More Than Words: Extra-Sylvian Networks Support Pragmatic Language Processing In Focal Dementia

Meghan L. Healey

University of Pennsylvania

Follow this and additional works at: https://repository.upenn.edu/edissertations

Part of the Clinical Psychology Commons, and the Neuroscience and Neurobiology Commons

Recommended Citation

https://repository.upenn.edu/edissertations/3906

This paper is posted at ScholarlyCommons. https://repository.upenn.edu/edissertations/3906
For more information, please contact repository@pobox.upenn.edu.
More Than Words: Extra-Sylvian Networks Support Pragmatic Language Processing In Focal Dementia

Abstract
The ability to communicate through spoken language is not only one of the most complex cognitive abilities we possess, but it is also the aspect of the brain that makes us uniquely human. While people communicate almost constantly in daily life—telling stories over dinner, gossiping over coffee, and so much more—the majority of previous work has failed to study language in this same real-world context and instead focuses on the representation of single words and sentences in isolation. Accordingly, and in an effort to expand upon existing models of language neurobiology, this dissertation will present a series of experiments examining how the brain supports everyday pragmatic discourse. In these experiments, I use a patient-lesion model and study non-aphasic patients with behavioral variant frontotemporal dementia (bvFTD)—a rare neurodegenerative disease characterized by social-executive deficits and atrophy in frontal and anterior temporal cortices. In Chapters 2-3, I examine the cognitive and neural substrates of social coordination and referential communication—that is, how a speaker describes an object so that a listener can identify that object. Across both experiments, I find that impaired referential communication in bvFTD is related cognitively to mental flexibility and anatomically to a social-executive network including non-language regions in prefrontal cortex. In Chapters 4-5, I turn from language production to language comprehension, examining the cognitive and neural substrates of indirect reply and indirect request comprehension, respectively. In doing so, I examine how listeners make pragmatic, bridging inferences to derive a speaker's true, intended meaning. Confirming my previous results, I find that patients with bvFTD struggle to interpret indirect speech due to social-executive deficits and degradation of a multimodal, extra-Sylvian network. The fifth and final experiment is more clinically-motivated, examining the progression of conversation difficulties in bvFTD and identifying potential prognostic markers. Here, I find that patients with poor executive function and focal disease in prefrontal cortex at baseline are likely to experience communication problems later in disease. Altogether, these findings help to define a more comprehensive model of language neurobiology that can account for the complexities of real-world communication from the perspective of both speakers and listeners.

Degree Type
Dissertation

Degree Name
Doctor of Philosophy (PhD)

Graduate Group
Neuroscience

First Advisor
Murray . Grossman

Keywords
dementia, indirect speech acts, language, neuroimaging, referential communication

Subject Categories
Clinical Psychology | Neuroscience and Neurobiology

This dissertation is available at ScholarlyCommons: https://repository.upenn.edu/edissertations/3906
MORE THAN WORDS: EXTRA-SYLVIAN NETWORKS SUPPORT PRAGMATIC LANGUAGE PROCESSING IN FOCAL DEMENTIA

Meghan Leigh Healey

A DISSERTATION

in

Neuroscience

Presented to the Faculties of the University of Pennsylvania

in

Partial Fulfillment of the Requirements for the

Degree of Doctor of Philosophy

2020

Supervisor of Dissertation

______________________

Murray Grossman, MD EdD
Professor of Neurology
University of Pennsylvania

Graduate Group Chairperson

______________________

Joshua I. Gold, PhD
Professor of Neuroscience
University of Pennsylvania

Dissertation Committee
Joseph Kable, PhD, Professor of Psychology, University of Pennsylvania
Roy Hamilton, MD MS, Associate Professor of Neurology, University of Pennsylvania
John Trueswell, PhD, Professor Psychology, University of Pennsylvania
Stephanie Cosentino, PhD, Associate Professor of Neuropsychology, Columbia Univ.
ACKNOWLEDGMENTS

In loving memory of Moose “The Mooseman” Healey.

I was still an infant when I entered a classroom for the first time. I may not have known it then, but at just a few weeks old, I had already found my place in the world. As the daughter of two remarkable teachers, my childhood was the definition of educational. I was constantly tagging along to school with my parents, playing in the sandbox on some days and recording my voice into assistive technology for children with developmental disorders on other days. Around age nine, I asked for a microscope and a model of the human body, and I spent numerous hours playing “Troglie Trouble Math.” So perhaps it should be no surprise that I have ended up on this journey. What is a surprise, however, is that I have now reached its end. I have countless people to thank for their role in supporting me in reaching this goal.

First and foremost, to my parents: thank you for inspiring my love of people and my love of communication. Thank you for indulging my endless curiosity, and in the words of the children’s music group Rosenshontz, thank you for always encouraging me to “G-O F-O-R I-T.” I never would have gone for this dream without you by my side. I am the luckiest girl in the world to call you mine.

To my siblings, Beth and Matt, thank you for putting up with your nerdy little sister. Your unwavering support and willingness to pick up the phone at all hours has been invaluable to me. Thank you, also, for countless dog pictures (Matthew) and that introduction to the Great British Bake Off (Beth).

Finally, thank you to my incredible and inspiring Nana. I love you, and I can only hope I age half as gracefully as you one day. Thanks for keeping me in the book.
I would be remiss if I did not thank all my friends at Penn, both inside and outside of the lab. You know who you are. Thank you for always being on Team Meghan— the matching t-shirts are coming soon.

Thank you also to my friends who have been following this journey from a distance— near, far, wherever you are. Sasha, Lauren, Andrew, Maggie, Melanie, Erin, Stephanie: I could not ask for better people to have by my side. I love you all. Special thanks also goes to Stephan Luma: I may not have started this journey with you, but I could not imagine completing it without you. Thank you for always being my biggest (read: loudest) cheerleader, no matter the circumstances. Jiffy pop.

And finally, thank you to my mentor, Dr. Murray Grossman. I will always appreciate your wisdom, your patience, and your endless optimism. Thank you for the many stories you have shared with me— about neuroscience, about baseball, and about life in general. I am only the scientist I am today because of you. Thank you.

It is truly impossible to mention all the people who have supported me during this rollercoaster of an adventure. To all of you who have touched my journey in some way, I am forever grateful.
ABSTRACT

MORE THAN WORDS: EXTRA-SYLVIAN NETWORKS SUPPORT PRAGMATIC LANGUAGE PROCESSING IN FOCAL DEMENTIA

Meghan Leigh Healey

Murray Grossman

The ability to communicate through spoken language is not only one of the most complex cognitive abilities we possess, but it is also the aspect of the brain that makes us uniquely human. While people communicate almost constantly in daily life—telling stories over dinner, gossiping over coffee, and so much more—the majority of previous work has failed to study language in this same real-world context and instead focuses on the representation of single words and sentences in isolation. Accordingly, and in an effort to expand upon existing models of language neurobiology, this dissertation will present a series of experiments examining how the brain supports everyday pragmatic discourse. In these experiments, I use a patient-lesion model and study non-aphasic patients with behavioral variant frontotemporal dementia (bvFTD)—a rare neurodegenerative disease characterized by social-executive deficits and atrophy in frontal and anterior temporal cortices. In Chapters 2-3, I examine the cognitive and neural substrates of social coordination and referential communication—that is, how a speaker describes an object so that a listener can identify that object. Across both experiments, I find that impaired referential communication in bvFTD is related cognitively to mental flexibility and anatomically to a social-executive network including non-language regions in prefrontal cortex. In Chapters 4-5, I turn from language production to language comprehension, examining the cognitive and neural substrates of indirect reply and indirect request comprehension, respectively. In doing so, I examine...
how listeners make pragmatic, bridging inferences to derive a speaker’s true, intended meaning. Confirming my previous results, I find that patients with bvFTD struggle to interpret indirect speech due to social-executive deficits and degradation of a multimodal, extra-Sylvian network. The fifth and final experiment is more clinically-motivated, examining the progression of conversation difficulties in bvFTD and identifying potential prognostic markers. Here, I find that patients with poor executive function and focal disease in prefrontal cortex at baseline are likely to experience communication problems later in disease. Altogether, these findings help to define a more comprehensive model of language neurobiology that can account for the complexities of real-world communication from the perspective of both speakers and listeners.
# TABLE OF CONTENTS

**ACKNOWLEDGMENTS** ........................................................................................................... II  

**ABSTRACT** ............................................................................................................................ IV  

**LIST OF TABLES** .................................................................................................................... VII  

**LIST OF FIGURES** ................................................................................................................ IX  

**CHAPTER 1: INTRODUCTION** .................................................................................................. 1  
- HISTORICAL APPROACHES TO LANGUAGE PROCESSING ............................................. 1  
- THE ADVENT OF DISCOURSE PRAGMATICS ............................................................... 5  
- OVERVIEW OF DISSERTATION STUDIES ..................................................................... 8  
- CASE STUDY I: REFERENTIAL COMMUNICATION ...................................................... 9  
- CASE STUDY II: INDIRECT SPEECH ACT COMPREHENSION ................................... 11  
- A PATIENT LESION MODEL APPROACH: INTRODUCTION TO BEHAVIORAL VARIANT 
  FRONTOTEMPORAL DEGENERATION .............................................................................. 16  

**CHAPTER 2: GETTING ON THE SAME PAGE: THE NEURAL BASIS OF SOCIAL 
COORDINATION DEFICITS IN BEHAVIORAL VARIANT FRONTOTEMPORAL DEMENTIA**  
........................................................................................................................................................ 20  

**CHAPTER 3: COGNITIVE AND NEUROANATOMIC ACCOUNTS OF REFERENTIAL 
COMMUNICATION IN FOCAL DEMENTIA** ............................................................................. 50  

**CHAPTER 4: BEYOND BROCA: EXTRA-SYLVIAN NETWORKS SUPPORT SPEECH ACT 
COMPREHENSION IN BEHAVIORAL VARIANT FRONTOTEMPORAL DEMENTIA** ............. 92  

**CHAPTER 5: A CALL TO ACTION: INDIRECT REQUEST COMPREHENSION IN 
BEHAVIORAL VARIANT FRONTOTEMPORAL DEMENTIA** .................................................. 137  

**CHAPTER 6: LONGITUDINAL TRAJECTORIES OF CONVERSATIONAL ABILITY IN 
BEHAVIORAL VARIANT FRONTOTEMPORAL DEMENTIA AND ALZHEIMER'S 
DEMENTIA** .............................................................................................................................. 172  

**CHAPTER 7: DISCUSSION** .................................................................................................... 204  

**REFERENCES** ......................................................................................................................... 212
LIST OF TABLES

Table 1. Demographics for Experiment 1 .......................................................... 27

Table 2. MNI Coordinates for Experiment 1 Imaging Results .......................... 39

Table 3. MNI Coordinates for Experiment 1 Condition-Specific Results ............. 40

Table 4. Demographics for Experiment 2 .......................................................... 57

Table 5. Correlation Results for Experiment 2 .................................................. 69

Table 6. Associations with Executive Function in Experiment 2 ....................... 70

Table 7. MNI Coordinates for Experiment 2 Imaging Results ......................... 75

Table 8. MNI Coordinates for Experiment 2 Condition-Specific Results ............ 77

Table 9. MNI Coordinates for Experiment 2 Conjunction Analysis ................... 79

Table 10. MNI Coordinates for Experiment 2 Diffusion Tensor Imaging Results .... 80

Table 11. Demographics for Experiment 3 ........................................................ 101

Table 12. Sample Stimulus Materials for Experiment 3 .................................... 101

Table 13. Correlation Results for Experiment 3 ................................................. 117

Table 14. MNI Coordinates for Experiment 3 Imaging Results ......................... 121

Table 15. MNI Coordinates for Experiment 2 Diffusion Tensor Imaging Results .... 125

Table 16. Demographics for Experiment 4 ........................................................ 147

Table 17. Sample Stimulus Materials for Experiment 4 .................................... 147

Table 18. Correlation Results for Experiment 4 ................................................. 156

Table 19. MNI Coordinates for Experiment 4 Imaging Results ......................... 159

Table 20. MNI Coordinates for Experiment 4 Diffusion Tensor Imaging Results .... 161

Table 21. Demographics for Experiment 5 ........................................................ 178

Table 22. Linear Mixed Effects Models for Experiment 5 ................................... 187

Table 23. Correlation Analyses for Experiment 5 ............................................. 188
Table 24. Predictive Model in bvFTD for Experiment 5..........................189
Table 25. Summary of Item Analysis in bvFTD versus AD..........................191
Table 26. MNI Coordinates for Experiment 5 Imaging Results..........................193
Supplementary Table S1. Item Analysis in bvFTD........................................200
Supplementary Table S2. Item Analysis in AD..............................................202
LIST OF FIGURES

Figure 1. Existing models of language neurobiology ........................................5
Figure 2. Design of Experiment 1 .................................................................30
Figure 3. Behavioral Results for Experiment 1 ............................................34
Figure 4. Error Analysis for Experiment 1 ..................................................36
Figure 5. Structural Neuroimaging Results for Experiment 1 ....................38
Figure 6. Condition-Specific Neuroimaging Results for Experiment 1 ....40
Figure 7. Design of Experiment 2 ...............................................................62
Figure 8. Behavioral Results for Experiment 2 ...........................................69
Figure 9. Performance across subgroups in Experiment 2 .........................72
Figure 10. Structural Neuroimaging Results for Experiment 2 ..................75
Figure 11. Condition-Specific Neuroimaging Results for Experiment 2 ....76
Figure 12. Conjunction Analysis for Experiment 2 .....................................78
Figure 13. White Matter Imaging Results for Experiment 2 .......................79
Figure 14. Response Accuracy Results for Experiment 3 .........................113
Figure 15. Response Latency Results for Experiment 3 .............................114
Figure 16. Structural Neuroimaging Results for Experiment 3 ..................120
Figure 17. Network Key for Experiment 3 ...............................................122
Figure 18. Experiment 3 Network Associations with Indirect Impairment ....123
Figure 19. White Matter Imaging Results for Experiment 3 .......................124
Figure 20. Behavioral Results for Experiment 4 .........................................156
Figure 21. Structural Neuroimaging Results for Experiment 4 ..................159
Figure 22. Experiment 4 ROI Associations with Indirect Impairment ........160
Figure 23. White Matter Imaging Results for Experiment 4 .......................161
Figure 24. Longitudinal change in conversation difficulties in bvFTD and AD........186

Figure 25. Behavioral Results for Experiment 5..................................................189

Figure 26. Structural Neuroimaging Results for Experiment 5..........................192

Figure 27. Proposed three-part model for processing language in context............207
CHAPTER 1: INTRODUCTION

Language comprehension in a real-world context extends beyond decoding the phonetic, semantic, and syntactic components of speech. Instead, to fully appreciate a speaker’s true, intended meaning, listeners must “read between the lines” and integrate non-linguistic, social information. Take, for example, the following scenario. Two friends, Sally and Betty, are both at a dinner party together, when Sally asks Betty, “Do you want some cake for dessert?” and Betty quickly responds, “Oh, I’m on a very strict diet right now.” While Betty has not answered Sally’s question directly (i.e. said “no”), most people can probably infer from her response that she is declining the offer of dessert. This is an example of pragmatic communication or discourse— an instance where the speaker’s words and their combined structure are insufficient in deriving meaning. Accordingly, in this chapter, I will review how the brain processes language in context— or in other words, how the brain transmits messages from speakers to listeners during everyday social interactions.

HISTORICAL APPROACHES TO LANGUAGE PROCESSING

Historically, our knowledge of language in the brain has been based primarily on the “Wernicke-Lichtheim-Geshwind” model (sometimes also “Broca-Wernicke-Lichtheim-Geschwind” model, or simply “Wernicke-Lichttheim model). This classic model of language processing, which has dominated the field since its inception in the latter half of the 19th century, was based on the pioneering work of physicians Paul Broca and Carl Wernicke, who conducted a series of post-mortem lesion studies in patients with acquired forms of aphasia. The French surgeon Broca described the following patient:
He could no longer produce but a single syllable, which he usually repeated twice in succession; regardless of the question asked him, he always responded: *tan, tan*, combined with varied expressive gestures. This is why, throughout the hospital, he is known only by the name *Tan*. (Broca, 1861).

When “Tan” died, an autopsy was performed and a lesion on the surface of the left frontal lobe was found, leading Broca to conclude that the faculty of “articulate language” was localized there. With the help of a second patient, whose speech was restricted to only five words, Broca clarified that it was “the third frontal convolution” in particular that was responsible for speech production.

In 1874, German neurologist Carl Wernicke added to the work of Broca, and suggested there was not one language center, but two, with the second involved in the perception of speech “sound images” and located in the rear of the temporal lobe. He described the symptoms associated with damage to this area:

> The patient is… neither able to repeat the spoken word, … nor to comprehend it. All the patient perceives of what is spoken to him is an indistinguishable noise which does not make any sense to him (Wernicke, 1874).

Years later in 1885, Ludwig Lichtheim predicted that injury to a pathway between these two language centers would allow the patient to hear and speak, but would interfere with the specific ability to repeat a word—a condition now known as conduction aphasia. According to Lichtheim’s connectionist model, the two language centers, one in the anterior of the brain and one in the posterior, were connected by a single white matter tract, the arcuate fasciculus. Finally, in the latter half of the twentieth century, the last eponymous contributor to the classic model-- American neurologist Norman Geschwind-- observed a patient with the exact opposite problem: he could only repeat. He could neither speak nor understand words because the lesion isolated an intact
Broca’s area-arcuate fasciculus-Wernicke’s area complex from the rest of the brain. Geschwind referred to this disorder as “isolation of the speech area.”

After these waves of growth and refinement, the final Wernicke-Lichtheim-Geschwind (WLG) model suggested that the human brain is anatomically modular and functionally specific, with language production localized to the inferior frontal gyrus (IFG), and language comprehension to the posterior-superior temporal gyrus (pSTG). While admittedly very useful in formulating the early studies of language neurobiology, the WLG view is not without major limitations. As summarized by Tremblay and Dick (2016), the WLG model 1) is based on outdated and spatially imprecise neuroanatomy, 2) does not adequately represent the broad network connectivity relevant to language, 3) suggests an overly modular view of the brain functioning, and 4) fails to incorporate non-cortical parts of the brain. With such a narrow view, the WLG model cannot possibly account for the complexities of real-world language and communication: how we integrate utterances with prior context, make inferences about speaker meaning, and engage in the rapid back and forth of conversation.

