impairments (Bouix et al., 2013; Riccardi et al., 2020; Weston et al., 2015). Regions within the stroke territory will have low FA, reflecting direct damage due to the stroke. However, FA can also measure structural integrity of perilesional and right hemisphere areas, which may have behavioral associates. FA values in areas outside of the stroke territory reflect microstructural variability across participants due to either the stroke (via long-range disruption or reorganization) or other etiologies (e.g., nonspecific atrophy, etc.). Again, using a mass univariate approach, a general linear model was constructed with region-wise FA scores being used to predict behavioral scores in all 20 left and 20 right hemisphere ROIs to detect where lower FA was related to task impairments, FWE corrected to $p < .05$ using 1000 permutations.

Results

Behavioral

Mean task performance and standard deviation (given as raw scores for PPT (max. 52), AWR (max: 60), and ON (max: 60) and proportion correct LD) were as follows; PPT (47.2 ± 4), AWR (52.8 ± 11.3), ON (43.9 ± 20.7), and LD (.93 ± .07).

Task Comparisons

The focus of the current study was to investigate neural correlates of relative impairments between tasks that varied in their lexical and semantic demands in the same group of participants. Results of the comparisons using LD as a baseline (L+S vs. L; S vs. L), and then using PPT as a baseline (L+S vs. S), are described below. Exact statistical values are provided in the corresponding tables for each analysis.

Results Controlling for Lexical Access

Auditory Word Recognition vs. Lexical Decision

VLSM: Worse AWR compared to LD was associated with damage to two voxel clusters: 1) extending from left AG down into posterior temporal gyri and STG/MTG proper, and 2) in the left ITG/MTGpole. No voxels were significant for LD.

RLSM: Worse AWR compared to LD was associated with lower FA in left AG, pMTG, and pSTG. No areas were significant for LD.

CLSM: Worse AWR compared to LD was associated with disruption of: 1) the left IFGorb to left pMTG, 2) left pSTG to right STG, and 3) left pMTG to right STG. No connections were significant for LD.

Table 2.2 Auditory word recognition vs. lexical decision

	VLSM			RLSM		CLSM	
Condition	Peak Location	Peak Z-score	Cluster size	Location	Z-score	Connection	Z-score
AWR	L pSTG	-5.7	20087	L pMTG	3.3	L pSTG – R STG	4.2
	L MTGpole	-5.2	1946	L pSTG	3.2	L pMTG – L IFGorb	3.9
				L AG	3.1	L pMTG – R STG	3.7
				L STG	2.9		
LD	-	-	-	-	-	-	-

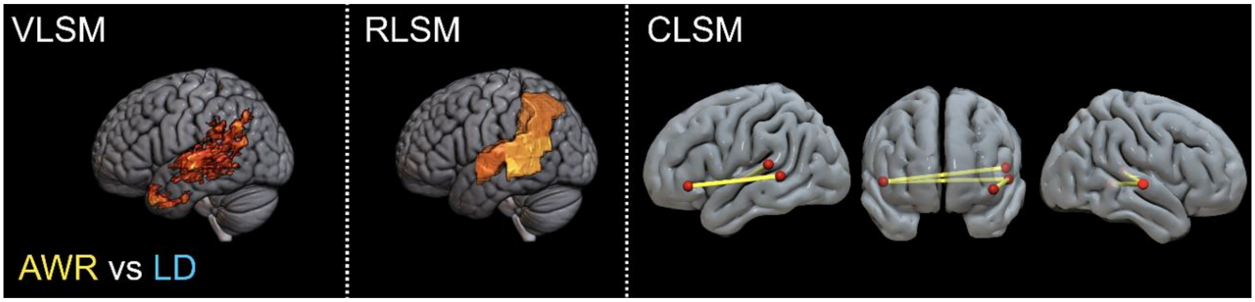

Figure 2.3 Auditory word recognition vs. lexical decision

Object Naming vs. Lexical Decision

VLSM: Worse ON was associated with damage to the left ITG and anterior temporal pole, as well as a cluster of voxels extending from the STG/MTG into the inferior parietal lobe. No voxels were associated with worse LD.

RLSM: No results survived for either ON or LD.

CLSM: Worse ON was associated with lower connectivity between the left IFGorb and left pMTG.

Table 2.3 Object naming vs. lexical decision

	VLSM			RLSM		CLSM	
Condition	Peak Location	Peak Z-score	Cluster size	Location	Z-score	Connection	Z-score
ON	L pSTG	-5.1	11125	-	-	L pMTG – L IFGorb	3.7
	L STGpole	-4.6	1139				
LD	-	-	-	-	-	-	-

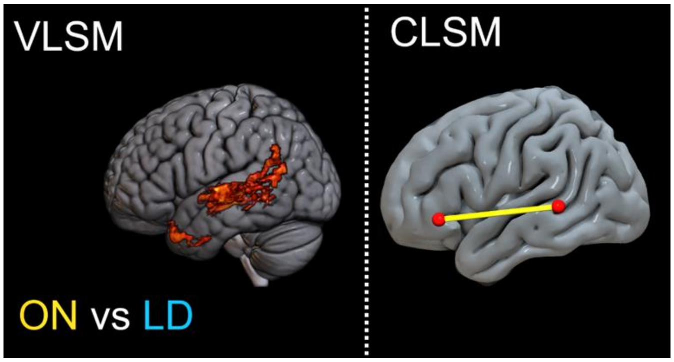

Figure 2.4 Object naming vs. lexical decision

Pyramids and Palm Trees vs. Lexical Decision

VLSM: Worse PPT relative to LD was associated with damage to a cluster of voxels in the AG. Worse relative LD was associated with damage to the left ITG/MTGpole.

CLSM: No connections survived for either task, even at more lenient threshold of p < .1.

RLSM: Worse PPT relative to LD was associated with lower FA in the left pSTG and AG.

Table 2.4 Pyramids and Palm Trees vs. lexical decision

	VLSM			RLSM		CLSM	
Condition	Peak Location	Peak Z-score	Cluster size	Location	Z-score	Connection	Z-score

PPT	L SMG	-4.1	849	L AG	2.8	-	-
				L pSTG	2.8	-	-
LD	L MTGpole	-4.3	1833	-	-	-	-

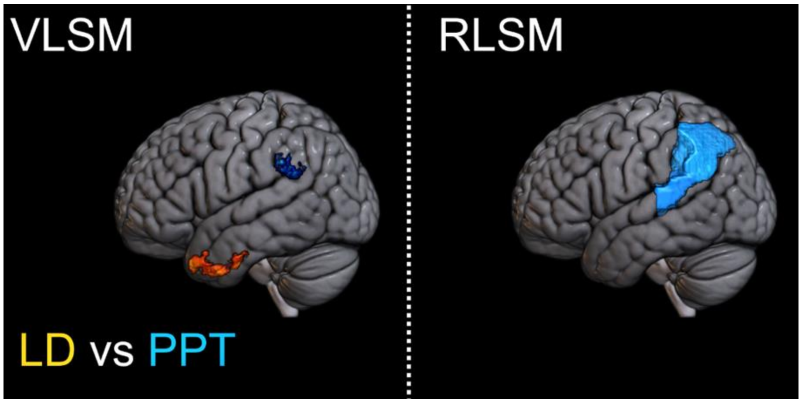

Figure 2.5 Lexical decision vs. pyramids and palm trees

Results Controlling for Nonverbal Semantics

Auditory Word Recognition vs. Pyramids and Palm Trees

VLSM: Worse AWR was associated with damage to voxels in STGpole/MTGpole, extending posteriorly into the temporal lobe. Worse PPT was associated with damage to left frontal voxels, including middle frontal gyrus and prefrontal cortex.

RLSM: Worse AWR was associated with lower FA in left STG, ITG, pSTG, and pMTG. Worse PPT was associated with lower FA in right pMTG.

CLSM: No connections survived for AWR controlling for PPT. Worse PPT was associated with lower connectivity from left to right FuG, and from left superior frontal gyrus to left precentral gyrus.

Table 2.5 Auditory word recognition vs. pyramids and palm trees

	VLSM	RLSM	CLSM

Condition	Peak Location	Peak Z-score	Cluster size	Location	Z-score	Connection	Z-score
AWR	L STGpole	-5.3	12385	L pMTG	3.8	-	
				L STG	3.3		
				L pSTG	3.3		
				L ITG	3.0		
PPT	L SFG (posterior)	-4.7	4656	L PrCG	2.7	L FuG – R FuG	4.5
				R pMTG	2.6	L SFG (posterior) – L PrCG	3.6

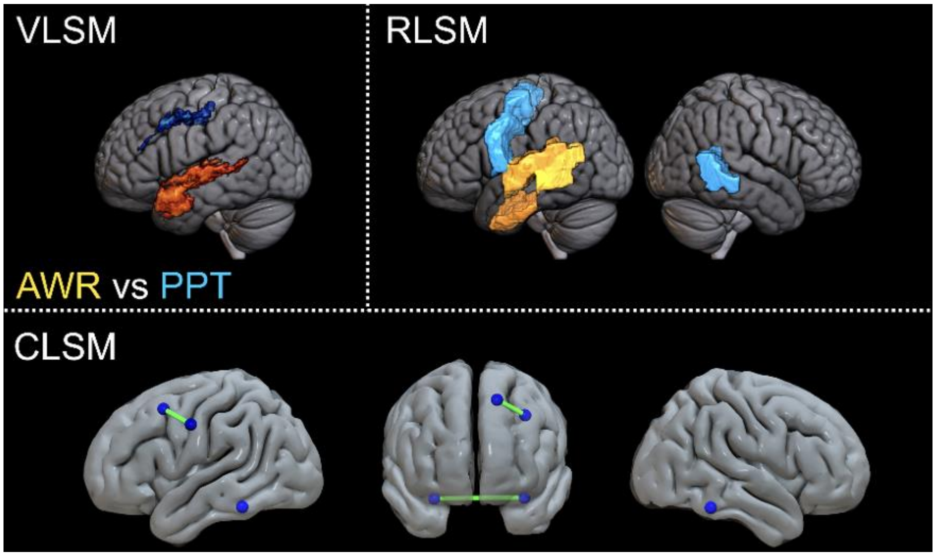

Figure 2.6 Auditory word recognition vs. pyramids and palm trees

Object Naming vs. Pyramids and Palm Trees

VLSM: Worse ON relative to PPT was associated with damage to voxels in the STGpole/MTGpole, extending into the STG. Worse PPT was associated with damage to a cluster of frontal voxels in premotor and motor cortex.

RLSM: Worse relative ON was associated with lower FA in left ITG. No regions were associated with PPT.

CLSM: No connections were associated with ON. Worse relative PPT was associated with lower connectivity between left and right FuG.

Table 2.6 Object naming vs. Pyramids and Palm Trees

	VLSM			RLSM		CLSM	
Condition	Peak Location	Peak Z-score	Cluster size	Location	Z-score	Connection	Z-score
ON	L STG	-4.7	4201	L ITG	2.9	-	-
PPT	L PrCG	-4.6	1888	L PrCG	2.7	L FuG – R FuG	4.1

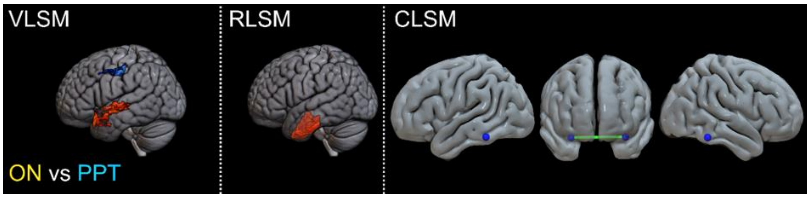

Figure 2.7 Object naming vs. pyramids and palm trees

Auditory Word Recognition vs. Object Naming

VLSM: No voxels survived at p < .05. A more lenient threshold of p < .1 revealed a small cluster of voxels in left MTG/pMTG associated with relatively worse AWR.

RLSM: Worse AWR was associated with lower FA in left pMTG. Worse ON was associated with lower FA in right STG, STGpole, and ITG.

CLSM: Worse relative AWR was associated with worse connectivity between left and right STG. Worse relative ON was associated with left MFG (dorsal prefrontal cortex) and right superior parietal gyrus.

Table 2.7 Auditory word recognition vs. object naming

	VLSM			RLSM		CLSM	
Condition	Peak Location	Peak Z-score	Cluster size	Location	Z-score	Connection	Z-score
AWR	L pMTG*	-5.4*	689*	L pMTG	3.6	L STG - R STG	4.1
ON	-	-	-	R STG	3.0	L MFG (dorsal prefrontal) – R SPG	3.7
				R ITG	2.9		
				R STGpole	2.8		

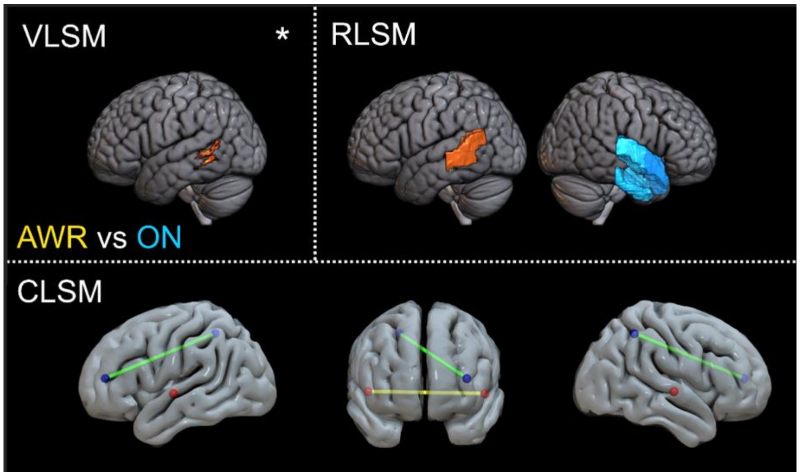

Figure 2.8 Auditory word recognition vs. object naming

Discussion

By using tasks that vary in their lexical and semantic demands, we interrogated the relative contributions of ATL, TPJ, and other language-specific and domain-general areas to these respective processes. Overall, damage to the left ATL was associated with worse performance on all tasks requiring lexical access/retrieval, even in a task with low semantic demands (LD) or after controlling for nonverbal semantic knowledge. Damage to the left AG and posterior temporal gyri was associated with worse performance on tasks with higher semantic demands. Disrupted connectivity of left pMTG/pSTG correlated with impairments on tasks with both lexical and semantic components (ON, AWR) relative to a primarily lexical task (LD). Further, R- and CLSM revealed the importance of microstructural integrity and interhemispheric connectivity of right hemisphere homologues, especially for tasks that require linking either lexical or semantic information to nonverbal stimuli (ON, PPT, AWR).

Anterior Temporal Lobe

Damage to the left ATL, specifically the anterolateral ITG, MTGpole, and STGpole, was associated with worse performance in tasks requiring lexical access/retrieval (LD, AWR, ON), even after controlling for non-verbal semantic performance using the PPT task as a covariate. Anterior temporal areas were not associated with the nonverbal semantic task in any of these analyses. These results support theoretical accounts that highlight the importance of the left ATL in lexical processing (Gainotti, 2007a; Gefen et al., 2013; Mesulam et al., 2013; Snowden et al., 2018; Tranel, 2009). In the present study, left ATL damage and microstructural integrity was associated with impairments to lexical tasks regardless of the level of semantic demands, whether the tasks required production (ON) or comprehension (AWR), or whether the tasks were written (LD) or auditory (AWR). These findings are consistent with several studies of individuals with stroke or PPA. Schwartz et al. (2009) found that in stroke survivors, ATL damage was predictive of the proportion of semantic errors in picture naming, after factoring out non-verbal semantics (assessed by a composite score from the PPT and Camel and Cactus Test). Hurley et al. (2012) examined patients with primary progressive aphasia (PPA) in groups either with mild or severe atrophy in ATL. In picture naming, mild patients could recognize but could not produce names, while severe patients were impaired in both naming and recognition. However, both groups could perform non-verbal semantic tasks such as visual association. N400 abnormalities emerged for lexical (picture-word), but not nonverbal (picture-picture) association tasks. Along similar lines, Mesulam et al. (2013) report PPA patients with ATL atrophy exhibited pure lexical retrieval failures, without a discernable semantic or associative component.

These findings also complement neuropsychological studies that show a relationship between left ATL and lexical demands for proper name retrieval. Those studies focused on patients with semantic dementia or temporal lobe resection, and primarily use lexical/semantic tasks that deal with unique, specific entities (e.g., famous or familiar person/place naming (Gainotti, 2007a; Gefen et al., 2013; Snowden et al., 2018)). Here, we expand that evidence by including tasks that use common names instead of proper names specifically (see also Desai et al. (2023b), where both proper and common names were used).

It is important to note that, while the present results support the hypothesis that the left ATL is especially important for lexical processing and not modality-invariant semantic knowledge representation per se, the results are not entirely incompatible with the 'hub and spoke' account (Ralph et al., 2017). The 'hub and spoke' model allows for 'graded specialization' wherein the left ATL is somewhat more important for processing lexical stimuli than the right ATL (although both left and right ATL functionally contribute to modality-invariant semantic representations; Rice et al. (2015b)). Graded specialization would predict that patients with unilateral left ATL damage could be relatively worse at ON and AWR than the non-verbal PPT task, in line with our current results. However, two of our LSM findings are more difficult to explain under the graded hub framework. Namely, it is not clear that the graded hub would predict that left ATL damage would impair a task with low semanticity/high lexicality (LD) relatively more than a highly semantic task (PPT), or that left ATL damage would have no relationship with performance in a highly semantic, non-verbal task (PPT). Many lines of evidence for the hub-and-spoke account comes from lexical tasks, or from non-lexical semantic tasks in PPA patients. When non-verbal semantic deficits are seen in PPA, the atrophy extends beyond the anterior one-third of temporal lobe. Deficits in visual semantic processing can be, for example, caused by damage to mid-fusiform gyrus. This region falls outside the definition of ATL used here (anterior one third of the temporal lobe) but might fall under ATL in a more expanded definition that includes half of the temporal lobe. An important caveat is also that the medial ATL, especially entorhinal and perirhinal cortex, has also been associated with non-verbal visual semantic processing (Clarke, 2020; Clarke & Tyler, 2014; Visser et al., 2012; Vonk et al., 2020). As is typical for MCA stroke, lesion coverage here does not extend medially. Therefore, present results are compatible with a model incorporating a lateral-medial distinction corresponding to verbal and non-verbal processing in the ATL. In conjunction with previous studies, the current findings suggest that lateral and polar left ATL regions are especially important for lexical access/retrieval.

Temporoparietal Junction

Damage to the left TPJ, including pMTG and AG, was associated with impaired performance on a non-verbal semantic task (PPT). Further, damage and disrupted connectivity of these regions, especially pM/STG, was also associated with worse performance on L+S tasks, when controlling for lexical (LD) or nonverbal semantic (PPT) abilities.

The first finding provides evidence that regions within the TPJ, such as the AG, are involved in semantic processing even in the absence of lexical demands. This aligns with TMS and neuropsychological evidence demonstrating that disruption of this region is associated with worse performance on nonverbal semantic tasks (Hoffman et al., 2012; Kemmerer et al., 2012; Noonan et al., 2009). On the other hand, AG damage was not associated with the task requiring the lowest semantic demands (LD). As such it is likely that the damage is related to nonverbal semantic representation, especially considering that TPJ damage was associated with worse performance on every task that required a nonverbal component (PPT, ON, AWR).

The second finding, that damage/disruption of left pM/STG, is associated with worse ON and AWR performance after controlling for lexical impairments and nonverbal semantics, aligns well with the hypothesis that these regions, especially pMTG, are involved specifically in linking phonological wordforms and their meanings, which are stored elsewhere in the brain (Bonilha et al., 2017; Hickok & Poeppel, 2004, 2007). Additionally, the damage to left ATL and pMTG displayed similar behavioral associates in the current task battery. In light of this, and considering the observed connectivity between left posterior temporal gyri and left inferior frontal cortex or right temporal lobe, we propose that the left ATL and pMTG work together in order to link lexical items to corresponding semantic information which may be represented in distributed brain areas.

Right Hemisphere Connectivity and Microstructural Integrity

C- and RLSM highlighted the importance of the right hemisphere in tasks involving nonverbal semantics. Bilateral visual ventral stream connectivity was associated with PPT, as was microstructural integrity of the right MTG. ON performance was related to microstructure of right ATL, and bilateral connectivity between posterior temporal regions was important for AWR. Taken together, these right hemisphere findings support theories similar to Paivio’s dual-coding model (Paivio, 1991). In this framework, the left hemisphere is important for verbal representations, while the right hemisphere works in conjunction with the left to support nonverbal conceptual processing or imagery. The current results suggest a stronger division of labor between the left and right ATLs than is suggested by the ‘graded specialization’ hypothesis. That is, ‘graded specialization’ would still predict that the nonverbal semantic task (PPT) should be associated with left ATL damage compared to a lexical task with minimal semantic demands (LD), while our results suggest the opposite.

Conclusion

Here, we used tasks that varied in their lexical and semantic demands to interrogate the specific roles of putative hubs within the lexicosemantic system. LSM revealed that damage to the left lateral ATL was associated with worse performance on all tasks requiring lexical access. Damage to the left ATL was not associated with a non-verbal semantic task, but right hemisphere language homologues, especially temporal areas, were related to tasks requiring linkages between lexical and semantic information and nonverbal stimuli. These findings support the hypothesis that the left lateral ATL is especially vital for lexical processing, and not necessarily modality-invariant semantic representations (Hickok & Poeppel, 2007; Mesulam et al., 2013; Snowden et al., 2018). A role for the right hemisphere in processing nonverbal semantics is also suggested. Damage to TPJ, especially the left AG, was associated with worse performance in all tasks that required a non-verbal semantic component. This provides further evidence that the left AG represents semantic information, even in the absence of a lexical component (Binder et al., 2009; Hoffman et al., 2012; Kemmerer et al., 2012).

CHAPTER 3

CANONICAL SENTENCE PROCESSING AND THE INFERIOR FRONTAL CORTEX

Introduction

Comprehending a spoken sentence is a neurobiologically complex process that requires coordination of multiple cognitive resources, such as phonological, executive, lexical, syntactic, and semantic functions. Reflecting this complexity, neuroimaging and neuropsychological studies demonstrate that numerous and distributed brain areas functionally contribute to sentence comprehension (Dronkers et al., 2004; Friederici, 2012; Hagoort & Indefrey, 2014; Walenski et al., 2019). Of these areas, the functional contribution of the lateral inferior frontal cortex (LIFC) in sentence comprehension remains particularly controversial.

Results of neuroimaging studies of sentence processing tasks in the LIFC, especially with respect to BA 44 and 45, have been inconsistent (for review see Kemmerer (2021)). A meta-analysis of 53 neuroimaging studies comparing sentence listening or reading to control conditions found that the inferior frontal gyrus pars opercularis (IFGoper) and pars triangularis (IFGtri) were only activated in 13 and 23 studies, respectively (Hagoort & Indefrey, 2014). However, an additional analysis within the same study compared sentences with high syntactic or semantic demands to comparatively simpler sentences and found that LIFC activation was reliably associated with more complex sentences.

Indeed, multiple neuroimaging studies have found that reading or listening to sentences passively does not activate the LIFC compared to word lists (Humphries et al., 2006; Mazoyer et al., 1993; Rogalsky & Hickok, 2009), yet it is recruited when the task requires the detection of semantic or syntactic violations (Rogalsky & Hickok, 2009). These findings suggest that LIFC involvement in sentence comprehension may be primarily driven by semantic/syntactic difficulty or executively related task demands, raising the question of whether the LIFC functionally contributes to the comprehension of declarative canonical sentences. On the other hand, some studies do indicate activation in LIFC even for relatively simple phrases and sentences. For example, Zaccarella and Friederici (2015) showed activation in BA 44 for two-word phrases (determiner, pseudoword) compared to two-word lists (noun, noun).

Neuropsychological studies also show inconsistent effects of LIFC damage on sentence processing. Multiple studies of patients with LIFC damage have demonstrated a relationship between LIFC damage and sentence comprehension, while others have found no association. For example, sentence comprehension is impaired in patients with focal gliomas located within the LIFC (Kinno et al., 2009; Kinno et al., 2014), but these impairments are limited mainly to noncanonical or semantically reversible sentences. Similar results have been found in studies of patients with primary progressive aphasia, with reduced functional or structural integrity of the LIFC being associated with worse sentence comprehension (Peelle et al., 2008; Wilson et al., 2016; Wilson et al., 2010), especially for complex sentences.

Alternatively, multiple studies of stroke survivors have failed to demonstrate a relationship between LIFC damage and sentence comprehension, regardless of complexity or canonicity. Using voxel-based lesion-symptom mapping (VLSM), Dronkers et al. (2004) found no relationship between damage to IFGoper or IFGtri and sentence-picture matching. Rogalsky et al. (2018) also found no association between LIFC damage and canonical or noncanonical sentence comprehension, even in a subset of patients with relatively focal lesions to LIFC. Instead, both of these studies found evidence that damage to areas proximal to the temporoparietal junction (TPJ), such as the posterior temporal and inferior parietal lobes, was related to worse sentence comprehension for canonical and noncanonical sentences (for similar results, see (Kristinsson et al., 2020; Matchin et al., 2020)).

To account for the inconsistent findings, multiple accounts have been proposed regarding the role of the LIFC in sentence comprehension. Here, we explore three hypotheses. First, the LIFC contributes to sentence processing via executive task-related demands. Evidence for this account comes from previously discussed neuroimaging findings suggesting that LIFC is mainly activated in sentence comprehension tasks that require special attention to syntactic or semantic information (Hagoort & Indefrey, 2014; Matchin et al., 2017; Rogalsky & Hickok, 2009). Additional evidence for the executive demand account comes from Rogalsky et al. (2018). They found that while LIFC damage was not associated with sentence comprehension, it was associated with response bias, indicating that LIFC contributions may be mainly task-related. Second, the LIFC may contribute to sentence comprehension through auditory-verbal short-term memory (STM). Evidence for this hypothesis comes from neuroimaging studies showing that some areas in the LIFC are activated by both syntax and STM (Rogalsky & Hickok, 2011; Rogalsky et al., 2008). Neuropsychological studies also find that LIFC damage is correlated with reduced digit span and impaired comprehension of sentences (Pettigrew & Hillis, 2014). Finally, the LIFC may be involved in lexical-semantic processes that contribute to sentence comprehension (Matchin et al., 2019; Newman et al., 2009; Segaert et al., 2013).

Here, we used voxel-, region-, and connectivity-based lesion symptom mapping (VLSM, RLSM, CLSM) in a group of unilateral left-hemisphere (LH) chronic stroke survivors to investigate comprehension of canonical sentences while controlling for lexical-semantic, executive, and phonological processes. Our specific focus was to investigate how damage and disrupted white matter connectivity of the LIFC and areas within two other language-related regions, the anterior temporal lobe (ATL) and temporoparietal junction (TPJ), affected canonical sentence comprehension. We used a sentence sensibility task on declarative sentences, combined with four control tasks with varying semantic, executive, and phonological demands to interrogate the LIFC's involvement in these sentence-related processes. A visual lexical decision task (LD) with low semantic, executive, and phonological demands was used to control for lexical access. Auditory word comprehension (AWC), which has relatively higher semantic, executive, and phonological demands was used to control for single word comprehension. A semantic similarity judgment (SSJ) task, which had the highest semantic and executive demands, but low phonological demands, was used to control for semantic retrieval. The forward digit span (FDS) task was used to control for auditory-verbal STM.

Materials and Methods

Participants

79 total participants (24 female) with unilateral LH stroke were recruited. Past power analysis has demonstrated that samples of ~50 or greater provide adequate power to detect medium-to-strong effects in the majority of brain areas (Kimberg et al., 2007a). Participants were at least 6 months post-stroke (4.14 years ± 4.52), and a mean age at time of testing of 58.87 y ± 9.61. All participants signed informed consent, and an Institutional Review Board approved the research.

Materials and Procedure

Sentence Sensibility (SS)

100 canonical declarative (*The janitor swept all the dirt away*) and 50 low-meaningfulness or nonsense sentences (*The tape rejected the air in the sky*) were presented auditorily to the participant. Half of the sensible sentences were literal, while the other half were figurative, but for the current purposes both types are collapsed together. The participant was instructed to determine as quickly and accurate as possible whether the sentence made sense or not by pressing one of two response buttons. Participants had five seconds to respond.

Visual Lexical Decision (LD)

LD consisted of 80 verbs, 80 nouns, and 160 phonologically plausible pseudowords used in a previous study (Desai et al., 2015). Pseudowords were chosen from the English Lexicon Project (ELP) database (http://elexicon.wustl.edu; (Balota et al., 2007)). Words and pseudowords were matched in number of letters, bigram frequency, orthographic neighborhood size, and LD accuracy.

Table 3.1 Psycholinguistic variables

	Words	Nonwords	T-test *p*
Length	5.53 (1.48)	5.36 (1.74)	.51
Orthographic Neighborhood	3.75 (4.85)	3.59 (3.92)	.81
Bigram Freq.	1607.78 (713.06)	1580.48 (738.27)	.81
ELP Lexical Decision Accuracy	.96 (.05)	.97 (.03)	.33

LD consisted of presentation of a fixation cross (500 ms), a mask (‘########’, 100 ms), a prime (50 ms), mask (100 ms), followed by the target. Participants were instructed to indicate as quickly and as accurately as possible whether the target was a real word or not by pressing one of two buttons. Participants had five seconds to respond. The prime was the same as the target word/pseudoword in capital letters for half of the stimuli, and a consonant string also in capital letters for the other half. For the purposes of the present investigation, we do not investigate priming effects. There were 160 trials, divided equally between words and pseudowords, in both the verb and noun versions of the LD task.

Visual Semantic Similarity Judgment

The SSJ task consisted of sets of 240 verbs and 240 nouns used in two previous studies (Riccardi et al., 2020; Riccardi et al., 2019). Each set was organized into 80 verb and 80 noun triplets such that, for each triplet, the target word was more similar in meaning to one of the two choices (e.g., ***to thrill****, to excite, to harm*; bold indicates the target word). The task was presented on a laptop PC running E-prime software (version 1.2, Psychology Software Tools, Inc.). Participants indicated their response by pressing one of two buttons. The position of the bottom words was counterbalanced across participants. Participants could use whichever hand they preferred and were asked to respond as quickly and accurately as possible. The words remained on the screen for five seconds, after which the next triplet was presented. There were 80 trials in both the verb and noun versions of the SSJ task.

Auditory Word Comprehension

AWC was administered by a licensed speech pathologist as part of the WAB (Kertesz, 2007). It consists of 60 real objects and pictures coming from ten categories: real objects, drawn objects, forms, letters, numbers, colors, furniture, body parts, fingers, and right-left body parts. There are six stimuli per category. The speech pathologist speaks aloud the name of one of the pictures/objects, and the participant must point to the correct item. Participants are given a point for each item that they correctly point to, for a maximum of 60 points.

Forward Digit Span

A series of digits (1 through 9) were read aloud to the participant. The participant was instructed to repeat as many of the digits as they could, in order, with series length increasing after successful repetition.

MRI Data Acquisition

MRI data were attained with a Siemens 3T Trio System with a 12-channel head coil (59 participants) and a Siemens 3T Prisma System with a 20-channel coil (20 participants). Participants underwent two anatomical MRI sequences: (i) T1-weighted imaging sequence with an MP-RAGE (magnetization-prepared rapid-gradient echo) [TFE (turbo field echo)] sequence with voxel size = 1 mm3, FOV (field of view) = 256 × 256 mm, 192 sagittal slices, 9° flip angle, TR (repetition time) = 2,250 msec, TI (inversion time) = 925 msec, TE (echo time) = 4.15 msec, GRAPPA (generalized autocalibrating partial parallel acquisition) = 2, and 80 reference lines; and (ii) T2-weighted MRI with a 3D sampling perfection with application optimized contrasts by using different flip angle evolutions protocol with the following parameters: voxel size = 1 mm3, FOV = 256 × 256 mm, 160 sagittal slices, variable flip angle, TR = 3,200 msec, TE = 212 msec, and no slice acceleration. The same slice center and angulation were used as in the T1 sequence.

Preprocessing of Structural Images

Lesions were defined in native space by a neurologist (L. Bonilha) in MRIcron (Rorden et al., 2012) on individual T2-weighted images. Preprocessing started with coregistration of the T2-weighted images to match the T-weighted images, allowing the lesions to be aligned to native T1 space. Images were warped to standard space using enantiomorphic (Nachev et al., 2008) segmentation-normalization (Ashburner & Friston, 2005) custom Matlab script (https://github.com/rordenlab/spmScripts/blob/master/nii_enat_norm.m) to warp images to an age-appropriate template image found in the Clinical Toolbox. The normalization parameters were used to reslice the lesion into standard space using linear interpolation, with subsequent lesion maps stored at 1 × 1 x 1-mm resolution and binarized using a 50% threshold (because interpolation can lead to fractional probabilities, this step confirms that each voxel is categorically either lesioned or unlesioned without biasing overall lesion volume). Normalized images were visually inspected to verify quality.

Preprocessing of Diffusion Tensor Imaging (DTI) Data

Diffusion data are processed in the method described in Bonilha et al. (2015). MRTrix tools are used to perform Gibbs artifacts removal (Kellner et al., 2016) and de-noising (Veraart et al., 2016). FSL's TOPUP (Andersson et al., 2003) and eddy (Andersson & Sotiropoulos, 2015) were used to attenuate spatial distortion. FSL's dtifit computes tensors, FA, and MD maps, and bedpost (Hernandez et al., 2013) is used to model fibers. As discussed in the previous section, the T1 scan uses SPM's unified normalization and segmentation. This allows warping of atlases from standard space to the patients space. This is warped to native diffusion space by nonlinearly warping the T1 scan to the FA map (which has similar contrast). This allows back-projection of our regions of interest into the native diffusion space. Finally, probtrackx (Hernandez-

Fernandez et al., 2019) quantifies connectivity. This evaluates the connectivity between each and every region in the atlas.

DTI Connectome Creation

As described in Gleichgerrcht et al. (2017), a unique probabilistic DTI connectome was constructed for every participant using the 189 cortical regions defined by the Johns Hopkins University (JHU) atlas (Faria et al., 2012; Mori et al., 2005; Wakana et al., 2004); resulting in a 189 x 189 correlation matrix for each participant, where positive values signify greater white matter connectivity of two regions.

Regions of Interest

Nine regions of interest (ROI; Fig. 3.1), based on the Johns Hopkins University (JHU) atlas (Faria et al., 2012; Mori et al., 2005; Wakana et al., 2004), were used for lesion-deficit analysis. The LIFC/Broca's area consisted of the inferior frontal gyrus pars opercularis and triangularis (IFGoper, IFGtri) (described as LIFC henceforth). The ATL consisted of the middle and superior temporal poles (MTGpole, STGpole) and the anterior portion of the inferior temporal gyrus (ITG). The TPJ consisted of the posterior middle and superior temporal gyri (pMTG, pSTG), supramarginal gyrus (SMG), and angular gyrus (AG).

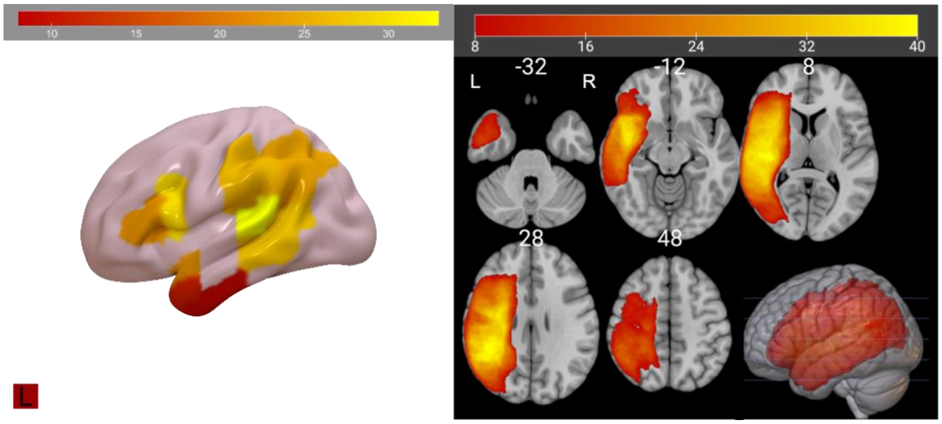

Figure 3.1 ROIs

Experimental design and statistical analysis

Behavioral Data

Our primary aim was to inspect the relative impairment of the sentence comprehension task (SS) factoring out the contribution of other tasks (LD, SSJ, AWC, FDS). For the SS and LD tasks, *d'* was calculated. A large *d'* score for a participant reflects a large separation between the number of correct 'hits' and 'false alarms'. For SSJ, proportion of correct responses was recorded. For AWC, total number of correct responses was used, and for FDS, the total number of digits correctly recalled, in order, was used.

Region- and voxel-based lesion-symptom mapping

RLSM was used within the LIFC, ATL, and TPJ ROIs (9 regions total) to identify damage related to greater impairment of the sentence comprehension task compared to the other four tasks by regressing out performance in one condition from the other using NiiStat software (www.nitrc.org/projects/niistat/). RLSM measures the relationship between percent of voxels damaged within an ROI and a behavioral measure. Nuisance regression used the Freedman-Lane method (Freedman & Lane, 1983), allowing for permutation-based control for family-wise error (Winkler et al., 2014). RLSM results were corrected for multiple comparisons using permutation analysis ($p < .05$, 1000 permutations). Permutation analysis is a nonparametric significance tests that compares a test statistic to a null distribution that is created by randomly permuting the real data (Baldo & Dronkers, 2018; Baldo et al., 2012; Kimberg et al., 2007a).

Given the theoretical importance of LIFC, to increase power to detect effects a more restrictive VLSM was used within the IFGoper and IFGtri to investigate whether damage to this region was associated with worse sentence comprehension. VLSM binarily demarcates each voxel as either lesioned or unlesioned and tests the probability that damage to a voxel is associated with behavioral performance (Bates et al., 2003). VLSM results were thresholded at $p < 0.001$ voxel-wise and cluster-corrected to $p < .05$ using permutation analysis as correction for multiple comparisons (1000 permutations). To improve power and minimize spatial bias, only voxels where at least 10% of patients had damage were considered (Baldo & Dronkers, 2018; Karnath et al., 2018). Region and voxelwise lesion incidence maps showed that we had sufficient coverage in all areas of interest (Fig. 3.1).

Connectivity-based lesion symptom mapping

CLSM was used to investigate whether white matter connectivity between all regions included in the LIFC, ATL, and TPJ network of interest (NOI) was specifically predictive of sentence comprehension impairment compared to the other tasks using nuisance regression, as described above. Left-to-left and left-to-right connections (117 in total) between the regions were considered to test for possible contributions from undamaged inter- or intra-hemispheric regions. White matter connectivity strengths were used in a general linear model to predict task performance. Alpha was set to .05, and significance was determined with permutation correction for multiple comparisons (1000 permutations).

Results

Behavioral

Mean task performance and standard deviations (given as *d'* for SS and LD, proportion correct for SSJ, total correct for AWC, and number of digits correctly recalled in order for FDS) were as follows; SS (1.87 ± 1.12), LD (3.54 ± 1.09), AWC (53.13 ± 11.26), and FDS (6.36 ± 2.12).

RLSM

We first examine regions associated with the SS task, without including the other behavioral tasks as covariates. SS performance was significantly associated with percent of voxels damaged in STGpole, SMG, AG, pSTG, and pMTG (Table 2; Fig. 2).

Next, we individually included data from each task as a covariate, partially accounting for potential contributions of auditory-verbal STM, lexical processing, executive function, and input modality (Table 3.2; Fig. 3.2). Worse SS performance, controlling for FDS (auditory-verbal STM), was significantly associated with percent of voxels damaged in the SMG, AG, pMTG, and pSTG. Worse SS performance, controlling for LD (lexical processing with relatively low executive demands), was associated with percent of voxels damaged in the pSTG and pMTG. Worse SS performance, controlling for SSJ (lexical processing with relatively high executive demands), was associated with percent of voxels damaged in the pMTG. No areas were significantly associated with worse SS performance when controlling for AWC (lexical task in the auditory modality with moderate executive demands).

Table 3.2 Significant RLSM regions

Condition	**Region**	**Z-score**
SS	STGpole	-2.7
	AG	-3.0
	SMG	-3.1
	pMTG	-3.4
	pSTG	-3.8
SS controlling for FDS	AG	-2.7
	SMG	-2.9
	pMTG	-2.9
	pSTG	-3.3
SS controlling for LD	pMTG	-3.2
	pSTG	-3.5
SS controlling for SSJ	pMTG	-2.5

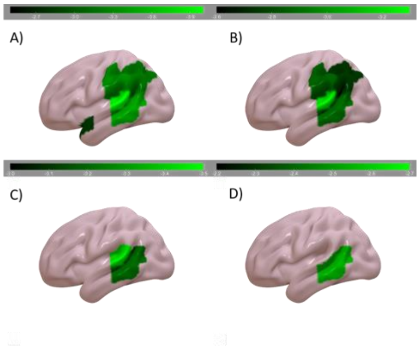

Figure 3.2 RLSM results

VLSM

VLSM, restricted to the LIFC, showed that no voxels were significantly associated with worse SS performance by itself, or when including any other tasks as covariates. However, worse SSJ performance, controlling for SS, was associated with a cluster of voxels in the LIFC (Table 3.3; Fig. 3.3).

Table 3.3 Significant VLSM peaks

Condition	**Location**	**Cluster Size (1 mm^3 voxels)**	**Peak z-score**	**X**	**Y**	**Z**
SSJ controlling for SS	IFGtri	364	-3.8	-27	18	16

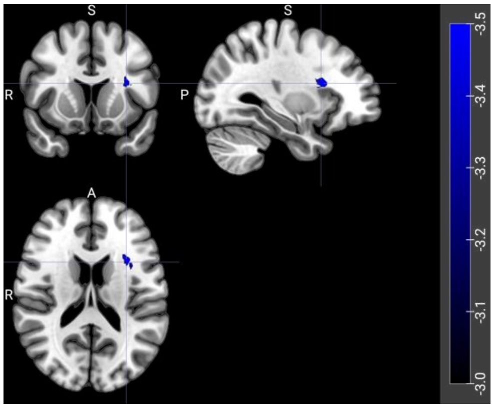

Figure 3.3 VLSM results for SSJ

CLSM

Worse performance in the SS task, without including the other behavioral tasks as covariates, was significantly associated with disruption of 10 white matter connections within the left hemisphere (Fig. 3.4). This included connections within and between LIFC, ATL, and TPJ.

Worse SS performance, when including FDS, LD, or AWC as nuisance covariates, was associated with disruption of the same seven white matter connections within the left hemisphere. This included connections within and between LIFC, ATL, and TPJ (Fig. 3.5). Worse SS performance, controlling for SSJ, was associated with disruption of a single white matter connection within the left hemisphere; SMG to pMTG (Fig. 3.6). CLSM results for all analyses are summarized in Table 4.

Table 3.4 Significant white matter connections

Condition	**Connection**		**Z-score**
SS	IFGoper	SMG	3.7
		AG	3.9
		MTGpole	4.0
	IFGtri	SMG	3.8
		AG	3.8
		pMTG	3.6
	SMG	AG	4.1
		STGpole	4.0
		MTGpole	3.6
	AG	pMTG	3.8
SS controlling for FDS, LD, or AWC	IFGoper	SMG	2.8
		AG	3.1
		MTGpole	3.0
	IFGtri	SMG	3.0
		AG	2.9
	SMG	AG	2.9
		MTGpole	2.7
SS controlling for SSJ	SMG	pMTG	2.9

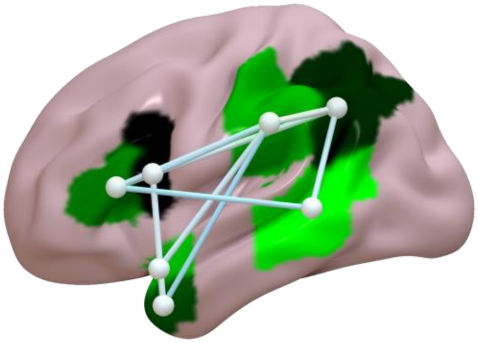

Figure 3.4 Significant SS white matter connections

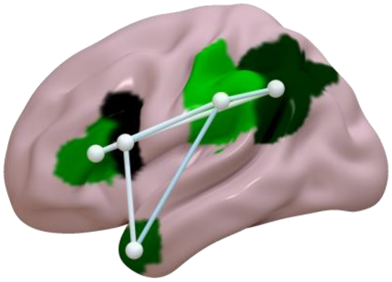

Figure 3.5 SS white matter connections,
controlling for other tasks

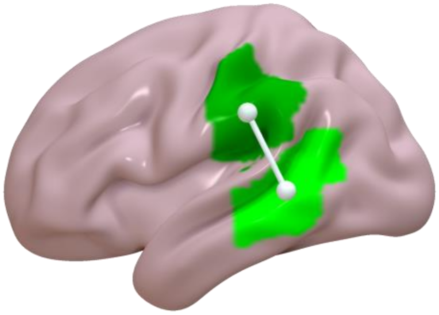

Figure 3.6 SS white matter, controlling for SSJ

Discussion

Sentence processing is a complex process that makes demands on multiple cognitive functions. By using tasks that vary in their executive, lexical, and phonological demands, we interrogated the contributions of the LIFC, and two other language-related regions, in sentence comprehension while controlling for these related cognitive processes.

LIFC

Focusing on pars opercularis and triangularis, we examined the effects of damage to LIFC itself, and also of lesions affecting the connectivity of LIFC. RLSM and VLSM provided little evidence supporting the contribution of the LIFC to canonical sentence comprehension. Damage to LIFC was not significantly associated with worse sentence comprehension in any of the analyses. Results here are similar to several prior studies (e.g., (Dronkers et al., 2004; Newhart et al., 2012; Rogalsky et al., 2018; Thothathiri et al., 2012); for a review of studies and theories of the potential role of LIFC in sentence comprehension, see Kemmerer (2021)). In the classic investigation by Dronkers et al. (2004) that included a number of different sentence types, damage to BA 44/45 was not associated with sentence comprehension deficits, only damage to BA47 was. In a follow-up investigation, Turken and Dronkers (2011) found that resting state connectivity with LIFC was associated with sentence comprehension deficits. More recently, den Ouden et al. (2019) reported similar results. They found that damage to LIFC was not predictive of sentence comprehension deficits. However, using CLSM, they found that structural connectivity of LIFC was important for comprehension. These results are consistent with Turken and Dronkers (2011) as well as the present study.

Here, we take these findings a step further from prior studies by including a lexical task with relatively high semantic and executive demands, SSJ. A more restrictive VLSM analysis, meant to increase power to detect effects within the LIFC, did not find a significant association between LIFC damage and sentence comprehension, even when not controlling for performance in the other tasks. However, damage to voxels within LIFC was associated with worse performance in the SSJ task. SSJ was the most semantically and executively demanding task included in our battery, suggesting a link between LIFC damage and impaired semantic control (Chiou et al., 2018; Jackson, 2021; Whitney et al., 2011). Additionally, CLSM revealed that connectivity of LIFC was predictive of sentence comprehension when factoring out performance on tasks that measured auditory-verbal STM, auditory word comprehension, and lexical access/retrieval.

When controlling for SSJ, however, this connectivity was not found to be predictive of sentence comprehension performance. These findings suggest that LIFC white matter connectivity is important for canonical sentence comprehension, but its role may be mainly related to general executive processes related to sentence processing and associated task demands.