As a result of these limitations, new, large-scale models of language neurobiology have been proposed in recent decades. For example, Hickok and Poeppel (Hickok and Poeppel, 2004, 2007), suggest the language system can be divided into two pathways, borrowing an idea from the organization of the cortical visual system. More specifically, they suggest a ventral pathway dedicated to auditory word comprehension and a dorsal pathway dedicated to auditory-motor interaction. Friederici (2012) also proposes a model with two major pathways: a bottom-up, input-driven pathway proceeding from auditory cortex to anterior superior temporal cortex to prefrontal cortex, and a top-down, predictive pathway from prefrontal cortex back to the temporal cortex. Finally, Hagoort (2005, 2013) proposed a three-component model of language
processing, known as the Memory-Unification-Control (MUC) model. According to this perspective, linguistic knowledge is encoded and consolidated in temporal cortex (i.e. the memory component). These lexical building blocks are then integrated into larger structures in Broca’s area and adjacent cortex (i.e. the unification component). Finally, executive control, mediated by dorsolateral prefrontal cortex and anterior cingulate cortex, is invoked in order to tailor language processes to the given context, as needed. See Figure 1 for a visual depiction of each of these models. While these models are more anatomically distributed than the WLG and can account for psycholinguistic phenomena including syntax and semantics, they remain undeniably limited as they are direct descendants of the classic model and based primarily on studies of single words and sentences. In other words, a model of language neurobiology based on studies of language in context and accounting for the full diversity of human communication is still needed. We attempt to address this gap in the literature in Chapters 2-6 of this Dissertation. Below I introduce the cognitive-linguistic framework for this development, and its neurobiological foundations.
THE ADVENT OF DISCOURSE PRAGMATICS

In recent years, recognition of the shortcomings of our extant models, coupled with technological advancements in neuroimaging techniques (e.g. fMRI, EEG, MEG, DTI), has led to somewhat of a paradigm shift in language science (Poeppel et al., 2012). Once considered too cumbersome and unwieldy, studies of discourse and pragmatic communication are now ripe for investigation. As discourse refers to the social use of language, it often takes a supra-sentential form, as seen in stories, narratives, and conversations. Consequently, speaker meaning may not be explicitly coded in the
semantic content of a single utterance, and additional cognitive and/or neural resources might be necessary for correct interpretation. Indeed, an influential model of discourse processing (van Dijk and Kintsch, 1983; Zwaan and Radvansky, 1998) suggests that text is processed at 3 levels of representation: the surface form, the text base, and the situation model-- where the surface form is the directly coded text, the text base is its propositional representation, and the situation model is an integrated cognitive representation of the event or action being described. More specifically, the surface form is the text’s literal wording-- a lexical-phonological representation of the discourse, with no further processing. The text base, then, is the semantic representation of the discourse with its associated syntax: the text's directly coded meaning is represented as a network of concepts and propositions. Finally, when text base elements are combined both with one another and embedded within information from the reader's internal stores (i.e. general world knowledge, social knowledge, autobiographical memory, etc.), a situation model arises. At this level, the discourse meaning is no longer dependent on structural features of the text, but rather on the inferred relationships between elements.

This raises the following question: as a reader or listener moves beyond the surface form to a text base and situation model, how might the core peri-Sylvian language regions described by Broca and Wernicke interact with other extra-Sylvian regions of the brain? Or in other words, how does the language network interact with other neural networks to facilitate communication?

Here, we suggest two candidate networks beyond the classic peri-Sylvian language network: a social brain network, and an executive brain network. Consider first the role of a social brain network. At its simplest, conversation in a real-world setting requires two or more individuals to take turns producing and interpreting language. In order to engage in this rapid back and forth smoothly, speakers and listeners must
continuously switch from one person’s point of view to another’s, constantly updating the situation model with new information content as they do so. Furthermore, according to well-known British philosopher Herbert Paul Grice and his “Cooperative Principle,” speakers and listeners can only reach mutual understanding in conversation by assuming that their partner is being cooperative (Grice, 1975), and that all contributions to the ongoing dialogue are thus relevant and meant to further the goal of successful communication. Therefore, when information is presented that seems to flout this principle (e.g. is off-topic or factually incorrect), the listener will go beyond the directly coded meaning (i.e. the text base) to incorporate non-linguistic, social information from the situation model (including knowledge about the speaker himself) in order to derive hidden meaning. Based on previous research on social cognition in both human and non-human primates alike, regions belonging to the social brain network and mediating these complex back-and-forth interactions include: medial prefrontal cortex, orbitofrontal cortex, precuneus, temporoparietal junction, and superior temporal sulcus (Amodio and Frith, 2006; Van Overwalle, 2009; Kennedy and Adolphs, 2012; Sliwa and Freiwald, 2017; Li et al., 2018). This same network of regions is also commonly known as the mentalizing or theory of mind network (Saxe and Powell, 2006; Carrington and Bailey, 2009; Schurz et al., 2014).

Next, consider the role of an executive brain network. According to the widely accepted model of executive function described by Miyake and colleagues (Miyake et al., 2000), there are three sub-domains of executive function: information updating and monitoring (i.e. working memory), mental set shifting, and inhibition of prepotent responses. Dyadic conversation likely requires all three of these postulated subdomains, as individuals must track multiple elements of the ongoing exchange in working memory, inhibit irrelevant information, and switch both from one person’s point of view to another,
and from literal interpretations of utterance meaning to non-literal ones. According to previous research, both in language and in other domains, these complex executive processes are subserved by a network of frontal and parietal regions, including dorsolateral prefrontal cortex, anterior cingulate cortex, pre- and supplementary motor areas, and inferior parietal lobule (Duncan and Owen, 2000; Cole and Schneider, 2007; Ye and Zhou, 2009; Fan et al., 2011; Niendam et al., 2012; Lemire-Rodger et al., 2019). We note here that this network of regions is also commonly referred to as the “multiple demand system” or “multiple demand network”—as its component regions are activated for a wide variety of tasks (Duncan, 2010; Fedorenko et al., 2013; Camilleri et al., 2018).

OVERVIEW OF DISSERTATION STUDIES

In order to test the roles of these two candidate networks in communication—the social/mentalizing network and the executive/multiple demand network, we developed a series of novel experiments, all aimed at answering the following overarching question: 

What are the cognitive and neural substrates necessary for processing the multiple levels of language representation that exist when language is used in a communicative, discourse context? For the sake of simplicity, we will refer to this as “language in context” for the remainder of this dissertation. More specifically, we are interested in two complementary phenomena. First, in the production domain, we ask: how does a speaker design a message so it will be understood by a given listener? To answer this question, we study social coordination and referential communication, or how a speaker describes an object so that a recipient (with a varying degree of shared knowledge) can identify that same object. We then seek commonalities in the comprehension domain, as we consider the reverse process: how does a listener understand the true intended meaning of a given speaker? To answer this question, we examine indirect speech acts,
which are ubiquitous in daily conversation but vastly understudied in the cognitive neuroscience literature. We will briefly review the pertinent background information relevant to each of these phenomena—referential communication and indirect speech act comprehension—in turn below.

CASE STUDY I: REFERENTIAL COMMUNICATION

According to well-known psycholinguist Herbert H. Clark and his theory of “common ground,” individuals engaged in the back and forth of conversation must share and coordinate knowledge in order to reach mutual understanding (Clark, 1985). He writes: “Common ground is important to any account of language use that appeals to “context”… Two people’s common ground is, in effect, the sum of their mutual common or joint knowledge, beliefs, and suppositions” (Clark, 1996). Accordingly to Clark, then, a speaker designs an utterance by making reference only to information that is shared in that common ground, and avoiding reference to information that is known only to one individual (in “privileged ground”).

According to Clark, one of the primary functions of language is to describe the world in front of us. Think of the number of times a day it is necessary for you to identify an object or referent, for example—“I’m driving the red car, not the black one” or “Can you pass me the water bottle that is to the left of the notebook—not the one behind the notebook?” We refer to this as referential communication—the ability to describe an object in such a way that a listener will be able to identify a specific, intended target. While we may take this ability for granted, as we do it almost effortlessly, referential communication is actually a perfect example of the coordination that Clark refers to.

We believe there are several advantages to studying referential communication over other types of discourse production. First, referential communication tasks can
require only minimal speech output and are thus less demanding on working memory than other speech production tasks. Similarly, the linguistic output of referential communication tasks can be easily scored according to objective and easily-identified features, such as adjective use. This is in stark contrast to other continuous speech tasks that have been used traditionally in studying conversational discourse, which require complex manual coding schemes that are both tedious and subjective. Next, referential communication tasks can be carefully designed to manipulate working memory and perspective-taking demands, which are two components of discourse production that are commonly conflated in the existing literature (Saxe et al., 2006; Wade et al., 2018). Finally, referential communication is a phenomenon we encounter in everyday life, and consequently, related tasks are sensitive to the type of difficulties that some people have in open-ended conversation.

Over the last several decades, the most common approach to studying referential communication has been variations of the so-called “director task”, originally developed by Krauss and Glucksberg (1977). In the original director task, participants sat on opposite sides of a blind and were asked to verbally coordinate to arrange a series of drawings according to a given chart, accessible to only one of them (“the director”). In the modified director task (Keysar et al., 2000, 2003), a participant was given instructions by a confederate as to how to move various objects around in a grid of squares. The confederate, however, could not see all of the objects, which the listener was supposed to keep in mind when interpreting his instructions. This modification, consequently, turned this primarily into a task of comprehension, and ultimately, selective attention (see Rubio-Fernández, 2017 for a comprehensive discussion of the director task). Given this significant flaw, we will address the need for a novel referential communication task in Chapters 2-3 of this Dissertation.
Beyond the aforementioned behavioral studies, there are only a limited number of neuroimaging studies examining perspective-taking during language use. In a recent fMRI experiment, Vanlangendonck et al. (2018) had subjects play a referential communication game, in which some subjects were in common ground and others in privileged ground. When subjects had to take their addressee’s needs into account and describe a target object that was in privileged ground, regions within the core mentalizing network, including mPFC, were activated. Similar results were obtained in two previous studies, both using a version of the director task adapted to improve task accuracy compared to previous behavioral versions (Dumontheil et al., 2010; Hillebrandt et al., 2013). Given the paucity of neuroimaging research on this topic, and flaws in the existing behavioral designs, additional work is clearly still needed to address how speakers design their utterances so they can be easily understood by their listeners.

CASE STUDY II: INDIRECT SPEECH ACT COMPREHENSION

Now that we have explored the processes required for a speaker to design a message for a given listener, we turn to the reverse— that is, the processes required for a listener to interpret the message of a given speaker. Speech act theory, developed by the philosophers J. L. Austin and John Searle, refers to the view that language can actually do more than simply describe the reality in front of us. Instead, it can perform a myriad of functions: it can assert or affirm, deny or reject, promise or request. Accordingly, when we are engaged in everyday conversations, we do not process just the words and sentences we hear, but also what they are meant to communicate. Here, we can distinguish between the locutionary and illocutionary acts of an utterance— or in other words, their direct and indirect meanings, respectively. Take for instance, the example Searle describes, where you are standing on a train platform and say to your
friend, “You’re standing on my foot.” Here, the locutionary act refers to actual utterance and its apparent meaning—a straightforward description of fact. The illocutionary act, however, is not the same. In this case, the utterance can also be interpreted as a request—you would like your friend to move his foot. Because there are two different acts being performed by a single utterance, we call this an indirect speech act. To use Searle’s own words:

In indirect speech acts the speaker communicates to the hearer more than he actually says by way of relying on their mutually shared background information, both linguistic and nonlinguistic, together with the general powers of rationality and inference on the part of the hearer. (Searle, 1979)

We choose to study indirect speech acts here because they are a relatively simple and “stripped down” example of discourse. As Searle notes, interpretation of an indirect speech act only requires:

…an ability on the part of the hearer to make inferences… It is not necessary to assume the existence of any conversational postulates… nor any concealed imperative forces or other ambiguities. (Searle, 1979)

We believe there are several advantages to studying indirect speech acts over other types of discourse. First, indirect speech acts are relatively short in length and can be carefully matched for linguistic variables and other features (e.g. word frequency, concreteness, imageability). This is generally not true of lengthy narratives, which are demanding on working memory and the content and structure of which varies greatly from one stimulus item to another. Second, most indirect speech acts are contextually-driven. They do not become “conventionalized” or “structurally” frozen due to frequent or repeated usage, as is the case with many forms of non-literal language including
metaphors or idioms, like “a broken heart” or “a fork in the road” (Note: studying various forms of non-literal language was one of the first approaches to studying discourse comprehension in the cognitive neuroscience literature). Comprehension of these rhetoric devices may depend instead on declarative memory retrieval, rather than online inferential processing. Next, indirect speech acts do not have a requisite affective component, which is often the case with subtypes of non-literal language including irony and sarcasm. Accordingly, appreciation of irony or sarcasm could be confounded by an individual’s emotional intelligence, as well as their ability to recognize co-occurring facial expressions and relevant acoustic properties of speech like pitch. Finally, indirect speech acts involve an interactive exchange between two or more conversational partners, which reflects how language is most commonly used in everyday life.

Also relevant to this discussion is the fact that there are (at least) two main categories of indirect speech acts: indirect replies and indirect requests. For our purposes, indirect replies and indirect requests can be differentiated based on who (speaker vs. addressee) actually uses the indirect speech. In the case of indirect replies, a speaker poses a question and the addressee replies using an indirect speech act—that is, they provide information that is both relevant and explanatory (i.e. answering a follow-up question such as “how” or “why”), but without answering the speaker’s question directly (e.g. Do you want to go to the movies tonight? / I have too much homework). In the case of indirect requests, the speaker initiates the exchange with an indirect speech act—a neutral statement that a listener can infer to be a request or “call to action” depending on the context (e.g. It’s cold in here. / Okay, I’ll open the window). Importantly, these two types indirect speech allow us to examine the same language phenomenon from different perspectives—speaker and listener—and gather evidence
for a model of language neurobiology that is not specific to a singular type of stimuli, but rather is broadly applicable to discourse as a whole.

Despite these many advantages, only a limited number of studies to date have examined the neural basis of indirect speech act comprehension (Shibata et al., 2011; Van Ackeren et al., 2012; Basnáková et al., 2013; Jang et al., 2013; van Ackeren et al., 2016; Feng et al., 2017). In terms of indirect replies, both Shibata et al. and Basnáková et al. used tasks that involve reading a short narrative to establish background context, followed by a brief exchange between two speakers. Jang et al., on the other hand, manipulated question-answer dialogues so that answers can be categorized as explicit, moderately implicit, or highly implicit, depending on the presence of binding words. Across the studies, consistent activations were observed in language regions, such as IFG and MTG, and social regions, including mPFC and TPJ. While promising, these studies are not without methodological limitations. For example, all the indirect stimuli used by Shibata et al. had a negative connotation, whereas all the literal stimuli had a positive connotation. This systematic difference in stimulus valence could contribute to the observed effects. Task design can also influence patterns of neural activity. For example, using narratives to establish context may introduce carry-over effects that make it difficult to dissociate inferential processing from story processing and artificially increase working memory demands as the participant tries to recall the preceding contextual information. Finally, none of these studies examined the patterns of functional connectivity necessary to support successful comprehension.

There are only two neuroimaging studies to date that have examined indirect request comprehension. In two complementary studies, van Ackeren and colleagues (2012, 2016) demonstrated that indirect requests activate social regions, including
mPFC, TPJ, and precuneus, as well as cortical motor regions including precentral gyrus (likely due to the implicit motor command contained within an indirect request) and executive regions including inferior parietal lobule. While largely consistent with the indirect reply literature, these studies are also not without methodological limitations. For example, in the initial experiment (van Ackeren et al., 2012), the stimuli were auditory sentences paired with simple, static pictures (e.g. “It’s very hot here,” paired with a picture of a desert or a picture of a room with a closed door). The pictures, which did not include any human interlocutors, were only correctly classified either direct or indirect requests 70% of the time. In the follow-up experiment (van Ackeren et al., 2016), the stimuli were perhaps more ecologically valid as they did include an exchange between two interlocutors, but they were constructed such that they were more similar to indirect replies than indirect requests. As mentioned above, we typically classify indirect requests as speaker-initiated. In this experiment, however, the speaker asked a question about an action (e.g. “Shall I move the television closer to the sofa?”) and it was the listener who responded with indirect speech meant to indicate either agreement or disagreement with that proposed action (e.g. “It is quite far away.”) Based on these preliminary studies, additional work and the development of new stimuli is still necessary.
A PATIENT LESION MODEL APPROACH: INTRODUCTION TO BEHAVIORAL VARIANT FRONTOTEMPORAL DEGENERATION

With the advent of functional brain imaging techniques towards the end of the 20th century, contemporary research on the neurobiology of language has typically focused on studies in healthy adults using techniques like functional magnetic resonance imaging (fMRI), positron emission tomography (PET), electroencephalography (EEG), and magnetencephalography (MEG). While significant progress has been made with these advanced technologies, it is important to remember that the initial and foundational work of Broca and Wernicke was not based on how the healthy brain processes language, but rather on how the diseased brain interrupts language processing. Indeed, studying the effects of brain lesions on behavior is one of the most longstanding and influential methods in all of cognitive neuroscience, not only in language but also in memory, vision, and motor control. Accordingly, there has been a recent call to return to this time-honored methodology (Adolphs, 2016; Vaidya et al., 2019) because of the unique evidence these types of studies can provide. For example, while fMRI, PET, EEG, and MEG provide only correlative evidence that a certain region is activated during a certain task, studies of humans with focal brain damage can provide causal evidence regarding the necessity of a certain brain region for a certain task. Patient “lesion” studies are also advantageous because they can 1) reveal dissociations in function that cannot be demonstrated with purely correlative approaches and 2) provide clinically valuable information about the type of impairments characteristic of a disease state and their change (and possible resolution) over time.

With these advantages in mind, the work contained herein will adopt a patient-lesion model approach, having carefully selected the behavioral variant of frontotemporal degeneration (bvFTD) as the primary population of interest. A rare, young-onset
neurodegenerative disease, FTD is the second most common cause of dementia after Alzheimer's disease. Characterized by progressive changes in social comportment, personality, and executive functioning, patients with bvFTD show focal disease in the frontal and anterior temporal lobes of the brain. Importantly, these patients do not have aphasia, so a primary language impairment such as word comprehension difficulty is unlikely to confound performance. Considering this particular constellation of symptoms, bvFTD is considered well-suited to studies of language in context and/or everyday conversation (Grossman, 2018), as we again predict the involvement of social and executive regions beyond the classic language regions.

SPECIFIC AIMS

To summarize, in this thesis I present a series of experiments that address the following neurobiological question: What brain networks are necessary for processing language in context? I approach this problem using a combination of structural magnetic resonance imaging and diffusion tensor imaging techniques in patients, which allows me to characterize both the cortical nodes involved in communication and the white matter projections that connect them. Overall, I hypothesize that processing language in context requires the interaction of brain regions that are not traditionally incorporated in neuroanatomic models of language, including prefrontal regions belonging to the social and executive brain networks.

The first section of this thesis (Chapters 2 and 3) finds data largely consistent with this hypothesis, as we examine the neural basis of referential communication and social coordination. In Chapter 2, we examine continuous speech production, and find that non-language brain regions in medial, orbital, and dorsolateral prefrontal cortices are critically involved in a speaker's ability to design an utterance for a listener. In
Chapter 3, we extend upon the work of Chapter 2 by examining the cognitive factors that mediate referential communication and modifying the paradigm to minimize the task-related demands associated with overt speech. In addition to confirming our previous results regarding the role of prefrontal cortices in coordination, we also implicate an individual’s mental flexibility in their ability to communicate successfully.

In the following section, Chapters 4 and 5, we turn from language production to language comprehension. Do the same mechanisms apply when a listener interprets the utterance of a given speaker, as when a speaker designs an utterance for a given listener? In Chapter 4, we examine the comprehension of indirect replies in patients with bvFTD compared to healthy controls, as well as brain-damaged controls with amnestic mild cognitive impairment. In Chapter 5, we seek converging evidence for the results we obtain in Chapter 4, by examining a different type of speech act known as indirect requests. Similar to our work on referential communication, we find evidence across both studies that regions belonging to the social and executive brain networks are implicated in the correct interpretation of indirect speech.