As mentioned in the Introduction, neuroimaging results with respect to LIFC are inconsistent. An interesting hypothesis regarding the role of LIFC is that it is involved in the ‘merge’ operation. For example, Zaccarella and Friederici (2015) found that a specific region within BA44 was activated by two-word phrases (‘this flirk’) compared to lists (‘apple flirk’). The ‘merge’ operation is essential to processing even canonical sentences, and hence it is not clear why several neuropsychological studies have found no relation between BA44/45 damage and sentence comprehension. Zaccarella et al. (2017) performed two meta-analyses to address this question. In the meta-analysis of studies that compared sentences with lists containing both open- and closed-class words, no activation in BA 44 was found. In the other meta-analysis that contained just content words or just function words in the control condition, activation in BA 44 *was* found. This suggests that the lack of activation seen in many studies may be due to the fact that even control conditions invoke the ‘merge’ operation when they contain a mix of content and function words even in a random order. Another possibility is that the role of BA44 may be related to syntactic prediction (Matchin et al., 2017). The task in the Zaccarella and Friederici (2015) study was to determine if a licit phrase was formed, and syntactic prediction may be used to a greater extent for phrases compared to lists.

TPJ

Damage to the TPJ, including the pMTG, was significantly associated with worse sentence comprehension, even after controlling for performance on tasks that measured auditory-verbal STM, semantic knowledge, executive function, and lexical access/retrieval. This aligns with the previously discussed neuropsychological evidence suggesting that the TPJ is involved in sentence processing, even for relatively simple canonical sentences (Dronkers et al., 2004; Rogalsky et al., 2018).

There are multiple hypotheses regarding the contribution of areas within the TPJ to processes that are required for successful sentence comprehension, including that they are involved in auditory-verbal STM (Leff et al., 2009; Richardson et al., 2011), linking wordforms to their meanings (Hickok & Poeppel, 2004, 2007), general semantic knowledge (Binder & Desai, 2011; Binder et al., 2009), or semantic control (Ralph et al., 2017). In the current study, damage to the TPJ was associated with worse sentence comprehension even after controlling for these demands, suggesting that the role of the TPJ in sentence comprehension may go beyond any of those individual processes. For example, it could also contribute to syntactic or thematic processing (Matchin et al., 2019; Matchin et al., 2017) or via functional or structural connectivity with other language-related regions (Turken & Dronkers, 2011).

Within the TPJ, the pMTG in particular has been identified as an important area for sentence processing, with its role being proposed as mapping wordforms to their meanings (‘lexical interface’; (Hickok & Poeppel, 2004, 2007)), processing syntax (Griffiths et al., 2013; Snijders et al., 2009), and representing semantic knowledge (Binder & Desai, 2011; Binder et al., 2009). RLSM revealed that damage to pMTG was associated with worse sentence comprehension when controlling for all tasks except for auditory word comprehension, a task with relatively high phonological and semantic demands. Additionally, CLSM revealed that pMTG connectivity was part of a large-scale network subserving sentence comprehension, but this pMTG connectivity disappeared when controlling for performance in LD, FDS, or AWC. When controlling for SSJ, disruption of a single connection (pMTG to SMG) was associated with worse sentence comprehension. Considering that the pMTG did not survive any analysis using auditory word comprehension as a covariate, our results suggest that the pMTG may be a common neural substrate for auditory single-word and sentence comprehension. This aligns with the ‘lexical interface’ hypothesis (Hickok & Poeppel, 2004, 2007), as well as studies suggesting that the pMTG may play a special role in specifically auditory language comprehension (Pillay et al., 2017). However, given the wealth of processes attributed to the pMTG, it is also possible that this area performs many different functions or that it serves as a general hub of connectivity within the language network (Turken & Dronkers, 2011).

ATL

RLSM revealed that damage to the STGpole was associated with worse sentence comprehension when not controlling for the other behavioral measures. This finding lends support to theories that implicate the ATL in sentence processing (Brennan et al., 2012; Brennan & Pylkkanen, 2017; Humphries et al., 2005; Humphries et al., 2001). However, the fact that ATL damage was not associated with worse sentence comprehension when adding the other behavioral measures as covariates could reflect that the ATL contributes to multiple processes in addition to sentence processing, such as lexical or semantic retrieval (Mesulam et al., 2013; Ralph et al., 2017). It is also possible that regions specialized for sentence-related syntactic processing are located more inferiorly in the ATL (Humphries et al., 2005), where relatively few patients had damage, limiting our power to detect effects.

In sum, the V- and RLSM results did not provide evidence that damage to LIFC is associated with impaired comprehension of canonical sentences. Instead, damage to TPJ regions, including the pMTG, was predictive of sentence comprehension impairments after controlling for tasks measuring lexical access, semantic knowledge, cognitive control, and auditory-verbal STM. This highlights the importance of the TPJ in canonical sentence comprehension, aligning with previous work (Dronkers et al., 2004; Rogalsky et al., 2018). However, the CLSM results, discussed below, revealed a more extensive network of left-hemisphere regions that serve sentence comprehension.

CLSM

CLSM revealed a left-lateralized network consisting of white matter connections within and between the LIFC, ATL, and TPJ that, when disrupted, are associated with worse sentence comprehension, not controlling for other tasks. After controlling for LD, FDS, and AWC, seven white matter connections, again consisting of links between the left LIFC, ATL, and TPJ, remained significantly associated with sentence comprehension specifically. When controlling for SSJ, the task with the highest executive and semantic demands, a single connection between the left SMG and pMTG was associated with sentence comprehension.

These findings demonstrate that connections between multiple left-hemisphere brain areas are important for canonical sentence comprehension, likely reflecting that successfully comprehending a sentence requires the coordination of numerous cognitive processes (e.g., syntactic analysis, semantic knowledge, phonology, etc.). Importantly, the LIFC was part of this network after controlling for auditory word comprehension, phonological demands, lexical access, and auditory-verbal STM. This suggests that the role of the LIFC within the sentence comprehension network goes beyond those demands. These findings do not rule out the contribution of the LIFC to these sub-processes, but they do suggest that the LIFC contributes to canonical sentence comprehension in an additional way. Using the SSJ task as a covariate allowed control for semantic and executive performance, resulting in the absence of LIFC and ATL connections that were uniquely associated with sentence comprehension. This suggests that the LIFC and ATL contribute to canonical sentence comprehension via semantic access/retrieval and executive processes, likely associated with the task demands of the sentence sensibility task. The sentence sensibility task oriented attention to the semantic content of the sentences, requiring participants to identify sentences where the words were semantically congruent/incongruent. As such, our findings align closely with previous neuroimaging research suggesting that the LIFC is especially involved in sentence comprehension when the task explicitly focuses attention on semantics or is semantically demanding (Hagoort & Indefrey, 2014; Rogalsky & Hickok, 2009). Considering the already well-established role of the ATL in lexical-semantic access and retrieval (Mesulam et al., 2013; Ralph et al., 2017), we interpret the role of the LIFC in canonical sentence comprehension as being related to general executive processes related to sentence analysis and task performance.

Limitations

The current study consisted entirely of canonical declarative sentences. Inclusion of other types of sentences, including non-canonical and more syntactically complex sentences would provide valuable information about neural substrates of sentence comprehension when syntactic demands are manipulated. Similarly, a single meaningfulness judgment task was used. Adding multiple tasks, such as sentence-picture matching, could better enable examination of task type and demands. Additionally, ‘executive control’ involves many processes, and having multiple control tasks in conjunction with SSJ to probe those specific processes would be helpful in understanding the specific role of the LIFC. Finally, the spatial resolution of lesion studies is inherently limited, and a fine-grained (e.g., millimeter scale) organization of function is better studied with methods such as fMRI.

Conclusion

VLSM and RLSM analyses suggest that the left pars opercularis and triangularis regions, by themselves, are not critical to canonical sentence comprehension. LIFC damage was associated instead with impairments in a semantic similarity judgment task that required high semantic and executive demands. Damage to the TPJ, including pMTG, predicted worse sentence comprehension after controlling for lexical access, semantic knowledge, and auditory-verbal STM, supporting findings suggesting that the TPJ contributes to sentence comprehension beyond those processes. Contrasting with the findings using VLSM and RLSM, CLSM revealed that disruption of left-lateralized white matter connections from LIFC to ATL and TPJ was associated with worse sentence comprehension after controlling for performance in tasks related to lexical access, phonology, and auditory-verbal STM. However, the LIFC connections were accounted for by the semantic similarity judgment task, which had high semantic and executive demands. These results suggest that the connectivity with LIFC is relevant to sentence comprehension, but that this involvement may be limited to general executive processes and task demands.

CHAPTER 4

DISSOCIATING ACTION AND ABSTRACT VERB COMPREHENSION POST-STROKE

Introduction

The role of sensory-motor systems in semantic processing remains a topic of debate. A large body of evidence suggests that conceptual processing is at least partially reliant on distributed sensory-motor cortices (Barsalou, 2009; Gallese & Lakoff, 2005; Martin, 2007; Meteyard et al., 2012). These findings diverge from models wherein cognition is largely independent from sensory-motor systems (Fodor, 1983; Mahon & Caramazza, 2008).

Evidence stemming from a range of methodologies has provided support for theories of grounded cognition. For example, behavioral and functional neuroimaging experiments have repeatedly established a close link between cognitive and sensory-motor processes (Binder & Desai, 2011; Fischer & Zwaan, 2008; Meteyard et al., 2012). While these findings suggest that sensory-motor systems are involved in cognition, they do not demonstrate that these systems are required for cognition.

Causal evidence demonstrating that disruption of a sensory-motor area results in semantic impairments of the corresponding conceptual modality has been provided by transcranial magnetic stimulation (TMS) and patient studies. For example, TMS studies have found that stimulation of motor and premotor cortices differentially affects processing of action-oriented words compared to other types of words (Cacciari et al., 2011; Vukovic et al., 2017; Willems et al., 2011), with at least one such study finding evidence of somatotopic organization of effector-specific concepts in the motor cortex (Pulvermuller et al., 2005).

Further, patient studies in populations with motor disorders such as Parkinson's or motor neuron disease have shown selective impairment of action relative to non-action semantics (Bak & Hodges, 2004; Bak et al., 2001; Cotelli et al., 2006; Cotelli et al., 2007; Grossman et al., 2008; Peran et al., 2013). Taken together, these studies show a relationship between the degradation of the motor system and deficits in verb comprehension, suggesting a causal brain-behavior relationship. It is important to note that while many of these studies compare action verbs to nouns, leaving open the possibility that the impairment is related to the grammatical class of verbs and not to action semantics per se, the effects are also found in studies that perform within-class comparisons (Desai et al., 2015; Fernandino et al., 2013b).

Compared to investigations of patients with motor disorders, the results of lesion-deficit studies have been somewhat inconsistent. Numerous studies have failed to find evidence for a causal relationship between sensory-motor systems and conceptual understanding of actions or objects (Halsband et al., 2001; Mahon et al., 2007; Negri et al., 2007; Papeo et al., 2010; Rosci et al., 2003; Rumiati et al., 2001). Generally, these studies have found behavioral or anatomical dissociations between action execution/imitation and conceptual knowledge of actions or objects, suggesting that motoric simulations are not as involved in conceptual processing as embodied theories would predict. It is important to note, however, that the motor system is composed of many parts, and it stands to reason that not all of these components are equally involved in conceptual processing, making behavioral or anatomical dissociations possible. Further, as will be discussed later, the role of post-stroke reorganization remains understudied, and it is likely that sensory-motor and lexico-semantic systems have differential reorganization following stroke, providing another avenue for dissociations to occur.

Conversely, many other studies have found evidence of selective conceptual impairments corresponding with damage to sensory-motor systems, substantiating grounded cognitive theories (Arevalo et al., 2007; Arevalo et al., 2012; Bonner & Grossman, 2012; Buxbaum & Saffran, 2002; Desai et al., 2015; Dreyer et al., 2015; Kemmerer et al., 2012; Trumpp et al., 2013). For example, Desai et al. (2015) used an exoskeleton robot to measure manual reaching abilities in stroke patients and found that action word processing was predicted by the degree of impairment in reaching performance, while abstract words were not. Additionally, Bonner and Grossman (2012) and Trumpp et al. (2013) both found that damage to the auditory association cortex appears to be causally related to the loss of sound concepts specifically, with relative preservation of other types of concepts.

Another example of lesion-deficit evidence in support of grounded cognition comes from a large scale study by Kemmerer et al. (2012). Six tasks were used to investigate lexical retrieval and conceptual knowledge of action concepts in 147 patients with unilateral left or right hemisphere (LH, RH) lesions.

They found that damage to a left-lateralized network consisting of the inferior frontal gyrus (IFG), precentral and postcentral gyri (PrC, PoC), supramarginal gyrus (SMG), posterior middle temporal gyrus (pMTG), and posterior ventral temporal areas resulted in impoverished performance on one or more tasks in the action knowledge battery. This finding was largely consistent with previous studies using similar tasks and overlapping patient populations (Tranel et al., 2001; Tranel et al., 2003; Tranel et al., 2008). Damage to the IFG and PrC was associated with impaired performance across all six tasks, demonstrating that these areas are likely involved in action concept representation regardless of specific task demands. This finding is consistent with evidence implicating the IFG in the production and perception of hand-related actions (Grafton, 2009; Kemmerer et al., 2012; Tranel et al., 2003), as well as the fMRI (Aziz-Zadeh et al., 2006; Hauk et al., 2004) and TMS (described above) evidence implicating the PrC as an area of overlap between action conceptualization and execution. However, while the Kemmerer et al. (2012) investigation provides evidence for a network that facilitates lexical and conceptual knowledge of actions, it remains unclear whether this network is involved specifically in actions or in verbs more generally, given that the study was not designed to test non-action verbs.

Few studies have directly compared the neural substrates of action and abstract verb comprehension post-stroke. For example, while some studies have explored the ‘concreteness effect’ wherein highly concrete and imageable words tend to be processed more accurately in brain damaged populations, the majority of these studies either compared verbs to nouns (Bird et al., 2000, 2001, 2003) or were confined to patients with anterior temporal lobe (ATL) atrophy due to semantic dementia (Jefferies et al., 2009; Reilly et al., 2006). An exception is a recent study that directly investigated the neural correlates of action and abstract verb comprehension post-stroke (Alyahya et al., 2018). Using voxel-based correlation and a synonym judgment task, they found that greater relative impairment to concrete verb comprehension was associated with damage to a wide swath of the left hemisphere, extending from the lateral occipital cortex to the anterior middle temporal gyrus. Greater relative impairment to abstract verb comprehension was predicted by damage to the middle and inferior frontal gyri. These results were interpreted as indicating that concrete concepts rely more on sensory areas found in the posterior temporo-occipital junction while abstract concepts, which often require more contextual orientation than concrete concepts, rely more on executive control functions associated with the inferior frontal gyrus.

Along with the scarcity of information about the neural correlates of action and abstract verb comprehension post-stroke, the issue of post-stroke reorganization and compensation warrants closer examination. Conclusions from lesion-deficit associations alone can be misleading due to other brain regions subsuming the duties of the damaged area, or residual function of undamaged areas preventing detection of behavioral impairments (Hillis et al., 2017; Price & Friston, 2002). For example, it has been shown that post-stroke neural plasticity sometimes allows for recovery of lost functions, with full or partial recovery of language capabilities after LH unilateral stroke being associated with upregulation or increased connectivity to RH areas (Heiss et al., 1999; Richter et al., 2008; Saur et al., 2006; Skipper-Kallal et al., 2017; Thulborn et al., 1999). This can lead to false negatives, where there is damage to an area that would otherwise be implicated in a certain process but no (or little) behavioral deficit due to compensation from other areas. One way to address this is to consider functional connectivity alongside traditional lesion-deficit association, given that functional connectivity can sometimes be a better predictor of post-stroke deficits than lesion location alone (Siegel et al., 2016). To the best of our knowledge, no previous studies have examined post-stroke resting-state functional connectivity (RSFC) in the context of categorical semantic deficits in verbs.

Here, we used two complementary methodologies, lesion-symptom mapping and RSFC, in a group of LH stroke patients to investigate whether lesions or RSFC predict differential semantic performance for action and abstract verbs. We used voxel-based lesion-symptom mapping (VLSM) at the whole brain level, as well as region-based lesion-symptom mapping (RLSM) and RSFC analysis in two *a priori* networks-of-interest (NOI) containing areas hypothesized to have relatively more involvement in either action or abstract conceptual processing. We predicted that impaired connectivity between the LH and the intact RH, involving motor areas, would affect action language comprehension to a greater degree than abstract comprehension, suggesting a compensatory role of the RH with damage to the LH. Similarly for abstract concepts, we examined whether connectivity or damage to fronto-temporal regions associated with abstract concept comprehension in neuroimaging studies (Binder et al., 2009;

Binder et al., 2005; Noppeney & Price, 2004; Wang et al., 2010) impairs their processing to a greater degree than action concepts.

Materials and Methods

Participants

Forty-eight participants (19 female) with unilateral LH stroke had resting-state data and met our semantic task accuracy criteria. Participants were at least 6 months post-stroke (M = 4.28 years, SD = 4.07) with a mean age at the time of stroke of 55.03 years old (SD = 10.03) and time of testing of 59.32 years (SD = 9.22). The Western Aphasia Battery was administered to all patients, with a mean aphasia quotient of 79.49 (SD = 22.64). All participants signed an informed consent, and the University of South Carolina Institutional Review Board approved the research.

Materials

A semantic similarity judgment (SSJ) task was used, which was identical to the one used in Fernandino et al. (2013a). A set of 120 action verbs ("to throw") and a set of 120 abstract verbs[3] ("to excuse") were organized into 40 triplets each such that two of the verbs had similar meanings in every triplet. For each of the 80 trials, three verbs were presented simultaneously in a triangular arrangement (Fig. 4.1). All three verbs were of either the abstract or action condition. An example action triplet would be the top (target) item, "to throw", with the bottom two items being "to pitch" and "to juggle". Participants must choose

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[3] Here, we defined 'abstract' verbs as those with relatively low action-relatedness rating. Abstract words can be divided into many sub-categories, such as cognition, emotion, or temporal words. These sub-types were not considered here.

which of the bottom two words is most similar in meaning to the top (e.g., “to pitch”). The action and abstract conditions were matched in number of letters, phonemes, syllables, orthographic and phonological neighbors, and lemma frequency (Table 4.1). They were also matched in argument structure, mean naming response times (RT), and mean Lexical Decision RT and Accuracy using measures from the English Lexicon Project (Balota et al., 2007).

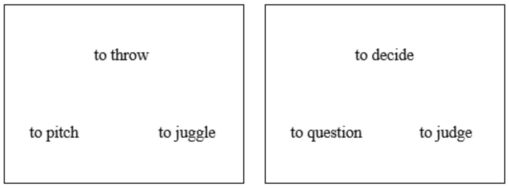

Figure 4.1 SSJ trials

Table 4.1 Psycholinguistic variables

	Action	**Abstract**	**T-test (p-value)**
Letters	5.33 (0.18)	5.32 (0.13)	0.97
Phonemes	4.22 (0.15)	4.25 (0.13)	0.86
Syllables	1.33 (0.06)	1.42 (0.05)	0.30
Log frequency	1.22 (0.06)	1.27 (0.07)	0.60
Ortho neighbor	4.89 (5.02)	4.09 (4.78)	0.21
Phono neighbor	10.77 (10.42)	8.72 (9.44)	0.11
LD RT	662 (46)	650 (40)	0.21
LD Acc	0.94 (0.06)	0.94 (0.07)	0.97
Naming RT	637 (46)	624 (27)	0.13
SemD	1.70 (0.15)	1.84 (0.15)	**< 0.001**

Procedure

The SSJ task was part of a larger neuropsychological test battery to assess speech and language capabilities of the participants. This battery was administered in a separate session from the functional magnetic resonance imaging (fMRI). The task was presented on a laptop PC running E-prime software (version 1.2, Psychology Software Tools, Inc.).

Participants indicated their SSJ response by pressing one of two corresponding buttons. Position of the bottom words was counterbalanced across participants. Participants could use whichever hand they preferred and were instructed to respond as quickly and accurately as possible. The words remained on the screen for five seconds, and failure to respond in that time resulted in presentation of the next triplet.

MRI Data Acquisition

MRI data were acquired using a Siemens 3T Trio System with a 12-channel head coil. Participants underwent scanning that included two anatomical MRI sequences: (*i*) T1-weighted imaging sequence using an MP-RAGE (magnetization-prepared rapid-gradient echo) [TFE (turbo field echo)] sequence with voxel size = 1 mm^3, FOV (field of view) = 256 × 256 mm, 192 sagittal slices, 9° flip angle, TR (repetition time) = 2,250 ms, TI (inversion time) = 925 ms, TE (echo time) = 4.15 ms, GRAPPA (generalized autocalibrating partial parallel acquisition) = 2, and 80 reference lines; and (*ii*) T2-weighted MRI with a 3D sampling perfection with application optimized contrasts by using different flip angle evolutions protocol with the following parameters: voxel size = 1 mm^3, FOV

= 256 × 256 mm, 160 sagittal slices, variable flip angle, TR = 3,200 ms, TE = 352 ms, and no slice acceleration. The same slice center and angulation were used as in the T1 sequence.

Images were acquired to assess functional connectivity using an EPI sequence with FOV = 208 x 208 mm, 64 x 64 matrix size, 75° flip angle, 34 axial slices (3 mm thick with 20% gap yielding 3.6 mm between slice centers, TR = 1850 ms, TE = 30 ms, GRAPPA = 2, 32 reference lines, sequential descending acquisition, 196 volumes acquired.

Preprocessing of Structural Images

Lesions were demarcated in native space by a neurologist (L. Bonilha) in MRIcron (Rorden et al., 2012) on individual T2-weighted images. Preprocessing began with the coregistration of the T2-weighted images to match the T-weighted images, allowing the lesions to be aligned to native T1 space. Images were warped to standard space using the enantiomorphic (Nachev et al., 2008) segmentation-normalization (Ashburner & Friston, 2005) custom Matlab script (https://github.com/rordenlab/spmScripts/blob/master/nii_enat_norm.m) to warp the images to an age-appropriate template image included with the Clinical Toolbox. The normalization parameters were used to reslice the lesion into standard space using linear interpolation, with the resulting lesion maps stored at 1 x 1 x 1-mm resolution and binarized using a 50% threshold (because interpolation can lead to fractional probabilities, this step ensures that each voxel is categorically either lesioned or unlesioned without biasing overall lesion volume). Normalized images were visually inspected to verify the quality of preprocessing.

Preprocessing of RSFC Data

fMRI data were corrected for motion using the SPM12 “realign and unwarp” procedure with default settings. Brain extraction was performed using the SPM12 script pm_brain_mask with default settings. Slice correction was completed with SPM12. The mean fMRI volume for each participant was aligned to the corresponding T2-weighted image to compute the spatial transformation between the fMRI data and the lesion mask. The fMRI data were then spatially smoothed with a Gaussian kernel with full width at half maximum of 6 mm.

To remove artifacts driven by lesions, the procedure described in (Yourganov et al., 2018a) was used. We applied FSL MELODIC package to decompose the data into independent components and to compute the Z-scored spatial maps for each independent component. These spatial maps were thresholded at $p < 0.05$ and compared with the lesion mask for that participant. If the spatial overlap (measured with Jaccard index) between the lesion mask and the thresholded IC map was greater than 5%, the corresponding component was deemed to be significantly overlapping with the lesion mask. All such components were then regressed out of the fMRI data using the fsl_regfilt script from the FSL package.

RSFC Connectome Creation

An individual RSFC connectome was built for each patient with the following steps: 1) segmentation of the probabilistic grey matter map from T1-

weighted images; 2) division of grey matter map into 189 regions of interest (ROI) based on the Johns Hopkins University (JHU) atlas (Faria et al., 2012; Mori et al., 2005; Wakana et al., 2004); 3) computation of ROI-specific time courses of the blood-oxygen level-dependent (BOLD) signal by averaging time courses across the voxels within each ROI; 4) generation of 189 x 189 RSFC correlation matrix for each patient, where positive values represent temporally synchronous co-activation of two regions.