Finally, in Chapter 6, we adopt a different, more-clinically motivated approach. As mentioned previously, in addition to advancing our theoretical knowledge of brain-behavior relationships, one of the benefits of patient-centric studies is that they can provide practical, prognostic information for patients about their expected disease course. In Chapter 7, we compare the longitudinal trajectories of conversational ability in bvFTD compared to Alzheimer’s disease (AD), finding a significant rate of decline in bvFTD but not AD. Within bvFTD, we then examine the cognitive and neural factors that can predict a faster rate of decline. Consistent with our previous findings, we find that bvFTD patients with poor executive functioning and focal atrophy in prefrontal cortex are more likely to experience communication problems later on in disease course.
We conclude in Chapter 7, with a discussion of our overall results and possibilities for future research. Altogether, our work argues for an updated model of language neurobiology that, beyond a core language network, also incorporates both social and executive components.
CHAPTER 2: Getting on the same page: The neural basis of social coordination deficits in behavioral variant frontotemporal dementia


ABSTRACT

For social interactions to be successful, individuals must establish shared mental representations that allow them to reach a common understanding and “get on the same page”. We refer to this process as social coordination. While examples of social coordination are ubiquitous in daily life, relatively little is known about the neuroanatomic basis of this complex behavior. This is particularly true in a language context, as previous studies have used overly complex paradigms to study this. Although traditional views of language processing and the recent interactive-alignment account of conversation focus on peri-Sylvian regions, our model of social coordination predicts prefrontal involvement. To test this hypothesis, we examine the neural basis of social coordination during conversational exchanges in non-aphasic patients with behavioral variant frontotemporal degeneration (bvFTD). bvFTD patients show impairments in executive function and social comportment due to disease in frontal and anterior temporal regions. To investigate social coordination in bvFTD, we developed a novel language-based task that assesses patients’ ability to convey an object’s description to a conversational partner. Experimental conditions manipulated the amount of information shared by the participant and the conversational partner, and the associated working memory demands. Our results indicate that, although patients did not have difficulty identifying the features of the objects, they did produce descriptions that included insufficient or inappropriate adjectives and thus struggled to communicate effectively.
Impaired performance was related to gray matter atrophy particularly in medial prefrontal and orbitofrontal cortices. Our findings suggest an important role for non-language brain areas that belong to a large-scale neurocognitive network for social coordination.
INTRODUCTION

As humans, we navigate a complex world of social interactions, from negotiating with colleagues at work to gossiping with friends over coffee. For these interactions to be successful, individuals must establish shared mental representations to mediate common understanding. Behavioral game theory, rooted in principles of rational decision-making and strategy, refers to this process as social coordination (Clark, 2011). While examples of social coordination dominate our daily lives, surprisingly little is known about the neural mechanisms supporting this complex behavior. This is particularly true within the domain of language, which is the most common way in which we exchange information. In this study, we examine the neural basis for social coordination by studying semi-structured conversational exchanges in patients with behavioral variant of frontotemporal degeneration (bvFTD).

Traditional views of language suggest the core processing regions reside in left hemisphere peri-Sylvian cortex. Based primarily on studies of segmental language, this classic model fails to account for the complexities of real-world communication. Indeed, some recent models of language processing suggest prefrontal cortex and areas associated with cognitive control and social cognition are needed to supplement core language processing regions (Cooke et al., 2006; Novais-Santos et al., 2007; Ferstl et al., 2008; Troiani et al., 2008; Hagoort, 2014).

We examine this possibility here and investigate the neural basis for social coordination during conversation by studying patients with behavioral variant frontotemporal degeneration (bvFTD). bvFTD is a rare neurodegenerative disease characterized by executive and social limitations due to progressive atrophy in frontal and temporal regions (Rascovsky et al., 2011). Patients with bvFTD demonstrate
relatively preserved language, although higher-order narrative deficits have been reported (Ash et al., 2006; Cosentino et al., 2006; Farag et al., 2010). Because segmental language function is largely spared and patients are considered non-aphasic, these narrative deficits are often attributed to executive and social difficulties. A recent study using a single-word task also demonstrated impaired social coordination in bvFTD (McMillan et al., 2012). In this study, bvFTD patients differed from healthy controls in providing responses (e.g. a boy’s name) that “others just like themselves” might provide. It remains unknown whether deficits in social coordination also contribute to difficulty with conversational discourse.

Here, we investigate social coordination using a novel, language-based task that involves describing a single object to a conversational partner. Much of the previous work examining perspective-taking during language use has employed complex narratives, many illustrating false beliefs or social faux pas. These studies consistently demonstrate a deficit in bvFTD (Gregory et al., 2002; Kipps and Hodges, 2006; Lough et al., 2006; Torralva et al., 2007, 2009; Fernandez-Duque et al., 2009; Kipps et al., 2009; Freedman et al., 2013). These narrative-based measures, however, require patients to track complex activities that involve multiple actors and extend over time. Since executive and working memory limitations have been documented in bvFTD (Kramer et al., 2003; Libon et al., 2007), the results of these demanding studies are controversial and potentially confounded (Henry et al., 2014). For instance, some studies have suggested that the results of these traditional, story-based, theory of mind tasks may reflect deficits related to task demands and executive functioning, rather than mentalizing or social cognition per se (Fernandez-Duque et al., 2009; Le Bouc et al., 2012). Such a relationship between executive function and theory of mind in bvFTD remains a source of contention, however, with a number of studies reporting that the two
deficits are dissociable and independent. For example, Torralva et al. (2007) report a deficit in theory of mind in bvFTD patients that is consistent across the Reading the Mind in the Eyes and faux pas tasks but independent of a general deficit in decision making. Similarly, Freedman et al. (2013) found significant deficits in second-order false belief performance that persisted when controlling for deficits in executive function. In the latter study, the authors also demonstrated that the patient deficit was specific: no deficits in visual perspective-taking were observed.

Beyond the potential confounds related to executive function, the existing theory of mind tasks are also limited in their ecological validity. These comprehension-based tasks only ask patients to be passive observers; they do not require subjects to play an active role in the experimental situation and use their understanding of a conversational partner’s perspective.

To our knowledge, this study is the first to examine social coordination in a natural, semi-structured discourse context. Furthermore, we manipulate two aspects of coordination. The first is perspective-taking, or the ability to adopt another’s point of view. We examine perspective-taking by assessing the patient’s sensitivity to the amount of information available to the conversational partner. Second, we examine the resource demands associated with tracking the multiple elements of a conversation. We independently examine the effect of resource demands by manipulating the number of objects sharing perceptual features and competing with the target object described by the patient.

Previous work in bvFTD has related both narrative (Ash et al., 2006; Farag et al., 2010) and social (Eslinger et al., 2007; Kipps et al., 2009; Mendez and Shapira, 2009; Grossman et al., 2010; Couto et al., 2013) deficits to prefrontal disease. fMRI studies of non-verbal coordination in healthy adults also implicate prefrontal regions (Kuo et al.,
Accordingly, our model of coordination predicts essential roles of medial prefrontal (mPFC), dorsolateral prefrontal (dLPPC), and orbitofrontal cortices (OFC), areas associated with mentalizing/perspective-taking, working memory, and decision-making, respectively (Amodio and Frith, 2006; Wallis, 2007; Badre, 2008). Therefore, in the context of the current experiment, we predict a priori that impaired behavioral performance on the social coordination task in bvFTD will be related to reduce gray matter density in these regions.

The interactive-alignment account provides an alternative, although not necessarily mutually exclusive, hypothesis (Pickering and Garrod, 2004). According to this perspective, effective interpersonal communication results from alignment at multiple levels of linguistic representation, including lexical selection and syntactic construction. Citing evidence that speakers and listeners both activate peri-Sylvian regions and show correlated brain activity during communication, Menenti et al. (2012) propose co-activation of the language network as a mechanism for conversational alignment.

Relatedly, simulation theory suggests that social interactions are supported by mirror neuron activity in premotor areas (including Broca’s area) (Gallese, 2007). The present investigation may help clarify the relative contributions of social processing dependent upon prefrontal regions (coordination) versus linguistic priming dependent upon peri-Sylvian language-specific regions (interactive-alignment) and simulation dependent upon premotor regions (mirror neurons) to communication.
MATERIALS AND METHODS

Participants

Participants included twelve patients with bvFTD who were demographically-comparable with fourteen healthy seniors in terms of age, education, and gender. Demographic and clinical characteristics are summarized in Table 1. Patients with bvFTD were diagnosed by board-certified neurologists (M.G., D.J.I) using a consensus procedure and published criteria (Rascovsky et al., 2011). Alternative causes of cognitive difficulty due to other neurodegenerative conditions such as Alzheimer’s disease, hydrocephalus, stroke or head trauma were excluded by clinical exam, neuroimaging, CSF, and blood tests. As summarized in Table 1, severity of overall cognitive impairment was assessed in patients using the Mini-Mental State Examination. On average, patients were not in the demented range (mean MMSE=25.75, SD=3.47), and individual scores all fell in the range of minimal to mild impairment (range: 18-29). To test specificity and ensure that any observed deficits in social coordination were not the result of linguistic deficits, patients with bvFTD also completed a short battery of language tests. These tests included an abbreviated version of the Boston Naming Test (Kaplan, Goodglass, and Weintraub, 1983), a test of lexical retrieval in which participants name 30 black and white line drawings of objects that are graded in difficulty; the language section of the Philadelphia Brief Assessment of Cognition (PBAC), which yields a composite measure based on a broad spectrum of language skills including lexical retrieval, semantic knowledge, conversational fluency, reading, writing, and repetition (Avants et al., 2014; Libon et al., 2011); and the Pyramid and Palm Trees test (Howard and Patterson, 1982), a test of semantic access in which participants must identify the word or picture that is associated with the presented target. Finally, patient
caregivers were administered the Neuropsychiatric Inventory (Cummings et al., 1994), which is a commonly used tool assessing the severity and frequency of neuropsychiatric symptoms (including apathy/indifference) in patients with dementia.

Informed consent was obtained from all participants according to a protocol approved by the Institutional Review Board at the University of Pennsylvania.

Table 1. Demographics for Experiment 1. Mean (±SEM) demographic and neuropsychological data for behavioral variant frontotemporal degeneration and control groups.

<table>
<thead>
<tr>
<th>NOTEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. bvFTD patients and healthy seniors did not significantly differ in terms of age [t(24) = 1.82; p = 0.08], education level [t(23) = 0.12, p = 0.85 ], or gender [χ²=2.74, p = 0.13].</td>
</tr>
<tr>
<td>2. Mini Mental State Examination: Overall measure of cognitive impairment</td>
</tr>
<tr>
<td>3. Boston Naming Test: Picture naming task that assesses word retrieval and semantic impairment.</td>
</tr>
<tr>
<td>4. Language Scale, Philadelphia Brief Assessment of Cognition: Composite measure of overall language functioning</td>
</tr>
<tr>
<td>5. Pyramids and Palm Trees: Semantic association task.</td>
</tr>
</tbody>
</table>

Discourse Social Coordination Task
Participants were presented with two-scene stories illustrating the movement of a target toy animal. In each story, the target animal was moved from the floor to a shelf (i.e. a three by four grid) of competing objects variably sharing color, size, and pattern features with the target object (see Figure 2). Participants were asked to describe the scene with sufficient detail so a conversational partner (an avatar visible behind the shelf) could correctly identify the moving animal.

To assess coordination and perspective-taking, trials varied in the amount of information available to the avatar. In “common ground” trials, the avatar had equal access to visual information. In “colorblind” trials, the avatar was said to be completely colorblind (i.e. only able to see in grayscale). In “privileged ground” trials, there was a physical obstruction blocking the avatar’s view of selected portions of the shelf so that only the participant could see some objects. The latter two conditions were hypothesized to put increasing demand on the participant’s perspective-taking ability. In the privileged ground condition, there was a physical reminder of the different perspectives available to the participant and the avatar; in the colorblind condition, there was no such physical reminder, and instead the phrase “colorblind” was placed in front of the participant.

In order to manipulate resource demands, the stimuli differed according to the number of competitors (i.e. objects displaying a shared feature). The number of competitors visible in the scene (0, 1, or 3) partially determined the number and type of adjectives necessary for the participant to adequately distinguish the target animal when describing its movement to the avatar.

Following presentation of each story, the subject was asked to describe the scene with sufficient detail so that the avatar could identify which animal was moving. There were eight stories for each level of competitor (0, 1, 3) for each condition.
(common ground, colorblind, privileged ground), with a total of 72 stimuli equally distributed across conditions. Stimuli were presented in a pseudo-randomized order to ensure that a single condition was not repeated across consecutive trials. Subjects were trained prior to testing by familiarizing them with task materials and providing feedback to their responses. All patients appeared to understand the task. In total, task administration took approximately one hour.

Subject responses were digitally recorded and later transcribed using the speech analysis program Praat. Responses were coded by the first author, who was blind to group membership. Responses were categorized as precise, superfluous, or insufficient, depending on the adjectives used to describe the moved object. Precise responses used the exact number of adjectives necessary to distinguish the target animal; superfluous responses used an excess number of adjectives, and insufficient responses were lacking necessary adjectives. For example, when the target animal differed from its competitors only in terms of color, the precise response would be “the red pig moved…”, a superfluous response would be “the solid red pig moved…”, and an insufficient response would be “the pig moved…”. Precise and superfluous responses were also summed to create an overall accuracy score, since both types of responses would allow the avatar to correctly identify the target animal. We used non-parametric statistics to analyze behavioral performance because the data were not normally distributed according to Levene’s tests.
Figure 2. Design of Experiment 1. Participants were presented two-scene stories in which a target animal moves from one location to another. We illustrate this with sample stimuli from the three conditions (A: common ground, B: colorblind, C: privileged ground). The stimuli above also vary in the number of competitors (i.e. animals of the same species as the target animal) visible in the scene (A: 0 competitors, B: 1 competitor, C: 1 competitor).
competitor, C: 3 competitors). Target responses are indicated in the lower right hand corner of each panel.

Imaging Procedure and Analysis

High-resolution volumetric T1-weighted MRI was available within an average of 6.04 months (SEM=1.95 months) from the date of behavioral testing for 9 bvFTD patients. MRI images were not available for a subset of individuals with bvFTD (n=3) for health and safety reasons, including claustrophobia and metallic implants (e.g. pacemakers, shrapnel) in the body. MRI volumes were acquired using an MPRAGE sequence from a SIEMENS 3.0T Trio scanner with an 8-channel head coil and the following acquisition parameters: repetition time=1620 msec; echo time=3.87 msec; slice thickness=1.0 mm; flip angle=15°; matrix=192×256, and in-plane resolution=0.98×0.98 mm. Whole-brain MRI volumes were preprocessed using PipeDream (https://sourceforge.net/projects/neuropipedream/) and Advanced Normalization Tools (http://www.picsl.upenn.edu/ANTS/) using a state-of-the-art procedure described previously (Avants et al., 2008; Klein et al., 2010; Tustison et al., 2014). Briefly, PipeDream deforms each individual dataset into a standard local template space. A diffeomorphic deformation was used for registration that is symmetric to minimize bias toward the reference space for computing the mappings, and topology-preserving to capture the large deformation necessary to aggregate images into a common space. Template-based priors are used to guide GM segmentation and compute GM probability, which reflects a quantitative measure of GM density. Resulting images were warped into MNI space, smoothed using a 5 mm full-width half-maximum Gaussian kernel and downsampled to 2 mm resolution to account for variation in individual gyral anatomy. Permutation-based imaging analyses were performed with threshold-free cluster enhancement using the randomise tool in FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki). Briefly, permutation-based t-tests evaluate a true assignment of GM density across
groups (signal) relative to many (10,000) random assignments of GM density across groups (noise) and thus is a statistically robust procedure that is much less susceptible to multiple comparisons problems compared to traditional parametric-based t-tests. GM density was compared in patients relative to healthy seniors (an independent group of 35 healthy seniors with imaging who were comparable to the patient group for age \( t(42)=0.52, \text{ ns} \) and education \( t(42)=0.86, \text{ ns} \). Analyses were run with 10,000 permutations and restricted to voxels containing GM using an explicit mask generated from the average gray matter probability map of all groups. We report clusters that survived a threshold of \( p<0.005 \) (uncorrected) and containing a minimum of 200 adjacent voxels.

To relate behavioral performance to regions of significant GM disease, we used regression analyses with the randomise tool of FSL and threshold-free cluster enhancement, as described above. Permutations were run exhaustively up to a maximum of 10,000 for each analysis. To constrain our interpretation to areas of known GM disease, we restricted our regression analyses to an explicit mask containing voxels of GM atrophy in the patients as defined in the group comparison. Regressions outside these regions of known disease would be difficult to interpret since they could be attributed to a variety of factors associated with individual differences in GM density, including healthy aging and genetic factors. We report clusters surviving a height threshold of \( p<0.005 \) (uncorrected) and containing a minimum of 10 adjacent voxels.

RESULTS
Behavioral Results

Our first analysis focused on overall accuracy (whether or not participants correctly produced necessary adjectives) and revealed that patients with bvFTD (mean=52.03% correct, SD=8.65) are less accurate overall compared to healthy seniors [mean=78.45% correct, SD=11.04, U(24)=6.00, p<0.001]. Correlation analyses using Spearman’s rank correlation coefficient indicated that accuracy in patients did not correlate with MMSE (r=0.174, p=0.588), any of the language measures [Boston Naming Test: r=0.51, p = 0.09; Language Scale, PBAC: r=0.44, p=0.150; Pyramids and Palm Trees: r = -0.45, p = 0.167], or with the caregiver-based apathy measure (total frequency x severity domain score) of the Neuropsychiatric Inventory (r=0.13, p=0.685). These data suggest that performance was not related to a language-specific impairment or to apathetic behavior.

When conditions were compared using a Friedman test, we found a significant difference performance across common ground, colorblind, and privileged ground conditions (Q=12.58, p<0.01). As illustrated in Figure 3A, subsequent Mann-Whitney tests investigating group differences within each condition showed that patients with bvFTD are significantly less accurate than healthy seniors in describing the movement of a target animal in both the common ground (U(24)=12.00, p<0.001) and colorblind conditions (U(24)=3.00, p<0.001). Patients did not differ significantly from healthy seniors in the privileged ground condition (U(22)=35.50, Z=1.843, p=0.10), suggesting that the physical reminder of the avatar’s obstructed view prompted patients to be more sensitive to a conversational partner.
Figure 3. Behavioral Results for Experiment 1. A: Mean (±SEM) percent accuracy of responses in common ground, colorblind, and privileged ground conditions for health seniors (dark gray) and bvFTD patients (light gray). bvFTD patients performed significantly worse than healthy controls on common ground and colorblind trials, but not on privileged ground trials. B: Mean (±SEM) percent responses classified as precise, superfluous, and insufficient for health seniors (dark gray) and bvFTD patients (light gray). bvFTD patients provide significantly more insufficient responses than healthy seniors.

Next, we conducted a qualitative error analysis by investigating the types of responses that patients produced when they erred, collapsing across all conditions. The results of this analysis, illustrated in Figure 3B, demonstrated that patients are significantly more likely than controls to give responses that are categorized as insufficient (U(24)=6.00, Z=44.02, p<0.001). Thus, patients omitted adjectives that would have been useful in identifying the target object for a conversational partner. Importantly, patients never gave responses that include factually incorrect information (e.g. misidentifying blue as green), which provides further evidence that the observed social coordination deficits are not related to lexical retrieval or visuospatial difficulty.
Within-group comparisons using Wilcoxon signed ranks test revealed that patients are equally impaired on common ground and colorblind trials ($Z=-1.56$, $p=0.120$), despite the hypothesized difference in perspective-taking demands associated with these conditions. Therefore, we conducted a follow-up analysis specifically examining the use of superfluous color terms across conditions. In common ground and privileged ground trials, the use of a color term was superfluous if it was not needed for the conversational partner to identify the target. In colorblind trials, use of color terms was always superfluous. As illustrated in Figure 4, we found a significant difference for the colorblind condition ($U(24)=24.00$, $p<0.01$). Patients demonstrated their insensitivity to the colorblindness of the conversational partner by using superfluous color terms significantly more often than healthy seniors. Indeed, according to within-group comparisons using the Wilcoxon signed ranks test, they used color terms in the colorblind condition as often as they did in the common ground condition, where color terms are informative and appropriate ($Z=-0.51$, $p=0.959$). Healthy seniors, on the other hand, adopted an effective strategy and decreased their use of color terms in the colorblind condition compared to the common ground condition ($Z=-2.20$, $p<0.05$). There were no group differences in color term use for the common ground condition ($U(26)=82.00$, $p=0.940$) or the privileged ground condition ($U(23)=52.00$, $p=0.446$). Finally, we examined the effect of resource demands across groups. No difference in performance was observed across groups for 0-competitor trials. This confirms that patients understood the task structure and were capable of visualizing and describing the materials appropriately. We computed a normalized difference score by calculating the percent difference in accuracy between 3-competitor and 1-competitor trials, and dividing this by percent accuracy in 1-competitor trials ($[3\text{COMP} - 1\text{COMP}] / 1\text{COMP}$), in order to account for differences in baseline performance across subjects and groups.
We found that bvFTD patients (mean= -79.77%; SD=18.22) are significantly more affected by resource demands than healthy seniors (mean= -46.04%; SD=27.03; U=27.50, p<0.01). However, Wilcoxon tests for within-group comparisons revealed that there are no significant differences across coordination conditions for either group (healthy seniors: p=0.40, bvFTD: p=0.50). Therefore, bvFTD patients showed reduced working memory, but this did not appear to interact with coordination and perspective-taking, suggesting the deficit observed during social coordination is largely independent of a limitation in executive resources per se.

Figure 4. Error Analysis for Experiment 1. Mean (±SEM) percent responses that include a superfluous color term in common ground, colorblind, and privileged ground conditions for healthy seniors (dark gray) and bvFTD patients (light gray). Patients use significantly more color terms in colorblind trials than healthy controls, but not in common ground or privileged ground trials.
Imaging Results

We contrasted GM density in bvFTD patients relative to healthy seniors. This revealed significantly reduced GM density throughout the frontal and temporal lobes, as summarized in Table 2 and illustrated in Figure 5A. To relate deficits in coordination to GM density, we performed a regression analysis within patients using the accuracy score from all trials as the independent variable and restricted to regions of known GM disease. This analysis revealed that impaired performance on the coordination task is associated with reduced GM density in medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (dIPFC), and anterior cingulate cortex (ACC) (see Table 2 and green regions in Figure 5B).

To specifically examine the neuroanatomic basis for coordination and perspective-taking, we performed regression analyses using the accuracy scores from the colorblind and privileged ground conditions, both of which were hypothesized to put increasing demand on perspective-taking due to differences in the information available to the patient and conversational partner. Results indicated that performance in the colorblind condition was uniquely related to reduced GM density in OFC and mPFC, as well as portions of ACC and inferior temporal gyrus (see Table 3 and green regions in Figure 6A). The privileged ground condition implicated a unique, non-overlapping set of brain regions, including dIPFC (see Table 3 and green regions in Figure 6B).
Figure 5. Structural Neuroimaging Results for Experiment 1. A: Surface renderings depicting regions of significantly reduced GM density in bvFTD patients relative to healthy seniors (red areas). B: Regions of significantly reduced GM density in bvFTD patients relative to healthy seniors (all colored areas) and regions of significantly reduced GM density associated with impaired social coordination (accuracy score across all trials) in bvFTD patients (green areas, circled).
<table>
<thead>
<tr>
<th>Neuroanatomic Region (BA)</th>
<th>L/R</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>p value</th>
<th>voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clusters of reduced gray matter density in patients with bvFTD relative to controls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>orbitofrontal cortex (11)</td>
<td>R</td>
<td>26</td>
<td>34</td>
<td>-16</td>
<td>&lt;0.001</td>
<td>29,345</td>
</tr>
<tr>
<td>fusiform gyrus (37)</td>
<td>R</td>
<td>40</td>
<td>-50</td>
<td>-16</td>
<td>&lt;0.001</td>
<td>145</td>
</tr>
<tr>
<td>fusiform gyrus (37)</td>
<td>L</td>
<td>-46</td>
<td>-54</td>
<td>-20</td>
<td>&lt;0.001</td>
<td>124</td>
</tr>
<tr>
<td>inferior temporal gyrus (37)</td>
<td>R</td>
<td>50</td>
<td>-66</td>
<td>-14</td>
<td>&lt;0.001</td>
<td>77</td>
</tr>
<tr>
<td>posterior cingulate gyrus (23)</td>
<td>R</td>
<td>20</td>
<td>-64</td>
<td>4</td>
<td>&lt;0.001</td>
<td>56</td>
</tr>
<tr>
<td><strong>Clusters of reduced gray matter density related to overall accuracy in patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dorsolateral prefrontal cortex (46)</td>
<td>L</td>
<td>-46</td>
<td>22</td>
<td>26</td>
<td>&lt;0.001</td>
<td>45</td>
</tr>
<tr>
<td>anterior cingulate cortex (24)</td>
<td>L</td>
<td>-6</td>
<td>36</td>
<td>-4</td>
<td>0.001</td>
<td>32</td>
</tr>
<tr>
<td>superior frontal gyrus (6)</td>
<td>R</td>
<td>24</td>
<td>10</td>
<td>52</td>
<td>0.001</td>
<td>22</td>
</tr>
<tr>
<td>anterior cingulate cortex (32)</td>
<td>L</td>
<td>-4</td>
<td>30</td>
<td>30</td>
<td>&lt;0.001</td>
<td>18</td>
</tr>
<tr>
<td>orbitofrontal cortex (11)</td>
<td>L</td>
<td>-28</td>
<td>44</td>
<td>-16</td>
<td>0.001</td>
<td>18</td>
</tr>
<tr>
<td>anterior cingulate cortex (32)</td>
<td>R</td>
<td>10</td>
<td>32</td>
<td>28</td>
<td>0.002</td>
<td>17</td>
</tr>
<tr>
<td>orbitofrontal cortex (47)</td>
<td>L</td>
<td>-36</td>
<td>32</td>
<td>-14</td>
<td>0.001</td>
<td>17</td>
</tr>
<tr>
<td>dorsolateral prefrontal cortex (8)</td>
<td>R</td>
<td>30</td>
<td>30</td>
<td>46</td>
<td>&lt;0.001</td>
<td>15</td>
</tr>
<tr>
<td>medial prefrontal cortex (10)</td>
<td>L</td>
<td>-12</td>
<td>50</td>
<td>6</td>
<td>0.001</td>
<td>11</td>
</tr>
<tr>
<td>middle frontal gyrus (9)</td>
<td>R</td>
<td>30</td>
<td>36</td>
<td>34</td>
<td>&lt;0.001</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 2. MNI Coordinates for Experiment 1 Imaging Results. Clusters or reduced gray matter density in patients with bvFTD relative to healthy seniors, and clusters of reduced gray matter density related to performance (accuracy score across all trials) in bvFTD patients. BA, Brodmann Area; MNI, Montreal Neurological Institute.
Figure 6. Condition-Specific Neuroimaging Results for Experiment 1. Regions of significantly reduced GM density (green areas, circles) selectively related to performance in colorblind (panel A) and privileged ground (panel B) conditions. Red areas represent regions of significantly reduced GM density in bvFTD patients relative to healthy controls.
### Table 3. MNI Coordinates for Experiment 1 Condition-Specific Results

Clusters of reduced GM density related to patient performance in the colorblind condition.

<table>
<thead>
<tr>
<th>Neuroanatomic Region (BA)</th>
<th>L/R</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>p value</th>
<th>voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>orbitofrontal cortex (11)</td>
<td>L</td>
<td>-14</td>
<td>14</td>
<td>-24</td>
<td>&lt;0.001</td>
<td>112</td>
</tr>
<tr>
<td>anterior cingulate cortex (24)</td>
<td>L</td>
<td>-2</td>
<td>24</td>
<td>20</td>
<td>&lt;0.001</td>
<td>23</td>
</tr>
<tr>
<td>medial orbitofrontal cortex (11)</td>
<td>R</td>
<td>10</td>
<td>52</td>
<td>-4</td>
<td>0.002</td>
<td>22</td>
</tr>
<tr>
<td>orbitofrontal cortex (11)</td>
<td>R</td>
<td>8</td>
<td>44</td>
<td>-20</td>
<td>0.002</td>
<td>20</td>
</tr>
<tr>
<td>orbitofrontal cortex (47)</td>
<td>L</td>
<td>-28</td>
<td>22</td>
<td>-16</td>
<td>0.001</td>
<td>18</td>
</tr>
<tr>
<td>middle frontal gyrus (8)</td>
<td>R</td>
<td>20</td>
<td>20</td>
<td>46</td>
<td>0.002</td>
<td>16</td>
</tr>
<tr>
<td>orbitofrontal cortex (11)</td>
<td>L</td>
<td>-28</td>
<td>44</td>
<td>-14</td>
<td>0.002</td>
<td>13</td>
</tr>
<tr>
<td>anterior cingulate cortex (32)</td>
<td>R</td>
<td>10</td>
<td>24</td>
<td>38</td>
<td>0.002</td>
<td>11</td>
</tr>
<tr>
<td>medial orbitofrontal cortex (11)</td>
<td>R</td>
<td>4</td>
<td>58</td>
<td>-16</td>
<td>0.001</td>
<td>10</td>
</tr>
<tr>
<td>orbitofrontal cortex (11)</td>
<td>L</td>
<td>-6</td>
<td>46</td>
<td>-22</td>
<td>0.001</td>
<td>10</td>
</tr>
<tr>
<td>inferior temporal gyrus (20)</td>
<td>L</td>
<td>-64</td>
<td>-6</td>
<td>-24</td>
<td>0.001</td>
<td>10</td>
</tr>
</tbody>
</table>

Clusters of reduced GM density related to patient performance in the privileged ground condition.

<table>
<thead>
<tr>
<th>Neuroanatomic Region (BA)</th>
<th>L/R</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>p value</th>
<th>voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>dorsolateral prefrontal cortex (46)</td>
<td>L</td>
<td>-46</td>
<td>18</td>
<td>26</td>
<td>0.001</td>
<td>21</td>
</tr>
<tr>
<td>superior frontal gyrus (10)</td>
<td>L</td>
<td>-32</td>
<td>56</td>
<td>2</td>
<td>&lt;0.001</td>
<td>20</td>
</tr>
<tr>
<td>inferior frontal gyrus (44)</td>
<td>L</td>
<td>-58</td>
<td>18</td>
<td>12</td>
<td>0.001</td>
<td>13</td>
</tr>
<tr>
<td>orbitofrontal cortex (47)</td>
<td>L</td>
<td>-30</td>
<td>32</td>
<td>-12</td>
<td>0.003</td>
<td>12</td>
</tr>
</tbody>
</table>

*BA, Bromdann Area; MNI, Montreal Neurological Institute.*
DISCUSSION

This study examined the neuroanatomic basis of social coordination deficits observed in bvFTD. We used a novel task that actively engages patients in demonstrating their perspective-taking by asking them to describe an object, and we carefully minimized task-related demands. Our results suggest that bvFTD patients have perspective-taking difficulties, offering insufficient descriptions of the given conversation topic and providing colored attributes that were inaccessible to a colorblind partner. This impairment was related to reduced GM density in medial, dorsolateral, and orbital frontal cortices. Performance on colorblind trials was specifically related to mPFC and OFC, suggesting roles for these areas in social perspective-taking. Overall, these results are consistent with social coordination theory and support the view that successful communication involves social processing and is supported in part by prefrontal activity. We discuss the behavioral and anatomic results in turn below.

Social coordination during discourse in behavioral variant frontotemporal degeneration

Only a limited number of studies to date have examined perspective-taking in a communicative context (Dumontheil et al., 2010; Hillebrandt et al., 2013; Wardlow, 2013; Wardlow et al., 2014). For example, in an fMRI study of healthy volunteers, Dumontheil et al. (2010) used a variant of the director task, originally described by Keysar and colleagues (Keysar et al., 2000, 2003). The authors report activation in mPFC and left temporal pole for the critical condition (director present, 3-objects), which partially overlaps with our findings. In a follow-up study, Hillebrandt et al. (2013) used dynamic causal modeling to show that the social demands of the task modulate backward connections from mPFC. The paradigm in both studies, however, is comprehension-
based and requires subjects to identify the target object via a motor response. Some referential communication studies in healthy adults and patients with Alzheimer’s disease (Wardlow, 2013; Wardlow et al., 2014) do involve overt speech responses, but not embedded within a discourse context. These studies also used smaller arrays of objects that may not adequately mimic the complex nature of real-world conversation. Therefore, while the current study constrains conversation to brief exchanges, it benefits from increased ecological validity as natural, self-generated speech is used to describe the stimuli to a conversational partner.

Our results suggest that bvFTD patients, who provide too few adjectives for a conversational partner to correctly identify the target animal, have perspective-taking limitations. This cannot be fully explained by a language deficit since the patients show largely intact language as assessed by a brief battery of language tests (i.e. Boston Naming Test, Philadelphia Brief Assessment of Cognition, Pyramids and Palm Trees). Moreover, their performance matched controls’ performance when no competitors were present. Apathy is frequently documented in bvFTD (Massimo et al., 2009), and we cannot entirely dismiss its contribution to the phenotype observed here. However, the lack of correlation between the Neuropsychiatric Inventory’s apathy score and performance on the coordination task suggests that apathy alone is also unlikely to explain the patients’ reduced production of adjectives.

Additional support implicating limitations in perspective-taking comes from the novel ‘colorblind’ condition. Previous studies examining perspective-taking (Dumontheil et al., 2010; Hillebrandt et al., 2013; Wardlow, 2013; Wardlow et al., 2014) used stimuli that physically obstruct one partner’s view, much like our privileged ground condition. However, the perspective-taking required during most conversations involves not necessarily the alignment of visuospatial references, but rather the alignment of mental
representations and situation models. The colorblind condition utilized here, which is identical in visual appearance to the common ground condition and does not include any physical reminder of the avatar’s limited knowledge state beyond the written condition label, requires the subject to consider which attributes will be informative for the avatar. In this sense, the colorblind condition involves appreciating the avatar’s mental state and recognizing shared information. This is a more complex and abstract form of social perspective-taking that may account for the dissociation we observe behaviorally: while patients perform as well as healthy seniors on privileged ground trials when there is a physical prompt (i.e. the opaque portions of shelf), they are significantly impaired on colorblind trials.

Although patients appeared to perform comparably on common ground and colorblind trials, closer examination revealed a crucial distinction. An error analysis evaluating use of color terms demonstrated that patients are essentially insensitive to the avatar’s colorblind status and refer to color terms significantly more than healthy seniors in the colorblind condition. Furthermore, while healthy seniors showed evidence of perspective-taking and decreased color term use in the colorblind versus common ground condition, patients showed no such modulation of behavior.

While our behavioral results align well with the existing literature on ToM, the design used here represents an important methodological improvement. Many previous studies on ToM used “false belief” and other story-based paradigms that involve extensive task-related performance demands, including maintaining complex relationships between actors throughout multi-sentence narratives. Caution must be used when interpreting the results of such tasks as they may have conflated theory of mind with executive function. Our measure minimized such confounds, as patients were merely asked to describe a target object using one or two adjectives and natural self-
generated speech. Furthermore, we manipulated perspective-taking (i.e. the knowledge state of the avatar) and working memory (i.e. number of competitors) independently, finding that patients show a greater decrease in performance relative to healthy seniors as working memory demands (i.e. competitor number) increased. This is consistent with previous observations of bvFTD patients (Kramer et al., 2003; Libon et al., 2007).

Nevertheless, we failed to observe an interaction between working memory and perspective-taking, since patients did not appear to show an effect of increased competitor number for a specific coordination condition. Thus, we were able to demonstrate more conclusively that patients with bvFTD do have a deficit in perspective-taking per se that is largely independent of any deficit in executive function. Additional work is needed to assess the subtle ways in which social perspective-taking and executive resources may interact during social coordination.

Neuroanatomic basis for social coordination during discourse in behavioral variant frontotemporal degeneration

We identified a large-scale neural network associated with task performance that encompassed dIPFC, mPFC, OFC, insula and ACC. These areas are elements of the “social brain network” described previously by others (Adolphs, 2003; Frith and Frith, 2007). Interestingly, even though we examined spoken discourse, these areas overlap minimally with the peri-Sylvian language network. These data are consistent with our conclusion that, the limitations in perspective-taking we observed during discourse in bvFTD cannot by entirely explained by a language deficit. Accordingly, our data are less consistent with strict interpretations of interactive-alignment, which hypothesizes that alignment in conversation is supported predominantly by co-activation of the language network (particularly BA44 and BA21) in speakers and listeners (Menenti et al., 2011,
2012). Although language clearly contributes to conversational competence, areas beyond the traditional language network alone appear to be involved in real-world communication. Our findings are also somewhat inconsistent with the idea that successful communication is purely the result of simulation that is driven by mirror neuron activity in premotor cortex. Instead, our data appear to be more consistent with social coordination theory and suggest that successful communication is at least partially dependent upon additional prefrontal regions that supplement traditional brain regions thought to support language processing. It is important to emphasize that these accounts (i.e. social coordination theory, interactive alignment, simulation theory) are not necessarily mutually exclusive but may operate in concert. Future fMRI studies in healthy adults using a whole-brain approach can address the possibility that both linguistic and social neuroanatomic networks contribute to the success of communication and mutual understanding between two or more partners.

Subsequent regression analyses examined the potential role that these frontal regions may play in social coordination in more detail. Accuracy on colorblind trials was specifically associated with reduced GM density in mPFC and OFC. mPFC has been implicated consistently in fMRI studies of healthy adults examining ToM and the ability to interpret other’s beliefs or intentions (Gallagher and Frith, 2003; Saxe and Kanwisher, 2003; Van Overwalle, 2011). OFC, on the other hand, has been implicated in decision-making, including the ability to encode stimulus-outcome contingencies, assess potential risk and reward, and perform tasks involving reversal learning or response inhibition (Murray et al., 2007; Viskontas et al., 2007; Wallis, 2007). In the current experiment, OFC damage may thus contribute to the inappropriate and superfluous references to color seen in patients in the colorblind condition. Furthermore, the current data may also implicate OFC in social perspective-taking, a multi-component process that likely
involves several of the aforementioned functions. Indeed, some have considered perspective-taking to be a two-stage process: 1) inhibiting one’s own perspective and 2) belief reasoning (i.e. interpreting and adopting another’s perspective) (van der Meer et al., 2011). Although findings have been inconsistent, other studies assessing perspective-taking and mentalizing in clinical populations have also suggested a role for OFC (Stone et al., 1998; Sabbagh, 2004; Channon et al., 2007; Kipps et al., 2009; Goodkind et al., 2012). For example, patients with OFC disease appear to have difficulty tracking the dynamically changing emotions of a character in a film clip (Goodkind et al., 2012) and deciding whether an actor in a video is expressing sarcastic or sincere statements (Kipps et al., 2009). Interestingly, these areas implicated in the colorblind condition are unique when compared to those implicated by the privileged ground condition. This again confirms our conclusion that social but not visual perspective-taking is specifically impaired in bvFTD and associated with a partially distinct cortical network.

As described above, the regression on performance across all trials also implicated the dlPFC and ACC. Briefly, the dlPFC is classically associated with top-down attentional regulation, working memory, and selection amongst competing responses (Petrides, 2005; Suzuki and Gottlieb, 2013). Additional research has suggested that dlPFC is associated with second-order relational complexity and assessing concrete relationships amongst objects, which is relevant in the given context, as subjects needed to identify which features of a given object were shared versus unique (Badre, 2008). The ACC was also related to performance across all trials and is commonly associated with error detection, response conflict, and performance monitoring (Chang et al., 2013; Alexander and Brown, 2010; Carter et al., 1998).
It is important to point out that previous work has demonstrated that right anterior temporal regions may also contribute to social and emotional processing (Olson et al., 2007; Wong and Gallate, 2012; Irish et al., 2014). Interestingly, we find little evidence for ATL involvement in social coordination, suggesting that perhaps its function is more tied to social knowledge rather than coordination and perspective-taking per se.