Experimental Design and Statistical Analysis

Behavioral Data

Trials with missing responses were excluded from analysis. Because our primary aim to was examine differences in action and abstract performance, eight original participants were excluded due to failure to achieve significantly above chance accuracy on at least one of either the action or abstract conditions (60%, $p < .05$). This criterion was chosen for two reasons. First, it ensures that patients who were unable to understand or perform the task would be excluded, thereby preventing spurious conclusions about differences in action or abstract performance based on chance performances from patients who could not adequately perform either condition, as a severe global deficit would not provide meaningful information distinguishing the two conditions. Second, it ensures that patients with severe deficits in one condition but relatively preserved performance in the other would be included in the analysis, as these patients can be the most informative with respect to dissociating the conditions. For each participant, average accuracy (Acc) was calculated for the action and abstract conditions individually. The main results of interest are from the residuals for each condition when the performance in the other condition is regressed out (ResidAction and ResidAbstract), thereby providing the critical test of a semantic category-relative deficit while controlling for other factors such as general semantic deficits or task demands.

RSFC Networks of Interest

Two NOIs were extracted from the original 189 x 189 correlation matrix for RSFC analysis: an action NOI and an abstract NOI (Fig. 4.2). The action NOI consisted of seven regions, chosen for being part of primary or higher order motor cortices, and included the bilateral inferior frontal gyrus pars opercularis and pars triangularis (IFGoper, IFGtri), precentral gyrus (PrC), postcentral gyrus (PoC), supramarginal gyrus (SMG), posterior middle temporal gyrus (pMTG), and the posterior inferior temporal gyrus (pITG). These regions were chosen for being consistently involved in action performance and action semantics (Binder & Desai, 2011; Binder et al., 2009; Desai et al., 2013; Kable et al., 2005; Kemmerer et al., 2012; Longo et al., 2010). The abstract NOI consisted of six regions, chosen for consistent association with abstract semantics across multiple studies (Binder et al., 2005; Noppeney & Price, 2004) as well as meta-analyses contrasting abstract and concrete semantics (Binder et al., 2009; Wang et al., 2010). This bilateral network included the IFGoper, IFGtri, middle and superior temporal gyri (MTG, STG), and the middle and superior temporal poles (aMTG, aSTG). Further, the action and abstract NOIs defined here closely match previously identified sensory-motor and language resting state networks, respectively (Chai et al., 2016; Lee et al., 2012; Pool et al., 2015; Tie et al., 2014). While these two NOIs were hypothesized to be differentially involved in either action or abstract semantics, we tested and report residuals for both action and abstract accuracies in both networks to assess relative selectivity (with the abstract condition serving as a control for the action NOI, and vice versa).

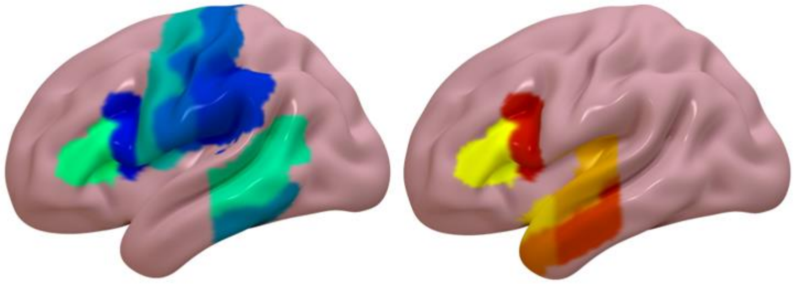

Figure 4.2 ROIs

Left-to-left, left-to-right, and right-to-right connections were considered for analysis in both NOIs, such that the resulting correlation matrix consisted of 91 connections for the action NOI and 66 for abstract. Because the representation of both concrete and abstract concepts is widely distributed (Binder et al. 2009, Desai et al. 2018), arguments can be made for inclusion of additional brain areas in these networks. However, due to the necessity for rigorous correction for multiple comparisons, type II errors increase as more and more areas are included. This is especially true for connectivity analyses, given that the number of connections increases nonlinearly with the number of areas (e.g., increasing NOI size from six regions to seven introduces 25 new connections). Hence, these NOIs were selected by balancing the need to examine areas consistently and differentially associated with action and abstract concepts, while providing sufficient power to detect effects.

The RSFC connection strengths from each NOI were used in a general linear model (GLM) regressing out performance in one condition from the other (ResidAction; ResidAbstract), using NiiStat software (http://www.nitrc.org/projects/niistat/). A decline in individual action or abstract scores can be observed for multiple reasons, including a deficit in the respective semantic type, general semantics, or executive function, and is thus more likely to be observed following lesion. Hence, regressing out performance in one condition from the other provides the critical test of a semantic category-relative deficit. RSFC analyses were conducted while including time post-stroke as a nuisance regressor. Alpha was set to 0.01 and significance was determined via permutation analysis to correct for multiple comparisons (5000 permutations). Because the current analysis compares two similar conditions within subjects, general effects of lesion size, such as greater global cognitive decline due to larger lesions, are controlled for. Nonetheless, RSFC analyses were also conducted with an additional lesion size covariate, and no connections survived in this analysis.

Lesion-Symptom Mapping

Whole brain voxel-based lesion-symptom mapping (VLSM) was used to identify brain damage associated with ResidAction and ResidAbstract after regressing out lesion size using NiiStat. VLSM shows the statistical likelihood that damage to a given voxel predicts performance on a behavioral measure, where each voxel is binarily demarcated as either damaged or undamaged (Bates et al., 2003). Region-based lesion-symptom mapping (RLSM) based on the *a priori* NOIs described above was used in order to investigate the effects of damage specifically to grey matter areas. RLSM differs from VLSM in that instead of using binary voxel-wise values, it uses the percent of voxels damaged within each ROI as the predictor of the behavioral score. This provides the advantage of analyzing the effects of damage over an entire region without requiring overlapping damage at the individual voxel level, losing spatial specificity. RLSM was used with the action (7 LH ROIs) and the abstract (6 LH ROIs) NOIs. VLSM results were thresholded at $p < 0.0005$ voxel-wise and cluster-corrected to $p < 0.05$, determined via permutation analysis to correct for multiple comparisons (5000 permutations). Only voxels (or regions for RLSM) where at least five patients had damage were considered; all regions used in the RLSM analysis passed this threshold.

Results

Behavioral

Mean Action Acc was 81% (SD = 16%) and mean Abstract Acc was 81% (SD = 15%), demonstrating that the conditions had similar levels of difficulty, and thus relative deficits are unlikely to be due to impaired performance on a generally more difficult task.

Functional Connectivity

Both Action and Abstract NOIs were examined for ResidAction and ResidAbstract. ResidAction: In the Action NOI, disruption of six interhemispheric RSFC links were significant predictors of worse action relative to abstract performance. These connections were 1) the left IFGoper to the right PrC, SMG, IFGoper, and IFGtri and 2) the left IFGtri to the right PrC and SMG (all $p < 0.0001$; Table 4.2, Fig. 4.3). In the Abstract NOI, only the left-to-right IFG connections (which were also part of the action NOI) were significant for ResidAction.

ResidAbstract: No connections survived in either the Abstract or Action NOI. A more lenient threshold ($p < 0.1$) also revealed no connections.

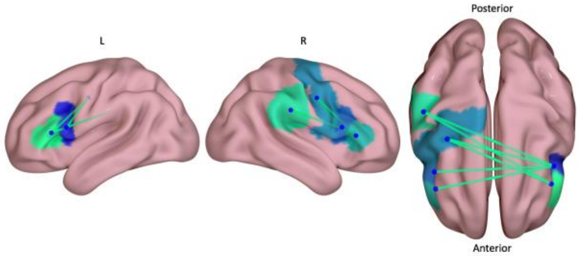

Figure 4.3 RSFC results for ResidAction

Table 4.2 Significant functional connections for ResidAction

Condition	**Connection**		**z-score**
Action > Abstract	L IFGoper	R IFGoper	4.6
		R IFGtri	3.8
		R PrC	4.6
		R SMG	4.5
	L IFGtri	R PrC	4.6
		R SMG	3.9

We also examined Action and Abstract accuracies individually (i.e. without regressing the conditions from each other) in their respective NOIs. Significant connections were revealed for both.

Lesion-Symptom Mapping

After excluding voxels lesioned in fewer than five patients, the lesion overlay map in Fig. 4.4 reveals coverage typical for patients with middle cerebral artery (MCA) stroke (Fridriksson et al., 2016). ResidAction: Whole-brain VLSM revealed a cluster of frontal white matter voxels (peak $z = -4.77$, $p < 0.00001$; Fig. 4.5, Table 4.3) estimated to be located in the anterior corona radiata and extending towards the inferior frontal gyrus that predicted greater relative impairment of action verb comprehension compared to abstract. Investigation of grey matter damage using RLSM revealed no ROIs that were significantly associated with ResidAction the action or abstract NOI mask.

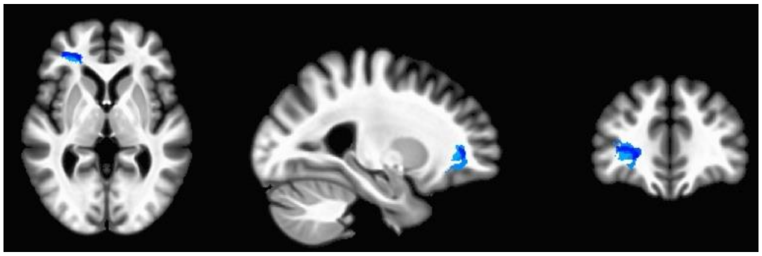

Figure 4.4 Whole-brain VLSM results for ResidAction

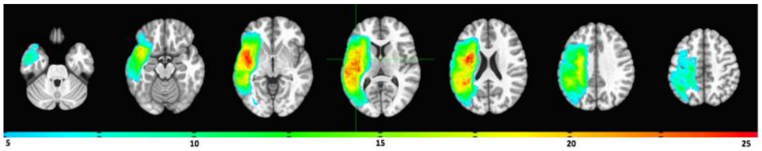

Figure 4.5 Lesion overlay map

Table 4.3 Significant clusters for ResidAction

Condition	**Location**	**Cluster size (1 mm^3 voxels)**	**Peak z-score**	**X**	**Y**	**Z**
Action > Abstract	Anterior corona radiata	1,475	4.79	-25	38	0

ResidAbstract: Whole-brain VLSM were not significant. RLSM within the abstract NOI revealed that damage to the aMTG predicted worse performance for abstract verbs compared to action (z = -2.44, p = 0.007; Fig. 4.6 and 4.7). RLSM within the action NOI was not significant.

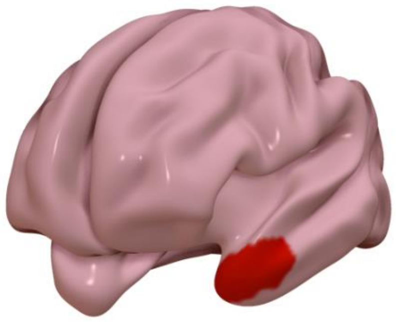

Figure 4.6 RLSM results for ResidAbstract

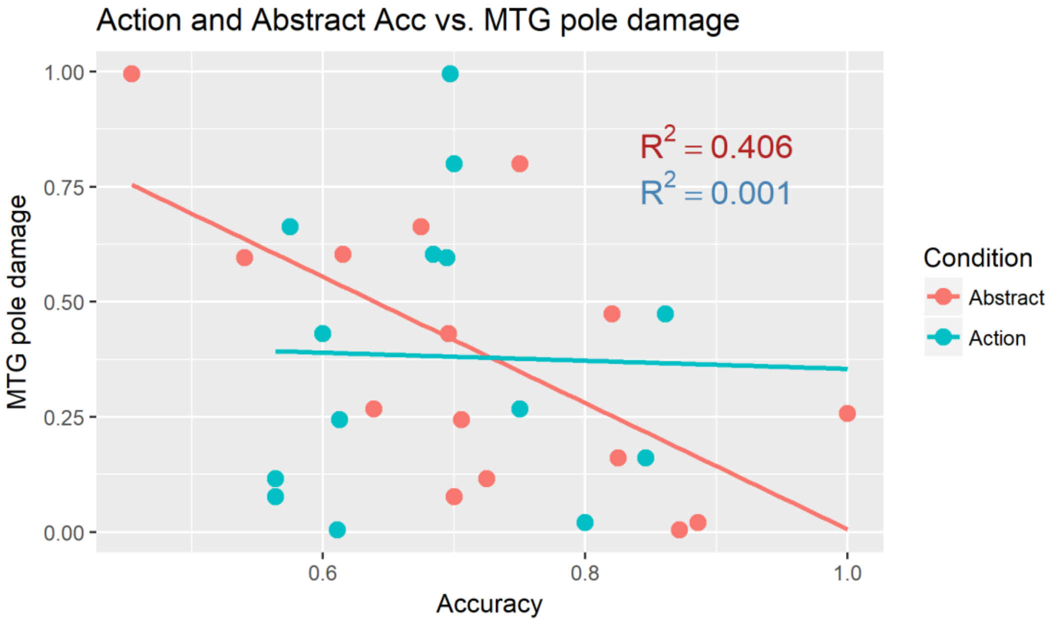

Figure 4.7 Action and Abstract accuracy as a function of MTG pole damage

Discussion

The results reveal that there is lesion-deficit and RSFC evidence for partially dissociable networks underlying action and abstract conceptual processing. While damage to these networks will likely impair overall semantic performance, the impairments will be relatively greater for action or abstract processing depending on the damaged areas and levels of interhemispheric functional connectivity. The results also show that both hemispheres can contribute to semantic processing and, following damage to the usually dominant LH, the RH appears to at least partially compensate for functional deficits via interhemispheric connectivity. When this interhemispheric connectivity is compromised, compensation is affected, and semantic deficits are seen.

Action Semantics

Whole-brain VLSM revealed a cluster of frontal white matter voxels extending towards the IFG that predicted worse relative action comprehension compared to abstract. RLSM with the grey matter action NOI mask revealed no areas of significance, demonstrating that the predictive damage was confined primarily to frontal white matter tracts. According to the JHU white matter atlas, the significant cluster of voxels corresponded to the anterior corona radiata (CR).

The CR is a large white matter motor pathway that is associated with the corticospinal tract. In the anterior aspect, motor projections run from frontal, premotor, and primary motor cortices to subcortical structures such as the basal ganglia and, eventually, the spinal cord (Catani et al., 2002; Wakana et al., 2004). Damage to the CR is associated with poor motor outcomes (Cho et al., 2007; Shelton & Reding, 2001), with arm, hand, and facial movements being somatotopically represented primarily in the middle to anterior portions (Schaechter et al., 2009; Song, 2007). These results are consistent with the view that the disproportionate reliance on this motor pathway for action verb comprehension reflects its use in action simulations that aid conceptual understanding.

Another possibility is that the white matter damage observed in the VLSM represents the anatomical basis for the impaired functional connections that were disproportionately associated with action verb comprehension, especially considering 1) the close proximity of that voxel cluster to the IFG and 2) that functional connectivity to the IFG has greater relation with action than abstract verb comprehension. It is known that functional connectivity is constrained by the underlying anatomy of white matter tracts, although there is not a one-to-one relationship between the two (Honey et al., 2009; Koch et al., 2002; Park et al., 2008).

RSFC analysis revealed that disruption of interhemispheric connectivity between the right PrC, SMG, and IFG with the left IFGoper and IFGtri predicted worse action semantic performance compared to abstract, indicating that these areas have greater involvement in action-related semantics. These results substantiate the special contribution of distributed motor areas to action semantics specifically. The PrC is the location of the human motor homunculus (Penfield & Rasmussen, 1950), and is an area of overlap between action execution and observation, causing it to be considered part of the human mirror neuron system (HMNS) (Arevalo et al., 2012; Fernandino & Iacoboni, 2010; Hari et al., 1998; Tremblay et al., 2004). The PrC has been shown to be involved in the processing of action-oriented language using a range of methodologies (Boulenger et al., 2009; Buccino et al., 2005; Cacciari et al., 2011; Desai et al., 2013; Hauk et al., 2004; Kemmerer et al., 2012; Pulvermuller et al., 2005; Vukovic et al., 2017). The current results provide evidence for the involvement of the right PrC in an action semantic network in LH stroke patients. More speculatively, the PrC is well-suited for post-stroke compensation since it has been shown to be especially plastic, displaying rapid reorganization in both human and rat studies (Sanes & Donoghue, 2000; Volz et al., 2016).

The SMG, especially anteriorly, is considered part of the somatosensory association cortex, implicated in storing proprioceptive information for complex motor sequences, planning and performing skilled actions, and reaching and grasping. Lesions to the anterior SMG have been associated with action knowledge impairment, apraxia, and impairments in tool use (Buxbaum & Saffran, 2002; Buxbaum et al., 2000; Goldenberg & Spatt, 2009; Haaland et al., 2000b; Jax et al., 2006; Randerath et al., 2010; Tranel et al., 1997; Tranel et al., 2003). Imaging studies implicate anterior SMG and surrounding anterior inferior parietal cortex with complex actions (Brandi et al., 2014; Frey et al., 2005; Hermsdorfer et al., 2007; Johnson-Frey et al., 2005; Peeters et al., 2009) and action semantics (Binder et al., 2009; Desai et al., 2010; Desai et al., 2016; Desai et al., 2013; Kable et al., 2005; Noppeney et al., 2006; Rueschemeyer et al., 2010). The current findings provide evidence for a disproportionate role of the SMG in action compared to abstract semantic processing, demonstrating action-semantic impairments when connectivity is compromised between the right SMG and the left IFG.

The IFG is associated with a wide variety of executive and linguistic functions (Badre, 2008; Fadiga et al., 2009b; Grodzinsky & Santi, 2008; Hagoort, 2005; Hickok & Rogalsky, 2011). One of the major functions of the IFG relates to the production and perception of actions, especially hand-related ones, and is considered part of the HMNS (Buccino et al., 2004a; Buccino et al., 2004b; Caspers et al., 2010; Fazio et al., 2009; Fernandino & Iacoboni, 2010; Grafton, 2009; Hamzei et al., 2003; Randerath et al., 2010; Tranel et al., 2003). The posterior IFG has also been associated with the comprehension and production of action-related language (Aziz-Zadeh et al., 2006; Bak et al., 2001; Hauk et al., 2004; Kemmerer et al., 2012; Tettamanti et al., 2005; Thompson-Schill et al., 1998; Tranel et al., 2001). Thus, the IFG is also well-established as part of an action network involved in execution, observation, and semantics. However, the precise role of the IFG remains under debate. One interpretation is that its role is in the hierarchical sequencing of elements (Fadiga et al., 2009b; Fazio et al., 2009; Koechlin & Jubault, 2006). Similar to grammar, actions reflect hierarchical nesting of simpler elements. Here, the IFG may work as part of a bilateral system to integrate simpler motor representations represented in the right hemisphere primary (PrC) and higher order (SMG) motor cortex through functional connectivity. Our results align well with emerging evidence indicating that stronger interhemispheric connectivity between brain areas in the action/tool-use network (such as the PrC and SMG) predicts better skilled action performance in stroke patients (Watson et al., 2019). In the context of the current study, when connectivity in this bilateral network is impaired, action simulations used in the service of comprehension of actions verbs are compromised.

Our results regarding the disproportionate involvement of the IFG (in RSFC analysis) and surrounding white matter (in VLSM analysis) in action semantics diverge from the recent findings of Alyahya et al. (2018), who found that IFG damage predicted greater relative impairment of abstract semantics. They concluded that the IFG's role in executive functioning was vital for the comprehension of abstract words, which tend to be more contextually flexible than action words. In the present study, we think it is unlikely that the disproportionate IFG involvement in action semantics reflects purely executive processing demands. If executive processing demands were responsible for the current results, there would be no reason that connectivity specifically between the IFG and primary and secondary motor areas would significantly predict action semantic comprehension over and above abstract. Further, the abstract words used in the current study had significantly greater semantic diversity (SemD; see Hoffman et al. (2011)) than the action words ($p < 0.001$), and patients with executive dysfunction perform worse on words with greater SemD. This makes it unlikely that the IFG's role in action semantics in the current study reflects primarily executive processing.

Instead, considering that the patients of Alyahya et al. (2018) performed significantly worse on the abstract condition compared to action, while patients in the current study performed equally on both conditions, it is possible that underlying differences in the stimuli or task demands between the two experiments led to divergent results. For example, their synonym judgment task had two distractor items compared to our one, thus it is possible that there was an interaction effect of increased distractor number and SemD which disproportionately loaded the executive control demands required for abstract synonym judgment in their experiment. In this way, the results from the two experiments are not necessarily incompatible, and likely reflect task characteristics that differentially recruit multiple functions of the IFG.

Abstract Semantics

RLSM analysis using the abstract NOI mask revealed that damage to the aMTG impaired abstract semantic performance to a greater degree than action, providing evidence for the disproportionate contribution of the aMTG to abstract semantics. This is consistent with evidence from healthy subjects that implicates the anterior temporal lobe (ATL) in abstract semantics (Binder et al., 2009; Desai et al., 2018a; Kiehl et al., 1999; Noppeney & Price, 2004; Pobric et al., 2009; Wang et al., 2010). The ATL has been proposed as a semantic hub (Lambon Ralph et al., 2010b; Ralph et al., 2017), although its function remains controversial (Simmons & Martin, 2009; Wong & Gallate, 2012). Damage to the ATL has been shown to cause a range of semantic impairments (Lambon Ralph et al., 2007; Lambon Ralph et al., 2010b; Patterson et al., 2007; Warren et al., 2016), but other prominent functions associated with the ATL are naming and identification of unique entities (Damasio et al., 2001; Damasio et al., 2004; Tranel, 2006, 2009) and social and emotional processing (Olson et al., 2013; Olson et al., 2007). The role of the ATL specifically in abstract concept processing is not well understood. However, its association with social and emotional processing may be the most relevant in this context, as abstract concepts tend to have higher emotional content and could be partly grounded in emotional processing circuits of the brain (Kousta et al., 2011; Vigliocco et al., 2014).

Several studies of patients with ATL atrophy have shown ‘reverse concreteness’ effects where a disproportionate impairment in concrete semantics compared to abstract is seen (Bonner et al., 2009; Cousins et al., 2016; Macoir, 2009; Reilly et al., 2007; Reilly et al., 2006), although this effect is not always so clear-cut (Crutch & Warrington, 2006; Jefferies et al., 2009; Pulvermuller et al., 2010). Further, these investigations were conducted on patients with semantic dementia, a progressive neurodegenerative disease, so patients likely had very different damage and functional reorganization profiles than the MCA stroke patients from the current study (see Hoffman and Lambon Ralph (2011)). This possibility highlights the importance of network analyses to investigate functional connectivity. Additionally, the precise characteristics of the stimuli used for specific experiments are likely important, as abstract concepts do not form a unitary category (Barsalou et al., 2018b; Desai et al., 2018a). Abstract stimuli in many studies also have intermediate and highly variable concreteness (Pollock, 2018), which can introduce inconsistencies between studies.

Functional connectivity and lesion-deficit studies

The present study has implications for the interpretation of past, and the implementation of future, lesion-deficit studies. The findings, specifically for the action NOI, show that functional connectivity can be predictive of behavioral impairment despite the absence of a direct association between grey matter damage and impairment.

We suggest that it is desirable to include analyses of connectivity in order to explore the possibility of post-stroke compensation, especially before drawing conclusions from negative findings. Functional connectivity is well-suited for such analyses since it has been shown to be flexible and well-equipped for reorganization (Honey et al., 2009; Koch et al., 2002; Park et al., 2008), as well as significantly predictive of post-stroke deficits (Siegel et al., 2016). While the current study supports the idea that interhemispheric functional connectivity plays an important role in post-stroke compensation, much work remains to be done regarding questions about the laterality (or lack thereof) of resting state networks post-stroke, how the integrity of specific white matter tracts might influence post-stroke network connectivity, and how time post-stroke and therapeutic interventions might modulate these networks.