While these findings allow us to begin disentangling the roles of specific prefrontal regions in social coordination, several caveats should be kept in mind when interpreting our results. Despite observations consistent with our hypotheses, we studied a small group of these rare patients and used somewhat lenient statistical thresholds. Furthermore, given the wide range of observed MMSE scores, there may be subgroups present in our patient population, although we did not see evidence of this. As a result, replication in an independent cohort with a patient control group would be valuable. Converging evidence from fMRI studies in healthy adults using the same stimulus materials would also lend additional support to our findings. These future studies might also adopt a more exploratory, whole-brain approach and examine potential effects of aging and individual differences on social coordination. Next, while we performed a detailed analysis of non-aphasic patients’ speech production in a structured context, it would be valuable to develop a comprehension-based paradigm that further reduces task-related demands. Although we were able to demonstrate that performance on the current measure is not correlated with confrontation naming or semantic knowledge, a comprehension-based measure also would minimize any difficulties that could be attributed to impaired lexical retrieval. Finally, our paradigm was designed to directly engage patients in perspective-taking (versus passive observation), but we used an avatar to represent a conversational partner. Future studies might benefit from using paradigms that examine truly interactive exchanges between two (or
more) human partners. With these caveats in mind, our observations offer preliminary support for the claim that social coordination in a discourse context is compromised in bvFTD due to perspective-taking limitations and degradation of a prefrontal network that supports perspective-taking and social coordination.
CHAPTER 3: Cognitive and neuroanatomic accounts of referential communication in focal dementia


ABSTRACT

The primary function of language is to communicate--that is, to make individuals reach a state of mutual understanding about a particular thought or idea. Accordingly, daily communication is truly a task of social coordination. Indeed, successful interactions require individuals to 1) track and adopt a partner’s perspective, and 2) continuously shift between the numerous elements relevant to the exchange. Here, we use a referential communication task to study the contributions of perspective-taking and executive function to effective communication in non-aphasic human patients with behavioral variant frontotemporal dementia (bvFTD). Similar to previous work, the task was to identify a target object, embedded amongst an array of competitors, for an interlocutor. Results indicate that bvFTD patients are impaired relative to controls in selecting the optimal, precise response. Neuropsychological testing related this performance to mental set-shifting, but not to working memory or inhibition. Follow-up analyses indicated that some bvFTD patients perform equally well as controls, while a second, clinically-matched patient group performs significantly worse. Importantly, the neuropsychological profiles of these subgroups differed only in set-shifting. Finally, structural MRI imaging analyses related patient impairment to gray matter disease in orbitofrontal, medial prefrontal, and dorsolateral prefrontal cortex, all regions previously implicated in social cognition and overlapping those related to set-shifting. Complementary white matter analyses implicated uncinate fasciculus, which carries projections between orbitofrontal and temporal cortices. Taken together, these findings demonstrate that impaired referential communication in bvFTD is cognitively related to set-shifting, and
anatomically related to a social-executive network including prefrontal cortices and uncinate fasciculus.

**Significance Statement**

While traditional models of language processing focus on single word and sentence comprehension, successful communication during conversational exchanges may involve additional executive resources and social perspective-taking. Here, we report a novel study of non-aphasic patients with behavioral variant frontotemporal dementia (bvFTD), who have documented deficits in social and executive function but relatively preserved language. Our findings demonstrate that patients with bvFTD have difficulty coordinating perspectives with a conversational partner in a referential communication task. Patient impairment was related to disease in a network of prefrontal regions associated with social functioning and mental set-shifting, highlighting the essential contribution of non-language brain regions to daily communication.
INTRODUCTION

Language does not exist as some arbitrary, surface phenomenon, but rather serves a critical function: to communicate. Indeed, as much as 70% of our waking time is spent in some form of communication (Klemmer and Snyder, 1972): we chat on the phone with friends, give directions to strangers, and make presentations at work. When language is used in these contexts, functioning to communicate something to someone, it is inherently a task of social coordination (Clark, 2011, 2012). Indeed, for an interaction to be successful, speakers and addressees must establish shared mental representations and mutual understanding with one another. A canonical example of this is seen in referential communication, when a speaker must select the attributes of an object or referent in such a way that allows the addressee to identify that referent (Bowman, 1984). Accordingly, referential communication requires an individual to 1) track and adopt a conversational partner’s perspective and 2) maintain and shift between the numerous elements relevant to the ongoing exchange. In this sense, language use is strategic-- it is both socially and executively demanding. Therefore, we ask: how do social and executive processes contribute to daily communication skills?

Surprisingly little is known about the cognitive and neural mechanisms of referential communication. Early examinations of language neurobiology focused on two hubs in left peri-Sylvian cortex, including inferior frontal gyrus (“Broca’s Area”) and posterior superior temporal gyrus (“Wernicke’s Area”). This seminal view, however, was based primarily on studies examining single word and sentence processing and largely ignored how language operates in context. More recently, theoretical and technical developments have made it possible to investigate the neural basis of discourse processing—that is, the social use of language. For example, Xu et al. (2005) used fMRI
to compare the neural correlates of words, sentences, and narratives. The authors found that peri-Sylvian regions are active regardless of context, but regions outside of the core language network, including medial prefrontal cortex, temporoparietal junction, and precuneus, are only engaged for narratives. Few studies have examined the neural basis of referential communication per se, but one recent fMRI experiment manipulating common versus privileged ground information also suggests the mPFC comes online when language production necessitates speaker perspective-taking (Vanlangendonck et al., 2018). Similar findings have been reported in other narrative-based studies (Troiani et al., 2008; AbdulSabur et al., 2014; Saur et al., 2010). Here, we test this hypothesis that non-language brain regions in prefrontal cortex are critical to referential communication, using a lesion-model approach and a carefully-controlled experimental task.

While fMRI studies in healthy adults can associate patterns of neural activity with ongoing behavior, it is a correlative technique that cannot identify which brain regions are truly necessary for a given task. Therefore, it is important to complement fMRI studies with converging evidence from patient studies. Behavioral variant frontotemporal degeneration (bvFTD) is a young-onset neurodegenerative disease characterized by social and executive limitations due to progressive atrophy in frontal and anterior temporal cortices (Rascovsky et al., 2011). Importantly, despite disease in anatomically-relevant areas, linguistic ability is relatively preserved in bvFTD, which makes the group an ideal lesion-model for studies examining social and executive components of language (Kumfor et al., 2017). Previous work using this same logic has also examined social discourse and referential communication in patients with bvFTD (Rankin et al., 2009; Shany-Ur et al., 2011; McMillan et al., 2012; Gola et al., 2015; Healey et al., 2015). In one such study (Healey et al., 2015), patients had to generate brief speech samples
describing the movement of a target object to a conversational partner. Conditions manipulated perspective-taking demand (i.e. the amount and type of information available to both interlocutors) and executive demand (i.e. the number of competing objects in the array). Textual analyses indicated that patients with bvFTD produce descriptions that lack critical, distinguishing adjectives-- a speech pattern that would drive poor communication outcomes in a real-world setting. The observed impairment was further associated with disease in medial, dorsolateral, and orbitofrontal cortices, all regions associated with a social network thought to be compromised in bvFTD (Ibanez and Manes, 2012).

We build upon this previous work in four important ways. First, past research has suggested that bvFTD patients may be overwhelmed by the cognitive demands associated with continuous speech production, often showing a phenotype characterized by reduced rate, decreased information content, and abnormal prosody (Ash et al., 2006; Nevler et al., 2017; Vogel et al., 2017) Therefore, in order to isolate the social and executive components of referential communication from the underlying speech and motor components, we use a simple, forced-choice task in the present work.

Second, much of the existing work on referential communication has relied on a contrast between common ground information (mutually accessible to both interlocutors) and privileged ground information (accessible to only a single interlocutor) (e.g. Brown-Schmidt et al., 2008; Heller et al., 2008; Wardlow et al., 2014). The privileged ground condition traditionally uses stimuli that physically obstruct one partner’s view and as such, places high demands on visuospatial processing. Here, we contrast a novel “colorblind” condition with a visually-identical “sighted condition” in order to minimize experimental confounds and target social (rather than visual) perspective-taking.
Next, while deficits in executive function (EF) and working memory have been consistently demonstrated in bvFTD (Kramer et al., 2003; Libon et al., 2007), the relationship of these constructs with patients’ perspective-taking remains unclear (Bertoux et al., 2016). For example, while some work demonstrates that EF and theory-of-mind are closely related in bvFTD (Snowden et al., 2003), other work demonstrates that the two are independent and dissociable (Lough et al., 2006). To address this ongoing controversy, we adopt the widely accepted tripartite model of EFs described by Miyake and colleagues (Miyake et al., 2000), and separately probe the three postulated subdomains: mental set-shifting, information updating, and inhibition.

Finally, previous work, both in healthy and clinical populations, has focused primarily on gray matter (GM) contributions to language processing. However, white matter (WM) tracts also play a critical role in network activity by transmitting electrical signals across spatially separate brain regions. Therefore, even when GM regions are intact, synchronized network activity may be disrupted if there is significant WM damage. Accordingly, and because bvFTD is known to show significant WM disease (Agosta et al., 2012), we collect high-resolution diffusion tensor imaging. While the arcuate fasciculus (connecting Broca’s and Wernicke’s area) is the primary language-associated fiber pathway (Dick and Tremblay, 2012), we predict that additional tracts, including the uncinate fasciculus (connecting orbitofrontal and temporal cortices) will also mediate referential communication.

In sum, we hypothesize 1) bvFTD patients will have difficulty coordinating perspectives with a conversational partner during referential communication, 2) impairment will be related to some, but not all, domains of executive function, and 3) impairment will be related to disease in a prefrontal, social-executive network.
MATERIALS AND METHODS

Participants

Participants included 20 patients with bvFTD (16 male) and 20 healthy controls (14 male) who were demographically matched for age (t(38)=0.23, p=0.54), education (t(38)=0.74, p=0.47), and gender ($\chi^2(1)= 0.13, p=0.72$). See Table 4 for a summary of demographic and clinical characteristics. Patients with bvFTD were diagnosed by board-certified neurologists (M.G., D.J.I) using a consensus procedure and published criteria (Rascovsky et al., 2011). Patients were classified as non-aphasic by clinician judgment (following clinical examination and elicitation of speech samples), and any patients with symptomatic evidence of semantic variant primary progressive aphasia (svPPA, which can sometimes co-occur with bvFTD) were excluded from our sample. Alternative causes of cognitive difficulty (e.g. Alzheimer’s disease, hydrocephalus, stroke, or head trauma) were excluded by clinical exam, neuroimaging, and blood tests. As shown in Table 1, dementia severity in patients was assessed using the Clinical Dementia Rating, Global Score (CDR-Global Score) (Morris, 1993), as modified by the inclusion of two FTD-related scales (Knopman et al., 2011). Derived from a semi-structured patient interview, the global CDR assesses functional impairment across six domains using a 3-point scale: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. This is supplemented by domains querying language and social functioning. All patients scored in the mild to moderate range (range = [0.5, 2]; mean = 1.075). Informed consent was obtained from all participants according to a protocol approved by the University of Pennsylvania’s Institutional Review Board.

It is widely accepted that bvFTD is a heterogeneous disorder, with patients showing different behavioral profiles and corresponding patterns of neural atrophy.
Further inspection of individual patient profiles (e.g. examination of group boxplots and z-scores) suggested the presence of two subgroups within our patient sample.

Accordingly, we rank ordered our patients on the basis of overall performance (precise responses in the sighted and colorblind conditions, combined, see below) and divided the sample into two equal subgroups using a median split procedure. The resulting patient subgroups were matched for age (U=43.00, p=0.63), education (U=40.50, p=0.481), CDR-Global Score (U=26.00,p=0.075), and disease duration (U=44.00,p=0.684) (See Table 4).

<table>
<thead>
<tr>
<th>All Subjects</th>
<th>Patients (N=20)</th>
<th>Healthy Seniors (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.65 (9.10)</td>
<td>64.00 (11.05)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>16.30 (2.77)</td>
<td>15.75 (2.12)</td>
</tr>
<tr>
<td>Disease Duration</td>
<td>4.50 (3.24)</td>
<td>N/A</td>
</tr>
<tr>
<td>Clinical Disease Rating, Global Score</td>
<td>1.08 (0.54)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Subgroups</th>
<th>Poor (n=10)</th>
<th>Good (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.00 (4.52)</td>
<td>66.30 (12.18)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>16.00 (3.13)</td>
<td>16.60 (2.50)</td>
</tr>
<tr>
<td>Disease Duration (years)</td>
<td>3.80 (1.62)</td>
<td>5.2 (4.28)</td>
</tr>
<tr>
<td>Clinical Disease Rating, Global Score</td>
<td>1.3 (0.48)</td>
<td>0.85 (0.53)</td>
</tr>
</tbody>
</table>

**Table 4. Demographics for Experiment 2.** Mean (±SD) demographic information for behavioral variant frontotemporal degeneration and control groups.

**Neuropsychological Battery**
Patients were administered a targeted neuropsychological battery including both language and executive measures. Language measures included the Boston Naming Test (BNT; Kaplan et al., 1983), a confrontational naming test using a series of line drawings that are graded in difficulty, and a semantic word-picture matching task (Rogalsky et al., 2011), in which subjects are asked to identify which of two pictures represents a given word. These measures were normalized to 100 and subsequently averaged to yield the Language Composite. Executive measures were chosen to probe the three postulated subdomains of executive function, as described by Miyake et al. (2000). Mental set-shifting was assessed using the Visual-Verbal Test (Feldman and Drasgow, 1960), which requires subjects to identify two unique but partially-overlapping groupings from a given set. Information monitoring and updating (i.e. working memory) was assessed using the Backward Digit Span (Wechsler, 1997), which requires subjects to repeat an orally presented sequence of numbers in reverse order. Finally, inhibition of prepotent responses was assessed using the Disinhibition Subscore of the Neuropsychiatric Inventory (NPI-Disinhibition), which is a caregiver-based instrument assessing the frequency and severity of neuropsychiatric symptoms in a patient (Cummings, 1997). Finally, perspective-taking ability was assessed using the Perspective-Taking subscore of the Interpersonal Reactivity Index, an informant-based measure with 28 items assessing 4 domains of empathy (empathic concern, personal distress, fantasy, and perspective-taking) (Davis, 1983).

**Experimental Design and Statistical Analyses**

Participants were presented with brief, two-scene stories illustrating the movement of a target cartoon animal. On each trial, the target animal was moved from the floor to a shelf (i.e. a three by four array) of objects that shared some combination of
color, size, and pattern features with the target (see Figure 1). The participants’ task was to successfully communicate which animal in the final array had been moved. An avatar visible behind the shelves represented a human interlocutor. Participants were given a multiple-choice selection of adjectives below each stimulus to describe the target animal that had been moved. The multiple-choice selection consisted of a probe and four fill-in-the-blank answer choices. Participants were instructed to select the best response that would correctly distinguish the target animal, without using any unnecessary descriptors. Answer choices varied in the number and type of adjectives, but all answers referenced the correct species of animal. Answer choices were classified according to response type: precise, superfluous, insufficient, irrelevant, and violations. Precise responses constitute the optimal response, using only those adjectives that are necessary and no additional adjectives. Superfluous responses, while accurate, were defined as responses using an excess number of adjectives and therefore requiring gratuitous effort by both speaker and listener (e.g. for the target “red pig,” selecting “big red pig”). Insufficient responses are responses using too few adjectives (e.g. for the target “red pig,” selecting “pig”). In practice, insufficient responses lead to ineffective communication, as the avatar would be unable to identify the target animal. Irrelevant responses used the correct number of adjectives, but like insufficient responses, lacked critical adjectives necessary to distinguish the target object from its competitor(s) (e.g. for the target “red pig,” selecting “big pig” even though all the pigs in the array are the same size). Finally, violations used a factually incorrect adjective (e.g. for the target “red pig,” selecting “yellow pig”).

Trials varied in two dimensions. First, in order to manipulate perspective-taking demand, trials varied in the amount and type of information accessible to the avatar. In “sighted” trials, the avatar had full access to visual information. The sighted condition is
thus analogous to the common ground condition in previous research. In “colorblind” trials, on the other hand, the avatar was described as colorblind and seeing only in black-and-white/grayscale. In each of the colorblind trials, the target animal was unique in at least two dimensions, one of which was always color. Therefore, to correctly identify the target animal, the subject would have to reject the color-based answer in favor of the answer that referred to shape and/or size. This condition is thus analogous to a “privileged ground” condition, where there is unequal access to information between the two partners that must be taken into account when selecting the appropriate attributes. Our colorblind condition, however, better mirrors the type of perspective-taking typically engaged in daily conversation, compared to the traditional privileged ground conditions that involve a physical obstruction and significant visuo-spatial processing.

Second, in order to manipulate working memory demands, the stimuli also differed according to the number of competitors (i.e. animals of the same species, such as “pigs” or “elephants”) present in the array (0, 1, or 3). The number of competitors visible in the array thus determined the number of adjectives necessary for the participant to adequately distinguish the target animal when describing its movement to the avatar. Please see Figure 7 for an illustration of stimulus materials.

There were eight stories for each level of competitor for each condition, with a total of 48 stimuli equally distributed across conditions. Stimuli were presented in a pseudo-randomized order in order to ensure that a single condition (e.g. colorblind, 3-competitors) was not repeated across consecutive trials. Repetition of trial type could encourage perseveration or the formation of alternative strategies and heuristics, rather than online perspective-taking. In order to ensure comprehension of task instructions, subjects were trained prior to testing and given feedback on practice items. All
participants appeared to understand the task. In total, task administration took approximately one hour.

Subject responses were digitally recorded and classified according to response type: precise, superfluous, insufficient, irrelevant, or violation. Individual subject scores were then generated by dividing the number of responses given for each type (i.e. precise, superfluous, etc.) by the total number of trials in the given condition (or the experiment as a whole, as appropriate). Precise and superfluous responses were also summed to create an overall accuracy score, since both types of responses would allow the avatar to correctly identify the target animal.

We used non-parametric statistics to analyze behavioral performance, as all data were not normally distributed according to Shapiro-Wilks tests. Between-group comparisons used Mann-Whitney tests, and within-group comparisons used Wilcoxon tests. Correlation analyses were calculated using the Spearman method. All results were corrected for multiple comparisons using the Bonferroni procedure.
Figure 7. Design of Experiment 2. Participants were presented two-scene stories in which a target animal moves from one location to another. Above are two stimuli from two conditions (A: sighted, B: colorblind). The stimuli also vary in the number of competitors (i.e. animals of the same species as the target) visible in the scene (A and B both have 1 competitor). Participants were presented with a multiple-choice item below each stimulus, consisting of a probe and four fill-in-the-blank answer choices. Participants were asked to select the correct response that would identify the target (for the avatar visible behind the shelves) while using the minimal numbers of descriptors. The precise response for each trial is denoted with a single asterisk (*) and the superfluous response with a double asterisk (**).
Structural Imaging Procedure and Analysis

High-resolution volumetric T1-weighted MRI was available for 18 bvFTD patients (Note: these 18 patients did not differ from the original 20-patient cohort for all demographic variables and experimental outcomes, all p-values >0.5). MRI images were not available for two individuals with bvFTD (one “good” performer and one “poor” performer) for health and safety reasons, including claustrophobia and metallic implants (e.g. pacemakers, shrapnel) in the body. MRI volumes were acquired using an MPRAGE sequence from a SIEMENS 3.0T Trio scanner with an 8-channel head coil and the following acquisition parameters: repetition time=1620 msec; echo time=3.87 msec; slice thickness=1.0 mm; flip angle=15°; matrix=192×256, and in-plane resolution=0.9766×0.9766 mm. Whole-brain MRI volumes were preprocessed using Advanced Normalization Tools (https://github.com/ANTsX/ANTs) using the state-of-the-art antsCorticalThickness pipeline described previously (Avants et al., 2008; Klein et al., 2010; Tustison et al., 2014). Briefly, processing begins by deforming each individual dataset into a standard local template space. A diffeomorphic deformation was used for registration that is symmetric to minimize bias toward the reference space for computing the mappings, and topology-preserving to capture the large deformation necessary to aggregate images into a common space. Template-based priors are used to guide GM segmentation and compute GM probability, which reflects a quantitative measure of GM density. Resulting images are warped into MNI space, smoothed using a 2 sigma smoothing kernel and down-sampled to 2 mm resolution, which best reflects average cortical thickness across the brain and is often required to achieve statistical significance.

Permutation-based imaging analyses were performed using the randomise tool in FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki). Briefly, permutation-based t-tests evaluate a true
assignment of GM density across groups (signal) relative to many (10,000) random assignments of GM density across groups (noise) and thus is a statistically robust procedure that is much less susceptible to multiple comparisons problems compared to traditional parametric-based t-tests (Winkler et al., 2014). GM density was compared in patients relative to an independent cohort of 36 healthy age and education-matched controls from the surrounding community (age: mean = 62.36, sd = 7.35, p=0.4117; education: mean = 15.79, sd=2.17, p=0.36). Analyses were run with 10,000 permutations and restricted to voxels containing GM using an explicit mask generated from the average GM probability map of all groups. We report clusters that survived a threshold of $p < 0.001$, correcting for multiple comparisons using the family wise error (FWE) rate and threshold-free cluster enhancement (Smith and Nichols, 2009). Results were projected onto the Conte69 surface-based atlas using Connectome Workbench (http://www.humanconnectome.org/software/connectome-workbench.html).

To relate behavioral performance to regions of significant GM disease, we conducted regression analyses with the randomise tool of FSL. Permutations were run exhaustively up to a maximum of 10,000 for each analysis. To constrain our interpretation to areas of known GM disease, we restricted our regression analyses to an explicit mask containing voxels of GM atrophy in the patients as defined in the above group comparison. Results outside these regions of atrophy would be difficult to interpret since they could be attributed to a variety of factors not related to disease (e.g. healthy aging, genetic differences). We report clusters surviving a height threshold of $p<0.005$ and a minimum of 10 adjacent voxels, a joint threshold suggested for optimal balance of Type I and Type II error rates (Lieberman and Cunningham, 2009). Covariates were run separately for the sighted condition, colorblind condition, and Visual-Verbal Test. Conjunction analyses were conducted in FSL to identify significant
regions that were common to different tasks (i.e. sighted and VVT, colorblind and VVT). All regression results were projected onto slices using MRICron software (Rorden and Brett, 2000).

**Diffusion Tensor Imaging Procedure and Analysis**

Diffusion tensor imaging was available for the same 18 bvFTD patients with T1 imaging. A 30-directional DWI sequence was collected using single-shot, spin-echo, diffusion-weighted echo planar imaging (FOV=240 mm; matrix size =128x128; number of slices = 70; voxel size = 1 mm isotropic, TR = 8100 ms; TE = 83 ms; fat saturation). Thirty volumes with diffusion weight (b=1000 s/mm²) were collected along 30 non-collinear directions, and either one or five volumes without diffusion weight (b=0 s/mm²) were collected per subject. The PipeDream processing pipeline used ANTs (Tustison et al., 2014) and Camino (Cook et al., 2006) to preprocess DWI. Motion and distortion artifacts were removed using affine co-registration of each diffusion-weighted image to the average of the unweighted (b= 0) images. Diffusion tensors were calculated using a weighted linear least-squares algorithm (Salvador et al., 2005) implemented in Camino. Fractional anisotropy (FA) was computed in each voxel from the DT image, and distortion between the subject’s T1 and DT image was corrected by registering the FA to the T1 image. DTs were then relocated to the local template for statistical analysis by applying the FA-to-T1 and T1-to-local template warps, and tensors were reoriented using the preservation of principal direction algorithm (Alexander et al., 2002). Each participant’s FA image was recomputed from the DT image in local template space and smoothed using a 2-sigma smoothing kernel.

Like the pipeline for GM analysis, we used the randomise tool in FSL to compare FA in patients relative to the same cohort healthy age-matched controls. The two-sample
t-test of patients vs. controls was run with 10,000 permutations and restricted to voxels containing WM based on an explicit mask of high probability WM (minimum FA considered WM = 0.25). Results were again thresholded at p<0.001 and corrected for multiple comparisons using FWE and threshold-free cluster enhancement. Regression analyses then related patient impairment to reduced FA, using covariates for sighted, colorblind, and VVT performances, respectively. These regressions were restricted to the results of the previous analysis—that is, only voxels showing a significant effect of group. Consistent with the GM analyses, we report only clusters surviving a height threshold of p<0.005 and a minimum of 10 contiguous voxels.

RESULTS

Behavioral Results in Patients

To examine overall performance in patients, we first examined the distribution of response types, collapsed across both sighted and colorblind conditions (Figure 8a). For the purposes of this analysis, we excluded 0-competitor trials as filler trials and only looked at 1-competitor and 3-competitor trials. These 0-competitor trials, which serve as a baseline measure, are excluded because they do not include all types of response types (Note: “insufficient” responses do not exist for 0-competitor trials. Because 0-competitor trials only require the animal species be named correctly, no modifying adjective is necessary and insufficient responses with too few adjectives are an impossibility). Here, we found that patients selected significantly fewer precise responses than matched control subjects (U=67.00, p<0.001). Instead, patients opted for significantly more superfluous responses (U=92.00, p=0.003). It is important to note that while superfluous responses are not the optimal, strategic choice, they still do provide
the requisite information needed for a communicative partner to correctly identify the
target animal. Patients with bvFTD also selected significantly more insufficient and
irrelevant responses than healthy controls, both of which lack critical, discriminating
adjectives (insufficient: U=96.00, p=0.004; irrelevant: U=93.50, p=0.03). Finally, as
expected, patients and healthy controls did not differ in regards to violations (U=190.00,
p=0.799). This null result for violations suggests that any deficit observed in patients with
bvFTD is not due to a baseline language or perceptual impairment. Additionally, to
confirm that age, disease severity, and language ability did not account for the
decrement in patient performance, we calculated Spearman correlations for performance
within each condition (sighted, colorblind) with age, disease duration, and Language
Composite Score (combined scored generated from BNT and word-picture matching).
No significant correlations were observed (see Table 5). Considered as independent
metrics, our language measures also confirm that our bvFTD patients are non-aphasic:
patients scored within normal limits on both the BNT (mean=25.35 out of 30) and word-
picture matching (mean=19.89 out of 20). Taken together, these data suggest patient is
impairment is due to the social and/or executive characteristics of the disease, rather
than overall cognitive status or language ability. Finally, we also correlated performance
in each condition with the Perspective-Taking subscore of the Interpersonal Reactivity
Index, finding a positive association for the colorblind condition but not sighted condition.
These data (see Table 5), showing the ability to adapt to the characteristics of the avatar
is dependent on general perspective-taking ability, support the ecological and construct
validity of our task.

For subsequent analyses, we focused on the precise response type, which
represents the optimal selection choice. Here, we observed that patients with bvFTD
offered significantly fewer precise responses than controls in both the sighted and
colorblind conditions (sighted: U=88.50, p=0.002; colorblind: U=72.00, p<0.001) (see Figure 8b). In healthy control subjects, a within-group comparison showed that there is a significant modulation of performance by condition, such that the rate of precise responses is significantly greater in the colorblind condition (Z=-2.98, p=0.003). This suggests that healthy controls engage in active perspective-taking behavior and use the additional information provided to them in the colorblind condition to improve their selection process. In contrast, patients show no difference in performance across the sighted and colorblind conditions (Z=-1.51, p=0.13).

Next, we considered the potential modulatory effect of competitor number on performance (Figure 8c). We interpret the increase in competitor number as a manipulation of working memory demand, since there are more objects to be maintained and manipulated during the visual search. Here, we found that patients select significantly fewer precise responses than healthy controls in all three conditions (0-competitor: U=71.00, p=<0.001; 1-competitor: U=77.00, p=0.001; 3-competitor: U=73.00, p<0.001). While this analysis thus suggests that patients are impaired even in the baseline 0-competitor condition, we point out that bvFTD patients perform at ceiling in regards to accuracy (a combination of precise and superfluous responses, both of which allow the conversational partner to correctly identify the target animal) (mean accuracy=99.06, sd=3.06). Additionally, in healthy controls, even though performance is consistently above chance, a Friedman test indicated that performance worsens with increasing competitor number, ($\chi^2(2) = 21.30, p<0.001$). Patients showed no such modulation ($\chi^2(2) = 0.11, p = 0.95$), suggesting that working memory demands are not responsible for the decrement in patient performance.
Figure 8. **Behavioral Results for Experiment 2.** A: Distribution of mean (±SEM) responses, collapsed across all conditions (Prec = precise, Sup = superfluous, Insuff = insufficient, Irr = irrelevant, Viol = violation). Patients select significantly fewer precise responses than healthy controls and significantly more superfluous, insufficient, and irrelevant responses. There is no group difference in violations. B: Mean (±SEM) precise responses in sighted and colorblind conditions. Patients select significantly fewer precise responses than healthy seniors in both conditions. C: Mean (±SEM) precise responses in 0-competitor, 1-competitor, and 3-competitor conditions. Patients select significantly fewer precise responses than healthy controls in all three conditions. For all figures, healthy controls are shown in dark gray and bvFTD patients are shown in light gray. * indicates significant at p<0.05. ** indicates significant at p<0.01.

<table>
<thead>
<tr>
<th></th>
<th>Mean±SD</th>
<th>Sighted</th>
<th>Colorblind</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td>64.65 (9.10)</td>
<td>ρ=0.21, p=0.37</td>
<td>ρ=0.21, p=0.37</td>
</tr>
<tr>
<td><strong>Disease Duration (y)</strong></td>
<td>4.50 (3.24)</td>
<td>ρ =-0.30, p=0.19</td>
<td>ρ=0.14, p=0.56</td>
</tr>
<tr>
<td><strong>Language Composite</strong></td>
<td>92.04 (6.72)</td>
<td>ρ =0.12, p=0.63</td>
<td>ρ=0.32, p=0.20</td>
</tr>
<tr>
<td><strong>Perspective-Taking (IRI)</strong></td>
<td>17.75 (18.75)</td>
<td>ρ =-0.24, p=0.36</td>
<td>ρ =-0.55, p=0.02*</td>
</tr>
</tbody>
</table>

**Table 5. Correlation Results for Experiment 2.** Correlations of age, disease duration, Language Composite, and Perspective-Taking Score with performance in the sighted and colorblind conditions. * indicates significant at p<0.05. ** indicates significant at p<0.01.
Neuropsychological Correlations

Next, to examine the neuropsychological mechanism underlying the observed patient deficits, we administered a targeted neuropsychological battery probing 3 domains of executive function, as described by Miyake et al. (2000): mental set-shifting, information updating (i.e. working memory), and inhibition. These were assessed using the Visual-Verbal Test, Backward Digit Span, and NPI-Disinhibition, respectively. We used Spearman correlations to relate each of these measures to performance in the sighted and colorblind conditions, separately. While patient performance was not significantly different between these conditions, it remains possible that different mechanisms underlie performance in each. In line with the earlier behavioral findings (i.e. no effect of competitor number), results indicated that working memory capacity was not related to performance in either the sighted or colorblind condition. The same null result was found for NPI-Disinhibition. Mental set-shifting, however, as assessed by the Visual-Verbal Test, showed a robust effect and was positively correlated with performance in both conditions, suggesting a specific role for mental-set shifting in referential communication. For all neuropsychological data, please see Table 6.

<table>
<thead>
<tr>
<th></th>
<th>Mean±SD</th>
<th>Sighted</th>
<th>Colorblind</th>
</tr>
</thead>
<tbody>
<tr>
<td>Backward Digit Span</td>
<td>4.15 (1.27)</td>
<td>ρ = -0.44, p = 0.07</td>
<td>ρ = -0.35, p = 0.16</td>
</tr>
<tr>
<td>Visual-Verbal Test</td>
<td>7.79 (2.51)</td>
<td>ρ = 0.85, p = &lt;0.001**</td>
<td>ρ = 0.59, p = 0.006**</td>
</tr>
<tr>
<td>NPI-Disinhibition</td>
<td>1.875 (2.16)</td>
<td>ρ = 0.16, p = 0.442</td>
<td>ρ = 0.049, p = 0.81</td>
</tr>
</tbody>
</table>

Table 6. Association with Executive Function in Experiment 2. Correlations of the three executive function subdomains with performance in the sighted and colorblind conditions. * indicates significant at p<0.05 ** indicates significant at p<0.01.
Subgroup Analyses in Patients

Next, we divided the patient cohort into two subgroups (good performers and poor performers) on the basis of a median split, using the overall precise responses performance metric. Within the sighted condition, a Kruskal-Wallis test indicated that there were significant differences among the 3 groups ($H(2)=17.71, p<0.001$). Post-hoc comparisons revealed no differences between the healthy controls and the good performers (sighted: $U=128.5$, $p=0.215$; colorblind: $U=123.5$, $p=0.293$). In contrast, the poor performers were significantly worse than the controls (sighted: $U=182$, $p<0.001$; colorblind: $U=198.5$, $p<0.001$) and also significantly worse than the good performers, as expected (sighted: $U=1.50$, $p<0.001$; colorblind: $U=8.50$, $p=0.001$). Please see Figure 9a for a visual depiction of results. To confirm that the differences in performance across subgroups was not a result of differential language ability, we also computed linear models. For both the sighted and colorblind models (run separately), group was a significant predictor (sighted: $\beta=-38.19$, $p=0.002$; colorblind: $\beta=-50.13$, $p=0.003$) while Language Composite was not (sighted: $\beta=-70.19$, $p=0.40$; colorblind: $\beta=-64.14$, $p=0.57$).

To understand why some patients were able to maintain performance at normal levels while others were not, we next compared the good and poor performers on the basis of their executive functioning. These data are consistent with the earlier correlation analyses: there was no significant difference between subgroups in regards to Backwards Digit Span ($U=60.00$, $p=0.49$) or NPI-Disinhibition ($U=37.00$, $p=0.58$), but there was a highly significant difference in regards to Visual-Verbal Test ($U=80.00$, $p<0.003$). Please see Figure 9b.
Figure 9. Performance across subgroups in Experiment 2. A: Mean (±SEM) precise responses in common ground and colorblind conditions for healthy controls (dark gray), good performers (medium gray), and poor performers (light gray). Poor performers select significantly fewer precise responses than good performers and healthy controls in both conditions. B: Mean backward digit span (BDS), Visual-Verbal test (VVT), and Neuropsychiatric Inventory-Disinhibition Subscore (NPI-DIS) scores (±SEM) in good performers (dark gray) and poor performers (light gray). While there are no significant differences BDS or NPI-DIS, good performers have significantly better VVT scores than poor performers. * indicates significant at p<0.05. ** indicates significant at p<0.01.
Structural MRI Results in All Patients

Next, we addressed the question of whether atrophy in patients with bvFTD is related to impaired social coordination during referential communication. First, we contrasted GM density in bvFTD patients relative to an independent cohort of healthy controls. As expected, this analysis revealed significantly reduced GM density throughout the frontal lobes and anterior temporal lobes in bvFTD patients, consistent with disease diagnosis (please see Figure 10 and Table 7). To relate discourse deficits to GM density, we performed a regression analysis in the patient group, using the percent precise responses in the sighted and colorblind conditions as covariates in two separate analyses. The results were largely consistent across conditions, with similar effects found in the medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), and dorsolateral prefrontal cortex (DLPFC), as well as insula. Within DLPFC, Brodmann Area (BA) 46 was related to performance in the sighted condition, while Brodmann Area 9, which is anterior to BA46, was related to colorblind performance. Finally, the colorblind condition also show a unique relationship with inferior frontal gyrus pars triangularis. Please see Figure 11 and Table 8.

Given the neuropsychological findings and the purported role of mental-set shifting in referential communication, we also related performance on the Visual-Verbal test to GM atrophy (please see Table 8), and compared this to our previous imaging findings from both the sighted and colorblind conditions. Any overlap (sighted-VVT or colorblind-VVT) could be interpreted as evidence of a common neural correlate across tasks. Indeed, for the sighted condition, we found overlapping results throughout prefrontal cortex: OFC, mPFC, and DLPFC. Similarly, overlapping results between the Visual-Verbal test and colorblind performance were found in portions of OFC, mPFC,
and insula. These data again suggest that referential communication involves mental set-shifting. See Figure 12 and Table 9 for conjunction results.

Diffusion Tensor Imaging Results in All Patients

To our knowledge, the majority of studies on referential communication and other examples of language-based coordination tasks have focused primarily on the role of GM regions. In the current study, we adopted a multimodal approach and also collected high-resolution diffusion tensor imaging to examine the possible involvement of white matter projections across the brain. As illustrated in Figure 13 and Table 10, we found significantly reduced FA in portions of the corticospinal tract, corpus callosum, inferior longitudinal fasciculus, and uncinate fasciculus in bvFTD relative to healthy age-matched controls. In a series of post-hoc regression analyses, we identified significant associations between FA and performance in the uncinate fasciculus and corpus callosum, for each sighted, colorblind, and VVT. FA was also significantly associated with colorblind performance in WM of inferior frontal gyrus, and with VVT performance in the inferior fronto-occipital fasciculus.
Figure 10. Structural Neuroimaging Results for Experiment 2. Surface renderings depicting regions of significantly reduced gray matter density in bvFTD patients relative to age-matched healthy controls. Heat map intensity refers to t-statistic value.