Limitations

One limitation inherent to lesion-deficit studies is that the distribution of regions affected by MCA stroke is not uniform, and the power to detect effects is not equal in all regions of the brain. For example, there is evidence that areas peri-lesional to the typical MCA stroke territory, such as the lateral occipital and medial frontal cortex could be involved in action and abstract semantics, respectively (Alyahya et al., 2018; Desai et al., 2018a), and it is possible that the current sample lacked the power to detect those effects in the VLSM anlaysis.

Another limitation is that the resting-state scans were not optimized to detect signal in the ATL, which is subject to loss of signal especially in the ventromedial regions (Devlin et al., 2000). Hence, negative results regarding ATL connectivity are not conclusive and await future studies desiged spcifically to detect effects in the ATL. Finally, here we have taken the traditional approach to treating abstract verbs as a unitary category. However, abstract concepts are diverse, and different types of abstract concepts (e.g., those related to mental processes, emotions, morality, social cognition) are likely to have at least partially different neural basis (Desai et al. 2018). Targeting different types of abstract concpets will be a goal for future studies.

Conclusion

Here, we used lesion-symptom mapping and RSFC analysis to investigate the role of distinct neural systems in action and abstract semantic processing. Our results reveal that partially dissociable neural networks underlie action and abstract conceptual processing, and the former relies on the motor network of the brain. Further, the RSFC analysis suggests that RH areas can participate in comprehension following LH damage and, when this compensatory ability is disrupted through impaired connectivity, a decline in semantic processing is seen. The results highlight the role of network connectivity, and suggest that future lesion-deficit studies could incorporate connectivity analyses as a complimentary methodology to lesion-symptom mapping.

CHAPTER 5

DEGREDATION OF PRAXIS BRAIN NETWORKS AND IMPAIRED COMPREHENSION OF MANIPULABLE NOUNS IN STROKE

Introduction

Understanding the neural basis of conceptual knowledge remains a top priority for the field of neuroscience. Much research over the past two decades has given rise to the embodied cognition framework, which states that sensory-motor brain systems causally contribute to conceptual processing (Barsalou, 2008a; Gallese & Lakoff, 2005). Although this framework is supported by behavioral (Fischer & Zwaan, 2008) and functional neuroimaging research (Binder & Desai, 2011). However, causal evidence directly linking disruption of sensory-motor areas to specific conceptual deficits has been somewhat limited, especially in post-stroke patient populations (Meteyard et al., 2012). This gap in the literature has led some to argue that sensory-motor networks do not directly contribute to conceptual processing, and that they instead play an auxiliary or epiphenomenal role (for critical review, see: Caramazza et al. (2014)). For example, one could argue that the functional neuroimaging findings reveal that action concepts *involve* sensory-motor systems, but these findings do not prove that the sensory-motor networks are *required* for processing action concepts.

One way to address this issue is to use causal methods, such as transcranial magnetic stimulation (TMS) or patient studies, to assess the relationship between sensory-motor networks and conceptual processing. For example, a number of TMS studies have found that stimulating motor or premotor areas affects action-related word processing compared to other word types (Cacciari et al., 2011; Pulvermuller et al., 2005; Reilly et al., 2019; Vukovic et al., 2017; Willems et al., 2011). Notably, Oliveri et al. (2004) found that TMS to the primary motor cortex affected motor-evoked potentials (MEP) elicited by the first dorsal interosseous muscle when retrieving action, but not non-action, words. Gough et al. (2012) used similar methods to find that reading graspable nouns, but not ungraspable, modulated MEP potentials during TMS stimulation of the primary motor cortex. These data substantiate a role for motor and premotor areas in the retrieval and comprehension of action related words and manipulable objects specifically. However, because the majority of these neurostimulation studies have focused on the primary motor or premotor cortices, the role of the rest of the widely distributed action observation and execution network in manipulable concept representation still requires delineation.

Studies of patients with motor disorders such as Parkinson’s disease (PD) or amyotrophic lateral sclerosis have also revealed greater relative deficits to action-related compared to non-action concepts (Bak & Chandran, 2012; Bak & Hodges, 2004; Bak et al., 2001; Cardona et al., 2014; Fernandino et al., 2013a, 2013b; Grossman et al., 2008; Ibanez et al., 2013; Muftuoglu et al., 2004; Peran et al., 2013). These studies provide evidence that, as cortical and subcortical action execution networks deteriorate, processing of action-related words and concepts are impaired to a greater degree than other types of concepts.

However, one limitation of these findings is that some of these studies have directly compared verbs to nouns, meaning that the observed effects could be due to grammatical class and not action or motor properties. Comparing within grammatical class is vital for addressing this possible confound. Further, neurodegenerative studies, especially in PD, have focused on the processing of verbs specifically. As such, possible effects of damage to cortical and subcortical motor networks on manipulable object noun representations requires further investigation.

In addition to studies of neurodegenerative diseases, some lesion-deficit association studies have found evidence that damage to specific sensory-motor systems impair comprehension of corresponding conceptual modalities, providing evidence for embodied cognition (Arevalo et al., 2007; Arevalo et al., 2012; Bonner & Grossman, 2012; Buxbaum & Saffran, 2002; Desai et al., 2015; Dreyer et al., 2015; Kemmerer et al., 2012; Trumpp et al., 2013). For example, Desai et al. (2015) used an exoskeleton robot to measure fine-grained reaching performance in a group of left hemisphere (LH) stroke patients and found that greater motor impairment was associated with greater relative deficits to manipulable compared to non-manipulable noun comprehension, as measured by a semantic similarity judgment task. Relatedly, Buxbaum and Saffran (2002) demonstrated that, compared to non-apraxic stroke patients, individuals with apraxia were more impaired in semantic knowledge of tool manipulation and body parts, but not other categories, as measured by word and picture versions of a similarity judgement task. Taken together, these investigations provide evidence for a close relationship between praxis brain networks and semantic knowledge of manipulable objects. However, because these studies associated performance on one domain (manual reaching/tool-use) to another (semantic similarity judgment) without reference to fine-grained anatomical data, the specific neuroanatomical overlap between praxis and manipulable object comprehension still requires delineation.

Conversely, other lesion studies have failed to find a relationship between action or manipulable object comprehension and degradation of praxis brain networks (Halsband et al., 2001; Mahon et al., 2007; Negri et al., 2007; Papeo et al., 2010; Rosci et al., 2003; Rumiati et al., 2001). For example, Papeo et al. (2010) demonstrated double dissociations between the ability to use tools and performance in a tool word-picture matching task in LH stroke patients. Similarly, Rosci et al. (2003) found that apraxia was not associated with selective deficits to the processing of manipulable objects, as measured by word-picture matching and picture naming tasks. While these observations provide evidence of possible anatomical dissociations between praxis and manipulable object comprehension, some alternative explanations must be considered.

First, tasks like word-picture matching and picture naming do not require explicit retrieval of conceptual features. It is possible that deeper probing of semantic knowledge and associated concepts, such as through a semantic similarity judgement task, would reveal deficits for manipulable objects. Second, the brain networks underlying semantic knowledge and praxis are large and complex, meaning that behavioral or anatomical dissociations can be observed if non-overlapping parts of these networks are damaged. This issue is further complicated by the possibility of post-stroke compensation from undamaged parts of these networks (Hillis et al., 2017; Price & Friston, 2002), such as perilesional areas or contributions from right hemisphere (RH) homologues. This compensatory reorganization can mask brain-behavior relationships, with the reduction in statistical power resulting in type II error. For this reason, additional measures of network integrity, such as fractional anisotropy (FA) or resting state functional connectivity (RSFC), should be considered alongside traditional lesion-deficit measures like behavioral associations or voxel-based lesion-symptom mapping (VLSM). To the best of our knowledge, no previous studies have used these measures in conjunction to examine the relationship between explicit semantic knowledge of manipulable objects and the integrity of praxis networks.

Here, we used VLSM, RSFC, and FA analyses in a group of chronic LH stroke patients to investigate explicit semantic knowledge of manipulable nouns. Non-manipulable nouns matched for a wide variety of psycholinguistic variables served as a control condition to account for global executive or linguistic impairments, as general language difficulties can co-occur with damage to praxis brain networks (Goldenberg & Randerath, 2015; Weiss et al., 2016). The non-manipulable stimuli were built on a criterion of exclusion (i.e. nouns that are not manipulable) instead of being constructed under a unifying feature, a tradition that has been common to many studies of language processing (Barsalou et al., 2018a; Desai et al., 2018b). For this reason, the non-manipulable condition serves best as a control for general cognitive or semantic decline, and not as an explicit investigation of the sensory-motor, emotional, or other *sui generis* properties of the non-manipulable words. We used VLSM and FA to measure grey matter integrity, as well as RSFC in an *a priori* network of interest (NOI) comprised of brain areas associated with praxis.

Materials and Methods

Participants

Fifty-seven participants (female = 19) in the chronic stage (>6 months) of LH unilateral stroke had imaging data for at least one of the three measures used (VLSM, RSFC, FA) and met our inclusion criterion (see *Experimental Design: Behavioral Data*). Participants were scanned and tested at least 6 months post-stroke (M = 4.4 years, Min. = 0.67 y, Max. = 16.83 y) with a mean age at the time of stroke of 54.63 y (SD = 3.71 y). The mean aphasia quotient was 78.84 (SD = 20.74), as measured by the Western Aphasia Battery. Participants signed informed consent, and the University of South Carolina Institutional Review Board approved the research.

Materials

A semantic similarity judgment (SSJ) task was used (Fig. 5.1), consisting of 120 manipulable (“the pen”) and 120 non-manipulable nouns (“the basement”). The noun conditions were organized into 40 triplets each, such that in every triplet two of the nouns had similar meanings and one less-similar noun served as a distractor. For all 80 trials, three nouns were shown in a triangular format simultaneously. Every triplet was made entirely of manipulable or non-manipulable nouns (i.e., no mixed conditions). For example, a manipulable triplet would consist of a target item on top (“the shovel”), with the bottom two items being the distractor (“the rake”) and the correct answer (“the spade”).

The manipulable and non-manipulable conditions differed primarily according to their manipulability and by body-object interaction (BOI) ratings (Tillotson et al., 2008), with the manipulable condition having significantly higher BOI ($p < 0.0001$)[4]. The conditions were matched for several other variables, including number of letters, phonemes, syllables, lemma frequency, imageability, and semantic diversity (Table 1). Additionally, they were matched in mean naming response times (RT) and mean lexical decision RT and accuracy, provided by the English Lexicon Project (Balota et al., 2007).

Procedure

The SSJ task was administered in a separate session from the functional magnetic resonance imaging (fMRI) and was part of a neuropsychological test battery to assess the language and speech abilities of the patients. The SSJ task was presented on a laptop PC running E-prime software (version 1.2, Psychology Software Tools, Inc.).

Participants pressed one of two response buttons to indicate their response to the SSJ task. The position of the bottom two words was counterbalanced across participants. Participants were instructed to respond as accurately and quickly as possible using whichever hand they preferred. The

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[4] BOI ratings measure interaction with the whole body. In addition to manipulable items such as *spoon* or *crutch*, words such as *sofa* also receive high BOI ratings. Here, we only used objects that are typically manipulated with hand/arm, and did not include items such as furniture that are not typically manipulated.

words remained on the screen for five seconds, and no response within that time would result in the next triplet appearing.

Table 5.1 Psycholinguistic variables

	Manipulable Mean (Std. Dev.)	Non-manipulable Mean (Std. Dev.)	p-value
Length	5.7 (1.67)	5.68 (1.54)	1
# Phonemes	4.51 (1.34)	4.62 (1.55)	0.48
# Syllables	1.58 (0.62)	1.66 (0.75)	0.30
Lexical Decision RT	661.9 (73.08)	655.73 (64.02)	0.49
Lexical Decision Acc	0.94 (0.09)	0.95 (0.08)	0.61
Naming RT	637.75 (62.59)	630.05 (54.41)	0.29
Imageability	564.65 (45.77)	570.81 (44.68)	0.38
CobLog Frequency	0.99 (0.54)	1.07 (0.49)	0.20
Semantic Diversity	1.51 (0.23)	1.49 (0.22)	0.40
Body-Object Interaction	5.14 (1)	3.91 (1.30)	**< 0.0001**

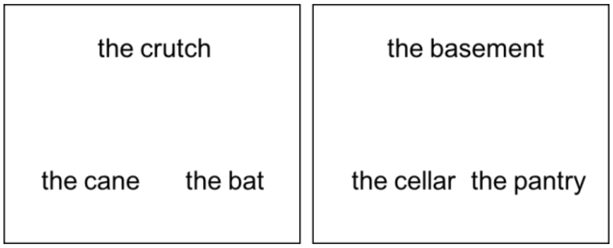


Figure 5.1 SSJ trials

MRI Data Acquisition

MRI data were gathered using a Siemens 3T system with initial participants scanned using the Trio configuration (using a 12-channel head coil) and later individuals scanned after the system was upgraded to the Prisma configuration (with a 20-channel coil). Scanning included two anatomical MRI sequences: (i) T1-weighted imaging sequence using an MP-RAGE (magnetization-prepared rapid-gradient echo) turbo field echo sequence with voxel size = 1 mm^3, FOV (field of view) = 256 × 256 mm, 192 sagittal slices, 9° flip angle, TR (repetition time) = 2,250 ms, TI (inversion time) = 925 ms, TE (echo time) = 4.15 ms, GRAPPA (generalized autocalibrating partial parallel acquisition) = 2, and 80 reference lines; and (ii) T2-weighted MRI with a 3D sampling perfection with application optimized contrasts by using different flip angle evolutions protocol with the following parameters: voxel size = 1 mm^3, FOV = 256 × 256 mm, 160 sagittal slices, variable flip angle, TR = 3,200 ms, TE = 212 ms, and GRAPPA = 2 (80 refernence lines). The same slice center and angle were used as in the T1 sequence.

Functional connectivity was assessed using resting-state fMRI imaging. For 37 participants (scanned on the Trio), images were acquired via an EPI sequence with FOV = 208 x 208 mm, 64 x 64 matrix size of 3.25 mm voxels, 75° flip angle, 34 axial slices (3 mm thick with 20% gap yielding 3.6 mm between slice centers), TR = 1850 ms, TE = 30 ms, GRAPPA = 2, 32 reference lines, sequential descending acquisition, 196 volumes acquired. For 16 participants (scanned on the Prisma), images were acquired via an multiband sequence (x2) with FOV = 216 x 216 mm, 90 x 90 matrix size of 2.4 mm voxels, 72° flip angle, 50 axial slices (2 mm thick with 20% gap yielding 2.4 mm between slice centers), TR = 1650 ms, TE = 35 ms, GRAPPA = 2, 44 reference lines, interleaved ascending acquisition, 427 volumes acquired.

Fractional anisotropy was computed using diffusion tensor imaging (DTI). For 42 participants (scanned the Trio), we used monopolar sequence with 82 isotropic (2.3 mm) volumes (x10 B = 0, × 72 B = 1000), TR = 4987 ms, TE = 79.2 ms, 90 × 90 matrix, with parallel imaging GRAPPA = 2, 50 contiguous slices. For 13 participants (scanned the Prisma), we used monopolar sequence with 86 isotropic (1.5mm) volumes (x14 B = 0, × 72 B = 1000), TR = 5250 ms, TE = 80 ms, 140× 140 matrix, 80 contiguous slices. For all participants, the sequence was acquired in two series (41 and 43 volumes in each series, respectively) with opposite phase encoding allowing us to spatially undistort the images with TOPUP.

Preprocessing of Structural Images

Lesions were defined in native space by a neurologist in MRIcron (Rorden et al., 2012) on individual T2-weighted images. Preprocessing started with coregistration of the T2-weighted images to match the T1-weighted images, permitting alignment of the lesions to native T1 space. Images were converted to standard space using the enantiomorphic (Nachev et al., 2008) segmentation-normalization (Ashburner & Friston, 2005) custom Matlab script (https://github.com/rordenlab/spmScripts/blob/master/nii_enat_norm.m) to warp the images to an age-appropriate template image contained within the Clinical Toolbox (Rorden et al., 2012). The lesion was resliced into standard space with linear interpolation, and the resulting lesion maps were stored at 1 x 1 x 1-mm resolution and binarized using a threshold of 50% (because interpolation can result in fractional likelihoods, this precaution guarantees that each voxel is categorically either lesioned or not without biasing total lesion volume). The tissue segmentation maps from the unified normalization-segmentation we used to create brain-extracted examples of the individuals T1 and T2 scans, which are leveraged for normalizing the other lower resolution modalities (as described below). Preprocessing quality of the normalized images was confirmed by visual inspection.

Preprocessing of RSFC Data

Motion correction for fMRI data was achieved using the SPM12 “realign and unwarp” procedure with default settings. Slice timing correction was performed with SPM12. Brain extraction was completed using the SPM12 script pm_brain_mask with default settings. The extracted mean fMRI volume for each subject was aligned to the equivalent extracted T2-weighted image to calculate the spatial change between the fMRI data and the lesion mask. The fMRI data were spatially smoothed with a Gaussian kernel with full width at half maximum of 6 mm.

The process outlined in Yourganov et al. (2018a) was used to eliminate artifacts driven by lesions. FSL MELODIC package was used to decompose the data into independent components and to calculate the Z-scored spatial maps for each component. The resulting maps were thresholded at $p < 0.05$ and juxtaposed with the lesion mask for that patient. If the overlap (measured with Jaccard index) between the lesion mask and the thresholded IC map was greater than 5%, the corresponding component was considered to have significant overlap with the lesion mask. Any components meeting this criterion were regressed out of the fMRI data using the fsl_regfilt script from the FSL package.

RSFC Connectome Creation

A unique RSFC connectome was constructed for every participant using the subsequent steps: 1) determination of the probabilistic grey matter map from T1-weighted images; 2) segmentation of the grey matter map into 189 regions of interest (ROI) according to the Johns Hopkins University (JHU) atlas (Faria et al., 2012; Mori et al., 2005; Wakana et al., 2004); 3) calculation of ROI-specific time courses of the blood-oxygen level-dependent (BOLD) signal by averaging across all voxels within each individual ROI; 4) creating a 189 x 189 correlation matrix for each participant, where positive values signify greater time-locked activation of two regions.

Fractional Anisotropy Preprocessing

The processing of diffusion-weighted images used the same pipeline described by Peters et al. (2018). Specifically, the diffusion images were undistorted using FSL's TOPUP and Eddy tools (Andersson, et al., 2003; Andersson and Sotiropoulos, 2016) with excess scalp removed using the FSL BET tool. FSL's dtifit tool was used to compute a fractional anisotropy (FA) map. In order to improve registration between T1 and DTI spaces, the scalp-stripped (based on segmentation estimates) T1 image was non-linearly normalized (using SPM12's 'old normalization' function) to match the undistorted FA image. This leverages the similarity of the image intensity in the T1 scan and the FA map, with the high resolution and tissue contrast allowing the T1 scan to achieve superior normalization accuracy. The same transformation matrix was applied to the map of segmented cortical ROIs and the probabilistic white matter map (which were in T1 space) to transform these maps into DTI space (using nearest neighbor interpolation to preserve discrete regions).

Experimental Design and Statistical Analysis

Behavioral Data

Our primary aim was to inspect the relative impairment of the manipulable compared to non-manipulable condition. The average accuracy (Acc) was calculated for the manipulable and non-manipulable conditions for each patient. Seven participants performed below chance (less than 60 % Acc, $p < 0.05$) in both conditions, indicating a general impairment (possibly resulting from impairment in, for example, reading, lexical processing, or executive demands of the SSJ task), and hence were omitted from subsequent analysis. This standard safeguards against the inclusion of participants who were unable to perform either task condition at an above-chance level. Condition-specific differences in such globally impaired patients performing below-chance are difficult to interpret meaningfully. Relatedly, this standard guarantees that patients with chance performance in one condition but relatively unimpaired or above chance performance in the other would be included, as these patients provide the most information about the differences between the conditions. Trials with missing responses were excluded from analysis. The results of central interest are the residuals for each condition when the performance in other condition is regressed out (ResidManip; ResidNonManip). By regressing the conditions out from each other, condition-relative deficits can be assessed while controlling for other confounds such as global impairment, general semantic deficits, or task demands.

Voxel-based Lesion-Symptom Mapping

Whole-brain VLSM was used to identify damage related to greater relative impairment of manipulable (ResidManip) noun comprehension compared to non-manipulable (ResidNonManip) by regressing out performance in one condition from the other using NiiStat software (http://www.nitrc.org/projects/niistat/). This examines condition-relative deficits while controlling for linguistic or executive confounds. VLSM marks each voxel as either lesioned or unlesioned and tests the probability that damage to a voxel is associated with performance on a behavioral measure (Bates et al., 2003). Nuisance regression used the Freedman-Lane method allowing permutation-based control for familywise error, as described by Winkler et al., 2014). VLSM results were thresholded at $p < 0.0005$ voxel-wise and cluster corrected to $p < 0.05$ using permutation analysis as correction for multiple comparisons (1000 permutations). Permutation analysis is a nonparametric significance test that compares a test statistic to a null distribution that is derived from randomly permuting the existing data. Permutation testing relies on minimal assumptions, approaches exact control of false positives, and is currently one of the most common statistical methods for conducting VLSM (Baldo & Dronkers, 2018; Baldo et al., 2012; Kimberg et al., 2007b). To maintain power, only voxels where at least five patients had damage were considered (improving statistical power and minimizing spatial bias, see

Karnath et al., 2018), according to the cut-off recommendation of 5-10% of the patient sample (Baldo & Dronkers, 2018).

Resting State Functional Connectivity: Praxis Network of Interest

A praxis network of interest (NOI) was extracted from the original 189 x 189 connectome for RSFC analysis. This NOI included the supramarginal gyrus (SMG), precentral and postcentral gyri (PrC, PoC), posterior middle and superior temporal gyri (pMTG, pSTG), and the lateral inferior occipital gyrus (IOG). These areas have been consistently implicated in praxis across a variety of methodologies (Borra & Luppino, 2019; Buxbaum & Kalenine, 2010; Hermsdorfer et al., 2007; Lingnau & Downing, 2015; Martin et al., 2017; Orban & Caruana, 2014). We hypothesized that disruption of RSFC links between areas within this NOI would result in worse performance in the manipulable (ResidManip) compared to non-manipulable condition (ResidNonManip), demonstrating a connection between praxis network integrity and the comprehension of manipulable object semantics specifically. Left-to-left, left-to-right, and right-to-right connections (66 total) were considered in order to account for possible contributions from undamaged homologues in the RH. The functional connectivity strengths were used in a general linear model (GLM) predicting ResidManip. Alpha was set to 0.05 and significance was determined with permutation correction for multiple comparisons (1000 permutations).

Fractional Anisotropy

FA is a measure of directional water diffusion that can be used to assess the integrity of underlying brain matter, with intact neural material being associated with more directional diffusion and higher FA (Beaulieu, 2002). FA and other measures of diffusivity are commonly used to investigate grey matter integrity in situations where there may or may not be direct grey matter atrophy, such as in presymptomatic stages of Alzheimer’s disease (Liu et al., 2006; Weston et al., 2015).Grey matter FA provides a promising additional measure to reveal brain-behavior relationships that might not be found using VLSM for two reasons. First, FA provides a continuous measure of damage compared to VLSM’s binary approach, allowing for detection of subtle changes to perilesional grey matter. Second, evidence suggests that even grey matter distant from the lesion site can undergo structural changes following stroke (Wang et al 2018, Abela et al 2014), and these changes would remain undetected if using VLSM alone. FA analysis was used for all 55 grey matter areas identified by the JHU atlas to detect areas where lower FA (i.e. compromised structural integrity) predicted ResidManip in a GLM using NiiStat. Alpha was set to 0.05 and significance was determined via permutation correction for multiple comparisons (1000 permutations).

Results

Behavioral

There was no significant difference between mean Acc in the manipulable (M = 81.8%, SD = 13.8%) and nonmanipulable (M = 83%, SD = 13.2%) conditions; t(56) = 0.67, p = 0.33 This indicates that the conditions were well-matched for difficulty, and that anatomical differences observed between the conditions are unlikely to be caused by general effects of difficulty.

Voxel-based Lesion-Symptom Mapping

Whole-brain VLSM for ResidManip revealed a cluster of voxels to which damage predicted worse manipulable noun comprehension compared to non-manipulable (peak z = -5.138, p < 0.0001). The main body of this cluster extended from the middle and superior temporal gyri posteriorly and into anterior inferior parietal areas such as the SMG, and small portions of the cluster reached medially into white matter such as the superior longitudinal fasciculus and subcortical areas such as the posterior insula (Table 5.2, Fig 5.2). No clusters were significant for ResidNonManip.

Table 5.2 VLSM results for ResidManip

Volume (1x1x1 mm)	**Region**
37,924	Superior Temporal Gyrus
	Posterior Superior Temporal Gyrus
	Middle Temporal Gyrus
	Posterior Middle Temporal Gyrus
	Supramarginal Gyrus
	Angular Gyrus
	Middle Occipital Gyrus
	Superior Longitudinal Fasciculus
	Posterior Insula
	Thalamus

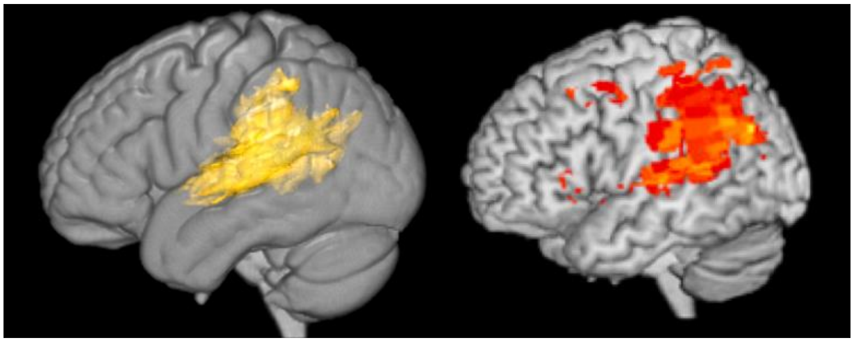


Figure 5.2 VLSM results for ResidManip and actual tool-use

Praxis Resting State Functional Connectivity Network

RSFC within the praxis NOI revealed three connections associated with ResidManip, with decreased functional connectivity in these regions being associated with worse relative performance on the manipulable condition (Table 5.3, Fig. 5.3). These connections were: 1) left postcentral to left supramarginal (z = 3.22, p = 0.0006), 2) left supramarginal to right supramarginal (z = 3.37, p = 0.0004), and 3) left posterior superior temporal to right posterior middle temporal (z = 3.24, p = 0.0006).

Table 5.3 Significant functional connections for ResidManip

Connection		Z-score
Left Supramarginal Gyrus	Left Postcentral Gryus	3.22
	Right Supramarginal Gyrus	3.37
Left Posterior Superior Temporal Gyrus	Right Posterior Middle Temporal Gyrus	3.24

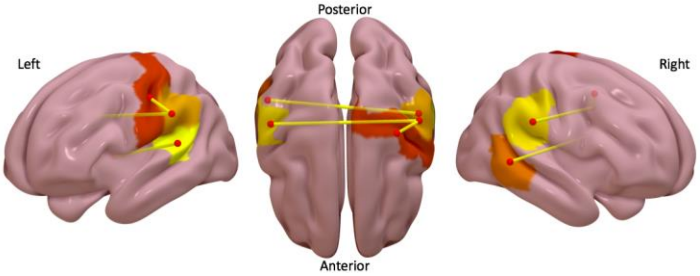


Figure 5.3 Functional connections for ResidManip

Fractional Anisotropy

FA of grey matter revealed eight cortical areas significantly associated with ResidManip, with decreased FA in these regions being associated with worse relative performance on the manipulable condition (Table 5.4, Figs. 5.4 &

5.5). These areas were the posterior middle frontal gyrus (pMFG), inferior frontal gyrus pars opercularis and pars triangularis (IFGoper; IFGtri), supramarginal gyrus, angular gyrus, superior temporal gyrus, and posterior middle and superior temporal gyri. Five subcortical areas were also found, consisting of the thalamus, hypothalamus, red nucleus, substantia nigra, and midbrain (all $p < 0.05$). No areas were significant for ResidNonManip.

Table 5.4 Regions where FA predicted ResidManip

Region	Z-score
Posterior Middle Frontal Gyrus	3.44
Inferior Frontal Gyrus pars Opercularis	3.36
Inferior Frontal Gyrus pars Triangularis	3.30
Supramarginal Gyrus	3.35
Angular Gyrus	3.40
Superior Temporal Gyrus	3.33
Posterior Middle Temporal Gyrus	4.05
Posterior Superior Temporal Gyrus	3.05
Thalamus	3.50
Hypothalamus	4.02
Red Nucleus	3.70
Substantia Nigra	3.77
Midbrain	3.58

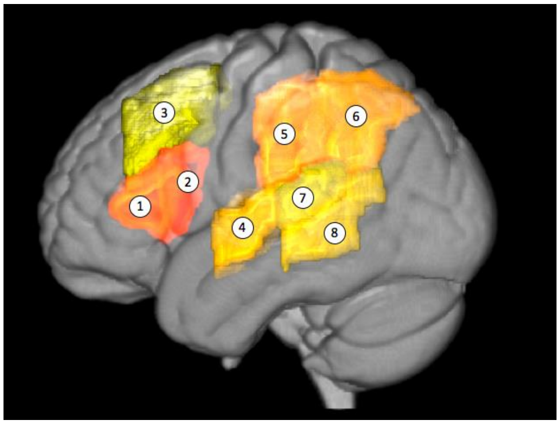


Figure 5.4 Lower FA and ResidManip

Discussion

The results provide clear evidence for the contribution of praxis-related brain areas to manipulable noun comprehension specifically. The three neuroanatomical measures (VLSM, FA, RSFC) revealed a relationship between the degradation of praxis networks and worse relative performance on the manipulable condition of the SSJ task, with the non-manipulable condition serving as a control for general deficits. Further, each of the three measures provided complementary, additive evidence that would not have been revealed by using any single method in isolation, highlighting the importance of using multiple measures of structural and functional integrity in patient studies when possible.

Damage to the Posterior Praxis Network and Manipulable Noun Comprehension

The VLSM results revealed that damage to anterior parietal (SMG) and posterior temporal (pMTG, pSTG) regions resulted in worse comprehension of manipulable compared to non-manipulable nouns. This swath of damage corresponds to the posterior portion of the praxis network (Borra & Luppino, 2019; Buxbaum & Kalenine, 2010), and it displays a remarkable resemblance to the results of lesion studies of impaired tool use (Martin et al., 2017; Salazar-Lopez et al., 2016).

The left anterior inferior parietal lobe (aIPL) is well-established as serving goal directed movement such as reaching-to-grasp and tool-use (Frey, 2008; Johnson-Frey, 2004). For example, lesions to the aIPL are associated with deficits in actual or pantomimed tool use (Goldenberg, 2009; Haaland et al., 2000a; Salazar-Lopez et al., 2016) and the production/imitation of object-related gestures (Buxbaum et al., 2007). TMS to the SMG, especially anterior portions, results in impaired judgment of whether objects are manipulated similarly (Pelgrims et al., 2011) and delayed grasp orientation for manipulable objects (McDowell et al., 2018; Potok et al., 2019). Neuroimaging studies also implicate the SMG and adjacent inferior parietal lobe with intricate actions (Brandi et al., 2014; Frey et al., 2005; Hermsdorfer et al., 2007; Johnson-Frey et al., 2005; Peeters et al., 2013) and the processing of action semantics (Binder et al., 2009; Desai et al., 2010; Desai et al., 2016; Desai et al., 2013).

Similarly, the posterior temporal lobe is often associated with action observation, gesture recognition, and retrieval of knowledge associated with actions and tools (Johnson-Frey, 2004). For example, a meta-analysis of 139 neuroimaging studies of action observation and imitation revealed a significant cluster in the pMTG (Caspers et al., 2010). Lesion evidence has indicated that the pMTG is critical in retrieving the meanings of actions (Kalenine et al., 2010) and to the recognition, but not production, of meaningful actions and their kinematics (Martin et al., 2017). This evidence, when considered alongside proposals that the pMTG serves as an integrative convergence zone (Binder et al., 2009; Willems et al., 2009), suggests that this region may be involved in assimilating multi-modal information, such as motion and visuo-spatial affordances, in order to retrieve the meanings of purposeful actions (Kalenine et al., 2010).

It is important to note that there is also evidence that damage to posterior temporal regions results in lexical impairment, especially when words are presented auditorily (Hillis, Rorden, & Fridriksson 2017). More specifically, pMTG damage has been associated with word comprehension difficulties even after factoring out object recognition. This suggests that the posterior temporal region may be involved in linking words to their concepts, which are then represented elsewhere in the cortex. This word-to-concept matching hypothesis for the pMTG is compatible with the current results under the interpretation that: 1) damage to the pMTG alone would impair the manipulable and nonmanipulable conditions roughly equally due to lexical impairment, but 2) further damage to the distributed action execution and observation regions implicated here would then selectively impair understanding of manipulable nouns due to impoverished conceptual representations. More research is needed to clarify the lexical versus conceptual nature of representations in the posterior temporal lobe.

In sum, evidence suggests that the aIPL supports high-level motor planning that aids body-object interactions, such as the orientation of grip in space. The posterior temporal lobe, on the other hand, is likely inolved in integrating motor-planning representations from the aIPL with other, multi-modal information such as visual motion in order to: 1) extract meaning during action observation or imitation and 2) form associations to related concepts, such as objects or communicative intentions that correspond to the action in question. The current results demonstrate that damage to these areas is associated with impairments to explicit semantic knowledge of manipulable nouns, substantiating an important role for these higher-order action observation and execution cortices in the conceptual representations of manipulable objects specifically.

Functional Connectivity within the Posterior Praxis Network is Associated with Manipulable Noun Comprehension

While tool-use is a largely left-lateralized process (Frey, 2008), recent evidence suggests that connectivity from the LH to homologues in the RH can play a role in praxis following left hemisphere stroke (Watson et al., 2019). As a whole, RSFC network integrity has been shown to be efficacious for predicting performance in a variety of tasks post-stroke (Siegel et al., 2016). RSFC analysis was used to examine how inter- and intrahemispheric connectivity within an *a priori* praxis NOI may contribute to manipulable noun comprehension specifically.

Disruptions of one intrahemispheric (left PoC to left SMG) and two interhemispheric (left SMG to right SMG; left pSTG to right pMTG) connections were associated with worse comprehension of manipulable nouns compared to nonmanipulable. Regarding the intrahemispheric connection, the PoC is the primary sensory cortex and is principally responsible for processing tactile sensations in a somatotopic fashion (Dreyer et al., 1975; Whitsel et al., 1971). Lesions to the PoC are associated with apraxia (Weiss et al., 2016), and neuroimaging studies have implicated the PoC in tool-use (Hermsdorfer et al., 2007) and action observation (Caspers et al., 2010). Additionally, the PoC displays strong connectivity to the aIPL (Ruschel et al., 2014), corresponding to the SMG, providing evidence that these areas form part of a coherent network in healthy brains. In the context of the current study, it is possible that connectivity between the left PoC and SMG helps integrate tactile and hand-orientation representations that serve explicit manipulable noun comprehension. When this connection is disrupted, performance in the manipulable condition declines to a greater degree than in the non-manipulable condition due to the greater sensory-motor and BOI associations for manipulable object concepts.

The interhemispheric connections, on the other hand, align well with those found by Watson et al. (2019), who demonstrated that patients with poorer interhemispheric connectivity between parietal and posterior temporal regions display more severe symptoms of apraxia compared to those with better interhemispheric connectivity. It is possible that the connections in the current study represent compensatory connectivity between undamaged RH hemisphere homologues and the surviving portions of the LH to aid comprehension. Studies of post-stroke language recovery have found that increased activity or connectivity to RH homologues is associated with better behavioral outcomes (Heiss et al., 1999; Richter et al., 2008; Saur et al., 2006; Skipper-Kallal et al., 2017; Thulborn et al., 1999). Similarly, post-stroke motor recovery has been shown to be reliant on connectivity between contralesional homologues and surviving portions of the ipsilesional cortex (Bestmann et al., 2010; Johansen-Berg et al., 2002; Kantak et al., 2012). Taken together, the current results suggest that disruption of connectivity within the LH or to RH homologues of the praxis network impairs manipulable noun processing especially, even after accounting for general executive or cognitive decline via the non-manipulable comparison condition.

Integrity of Frontal and Subcortical Motor Structures Predicts Worse Manipulable Noun Comprehension

Praxis is a complex and widely distributed process that involves contributions from cortical and sub-cortical structures. While the VLSM and RSFC results highlighted the contributions of posterior cortical areas to manipulable noun comprehension, FA provided complementary evidence by identifying structural changes to grey matter that were not established via traditional VLSM. The FA results: 1) added evidence suggesting that compromised integrity of subcortical and frontal structures also disproportionately impairs manipulable noun understanding compared to nonmanipulable and 2) replicated VLSM and RSFC results regarding the importance of the posterior praxis network (pMTG, SMG) for manipulable noun comprehension.

The FA analysis revealed that reduced integrity of subcortical areas, including the thalamus and midbrain structures, is associated with worse comprehension of manipulable nouns compared to non-manipulable. While the specific contributions of these areas to semantic processing is understudied, evidence from Parkinson’s disease (PD) suggests that degradation of the basal ganglia-thalamo-cortical network can selectively impair action-related language processing (Bocanegra et al., 2015; Fernandino et al., 2013a, 2013b). PD is associated with the degeneration of dopaminergic neurons in the midbrain, especially in the substantia nigra, causing multiple motor and cognitive impairments (Chinta & Andersen, 2005; Hoehn & Yahr, 1967). These midbrain areas, including the red nucleus, are important parts of the motor system (Herter et al., 2015; Hosp et al., 2011) and display connectivity to cortical motor areas in both human and animal models as part of the corticospinal tract (Habas & Cabanis, 2006; Hartmann-von Monakow et al., 1979; Humphrey et al., 1984). The current results demonstrate that, following stroke, reduced structural integrity of these subcortical motor areas is associated with impaired processing of manipulable nouns compared to non-manipulable. This is an addition to the literature regarding the possible contributions of the midbrain and other subcortical structures to action-related language processing, as most previous patient studies about the linguistic role of these structures have focused on verb processing in PD (see Buccino et al. (2018) for a recent exception).

However, a caveat should be noted concerning the subcortical FA results. Stroke is associated with ventricular enlargement (Hijdra & Verbeeten, 1991), and it is possible that low FA measures in subcortical areas, especially areas directly adjacent to the ventricles such as the thalamus, are driven by this enlargement rather than by direct degradation to the area in question. For this reason, the subcortical FA results should be treated with caution, and future studies should investigate the role of subcortical motor areas in action-related noun processing beyond the typical PD patient model.

Regarding frontal cortices, the analysis revealed that reduced FA in the posterior middle frontal gyrus (corresponding to the premotor cortex; PMc) and inferior frontal gyrus pars triangularis and opercularis (IFGtri; IFGoper) was associated with worse relative comprehension of manipulable nouns. These areas have been shown to be heavily involved in motor planning, execution, and observation, especially as it pertains to hand-related actions (Binkofski & Buccino, 2006; Caspers et al., 2010; Rizzolatti et al., 2001). PMc and IFG have also been implicated in the production and comprehension of action language. For example, words referring to face, leg, or arm actions are associated with somatotopically organized activations in the PMc (Aziz-Zadeh et al., 2006; Hauk et al., 2004). Further, deterioration of the IFG from amyotrophic lateral sclerosis is associated with selective impairments to action verbs, supporting a causal role for the IFG in the comprehension of action-related language (Bak & Chandran, 2012; Bak & Hodges, 2004; Bak et al., 2001). Finally, evidence from stroke patients implicates these frontal areas in lexical and conceptual knowledge of actions (Kemmerer et al., 2012; Tranel et al., 2001; Tranel et al., 2003). Many of these past studies focused specifically on action verbs or concrete objects without specifically addressing manipulability, leaving gaps in the patient literature regarding the neural substrates of nouns that are highly action-related. Our results help address this, demonstrating that reduced integrity of the PMc and IFG is associated with worse relative comprehension of manipulable objects compared to the nonmanipulable condition. Importantly, while the IFG is known to have many executive and linguistic functions (Badre, 2008; Fadiga et al., 2009a; Grodzinsky & Santi, 2008), the effect observed here is unlikely to be driven by these more general processes due to the matching of difficulty and psycholinguistic variables, such as semantic diversity, between the manipulable and non-manipulable conditions. Thus, it is likely that these frontal portions of the motor planning and execution network are especially involved in the representation of concepts with high motor or body-object interaction properties.

Negative Results for Non-manipulable Nouns

The analyses presented here did not reveal significant results for the ResidNonManip condition. This is likely due to the non-manipulable stimuli being built on a criterion of exclusion (i.e. nouns that are not manipulable) instead of being constructed under a unifying feature, a tradition that has been common to many past studies of language processing (Barsalou et al., 2018a; Desai et al., 2018b). Because of this, the non-manipulable condition serves best as a control for general cognitive, lexical, or semantic decline, and not as an overt exploration of the anatomical substrates of the sensory-motor, emotional, or other *sui generis* properties of the non-manipulable words. Future lesion studies should construct stimuli that are specifically meant to test salient features other than manipulability.

Limitations

This work has limitations. Damage from middle cerebral artery stroke does not usually extend to some areas that are implicated in action perception or execution, such as the lateral occipital cortex (Lingnau & Downing, 2015). This could limit the ability to test the contribution of these areas to semantic processing in MCA stroke patients. Further, the nature of MCA stroke means that certain regions are often damaged together, making it difficult to draw fine-grained anatomical boundaries for brain-behavior relationships. For example, STG damage was predictive of ResidManip in both the FA and VLSM analysis, but this region is commonly associated with general auditory and speech processing (Liebenthal et al., 2014). This is likely due to the superior temporal region and praxis-related ventral fronto-parietal regions being affected together in MCA stroke. In our sample, only three patients had damage to the STG without corresponding damage to the SMG, meaning that there were not enough patients with this pattern of damage to dissociate the function of these areas. This natural limitation of MCA stroke investigations is one possible reason why apraxia and general language difficulties often co-occur (Goldenberg & Randerath, 2015; Weiss et al., 2016). Future studies can make finer distinctions via more focal methods such as TMS or investigating patients with relatively localized lesions.

Conclusions

Here, using three complementary methods, we found striking evidence demonstrating that degradation of praxis brain networks especially impairs semantic processing of manipulable nouns compared to non-manipulable. This network mainly consists of the posterior temporal lobe, aIPL, and inferior frontal and premotor cortices. Further, RSFC analysis revealed that disrupted connectivity to RH homologues of this network was associated with worse relative performance on the manipulable compared to non-manipulable condition, demonstrating that disrupted connectivity to the RH is associated with semantic decline. Overall, these results suggest that brain areas underlying action planning and execution contribute to the representation of semantic information pertaining to words with high body-object interaction properties, providing novel support for the embodied cognitive framework.

CHAPTER 6

THE ANTERIOR TEMPORAL LOBE IDENTIFIES SPECIFIC ENTITIES

Introduction

The anterior temporal lobe (ATL) is an important part of the lexical semantic system (Ralph et al., 2017). Evidence from neuropsychological and neuroimaging investigations has demonstrated its role in other domains, such as social and emotional processing (Olson et al., 2013) and the naming of unique entities (Tranel, 2009). As a result, controversy persists regarding whether the ATL has an overarching function, and whether there are subdivisions of the ATL that are specialized for different functions (Simmons & Martin, 2009; Wong & Gallate, 2012).

Currently, there are three dominant theories about the function of the ATL. First, the semantic ‘hub’ model proposes that the ATL is a semantic hub region that stores coherent concepts (Lambon Ralph et al., 2010b; Patterson et al., 2007; Ralph et al., 2017). Second, the social processing account states that the ATL is involved in processing social concepts and linking perceptual information of persons to relevant biographical information such as name or occupation (Olson et al., 2013; Olson et al., 2007; Wang et al., 2017). Third, the unique entities hypothesis argues that the ATL is involved in processing unique, one-of-a-kind entities such as famous people or places, with its specific role being name retrieval (Tranel, 2009). Lines of research produced by these theories have provided contradictory results, making it difficult to interpret the true role of the

ATL within the semantic system. However, an additional fourth line of evidence that is comparatively underrepresented in the neuroimaging literature demonstrates that portions of the ATL serve more general memory processes (Bowles et al., 2007a; Jackson & Schacter, 2004b; Titiz et al., 2017), introducing the need to dissociate these memory processes from semantic, social, or name-retrieval confounds.

Much of the evidence for the semantic hub model comes from neuropsychological investigations of patients with semantic dementia (SD), a neurodegenerative disease characterized by ATL atrophy accompanied by severe anomia and nearly complete loss of semantic knowledge (Hodges & Patterson, 2007a; Hodges et al., 1992). However, patients with ATL damage from SD or other etiologies such as temporal lobe resection also often display severe behavioral issues such as withdrawal, compulsive behavior, and lack of empathy (Ghika-Schmid et al., 1995; Irish et al., 2014; Lilly et al., 1983; Snowden et al., 2001), substantiating claims that the ATL is involved in social processes (Olson et al., 2013). ATL damage from etiologies other than SD does not necessarily cause the category-general impairments of semantic knowledge seen in SD (see Shallice and Cooper (2011) for review; see Lambon Ralph et al. (2010a) for counterevidence). Instead, these patients can demonstrate category-specific semantic deficits (Capitani et al., 2003; Gainotti, 2000; Shallice & Cooper, 2011) or impairments in memory, recognition, or person/place name retrieval tasks (Bowles et al., 2007a; Damasio et al., 2004; Grabowski et al., 2001; Martin et al., 2011; Milner, 2003; Novelly et al., 1983; Samson & Zatorre, 1991; Tranel, 2006, 2009), supporting other interpretations of ATL function.

Similar to neuropsychological investigations, functional neuroimaging in healthy populations has led to contradictory results and interpretations of findings. Contrary to predictions generated by the semantic hub hypothesis, semantic tasks do not consistently lead to ATL activation (Simmons & Martin, 2009; Wong & Gallate, 2012), though semantic hub proponents argue that this is a function of poor functional magnetic resonance imaging (fMRI) signal from the ATL due to its proximity to sinus cavities (Devlin et al., 2000) and has been addressed via distortion correction and alterations of fMRI parameters (Visser et al., 2010a; Visser et al., 2010b).

Despite these corrective measures, there is still a relative scarcity of neuroimaging evidence in support of the semantic hub account. For example, an fMRI investigation of semantic fact encoding, with parameters optimized for capturing ATL signal, failed to find evidence for ATL involvement for the categories of buildings and tools, instead only finding evidence for the category of faces (Simmons et al., 2010). Additionally, multiple meta-analyses and reviews of neuroimaging studies have failed to find substantial evidence of ATL involvement in category-general semantic tasks (Binder & Desai, 2011; Devlin et al., 2002; Gerlach, 2007). Findings such as these are difficult to reconcile with the semantic hub account, especially when considered alongside the relatively extensive neuroimaging evidence substantiating the role of the ATL in other domains such as social and emotional processing (Olson et al., 2013; Olson et al., 2007; Tsukiura et al., 2008; Von Der Heide et al., 2013; Wang et al., 2017), naming unique entities (Damasio et al., 2004; Grabowski et al., 2001; Tranel, 2006, 2009; Tsukiura et al., 2006), or associative memory tasks (Jackson & Schacter, 2004b; Nieuwenhuis et al., 2012; Simmons et al., 2010), with example tasks from such experiments being to name or recall information associated with a stimuli.