<table>
<thead>
<tr>
<th>Neuroanatomic Region (BA)</th>
<th>L/R</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>t-stat</th>
<th>voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>temporal pole (38)</td>
<td>L</td>
<td>-30</td>
<td>16</td>
<td>-32</td>
<td>9.16</td>
<td>37,306</td>
</tr>
<tr>
<td>inferior frontal gyrus (47)</td>
<td>L</td>
<td>-24</td>
<td>12</td>
<td>-22</td>
<td>8.50</td>
<td>sub</td>
</tr>
<tr>
<td>insular cortex (13)</td>
<td>L</td>
<td>-32</td>
<td>24</td>
<td>6</td>
<td>8.43</td>
<td>sub</td>
</tr>
<tr>
<td>orbitofrontal cortex (47)</td>
<td>L</td>
<td>-30</td>
<td>34</td>
<td>-16</td>
<td>8.27</td>
<td>sub</td>
</tr>
<tr>
<td>anterior cingulate cortex (32)</td>
<td>R</td>
<td>0</td>
<td>36</td>
<td>14</td>
<td>8.15</td>
<td>sub</td>
</tr>
<tr>
<td>medial prefrontal cortex (11)</td>
<td>R</td>
<td>2</td>
<td>44</td>
<td>-16</td>
<td>7.75</td>
<td>sub</td>
</tr>
</tbody>
</table>

Table 7. MNI Coordinates for Experiment 2 Imaging Results. Peaks and subpeaks of reduced gray matter density in patients with behavioral variant frontotemporal degeneration. BA, Brdomann Area; MNI, Montreal Neurological Institute; sub, subpeak.
Figure 11. Condition-Specific Neuroimaging Results for Experiment 2. A: Yellow regions represent regions of reduced gray matter density related to performance in sighted trials. B: Green regions represent regions of reduced gray matter density related to performance in colorblind trials. Both A and B: Red regions represent areas of significantly reduced gray matter density in patients with behavioral variant frontotemporal degeneration relative to healthy controls.
### MNI Coordinates

<table>
<thead>
<tr>
<th>Neuroanatomic Region (BA)</th>
<th>L/R</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>t-stat</th>
<th>voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Clusters of reduced gray matter density related to sighted performance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dorsolateral prefrontal cortex (45)</td>
<td>L</td>
<td>-44</td>
<td>36</td>
<td>18</td>
<td>4.19</td>
<td>41</td>
</tr>
<tr>
<td>medial prefrontal cortex (11)</td>
<td>R</td>
<td>6</td>
<td>52</td>
<td>-14</td>
<td>3.59</td>
<td>21</td>
</tr>
<tr>
<td>orbitofrontal cortex (11)</td>
<td>R</td>
<td>10</td>
<td>44</td>
<td>-24</td>
<td>4.23</td>
<td>19</td>
</tr>
<tr>
<td>orbitofrontal cortex (11)</td>
<td>L</td>
<td>-10</td>
<td>44</td>
<td>-26</td>
<td>3.93</td>
<td>14</td>
</tr>
<tr>
<td>insula</td>
<td>L</td>
<td>-32</td>
<td>30</td>
<td>6</td>
<td>3.63</td>
<td>14</td>
</tr>
<tr>
<td>anterior cingulate cortex (32)</td>
<td>L</td>
<td>-4</td>
<td>50</td>
<td>4</td>
<td>3.40</td>
<td>10</td>
</tr>
<tr>
<td><strong>B. Clusters of reduced gray matter density related to colorblind performance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>orbitofrontal cortex (11)</td>
<td>L</td>
<td>-8</td>
<td>46</td>
<td>-24</td>
<td>4.51</td>
<td>34</td>
</tr>
<tr>
<td>medial prefrontal cortex (11)</td>
<td>R</td>
<td>6</td>
<td>52</td>
<td>-14</td>
<td>4.80</td>
<td>26</td>
</tr>
<tr>
<td>orbitofrontal cortex (11)</td>
<td>R</td>
<td>10</td>
<td>44</td>
<td>-22</td>
<td>4.24</td>
<td>24</td>
</tr>
<tr>
<td>dorsolateral prefrontal cortex (9)</td>
<td>L</td>
<td>-22</td>
<td>40</td>
<td>38</td>
<td>3.89</td>
<td>17</td>
</tr>
<tr>
<td>insula</td>
<td>L</td>
<td>-36</td>
<td>18</td>
<td>6</td>
<td>3.47</td>
<td>15</td>
</tr>
<tr>
<td>inferior frontal gyrus (45)</td>
<td>L</td>
<td>-52</td>
<td>38</td>
<td>2</td>
<td>5.66</td>
<td>11</td>
</tr>
<tr>
<td>insula</td>
<td>R</td>
<td>36</td>
<td>24</td>
<td>-10</td>
<td>3.49</td>
<td>10</td>
</tr>
<tr>
<td><strong>C. Clusters of reduced gray matter density related to Visual-Verbal test performance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>orbitofrontal cortex (11)</td>
<td>R</td>
<td>10</td>
<td>42</td>
<td>-24</td>
<td>5.48</td>
<td>97</td>
</tr>
<tr>
<td>insula</td>
<td>R</td>
<td>36</td>
<td>28</td>
<td>-4</td>
<td>5.63</td>
<td>84</td>
</tr>
<tr>
<td>orbitofrontal cortex (11)</td>
<td>R</td>
<td>22</td>
<td>32</td>
<td>-14</td>
<td>6.42</td>
<td>84</td>
</tr>
<tr>
<td>orbitofrontal cortex (11)</td>
<td>L</td>
<td>-12</td>
<td>40</td>
<td>-24</td>
<td>5.44</td>
<td>80</td>
</tr>
<tr>
<td>insula</td>
<td>R</td>
<td>32</td>
<td>18</td>
<td>6</td>
<td>5.02</td>
<td>53</td>
</tr>
<tr>
<td>caudate nucleus</td>
<td>R</td>
<td>10</td>
<td>10</td>
<td>6</td>
<td>5.17</td>
<td>52</td>
</tr>
<tr>
<td>insula</td>
<td>L</td>
<td>-32</td>
<td>14</td>
<td>4</td>
<td>4.01</td>
<td>41</td>
</tr>
<tr>
<td>insula</td>
<td>R</td>
<td>40</td>
<td>8</td>
<td>2</td>
<td>3.94</td>
<td>39</td>
</tr>
<tr>
<td>inferior frontal gyrus (45)</td>
<td>L</td>
<td>-30</td>
<td>30</td>
<td>8</td>
<td>3.75</td>
<td>39</td>
</tr>
<tr>
<td>inferior frontal gyrus (46)</td>
<td>L</td>
<td>-42</td>
<td>34</td>
<td>16</td>
<td>3.74</td>
<td>33</td>
</tr>
<tr>
<td>caudate nucleus</td>
<td>L</td>
<td>-10</td>
<td>14</td>
<td>2</td>
<td>4.46</td>
<td>22</td>
</tr>
<tr>
<td>medial prefrontal cortex (10)</td>
<td>R</td>
<td>14</td>
<td>44</td>
<td>10</td>
<td>4.86</td>
<td>18</td>
</tr>
<tr>
<td>anterior cingulate cortex (32)</td>
<td>L</td>
<td>-4</td>
<td>50</td>
<td>4</td>
<td>4.58</td>
<td>18</td>
</tr>
<tr>
<td>dorsolateral prefrontal cortex (9)</td>
<td>R</td>
<td>40</td>
<td>32</td>
<td>18</td>
<td>4.04</td>
<td>12</td>
</tr>
<tr>
<td>inferior frontal gyrus (46)</td>
<td>L</td>
<td>-46</td>
<td>46</td>
<td>4</td>
<td>4.04</td>
<td>10</td>
</tr>
</tbody>
</table>

**Table 8. MNI Coordinates for Experiment 2 Condition-Specific Results.** Regions of reduced gray matter density in patients with behavioral variant frontotemporal degeneration related to performance in sighted (A), colorblind (B), and Visual-Verbal test (C). BA, Brodmann Area; MNI, Montreal Neurological Institute.
Figure 12. Conjunction Analysis for Experiment 2. A. Conjunction of sighted (yellow) and VVT (blue) regressions. Overlap (i.e. regions where both tasks are significantly associated) is shown in orange. B. Conjunction of colorblind (“cblind”, green) and VVT (blue) regressions. Overlap is gain shown orange. See insets (labeled a, b) for close-up views of conjunction results in orbitofrontal and medial prefrontal cortex.
Table 9. MNI Coordinates for Experiment 2 Conjunction Analysis. Peak coordinates representing regions of overlap between sighted and VVT performance (A) and colorblind and VVT performance (B). BA, Brodmann Area; MNI, Montreal Neurological Institute.

<table>
<thead>
<tr>
<th>Neuroanatomic Region (BA)</th>
<th>L/R</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Conjunction of Sighted and VVT Performance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dorsolateral prefrontal cortex (46)</td>
<td>L</td>
<td>-42</td>
<td>38</td>
<td>12</td>
<td>23</td>
</tr>
<tr>
<td>orbitofrontal cortex (11)</td>
<td>R</td>
<td>10</td>
<td>42</td>
<td>-24</td>
<td>16</td>
</tr>
<tr>
<td>orbitofrontal cortex (11)</td>
<td>L</td>
<td>-6</td>
<td>42</td>
<td>-28</td>
<td>13</td>
</tr>
<tr>
<td>insula</td>
<td>L</td>
<td>-34</td>
<td>28</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>anterior cingulate cortex (32)</td>
<td>L</td>
<td>-2</td>
<td>50</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>medial prefrontal cortex (11)</td>
<td>R</td>
<td>6</td>
<td>52</td>
<td>-14</td>
<td>5</td>
</tr>
<tr>
<td>B. Conjunction of Colorblind and VVT Performance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>orbitofrontal cortex (11)</td>
<td>L</td>
<td>-8</td>
<td>40</td>
<td>-28</td>
<td>26</td>
</tr>
<tr>
<td>orbitofrontal cortex (11)</td>
<td>R</td>
<td>10</td>
<td>40</td>
<td>-24</td>
<td>21</td>
</tr>
<tr>
<td>insula</td>
<td>L</td>
<td>-34</td>
<td>14</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>insula</td>
<td>R</td>
<td>38</td>
<td>22</td>
<td>-12</td>
<td>10</td>
</tr>
<tr>
<td>medial prefrontal cortex (11)</td>
<td>R</td>
<td>6</td>
<td>50</td>
<td>-16</td>
<td>7</td>
</tr>
</tbody>
</table>

Figure 13. White Matter Imaging Results for Experiment 2. Slices depicting regions of reduced fractional anisotropy in bvFTD patients compared to healthy controls (red), overlaid by regions of reduced FA significantly related to task performance, as labeled. Sighted = yellow, Colorblind = green, VVT = blue. For all slices, z = -7.
<table>
<thead>
<tr>
<th>White Matter Projection</th>
<th>MNI Coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L/R</td>
</tr>
<tr>
<td>A. Regions of reduced FA in patients versus controls (red)</td>
<td></td>
</tr>
<tr>
<td>corticospinal tract</td>
<td>L</td>
</tr>
<tr>
<td>corpus callosum (frontal)</td>
<td>R</td>
</tr>
<tr>
<td>corpus callosum (frontal)</td>
<td>L</td>
</tr>
<tr>
<td>uncinate fasciculus</td>
<td>L</td>
</tr>
<tr>
<td>inferior longitudinal fasciculus</td>
<td>L</td>
</tr>
<tr>
<td>fusiform gyrus WM</td>
<td>L</td>
</tr>
<tr>
<td>B. Regions of reduced FA related to sighted performance in patients (yellow)</td>
<td></td>
</tr>
<tr>
<td>uncinate fasciculus</td>
<td>L</td>
</tr>
<tr>
<td>uncinate fasciculus</td>
<td>R</td>
</tr>
<tr>
<td>corpus callosum (frontal)</td>
<td>L</td>
</tr>
<tr>
<td>C. Regions of reduced FA related to colorblind performance in patients (green)</td>
<td></td>
</tr>
<tr>
<td>inferior frontal gyrus WM</td>
<td>L</td>
</tr>
<tr>
<td>inferior frontal gyrus WM</td>
<td>L</td>
</tr>
<tr>
<td>uncinate fasciculus</td>
<td>R</td>
</tr>
<tr>
<td>corpus callosum (frontal)</td>
<td>L</td>
</tr>
<tr>
<td>D. Regions of reduced FA related to VVT performance in patients (blue)</td>
<td></td>
</tr>
<tr>
<td>uncinate fasciculus</td>
<td>R</td>
</tr>
<tr>
<td>superior frontal gyrus WM</td>
<td>L</td>
</tr>
<tr>
<td>uncinate fasciculus</td>
<td>L</td>
</tr>
<tr>
<td>superior frontal gyrus WM</td>
<td>R</td>
</tr>
<tr>
<td>inferior fronto-occipital fasciculus</td>
<td>R</td>
</tr>
<tr>
<td>superior temporal gyrus WM</td>
<td>L</td>
</tr>
<tr>
<td>superior temporal gyrus WM</td>
<td>L</td>
</tr>
<tr>
<td>corpus callosum (frontal)</td>
<td>R</td>
</tr>
</tbody>
</table>

Table 10. MNI Coordinates for Experiment 2 Diffusion Tensor Imaging Results.
White matter tracts and peak coordinates of significantly reduced fractional anisotropy in bvFTRD patients compared to healthy controls (A) and regression of task performance with regions of reduced fractional anisotropy for sighted condition (B), colorblind condition (C), and VVT (D). MNI, Montreal Neurological Institute; sub, subpeak.
DISCUSSION

This study examined the cognitive and neuroanatomic bases of impaired referential communication in patients with bvFTD. Using a carefully-controlled experimental task, subjects were asked to indicate the movement of a target object to an interlocutor, who shared a variable amount of access to visual information. We found that bvFTD patients have deficits coordinating perspectives with a partner, due in part to deficits in mental flexibility and disease in a prefrontal network associated with social and executive functioning. These findings highlight the essential contribution of non-language brain regions to referential communication. We discuss our cognitive and anatomic results in turn below.

Referential communication is impaired in bvFTD

Overall, the behavioral results across both sighted and colorblind conditions indicated that bvFTD patients select significantly fewer precise responses than healthy controls, instead offering more superfluous, as well as insufficient and irrelevant responses. These results mirror the finding of decreased overall accuracy for bvFTD patients relative to controls on a task monitoring adjective use during overt speech production and using similar stimulus materials (Healey et al., 2015). The patients’ frequent selection of superfluous responses—that is, responses which are over-specified and include excess adjectives—is considered suboptimal here because they violate the Gricean maxim of quantity (i.e. be as brief as possible) (Grice, 1975). While some research has found that the inclusion of extra information during communication can facilitate object identification and promote learning (Maes et al., 2004; Arts et al., 2011), other studies have demonstrated that over-specified referring expressions can actually impair comprehension (Arbuckle et al., 2000; Engelhardt et al., 2006, 2011). For
example, in an event-related potential study examining how listeners process object descriptions with unnecessary modifiers (e.g. “red square” in a context where only one square was displayed), healthy participants were slower to orient to the target object when unnecessary modifiers were used (Engelhardt et al., 2011). Furthermore, an N400 effect, thought to index semantic integration difficulties (Kutas and Hillyard, 1980; Kutas and Federmeier, 2011), emerged 200 to 300 milliseconds after modifier onset.

Unlike superfluous responses, insufficient and irrelevant responses are missing critical, discriminating adjectives that would be necessary for the interlocutor to correctly identify the target. In a real-world context, these responses, which bvFTD patients selected more frequently than controls, would constitute a failure to communicate effectively. Importantly, patients did not select more violation responses than healthy controls, indicating that lexico-semantic or visuo-spatial deficits are unlikely to contribute to impaired performance. It is unlikely that language impairment can explain the bvFTD deficit, as they are non-aphasic and generally demonstrate relatively preserved language skills. Indeed, when we tested for a relationship between our composite language score and performance on the coordination task, we found no significant effect.

Interestingly, healthy controls, who showed performance well above chance in both conditions, showed significantly better performance for colorblind trials compared to sighted trials. This pattern suggests that healthy controls acted strategically and used the condition information to eliminate incorrect options using color terms (and thereby increased the chance of a precise response). Such an explanation aligns well with the previous literature showing that older adults tend to show an increased use of heuristics when problem solving compared to younger adults, who rely more on online analytical reasoning (Johnson, 1990; Kim and Hasher, 2005; Klaczynski and Robinson, 2000;
Rydzewska et al., 2018; Worthy and Maddox, 2012). For example, using a computer-based sequential choice task, Rydzewska et al. (2018) found that older adults adopt compensatory strategies during complex decision-making tasks and reduce the number of options they consider over time, without sacrificing performance.

Patients with bvFTD, on the other hand, were insensitive to the difference between conditions and did not modulate their use of color adjectives in the same manner as healthy controls. While the finding that bvFTD patients are not significantly more impaired on colorblind trials may seem counter-intuitive, it is not unexpected. We note here that both the sighted and colorblind conditions require perspective-taking. The interesting question is not which condition is more difficult, but whether or not patients can adapt their responses to the specific demands of a given trial—using color terms as appropriate in sighted trials, but never in colorblind trials. Indeed, our data show that patients fail to consider the characteristics of their conversational partner when planning their response—a phenomenon known as recipient design (Blokpoel et al., 2012). The absence of a condition effect in bvFTD again suggests that this group consistently responds in a superfluous way.

**Referential communication is related to mental flexibility**

Although previous studies have consistently reported executive deficits in patients with bvFTD (Kramer et al., 2003; Rosen et al., 2004; Libon et al., 2007; Possin et al., 2013; Baez et al., 2016), there has been conflicting evidence regarding the relationship between social cognition and executive function (Lough et al., 2006; Eslinger et al., 2007; Le Bouc et al., 2012; Bertoux et al., 2016). It is possible that these discrepant findings are a result of examining different sub-domains of executive function. For example, Eslinger et al. (2007) used the Visual-Verbal Test to probe executive
function, while Le Bouc et al. (2012) used the Stroop test, Trailmaking Test, and verbal fluency to assess executive function. In the current study, by specifically probing each of the three postulated domains of executive function described by Miyake et al. (2000), we may be able to resolve this debate in the context of communication. We also explicitly manipulated working memory demands by systematically varying the number of competitors (i.e. objects sharing a perceptual feature with the target object) present in the array. Results showed that while patients were impaired relative to controls in the 0-competitor, 1-competitor, and 3-competitor conditions, there was no modulatory effect of competitor number, suggesting minimal contribution of working memory. It is important to point out here that although patients selected significantly fewer precise responses than controls in the baseline, 0-competitor condition, they were still highly accurate (accurate responses are either precise or superfluous, both of which allow the interlocutor to correctly identify the target). The persistent use of superfluous descriptors across all conditions is nevertheless suboptimal according to Grice’s (1975) maxim of quantity, and consistent with previous reports in bvFTD documenting speech that is tangential and/or lacks essential meaning (Ash et al., 2006; Barsuglia et al., 2014; Mendez et al., 2017).

If the resource demands associated with increasing competitor numbers does not appear to relate to performance, then what does? We collected a targeted executive battery, including measures of working memory, inhibition, and set-shifting, to examine if any executive resources are related to referential communication. As suggested by the null results of competitor conditions, our neuropsychological data confirm that working memory, as measured by the Backwards Digit Span, is not associated with performance in the sighted or colorblind conditions. These results add to the growing body of evidence that perspective-taking does not depend upon working memory per se, either
in healthy adults (Lin et al., 2010; Cavallini et al., 2013; Healey and Grossman, 2016; Cane et al., 2017) or in patients with bvFTD (Freedman et al., 2013; Bertoux et al., 2016). With some evidence for a positive relationship between working memory and perspective-taking also reported for both groups (Fizke et al., 2014; Torralva et al., 2015), more research on this topic is still needed.

Like working memory, we also found no evidence for a relationship between inhibitory control and social coordination. This is somewhat surprising, given that social perspective-taking is hypothesized to involve two major components: 1) inferring the perspective of the other and 2) inhibiting one’s own perspective (Leslie et al., 2004, 2005; Samson et al., 2007; Le Bouc et al., 2012). It is possible that the type of inhibitory control measured here by the NPI, which represents limited control of social behavior and comportment (e.g. inhibiting outbursts, inappropriate comments, etc.), is functionally distinct from the type of cognitive inhibitory control needed for the prescribed perspective-taking task. Indeed, other studies have claimed that individual differences in inhibition can predict perspective-taking abilities both across the lifespan (Carlson and Moses, 2001; German and Hehman, 2006; Brown-Schmidt, 2009; Nilsen and Graham, 2009; Long et al., 2018) and in disease states (Le Bouc et al., 2012; Schroeter et al., 2014). We do note, however, that previous work on the relationship between different types of inhibition has suggested that resisting distractor interference (likely what our referential communication task assesses) and inhibition of action (likely what the NPI assesses) are strongly correlated and cluster as a single factor in a latent-variable analysis (Friedman and Miyake, 2004). Regardless, additional work is needed to investigate these discrepant findings, likely using a more representative inhibitory control task, such as the Go/No-Go or Hayling Sentence Test.
Importantly, we did observe a robust relationship between mental set-shifting (i.e. performance on the Visual-Verbal test) and referential communication ability (both conditions). In confirmation of these results, we also found that our bvFTD subgroups, good and poor performers, were significantly different from one another in mental-set shifting, but not other EFs. Positive results may have been observed here because the Visual-Verbal test (Feldman and Drasgow, 1960) is particularly appropriate for use in clinical populations: it is brief, non-social, non-verbal, and has minimal motor demands (Eslinger et al., 2007; Evans et al., 2015). Other authors have found similar results concerning the role of mental set-shifting in social behavior. Eslinger and colleagues, for example, reported that performance on the Visual-Verbal Test was predictive of social dilemma judgments in patients with bvFTD (Eslinger et al., 2007). Previous studies have also found similar results using alternative tasks, including the Wisconsin Card Sorting Test (Torralva et al., 2009, 2015; Flanagan et al., 2018).