In light of this evidence, a theory proposed by Tranel (2009) separates itself from both the semantic hub and social accounts by proposing that the ATL is involved specifically in name retrieval for any unique, concrete entities such as famous people or landmarks. Evidence for this proposal comes from investigations of both healthy and impaired brains. Neuroimaging studies in healthy participants found that the left ATL is significantly activated in both famous person and landmark naming tasks compared to face and place orientation judgement baseline tasks (Damasio et al., 1996; Grabowski et al., 2001). Further, a series of neuropsychological experiments of patients with ATL damage from various etiologies established that those with left temporal pole damage had significantly impaired naming of famous faces compared to both healthy controls and patients with lesions elsewhere in the brain (Damasio et al., 1996; Damasio et al., 2004; Tranel, 2006). This naming impairment was also shown for landmarks (Tranel, 2006), providing counterevidence to the social account by demonstrating that the deficit is not specific to faces.

These results were also found after controlling for semantic knowledge about the specific entities, that is, instances when the patient could demonstrate knowledge about the entity (i.e., famous basketball player for the Chicago Bulls) but could not retrieve the name (Michael Jordan). This demonstrates that 1) ‘naming’ and ‘knowing’ are dissociable processes that can be differentially impaired and 2) damage to the left ATL seems to selectively impair naming, but not knowing (Tranel, 2009). Additionally, (Damasio et al., 1996) failed to find evidence of naming deficits for other categories such as animals or tools in patients with left temporal pole damage. The category-specific nature of these deficits makes interpretation from a semantic hub account difficult since it predicts that all categories should be impaired, and deficits in landmark naming in addition to faces makes a purely social account of ATL function unlikely.

Tranel (2009) interpreted these findings as evidence that the left ATL is specifically involved in linking word forms of proper names to unique concrete entities, with the domain of unique entities being defined as numerous, visually similar items that can also be described as ‘one of a kind’ (such as famous faces, which share underlying visual features but differ according to specific qualities). However, this interpretation of ATL function is perhaps too limited considering a body of evidence in both animal (Baxter & Murray, 2001; Meunier et al., 1993; Mumby & Pinel, 1994; Murray et al., 2005; Nakamura & Kubota, 1996) and human studies that implicates the ATL in more general recognition and memory processes that, in the case of human studies, do not necessarily require an explicit naming task (Bowles et al., 2007a; Dolan et al., 2000; Elliot & Dolan, 1999; Ezzyat et al., 2018; Jackson & Schacter, 2004b; Milner, 2003;

Nieuwenhuis et al., 2012; Novelly et al., 1983; Samson & Zatorre, 1991; Titiz et al., 2017).

A number of studies have investigated memory impairments in human patients with ATL damage (Bowles et al., 2007a; Ezzyat et al., 2018; Milner, 2003; Titiz et al., 2017). For example, Titiz et al. (2017) found that microstimulation of the medial right ATL (specifically the entorhinal cortex) in neurosurgical patients significantly improved memory specificity, as measured by the ability to accurately recognize familiar persons while rejecting highly similar 'lure' persons. Ezzyat et al. (2018) found similar results in a verbal task, wherein closed-loop stimulation of more posterior portions of the left lateral ATL significantly improved performance on a simple word recall task. Finally, a case study by Bowles et al. (2007a) found that a patient with a left ATL lesion sparing the hippocampus was impaired at verbal familiarity tasks, but not episodic memory, further substantiating a role for the ATL in simple recognition and memory.

Neuroimaging investigations of healthy adults also support the involvement of the ATL in memory (Dolan et al., 2000; Elliot & Dolan, 1999; Jackson & Schacter, 2004b; Nieuwenhuis et al., 2012; Simmons et al., 2010; Tsukiura et al., 2006; Wang et al., 2017), although some of these experiments have used associative memory task paradigms. The use of associative memory tasks, where participants are trained to associate additional information to an original stimulus, sometimes makes it difficult to dissociate whether ATL involvement is due to recognizing specific, familiar entities or if it is due to the retrieval of the associated knowledge. For example, in a magnetoencephalography (MEG) experiment conducted by Nieuwenhuis et al. (2012), participants were trained to associate previously unknown faces with 1 of 6 screen locations and then were tested either 1 (recent) or 25 hours (remote) after completion of training. Comparison of the remote versus recent conditions demonstrated a significant reorganization of neocortical networks such that activation of the ATL for associative memories increases as a function of time (Nieuwenhuis et al., 2012). These results were found in the absence of an explicit naming task and, although stimuli were faces, there is no reason to believe that these results should be face-specific, especially considering the findings of studies using non-face stimuli (Dolan et al., 2000; Elliot & Dolan, 1999; Jackson & Schacter, 2004b).

In sum, research has shown that the ATL is associated with name retrieval for unique entities such as famous faces and landmarks (Tranel, 2009), as well as retrieving social information about familiar people (Olson et al., 2013; Olson et al., 2007). However, these findings can be partially accommodated under the semantic hub account when considering the fact that these entities are often part and parcel with rich semantic information (i.e., people tend to know a lot about famous or familiar people and places). As such, the factors of familiarity and semantic knowledge must be dissociated in order to clarify the true function of the ATL. Some prior studies that have used famous or personally familiar faces and landmarks have not been able to properly distinguish these two factors. Similarly, the ATL has been implicated in training studies wherein participants are trained to associate additional information with visual stimuli, but again it can be unclear if the ATL is involved specifically in the retrieval of associated information or in the identification of specific, familiar entities. The previously discussed body of evidence implicating the ATL in simple memory and familiarity processes establishes the need for an fMRI investigation that properly dissociates simple familiarity effects from associated information retrieval.

Thus, in a novel training study, participants were exposed to six different categories (persons, objects, buildings, words, non-words, and numbers) of non-famous visual stimuli prior to scanning, making those stimuli ‘familiar’. No additional semantic information was given about the items. These ‘familiar’ items were then presented to participants in the scanner along with ‘unfamiliar’ items (i.e. previously unseen stimuli) from the same categories. The hypothesis was that the ATL will be involved in the identification of familiar compared to novel entities, even when controlling for associated semantic content. This would demonstrate that, in some past studies, it might not be semantic knowledge that is driving ATL involvement but is instead the fact that the participant is identifying a familiar or specific entity among other visually similar items. This hypothesis differs from the semantic hub account, which would not predict significant differences within the ATL between the familiar and unfamiliar conditions, since both the familiar and unfamiliar stimuli have the same amount of semantic information attached to them. Further, it expands upon the unique entities account as proposed by Tranel (2009) in that it requires no explicit name retrieval. The hypothesis was tested via traditional univariate analysis comparing the blood oxygen-level dependent (BOLD) signals of familiar versus novel conditions, as well as multi-voxel pattern analysis (MVPA) which provides increased sensitivity by taking into account whole patterns of voxel activation (Combrisson & Jerbi, 2015; Mahmoudi et al., 2012; Norman et al., 2006).

A secondary area of interest pertains to the scope of the effect of familiarity. That is, will familiarity-related activation in the ATL be restricted to more socially salient stimuli such as persons, as predicted by the social processing account (Olson et al., 2013; Olson et al., 2007)? Or will the effect be seen for any type of entity, including more non-semantic stimuli such as non-words and numbers? Previous research has shown that left- or right-lateralization is possible depending on category type, with written stimuli being more associated with the left ATL (Rice et al., 2015a; Rice et al., 2015b; Tsukiura et al., 2006). Similarly, there is some evidence that indicates differential functional organization within the ATL depending on stimulus type (Murphy et al., 2017; Visser & Lambon Ralph, 2011). The wide range of categories used in the current experiment allows investigation of possible between-category differences.

Materials and Methods

Participants

Twenty-six participants (7 male, mean age = 20.9 years) were recruited from the University of South Carolina Department of Psychology undergraduate participant pool. This number of participants has been shown to provide adequate power for fMRI experiments (Desmond & Glover, 2002). All participants were right handed native English speakers with no history of neurological conditions. They signed an informed consent form and underwent appropriate fMRI safety screening. Participants were compensated for their time with course credit or financial reward.

Stimuli

Organization

720 stimuli were gathered, with 120 stimuli per 6 categories (persons, buildings, objects, words, non-words, numbers). The stimuli were pseudo-randomly broken into 5 groups, consisting of a) the *training* group, which participants were trained to recognize prior to scanning, b) three *test* groups, which were used against the training group to test the participants' familiarity with their training stimuli prior to scanning, and c) the *test-scan* group, which were novel stimuli used against the trained stimuli while in the scanner. The training and three test groups contained 24 stimuli per 6 categories, for a total of 144 stimuli per stimuli group. The test-scan group contained an extra category consisting of 24 scrambled images for a total of 7 categories and 168 stimuli. The scrambled images were for use in a different analysis that will not be discussed here.

Creation

Buildings and persons were gathered from a google image search of public domain websites and underwent pilot testing to ensure that no famous buildings or persons were included. Non-words were pronounceable constrained bi- and trigram based strings generated by the McWord wordform database (Medler & Binder, 2005). Words were real English nouns and adjectives gathered from a database of 40,000 English words lemmas (Brysbaert et al., 2014). Numbers were whole integers gathered using an online pseudo-random number generator (Haahr & Haahr, 2017). Objects were standardized images of tools, fruits/vegetables, and ‘building materials’ (fences, escalators, fountains, etc.) on a white background gathered from the Bank of Standardized Stimuli (BOSS) (Brodeur et al., 2010).

Matching

Buildings and persons were assigned to groups using a pseudorandom number generator. Words were matched using independent samples t-tests between each group for variables of concreteness/abstractness, emotional valence, word length, and frequency, $t(46)$, all $p > .05$. Non-words were first generated to match the length of the real words ($M = 7.13$, $SD = 1.81$), and then matched using independent samples t-tests between each group for word length, $t(46)$, $p > .05$. Numbers were perfectly matched between groups according to integer length such that each group contained 6 two-digit, 12 three-digit, and 6 four-digit integers. These integer lengths were chosen after a pilot study indicated that integers of four digits or greater are difficult for participants. Objects were matched between each group for familiarity, visual complexity, manipulability, percent of people who did not recognize the object, and percent of people who recognized the object but did not know the name (Brodeur et al., 2010) with independent samples t-tests, $t(46)$, all $p > .05$.

Alteration

Exactly half (chosen pseudo-randomly within each group) of the building, person, and object stimuli were altered visually by conducting at least two of any of the following; altering borders, contrast/saturation, brightness, sharpness, transparency, or flipping horizontally/vertically (Fig. 1). Alterations were conducted using Microsoft Word and a command-line image alteration software package (ImageMagick, 2017). No objects were altered in such a way as to make them unrealistic (e.g. buildings and persons were not flipped vertically) or unrecognizable compared to the unaltered image. After alterations, two versions of the training groups were created; one in which half of the stimuli were altered and half were unaltered, and another where this was reversed (i.e. if version 1 contained an altered wrench and unaltered hammer image, version 2 would contain the reverse). This was done so that, while in the scanner, participants would not see the exact same stimuli on which they had trained, but would instead need to display true recognition of the stimulus itself in order to determine if they are familiar with it. For words, non-words, and numbers, font was altered for each phase (e.g. training: times new roman, scanning: arial)

Procedure

Training and Testing

Participants were trained and tested at least two times prior to scanning, with a maximum of three training/testing sessions. Each time, they first trained on their *training* stimuli via self-paced navigation of the stimuli on a laptop, with the specific instructions being to view each item until they felt that they could sufficiently identify their training stimuli if presented alongside new stimuli. Once the participant indicated that they were done training, they were tested with novel stimuli randomly mixed in alongside their training set. For each item, they had to indicate with a yes/no response "Was this item on your original training list?" Every participant who underwent scanning had to achieve at least 85% accuracy on each stimuli category within three testing sessions, or else they were dropped from the fMRI portion of the study.

Scanning

Participants were brought to the scanner 24-48 hours after the final training session. This time window was chosen due to it being outside of any short-term memory window and based on the findings of the previously discussed Nieuwenhuis et al. (2012), which found increased ATL activation in a memory task at least 24 hours after training.

In the scanner, stimuli were presented in six runs of 13 blocks each (with one block being the scrambled image condition). Each block was made of four items of the same category and condition (e.g., four familiar buildings, four unfamiliar faces, etc.). At the beginning of each run, participants were instructed to use their index or middle finger to press a button if all the items in a block were familiar, while using the opposite finger to respond if all the items were unfamiliar. Participants indicated 'scrambled' with a third button press (ring finger) when presented with the scrambled stimuli block. Button presses and response hand were pseudo-randomly assigned to participants. Each item was presented for 1500 ms followed by a 100 ms fixation. At a randomly varying interval of between

4-8 s after the end of a block, a ‘?’ was displayed, at which point the participant responded with the appropriate button press. A total of 12 s separated each block.

Stimuli were assigned to blocks pseudo-randomly, and runs were presented randomly using the MATLAB psychophysics Toolbox-3 (Brainard, 1997; Kleiner et al., 2007; Pelli, 1997). The training, test, and test-scan stimuli groups were counterbalanced between participants such that half of all participants were trained on stimulus group A, with stimulus group B being presented as novel stimuli in the scanner, and the other half were trained on stimulus group B, with stimulus group A being presented as novel stimuli in the scanner.

fMRI parameters were chosen to maximize signal retention in the ATL (Devlin et al. (2000), fig. 6.1 shows coverage). Functional images were acquired on a Siemens PRISMA 3.0-T MRI system (Siemens, Erlangen, Germany) equipped with a 20-channel head coil. Blood oxygen-level dependent (BOLD) images were acquired using a single-shot gradient, multi-band EPI sequence (echo time/repetition time = 34/1500 ms, 50 interleaved slices via PAT GRAPPA, slice thickness = 2 mm, field of view (FoV) = 216 mm, flip angle = 72 degrees, voxel size = 2.4 x 2.4 x 2.0 mm^3). High-resolution anatomical images were acquired using a fast gradient echo sequence (echo time = 4.11 ms, voxel size = 1 x 1 x 1 mm^3, 192 sagittal slices, FoV = 256 mm).

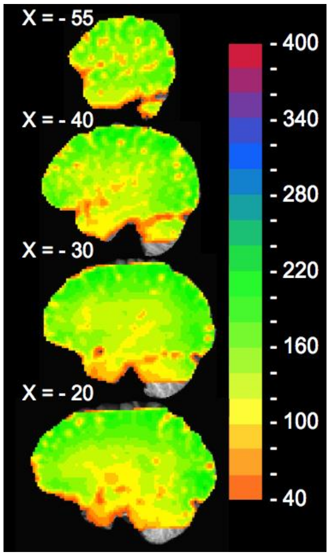


Figure 6.1 TSNR

Univariate and Multivariate fMRI Data Preprocessing

Functional data were preprocessed and analyzed with the Analysis of Functional NeuroImages (AFNI) software package (Cox, 1996). Standardized preprocessing consisted of registration of functional images to participant anatomy (Saad et al., 2009). Functional images were then co-registered (Cox & Jesmanowicz, 1999) and projected into standard stereotaxic space (Talairach & Tournoux, 1988). For univariate analysis, the images were smoothed with a 6-mm full width at half maximum (FWHM) Gaussian kernel. For multivariate, the images were smoothed with a 2-mm FWHM Gaussian kernel. The preprocessed fMRI time series were analyzed within-participants using a block design for voxelwise multiple linear regression with regressors for each category and condition (e.g., familiar buildings, unfamiliar buildings, familiar persons, etc.) and for the fixation jitter and button press time-points. Six motion parameters and the signal from cerebrospinal fluid were included as nuisance covariates.

Univariate Data Analysis

Within each category, the unfamiliar condition activations were subtracted from familiar (e.g., familiar persons minus unfamiliar persons, familiar buildings minus unfamiliar buildings, etc.). In a random effects analysis, the resulting activation maps were compared to a constant value of 0 to create group maps. These maps were thresholded at voxelwsie, one-tailed $p < .005$ because the prediction was that the familiar conditions should result in more activity in the ATL compared to unfamiliar. Correction for multiple comparisons was accomplished by removing clusters smaller than 276 microliters to achieve a map-wise corrected $p < .05$. This clusterwise threshold was determined via the *3dClustSim* command with 10,000 iterations, using Monte Carlo simulations that estimate the chance probability of adjacent voxels exceeding the voxelwise *p* threshold. The analysis was restricted to two ATL masks (Fig. 6.2), one for each hemisphere. These masks were based on the probabilistic Desikan–Killiany atlas (Desikan et al., 2006) and consisted of six ATL structures: entorhinal cortex (EC), fusiform gyrus (FFG), inferior temporal gyrus (ITG), middle temporal gyrus (MTG), superior temporal gyrus (STG), and temporal pole (TP).

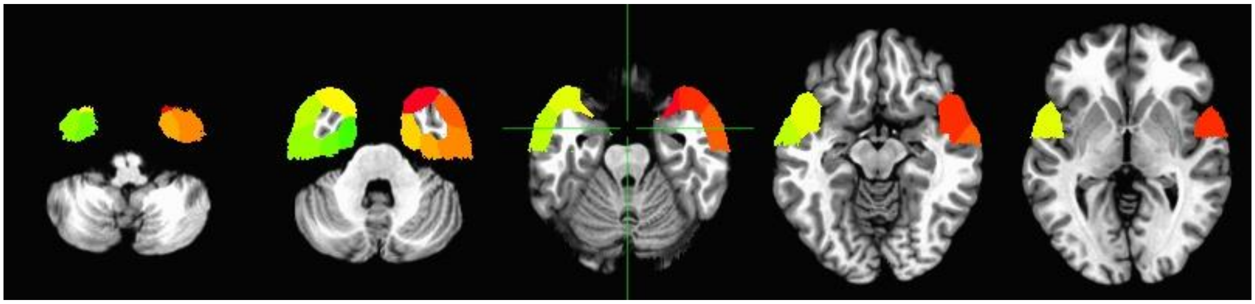


Figure 6.2 ATL mask

Multivariate Data Analysis

Searchlight (5 mm radius) MVPA was used within the bilateral ATL mask for each subject to train a linear support vector machine (SVM) model to classify stimuli as either ‘familiar’ or ‘unfamiliar’, using each participant’s time course-dependent voxel activations as input. Searchlight analysis passes a sphere over each voxel, performing a multivariate test of the activation patterns of all voxels within that sphere to generate a single value for the voxel at the center of that sphere (Kriegeskorte et al., 2006). This single value represents that voxel’s accuracy as it pertains to the classification goals of the model.

Classification results for the SVM model were evaluated within-subject using 6-fold, leave-two-out cross-validation wherein the model was trained on the voxel patterns from five familiar and five novel blocks of the same category and then asked to classify the two remaining blocks as either familiar or unfamiliar. Prediction accuracies were based only on test data and were independent of the training set. To evaluate significance of cross-subject model classification accuracy, the accuracies of every within-subject analysis were averaged for each category separately and subsequently tested against a simulated binomial cumulative distribution with a sample size of $n=26$ and 2-class classification. A binomial cumulative distribution was used instead of a traditional t-test against exact chance due to the binomial cumulative distribution being more statistically rigorous, thereby reducing the likelihood of obtaining false positives (Combrisson & Jerbi, 2015).

Informative voxel clusters were identified using the searchlight analysis output, which generated a classification accuracy for each individual voxel within the bilateral ATL mask for each participant. Similar to group analysis for the univariate method, these accuracies were used for voxel-by-voxel t-tests against a constant value of 0.65, which is significantly greater than binomial chance accuracy ($p < .05$), and subsequent voxelwise thresholding at one-tailed $p < 0.001$. Correction for multiple comparisons ($p < .05$) was accomplished via permuting the behavioral data 1000 times for each contrast and voxelwise thresholding the resulting maps in the same way as described for the unpermuted data, which provided a distribution of cluster sizes generated with the permuted data. In the real (unpermuted) data, for each contrast, we then only kept clusters that were larger than 95% of the permuted clusters.

Results

Behavioral

Participant accuracy in the scanner was high for each condition (mean accuracies: buildings = 99.4%, persons = 98.7%, nonwords = 97.8%, numbers = 89.1%, objects = 97.8%, words = 97.1%). This demonstrates that participants understood the task and were able to reliably identify the stimuli as either familiar or unfamiliar.

Univariate

An effect of familiarity was found for the nonwords and numbers categories (table 6.1). The left MTG was activated more for familiar nonwords compared to unfamiliar nonwords (fig. 6.3). The right TP was activated more for familiar numbers compared to unfamiliar numbers (fig. 6.4).

Table 6.1 Univariate results for familiar > unfamiliar

Condition	**Location**	**# of Voxels**	**Peak X**	**Peak Y**	**Peak Z**	**Value (z-score)**
Nonwords	L. MTG	39	-53	5	-24	3.64
Numbers	L. STG	41	59	1	-4	4.76

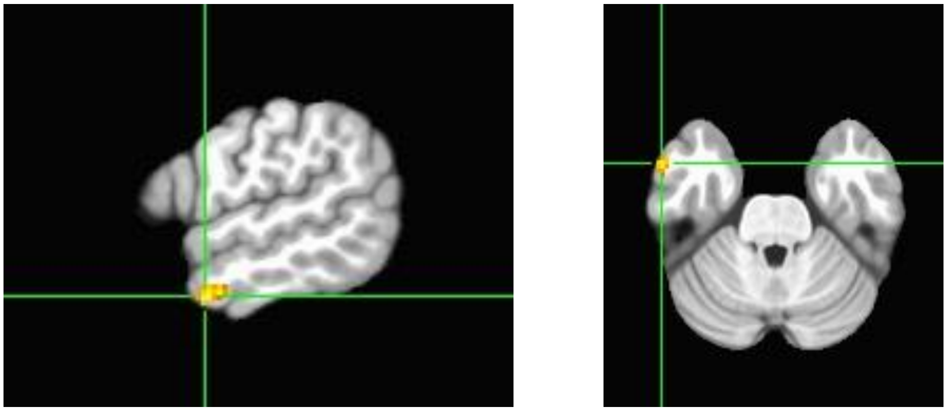


Figure 6.3 Univariate contrast of familiar > unfamiliar nonwords

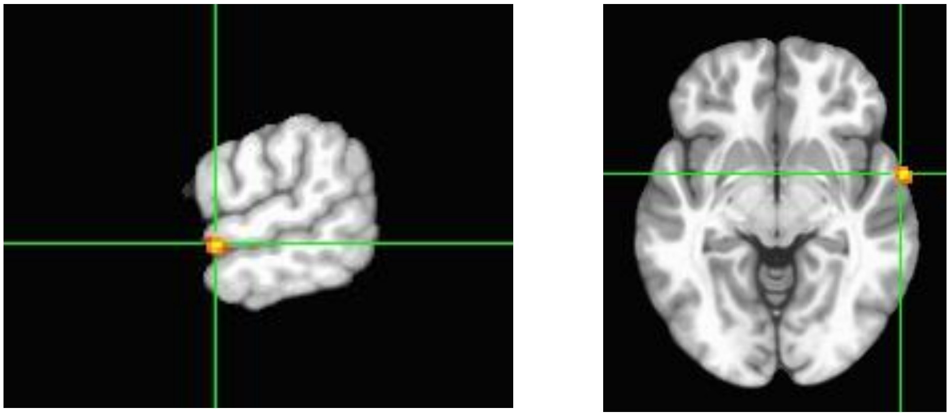


Figure 6.4 Univariate contrast of familiar > unfamiliar numbers

Model Classification Accuracy

Using activation patterns within the bilateral ATL as input, the SVM model was able to accurately discriminate between familiar and novel stimuli for all categories: persons (*82.7%,* $p < 0.001$), buildings (*82.7%,* $p < 0.001$), objects (*78.2%,* $p < 0.005$), words (*80.4%,* $p < 0.005$), nonwords (*83%,* $p < 0.001$), and numbers (79.5%, $p < 0.005$).

Searchlight Analysis

Searchlight analysis revealed cross-subject clusters of informative voxels for every category (table 6.2). The verbal categories of words, numbers, and nonwords each displayed a single, left-lateralized cluster of informative voxels (fig. 6.5). Words and numbers demonstrated a highly overlapping cluster in the anterior MTG (fig. 6.6). For nonwords, the most informative cluster was in the left EC.

Table 6.2 Searchlight multivariate results

Condition	**Location**	**# of Voxels**	**Center Mass X**	**CM Y**	**CM Z**	**Value (z-score)**
Words	L. MTG	34	-50	3	-14	6.21
Numbers	L. MTG	41	-54	-2.6	-15	4.27
Nonwords	L. EC	126	-21	-1	-30	4.89
Objects	R. TP	130	35	17	-23	4.55
	L. STG	36	-40	18	-22	4.89
Persons	L. STG	478	-43	10	-15	4.64
	R. STG	230	50	1	-11	5.26
	R. FFG	52	33	-11	-31	3.7
	L. TP	46	-29	15	-32	5.2
Buildings	R. FFG	269	32	-3	-32	3.9
	L. STG	186	-45	16	-18	5.17
	R. MTG	42	56	-8	-16	4.01
	L. EC	39	-20	-1	-30	3.67

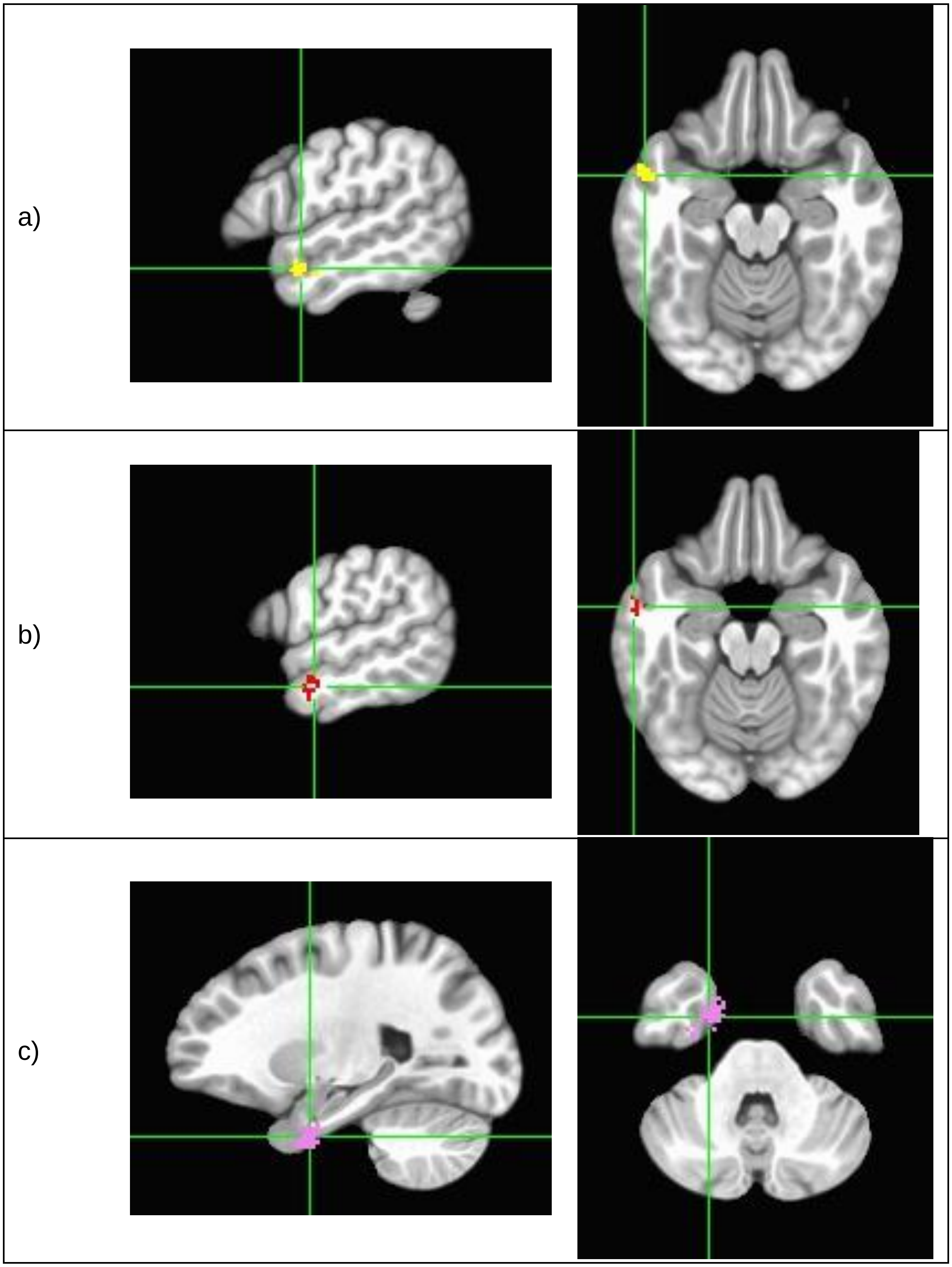


Figure 6.5 MVPA clusters for: a) Words, b) Numbers, and c) Nonwords

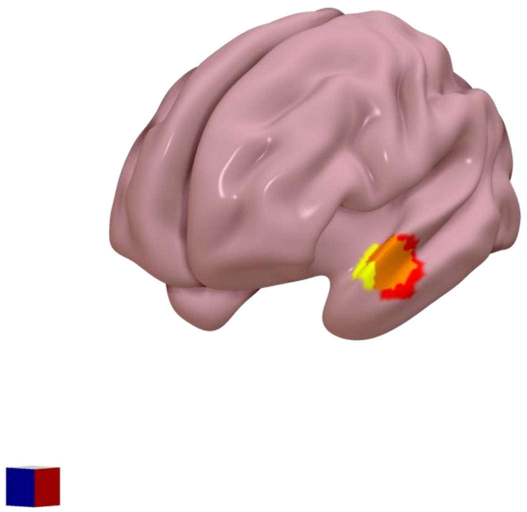
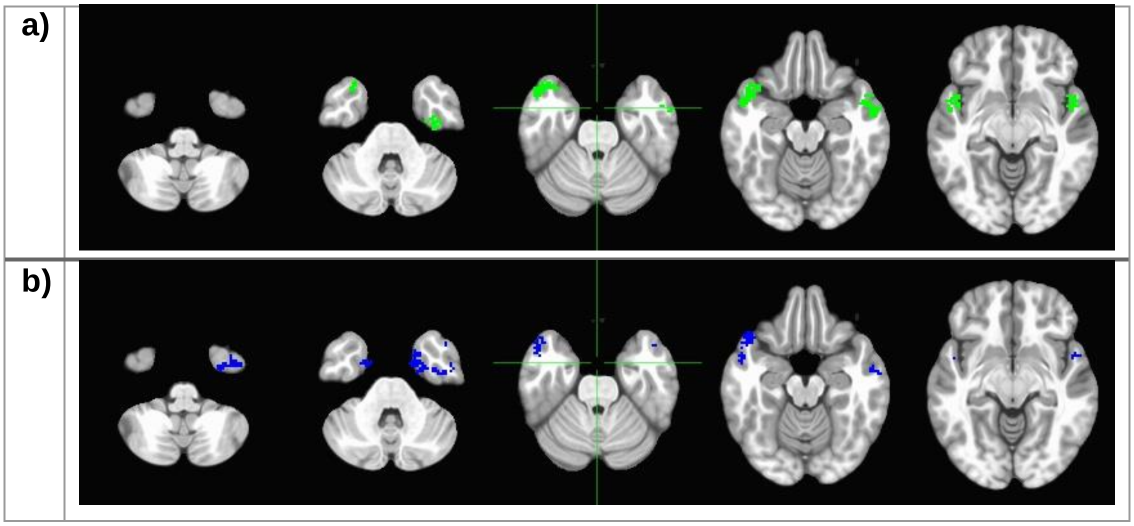


Figure 6.6 Clusters for words (yellow), numbers (red), and their overlap (orange)

The picture categories of persons, buildings, and objects each displayed bilateral clusters of informative voxels (fig. 6.7), with areas of overlap especially for buildings and persons.



c)

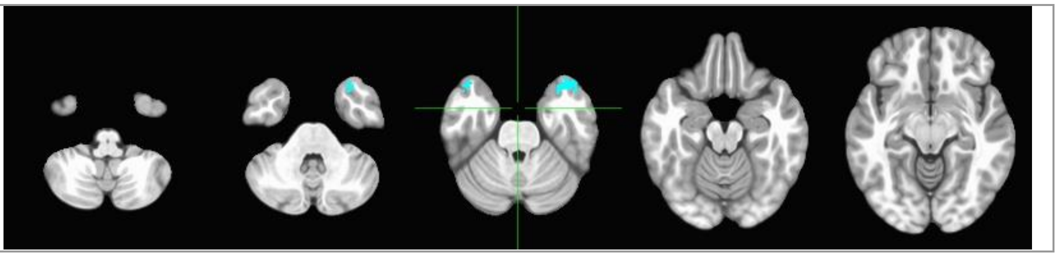


Figure 6.7 MVPA clusters for a) persons, b) buildings, and c) objects

Discussion

The current experiment explored the ATL's involvement in identifying specific entities or, more specifically, in identifying entities that were made familiar to the participant through training from novel, visually similar entities. A variety of stimuli categories were used, ranging from higher (words, objects) to lower (numbers, nonwords) inherent semantic value. Vitally, the effect of familiarity was isolated by having no differences in associated semantic information between the familiar and unfamiliar stimuli conditions, such that the results cannot be attributed to the retrieval of associated semantic information.

Univariate Analysis

The univariate results demonstrated that familiar entities elicited greater activity than unfamiliar in the left MTG for nonwords and in the right TP for numbers. A selective univariate effect for these categories was somewhat surprising. Numbers are commonly used as control conditions for semantic experiments involving the ATL, since number processing typically does not activate the ATL and is preserved in SD patients (Cappelletti et al., 2001; Jefferies et al., 2004; Pobric et al., 2007). Past experiments have shown that the highly semantic categories such as words, faces, and landmarks (the equivalent of buildings in this study) seem to take precedent in the ATL (Simmons & Martin, 2009; Wong & Gallate, 2012), with these categories being impaired by ATL damage or disruption while number processing and nonword reading are largely preserved (with the exception of atypical nonwords; see Woollams et al. (2007)).

However, the manipulation of this study—inducing familiarity through training—effectively encourages participants to identify their trained nonwords and numbers as specific, unique entities when compared to the untrained nonwords and numbers. Past research has demonstrated that damage to the ATL results in recognition impairments for unique, one-of-a-kind entities, although this effect has typically been shown for either familiar faces or landmarks (Gainotti, 2007a, 2007b; Tranel, 2009). A similar effect is seen within semantic categories such as animals, wherein the ability to name specific, atypical exemplars (such as penguins) is the first to be lost in early onset SD (Hodges & Patterson, 2007a; Hodges et al., 1992). Additionally, memory tasks, which have participants identify certain stimuli as 'unique' among visually similar distractors, use ATL structures as evidenced by patient and neuroimaging studies (Bowles et al., 2007a; Dolan et al., 2000; Elliot & Dolan, 1999; Martin et al., 2011; Milner, 2003).

For example, a case study by Martin et al. (2011) found that a patient with left medial temporal lobe resection sparing the hippocampus was impaired at a recognition and familiarity task for aurally presented nonwords. Although the univariate cluster of activity for familiar nonwords in the current study was the left lateral MTG instead of more medial temporal structures, this change could be due to differences in the time-course of the tasks used. In Martin et al. (2011), the participant had to recognize the nonwords only after a 5-minute delay, whereas participants in the current study performed the recognition task at least 24 hours after training. This especially makes sense when considering findings that implicate medial temporal structures in encoding (Jackson & Schacter, 2004b) or in memory tasks with relatively short delays, while the lateral temporal lobe has been implicated in memory tasks after at least 24 hours (Nieuwenhuis et al., 2012).

Regarding the numbers category, which elicited greater activation for the familiar compared to unfamiliar condition in the right temporal pole, it is possible that this right laterality is due to differences in how numbers are represented in the brain compared to words and word-like stimuli. While the language network is largely left-lateralized, activity in response to numbers is more bilateral (Kaufmann et al., 2011). Further, because numeric tasks such as reading numbers or performing calculations only rarely show activity in the temporal lobes (Kaufmann et al., 2011), this demonstrates that the task demands of identifying specific stimuli from similar distractors likely utilizes the ATL even for stimuli categories that do not typically rely on this area.

For the other categories, the lack of univariate results could be due to a few reasons. For words and objects, which are already ‘familiar’ to some extent to the participants even before training, it is possible that the training was not sufficient to make stimuli from these categories ‘unique’ enough to elicit substantially stronger activations during the familiarity judgment task. Indeed, during the training/testing sessions participants noted that familiarizing themselves with the words was harder than the nonwords since they ‘already knew all the words’. However, considering the lack of univariate results for buildings and persons (which do not suffer from the problem noted above for words and objects) and the significant multivariate results for every category, it is likely that the univariate analysis was simply not sensitive enough to the distributed patterns of activation elicited by the task.

Multivariate Analysis

In addition to high model classification accuracies for all categories, the searchlight MVPA revealed informative voxel clusters for every category. ‘Informative voxel clusters’ are here defined as voxels with surrounding patterns of activations that were able to classify the stimuli being either familiar or unfamiliar. Three main findings emerged from this analysis: 1) there was a lateralization effect based on presentation modality (i.e., verbal or nonverbal), 2) there were areas of overlap for the building and persons categories (and, to a lesser extent, objects) and for the words and numbers categories, and 4) the classification accuracy for all categories suggests a role for the ATL in identifying specific entities from novel, visually similar candidates that is dissociable from associative semantic, social, or name retrieval processes.

Regarding lateralization, picture stimuli elicited bilateral clusters whereas the verbal stimuli, including numbers, were left-lateralized. This finding is in line with meta-analyses of ATL functionality, which have shown that picture stimuli elicit bilateral activations while verbal stimuli tend to be more left lateralized

(Visser & Lambon Ralph, 2011). Similarly, patient evidence has supported this lateralization effect. For example, a case study by (Martin et al., 2011) demonstrated that a patient with left ATL lobectomy was impaired at a familiarity task for nonwords, but not abstract pictures or faces. Other studies have demonstrated that focal damage to the right ATL impairs recognition of famous faces and places when shown pictures, but not necessarily when presented with names or definitions (Gainotti, 2007a, 2007b; Gainotti et al., 2003; Gainotti et al., 2008). In one of those cases, the patient lost the ability to recognize the famous person by their name once the degenerative damage progressed into the left ATL (Gainotti et al., 2008). This meshes well with the body of evidence provided by Tranel (2009), which found that deficits to naming famous people or landmarks was associated with left ATL damage specifically. These findings, in conjunction with the current experiment, substantiate a bilateral, yet possibly right-lateralized, system that aids in the recognition of specific entities when presented pictorially, while the left ATL may be more important for identifying entities through their names.

Relatedly, the numbers and words categories showed substantial overlap in the left anterior MTG. Number-based processes do not typically activate the ATL, are spared in semantic dementia, and are used as control tasks for experiments probing semantic processing in the ATL (Cappelletti et al., 2001; Jefferies et al., 2004; Pobric et al., 2007). The current experiment provides evidence that the ATL contains information for the identification of specific, familiar numbers from novel ones, and that similar voxels are informative for number and word versions of this task. This evidence coincides with the previously discussed evidence that the left ATL is involved in name retrieval for specific entities (Tranel, 2009) or accessing information about specific entities through their names (Gainotti et al., 2008). However, it is important to note that, by nature, those tasks are associative because the specific entities were famous or personally familiar. The current experiment demonstrates that the ATL is involved in identifying specific words or numbers without extra associative semantic information since the familiar and unfamiliar conditions of numbers and words had roughly equivalent levels of semantic information.

Nonwords elicited a cluster of informative voxels in the entorhinal cortex that did not overlap with the other verbal stimuli of words or numbers. The entorhinal cortex is a major link between the hippocampus and the neocortex (Witter, 1993; Maass et al., 2015). It has been implicated in the encoding and retrieval of associative memories (Jackson and Schacter, 2004; Kirwan and Stark, 2004; Morrissey et al., 2012) as well as in 'feelings of familiarity' and recognition tasks in both human (Bowles et al., 2007; Yonelinas et al., 2007; Martin et al., 2011) and animal (Meunier et al., 1993; Mumby and Pinel, 1994; Murray et al., 2005) studies. This evidence, along with that provided by the current study, highlights a complex role for the left entorhinal cortex in encoding and retrieval of familiar entities, with perhaps increased reliance on this structure when recognition is driven by simple 'feelings of familiarity'—as could be case with meaningless stimuli such as nonwords.

Finally, the present experiment found bilateral clusters of overlap for the persons and buildings categories in the bilateral STG and right FFG, with the category of objects showing substantially smaller overlap with those two categories in the STG. This finding is well-supported by past research that has largely found that damage to the ATL causes impairments in both famous landmark and person naming or recognition, supporting the idea that specific entities from these categories are represented similarly in the ATL (Gainotti et al., 2008; Tranel, 2009). How objects play into this relationship is somewhat less clear because the impairments to landmarks and persons are not necessarily accompanied by impairments to object naming or identification (Gainotti, 2007a; Gainotti et al., 2008; Tranel, 2009). One interpretation is that, due to the nature of the stimuli, people and landmarks lend themselves well to tasks probing unique /specific entity identification. That is, there are simply not many famous or truly one-of-a-kind objects with which to construct a comparable task. However, the current experiment addresses this issue by training participants to recognize certain objects as unique or specific to them. Once this manipulation is made, the familiar/unfamiliar judgment for objects is represented by similar informative voxels to the buildings and persons categories, albeit with smaller clusters. This supports the idea that, while the ATL seems to have a large role in identifying specific people or places, this is partly a function of the natural tendency of those types of entities to be ‘one-of-a-kind’ compared to other categories.

Conclusion

In sum, the ATL contains information that identifies specific/familiar entities from novel entities that are visually similar, even when controlling for associated social and semantic content. This holds for a variety of categories, including those with low inherent semantic or social value such as nonwords and numbers. These findings support a role for the ATL in the identification of specific entities that can be dissociated from social, semantic, and name retrieval processes. As a result, investigations seeking to substantiate a special role for the ATL in semantics or social processing must carefully control both stimuli and task demands to dissociate those processes from the familiarity effects observed in the current study.

CHAPTER 7

GENERAL DISCUSSION

The current dissertation investigated the neural substrates of the lexical semantic system in the human brain. Specifically, we aimed to address the following questions: 1) what are the roles of the ATL, TPJ, and their subdivisions in tasks that vary in their lexical and semantic demands? (Chapter 2); 2) how do putative hubs, and especially the LIFC, contribute to canonical sentence comprehension and related cognitive subdomains? (Chapter 3); 3) do DAPS causally contribute to semantic representation of action-related concepts? (Chapters 4 and 5); 4) does the ATL contain information about 'unique' or 'familiar' entities, even when controlling for associated semantic information? (Chapter 6). To accomplish this, I used a variety of structural and functional neuroimaging techniques in both healthy and impaired populations. This included voxel-, region-, and connectome-based lesion-symptom mapping, as well as univariate and multivariate fMRI approaches.

Summary of Novel Findings

Chapter 2 revealed that damage to the left lateral ATL was associated with worse performance on tasks requiring lexical access. Damage to the left ATL was not associated with a non-verbal semantic task, but right hemisphere language homologues, especially temporal areas, were related to tasks requiring linkages between lexical and semantic information and nonverbal stimuli. These findings are important because they support the hypothesis that the left lateral ATL is especially vital for lexical processing, and not necessarily modality-invariant semantic representations. A role for the right hemisphere in processing nonverbal semantics is also suggested. Damage to TPJ, especially the left AG, was associated with worse performance in all tasks that required a non-verbal semantic component. This is important because it provides further evidence that the left AG represents semantic information, even in the absence of a lexical component.

In Chapter 3, VLSM and RLSM analyses suggested that the left pars opercularis and triangularis regions may not be critical to canonical sentence comprehension when damaged in isolation. LIFC damage was associated instead with impairments in a semantic similarity judgment task that required high semantic and executive demands. Damage to the TPJ, including pMTG, predicted worse sentence comprehension after controlling for lexical access, semantic knowledge, and auditory-verbal STM, supporting findings suggesting that the TPJ contributes to sentence comprehension beyond those processes. CLSM revealed that disruption of left-lateralized white matter connections from LIFC to ATL and TPJ was associated with worse sentence comprehension after controlling for performance in tasks related to lexical access, phonology, and auditory-verbal STM. However, the contribution of the LIFC connections were accounted for by the semantic similarity judgment task, which had high semantic and executive demands. These results are important because they suggest that the connectivity with LIFC is relevant to sentence comprehension, but that this involvement may be limited to general executive processes and task demands. This provides novel insight into how the LIFC contributes to language comprehension.

Chapters 4 and 5 showed that damage and disconnection of primary and higher-order DAPS are related to impairment in the comprehension of action-related words compared to non-action, for both nouns and verbs. These studies are important because they provide causal evidence in support of embodied cognitive theories. They are also, to our knowledge, the first studies to use multiple imaging methods post-stroke to test embodied cognitive hypotheses with stimuli that closely controlled for grammatical and psycholinguistic confounds.

Chapter 6 used a novel training paradigm in healthy adults to demonstrate that brain activity in the ATL contains information about unique, familiar entities while controlling for associative semantic confounds that had not been accounted for by previous studies. These findings held true even for categories with low-semanticity such as nonwords and numbers. This is important because it provides evidence against the 'hub-and-spoke' model, while supporting alternate theories of ATL functionality that are comparatively underrepresented in the literature.

Future Directions

These studies highlight the complexity and neuroanatomically distributed nature of the lexical semantic system. While the current studies provided valuable information about the organization of this system, many questions remain. In the coming years, it will be important to replicate and expand on these results using more methods.

First, some of the present studies used tests designed for clinical purposes (e.g., subtests of the WAB) in order to draw conclusions about the organization of the lexical semantic system. While these tests are invaluable in a clinical setting, and they are widely used for experimental purposes, they are perhaps not ideal for experimental settings due to lack of control over the psycholinguistic and conceptual properties of the stimuli within those tests (e.g., majority of items tend to be concrete, frequent, etc.). Future studies should seek to design carefully controlled stimuli that cover a wider range of psycholinguistic content in order to provide more generalizable conclusions. An alternative approach is to use more naturalistic tasks (Newman-Norlund et al., 2021; Riccardi & Desai, 2022), such as discourse production or comprehension, which provide ecological validity at the expense of control.

Second, while the present work provided insights into how damage or disruption of nodes within the semantic system affects behavioral performance, another question pertains to *how* these nodes interact with each other and the time-course of their involvement over the course of a given trial. That is, if left ATL is important for lexical access or basic identification of unique entities, we might expect it to be activated prior to 'deeper' semantic content being accessed in other brain areas. One could investigate this time-course with methods including electroencephalography or single-pulse transcranial magnetic stimulation, in which the timing of the pulses can be manipulated at the millisecond level. Alternative methods could also be explored, such as multivariate analysis of brain networks and blood flow (Sen et al., 2023) or brain age (Busby et al., 2023a; Busby et al., 2022; Busby et al., 2023b). Application of these methods to the language domain could provide novel information about the neural mechanisms of lexical semantics.

Third, regarding DAPS specifically, our studies provided causal evidence for their contribution to concept representation in a somewhat 'deep' semantic task (semantic similarity judgment). Future studies, perhaps using brain stimulation, could examine their contributions to action-related concepts during more shallow tasks that do not require explicit semantic access (e.g., lexical decision; (Johari et al., 2022)) or during sentence comprehension (Johari et al., 2021). If damage or disruption of DAPS is associated with impaired performance even in a variety of tasks, then it provides even stronger evidence for the fundamental contribution of DAPS to concept representation.

Lastly, more work needs to be done focusing on abstract concept representation. As mentioned previously, many of the tests we used tend to include concrete, imageable stimuli. Even in Chapters 4 and 5, where we explicitly probed abstract concept representation, those abstract stimuli were built on negative criteria (e.g., concepts that are not concrete). These limitations have been common in the field for decades. Abstract concepts likely have many sub-domains such as emotional, social, theory of mind, etc., which may be partially dissociable from each other in the brain. Alternatively, the representation of concepts related to time and space (Johari et al., 2023) or knowledge of people/places requires further investigation (Desai et al., 2023a). Future studies should seek to understand how these more specific types of concepts are represented, including any differences that may exist between those sub-domains.

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