A multi-modal, prefrontal network for referential communication

To examine the neuroanatomic basis for referential communication deficits in bvFTD, we conducted a series of structural imaging analyses. Unlike most previous studies, we examine patterns of both GM atrophy and WM damage in order to build a large-scale, multi-modal network associated with successful social communication. Using a whole-brain approach, we found that patients with bvFTD show widespread reductions in GM density in the frontal and anterior temporal lobes compared to healthy controls, with peaks in the left temporal pole, OFC, insula, and anterior cingulate cortex. This pattern of atrophy is consistent with the diagnostic criteria for “probable” bvFTD (Rascovsky et al., 2011).
Subsequent analyses examined the potential role that these frontal and temporal regions may play in referential communication more specifically. Parallel regression analyses (using performance either in the sighted or colorblind conditions) showed largely consistent results across conditions, with positive associations found between performance and GM density in OFC, mPFC, DLPFC, and insula. These results are well-aligned with previous observations relating narrative expression (i.e. overt speech) to frontal brain regions (Healey et al. 2015).

Our principal finding suggests primary roles for OFC and mPFC in cortical networks supporting referential communication. Take first OFC, which has been previously implicated in studies of set-shifting and cognitive flexibility (Badre and Wagner, 2006; Dajani and Uddin, 2015), as well as a range of social behaviors, including emotion and reward processing (Viskontas et al., 2007). Theories of OFC function suggest that this area contributes broadly to networks for everyday decision-making, including the ability to adapt to new environmental contingencies and reverse previous stimulus-reinforcement associations (Murray et al., 2007; Wallis, 2007). In the current paradigm, then, OFC damage may relate to the patients’ inability to adjust their strategy and use of color-based responses according to the given condition. Offering converging evidence for this interpretation is the finding of a common neural substrate for referential communication and VVT, both associated in part with OFC.

Proximal but dorsal to the observed OFC cluster is mPFC, a region included in networks for self-referential processing, perspective-taking, and theory of mind (ToM) (Gallagher and Frith, 2003; D’Argembeau et al., 2007; Van Overwalle, 2009) We note here that the observed cluster is located in the ventral portion of mPFC, a location that is sometimes considered overlapping or interchangeable with OFC in the clinical literature (Zald and Andreotti, 2010). Furthermore, some previous research suggests that the
mPFC functions may vary in part along a dorsal-ventral axis, such that ventral mPFC is involved in affective ToM and dorsal mPFC in cognitive ToM (Abu-Akel and Shamay-Tsoory, 2011). Given this perspective, additional work is still needed to clarify the organization of mPFC, as our cluster is predominantly ventral but our task predominantly cognitive. Alternatively, our data may be consistent with theories of mPFC suggesting that ventral portions are engaged during generation of explicit inferences about others (as required here), whereas dorsal portions are engaged during spontaneous or implicit inferences (Van Overwalle, 2009). Regardless, our findings are consistent with previous work demonstrating a role for vmPFC in social communication (Gordon et al., 2014; Healey et al., 2015; Spotorno et al., 2015; Stolk et al., 2015).

The observed results in DLPFC are also somewhat nuanced. Broadly speaking, the DLPFC is thought to subserve functions such as working memory, relational complexity, and selection amongst competing responses (Petrides, 2005; Badre and D’Esposito, 2007; Badre, 2008; Suzuki and Gottlieb, 2013), all of which are relevant to the task here. Although DLPFC was implicated in both the sighted and colorblind conditions, the relevant portions of DLPFC were somewhat unique: Brodmann Area 9 for sighted and Brodmann Area 46 for colorblind. These regions are thought to process different types of information. For example, Badre and others (2007, 2008) hypothesized a hierarchical rostro-caudal organization to the frontal lobes, such that more abstract information is processed in anterior regions and more concrete information in posterior regions. Our data are well-aligned with this account, as BA46, associated with colorblind performance, is anterior to BA 9, associated with sighted performance. The colorblind condition may be more abstract than the sighted condition, as it requires recognition of the avatar’s inability to appreciate color terms, a quality that is visually imperceptible and instead must be maintained in working memory. The sighted condition, on the other
hand, is more concrete, with all cues explicitly available in the color, size, and pattern features of the competing objects. Unsurprisingly then, it is the sighted condition that shows a preferential overlap with the VVT (which similarly requires no abstraction beyond the objective appearance of the stimulus sets).

Also related to aberrant referential communication was the insula, which has been previously implicated in bvFTD (Seeley, 2010; Mandelli et al., 2016). Previous work has suggested that the insula is involved in guiding goal-directed behavior in dynamic social contexts and/or detecting salient events (Menon and Uddin, 2010; Bernhardt and Singer, 2012; Gasquoine, 2014). Thus, the insula may play a domain-general role in communication, helping to detect salient features (i.e. an interlocutor’s affect, gender, or social status) against a busy and constantly changing environment.

We also note here that the colorblind condition showed a unique relationship with inferior frontal gyrus pars triangularis (BA 45), one of the primary nodes of the classic language network. While this region is known to be active in cases of semantic ambiguity and when syntactic demands are high (Rodd et al., 2005; Hagoort and Indefrey, 2014), our two conditions (sighted, colorblind) were perfectly matched in terms of semantic and syntactic load. Alternatively, our results seem to support previous work suggesting a role for the IFG in selection and interference resolution (Thompson-Schill et al., 2005; Nelson et al., 2009; Hagoort, 2014). Indeed, the colorblind condition is characterized by two opposing responses: both using the minimum number of requisite adjectives and identifying the target correctly, but one referring to color (to be rejected) and one referring to color or size (to be selected).

Finally, because diseases like FTD are thought to be network-based (Seeley et al., 2009; Pievani et al., 2011), our last set of analyses examined the role that WM tracts may play in social perspective-taking. Our analyses suggested that the unicinate
fasciculus, which connects OFC to portions of the anterior temporal lobe and is broadly involved in social-emotional processing (Von Der Heide et al., 2013), may also be involved in referential communication. This result, which is consistent across sighted and colorblind condition, as well as VVT, corresponds well to previous work showing that damage to the uncinate is predictive of bvFTD diagnosis (Agosta et al., 2012; Mahoney et al., 2014) and associated with both impaired sarcasm identification (i.e. another example of language-based social coordination) and altered emotional empathy (Downey et al., 2015; Oishi et al., 2015). While early research on the language connectome focused primarily on the arcuate fasciculus (part of the superior longitudinal fasciculus connecting Broca’s and Wernickes area), the uncinate has also been included as part of the ventral stream in contemporary models (Dick et al., 2014), with some evidence demonstrating that it plays a role in semantic processing and naming (Agosta et al., 2010; Catani et al., 2013). According to our data, and given its physical architecture (i.e. the regions it traverses and connects), the uncinate likely plays a key role in daily communication by facilitating cross-talk between the social and language networks.

Caveats and Future Directions

While the findings described here are robust, several caveats should be kept in mind when interpreting our results. Although we were able to test a relatively large group of rare patients, our cohort was not pathologically confirmed and we did not have a brain-damaged control group, both of which would improve the specificity of our results. fMRI and/or rTMS studies in healthy adults using the same stimulus materials could offer converging evidence for our findings from an independent source. Next, while we are able to contribute to the ongoing debate regarding the relationship between
executive function and social cognition in bvFTD, we did not examine comparative performance in younger adults, which would have helped us form a comprehensive model of referential communication in both healthy aging and disease. Similarly, we are unable to comment on the potential effects of gender or individual differences in attention. Finally, although previous work has demonstrated that language processing is comparable when interacting with a human-like avatar compared to a human partner (Heyselaar et al., 2017), the paradigm we developed used an avatar to represent a conversational partner. Future work might have greater ecological validity with truly interactive exchanges involving two human partners.

With these caveats in mind, the results of the present study support the view that impaired social coordination abilities in bvFTD are clearly evident in a novel referential communication task that carefully minimizes external task demands. Furthermore, the observed communicative impairment is due in part to limitations in mental set-shifting and involves degradation of a prefrontal gray and white matter network that extends beyond the traditional, left peri-Sylvian language network.
CHAPTER 4: Beyond Broca: Extra-Sylvian networks support speech act comprehension in behavioral variant frontotemporal dementia

Meghan Healey, Erica Howard, Molly Ungrady, Christopher Olm, David J. Irwin, Murray Grossman.

ABSTRACT

Indirect speech acts—responding “I forgot to wear my watch today” to someone who asked for the time— are ubiquitous in daily conversation, but cannot be easily explained by current models of language neurobiology. To comprehend an indirect reply like this one, listeners must not only decode the lexico-semantic content of the utterance, but also make a pragmatic, bridging inference. This inference allows listeners to derive the speaker’s true, intended meaning—in the above dialogue, for example, that the speaker cannot provide the time. In the present work, we address a major gap in traditional models of language neurobiology by examining this highly common but often overlooked inferential component. To do so, we developed a novel question-answer paradigm that assesses speech act comprehension in a conversational context. Adopting a patient-lesion model approach, we study both non-aphasic patients with behavioral variant frontotemporal dementia (bvFTD) and brain-damaged controls with amnestic mild cognitive impairment (MCI). Results demonstrate that bvFTD, but not MCI, subjects are selectively impaired in indirect relative to direct reply comprehension, due in part to their social and executive limitations. High-resolution structural MRI imaging associates the observed impairment in bvFTD not only to traditional language-associated regions, but also to fronto-parietal regions implicated in social brain and executive networks. Finally, diffusion tensor imaging analyses implicate white matter tracts in both dorsal and ventral projection streams, including superior longitudinal fasciculus, frontal aslant, and uncinate fasciculus. These results have strong
implications for updated models of language neurobiology and treatment studies in neurodegenerative patients.
INTRODUCTION

“The chief end of language in communication is to be understood, and words don’t serve well for that end—whether in everyday or in philosophical discourse—when some word fails to arouse in the hearer the idea it stands for in the mind of the speaker.”


To paraphrase the famed English philosopher John Locke, human communication does not depend on decoding the individual meanings of words per se, but rather decoding the speaker’s idea represented by those words. Indeed, we do not communicate by volleying single words back and forth in isolation: we communicate through stories, narratives, and conversations (Bell, 2002; Kellas, 2005). This is a critical point that bears significant implications for the experimental methodology adopted by neuroscientists and the theoretical frameworks they endorse in studying language. From this perspective, the methodology we have used to date—studying the neural basis of phonology, morphology, syntax, and semantics—may be too narrowly focused, as these elements alone are often insufficient for comprehension. Instead, when we consider language in an interactive real-world context—as language for communication—we recognize that language is polysemous and consequently, listeners must make pragmatic, bridging inferences in order to derive a speaker’s true meaning. In the present study, we address this major gap in traditional models of language neurobiology by focusing on the highly common but oft overlooked inferential component of conversational speech.
Indirect speech acts, which are ubiquitous in daily communication, are a canonical example of natural, inferential language. Consider, for instance, if Sally asks Betty, “Do you want some cake for dessert?” and Betty sadly replies, “I’m on a very strict diet right now.” In the given exchange, Sally can easily infer that Betty is declining the cake, even though it is not explicitly stated in her reply. Interestingly, although indirect speech epitomizes the resource-demanding, socially-constrained nature of language, its processing appears to be both quick and effortless (Clark, 1979). Still unknown, however, is how the brain accomplishes this remarkable feat: what are the cognitive and neural substrates of indirect speech act comprehension?

Historical investigations into the neurobiology of language have typically been limited to studies of speech sounds, words, and sentences. Pioneered by the physicians Paul Broca and Carl Wernicke, the resulting “Wernicke-Lichtheim-Geschwind” (WLG) model emphasizes two primary hubs in left hemisphere peri-Sylvian cortex: the inferior frontal gyrus, specific for language production, and the posterior superior temporal gyrus, specific for language comprehension. While we have now developed a more nuanced understanding of the contributions of these brain regions in supporting language, the WLG cannot fully account for the complexities of real-world language and communication—how we integrate utterances with prior context so effortlessly, make inferences about speaker meaning, and engage in the rapid back and forth of conversation (Tremblay and Dick, 2016; Hasson et al., 2018).

More recently, we have begun to study natural language discourse—that is, the social use of language, or language for communication. Discourse typically has a suprasentential structure, and consequently, may require additional neurocognitive resources to disambiguate meaning.
Surprisingly little attention, however, has been paid to indirect speech acts like the one above—communicative exchanges in which the intended speaker meaning is not directly coded in the lexico-semantic content of the utterance itself (Grice, 1975; Searle, 1975). To address this major gap in natural language use, we study indirect replies, a subtype of indirect speech that boasts several theoretical advantages: 1) they are relatively short and can be tightly controlled, unlike lengthy narratives; 2) their meaning does not become “frozen” due to repeated usage, as with metaphors, idioms, or proverbs; 3) they do not have an affective component, which typically characterizes irony and sarcasm; and 4) they involve an interactive exchange between speakers, which reflects how language is most commonly used. With these factors in mind, we developed a novel, question-answer paradigm manipulating inferential demand—whether a reply is conveyed directly or indirectly.

Unlike previous fMRI studies in healthy adults (Shibata et al., 2011; Basnáková et al., 2013; Jang et al., 2013; Feng et al., 2017), which are limited due to their correlative nature, we use a patient lesion-model to examine the neurobiological basis of indirect speech. Here, we study patients with behavioral variant frontotemporal dementia (bvFTD), who constitute an ideal cohort to study deficits in “real world” communication (Grossman, 2018). A young-onset neurodegenerative disease, bvFTD is characterized by changes in social comportment, personality, and executive function due to disease in frontal and temporal cortices. Importantly, while patients are grossly non-aphasic, they may show deficits at the discourse level of language: previous research has demonstrated that bvFTD speech is marked by poor narrative organization and limited appreciation of global meaning, abnormal prosody, simplified grammatical structures, and a reliance on concrete concepts and literal meaning (Ash et al., 2006; Farag et al., 2010; Charles et al., 2014; Cousins et al., 2017; Nevler et al., 2017).
Based on previous work from our laboratory and others, we predict that non-aphasic bvFTD patients will show deficits in indirect speech related in part to disease in brain regions associated with an “extended language network” encompassing social, executive, and language regions (Ferstl et al., 2008). We hypothesize further that critical white matter tracts linking these linguistic and extra-linguistic regions may also be disrupted in bvFTD. While the initial WLG model posited only a single white matter tract for language—the arcuate fasciculus, connecting Broca’s and Wernicke’s areas—more recent work has suggested that multiple tracts, including the superior longitudinal fasciculus, inferior longitudinal fasciculus, and uncinate fasciculus, are also critically involved (Saur et al., 2008; Friederici, 2015; Vassal et al., 2016). It is these tracts that would permit the traditional language network to interact with extra-Sylvian regions—namely, the executive control and social brain networks that are believed to play a role in discourse processing. Accordingly, and given that bvFTD is known to shown significant WM disease (Agosta et al., 2012), we adopt a multimodal approach and use a combination of high-resolution structural magnetic resonance imaging (sMRI) and diffusion tensor imaging (DTI) to expand our understanding of the neural correlates of real-world communication.

MATERIALS AND METHODS

Participants

Participants included 21 patients with bvFTD, 17 age and education-matched healthy controls, and 17 brain-damaged controls with amnestic mild cognitive impairment (MCI). See Table 1 for a summary of demographic and clinical characteristics. All patients (bvFTD, MCI) were diagnosed by board-certified neurologists.
(M.G. and D.J.I.) using published criteria and a consensus procedure (Albert et al., 2011; Rascovoy et al., 2011). As some bvFTD patients may develop language deficits associated with semantic variant primary progressive aphasia (svPPA), any patients with symptomatic evidence of svPPA or a score greater or equal to 1 on the Language Supplement of the Clinical Dementia Rating Scale (CDR) (Knopman et al., 2011) were excluded from the sample population. We note here that we chose MCI as our brain-damaged control group rather than svPPA since we wanted all patients to be non-aphasic and capable of performing the discourse task at a reasonable level of proficiency and without obvious language-related deficits. All alternative causes of cognitive difficulty (e.g. vascular dementia, hydrocephalus, stroke, head trauma, primary psychiatric disorders) were excluded by clinical exam, neuroimaging, CSF, and blood tests. As summarized in Table 1, severity of overall cognitive impairment was assessed in patients using the Mini-Mental State Examination (MMSE). On average, patient scores fell in the mild range. Healthy control subjects were verified through negative self-report of a neurological and psychiatric history and a score of greater than or equal to 28 on MMSE. All subjects were recruited from the Penn Frontotemporal Degeneration Center and gave informed consent according to a protocol approved by the Institutional Review Board at the University of Pennsylvania.

Experimental Design and Statistical Analyses

The stimulus materials consisted of 120 question-answer dialogues (60 experimental items and 60 filler items of similar structure). All questions were polar, such that the expected answer was either “yes” or “no.” Stimuli were presented as printed text in order to avoid any confounds introduced by prosodic cutes inherent in the speech stream.
Each question (n=30) was associated with two different replies, which systematically varied according to inferential demand (direct, indirect). The 60 filler items used the same questions, but presented both the indirect and indirect replies in succession (30 provided the direct reply first, and 30 provided indirect reply first). The filler items will not be discussed further here. See Table 12 for a description of each condition and sample stimuli. Note that indirect replies, as operationalized here, are equivalent to Grice’s notion of “conversational implicatures” (Grice, 1975).

Stimuli were carefully constructed to minimize linguistic variation within and across conditions. The direct and indirect items were matched within each item for number of syllables, mean word frequency (Brysbaert and New, 2009), and mean concreteness (Brysbaert et al., 2014). For word frequency and concreteness, a mean score was generated for each sentence by averaging across the individual scores of each content word. This careful matching procedure is meant to ensure that any differences in processing direct and indirect items are due to the manipulation of inferential demand, and not to any differences in linguistic difficulty.

Stimulus presentation, timing, and responses were controlled via E-Prime presentation software. On each trial, a fixation cross was presented (3 seconds), followed by the question (3 seconds), and then reply (3 seconds). The question remained on the screen as the reply appeared, in order to reduce any working memory demands. Following each trial, subjects were presented a probe: “Does the reply mean yes or no?” and given 10 seconds to respond via button press. Response accuracy and response time were recorded for each condition. Items were counterbalanced so that half the replies had a positive connotation (i.e. mean “yes”) and half the replies had a negative connotation (i.e. mean “no”). Participants were trained prior to testing and completed 12 practice trials. In total, task administration took approximately one hour.
We assessed performance using two independent metrics: response accuracy and reaction time, as well as two derivative measures: an impairment score and a slowing score. The impairment score, which was meant to quantify a patient’s degree of impairment in indirect speech processing specifically, was calculated by subtracting accuracy in the direct condition from accuracy in the indirect condition within each individual subject (impairment score per subject = indirect accuracy – direct accuracy). The slowing score is an analogous measure for reaction time (slowing score = indirect reaction time = direct reaction time). All analyses used non-parametric statistics as the data were not normally distributed according to Shapiro-Wilks tests. Such non-normality is common in clinical research. Between-group comparisons were performed with Mann-Whitney tests, and within-group comparisons with Wilcoxon tests. Correlations were calculated using the Spearman method. All statistical analyses were performed in R (https://cran.r-project.org/).

Prior to data collection, stimulus validity was confirmed via pre-testing. In a norming study, healthy, young adult subjects (n=10) were asked to read each dialogue and respond to a series of question via button press. As in the main experiment, subjects were first asked to indicate if the reply meant “yes” or “no”. Next, subjects were asked to rate how direct the reply sounded and how natural the dialogue sounded, both on a scale of 1 to 5 (where 1= very direct/natural and 5 = very indirect/unnatural). Overall, subjects performed at ceiling, with a mean accuracy of 97.87% (sd=0.05) across all items. Furthermore, there was no significant difference for accuracy [direct = 96.88(0.02), indirect=98.63(0.01); t=-1.9, p=0.07] or naturalness [direct = 1.45(0.64), indirect = 1.87 (0.51); p=0.12], in the direct and indirect conditions. Importantly, there was a significant difference between stimuli in terms of the directness rating [direct = 1.19(0.13), indirect = 3.50 (0.98); p=0.00003].
Table 11. Demographics for Experiment 3. Mean (±SD) of group demographic characteristics. *bvFTD: behavioral variant frontotemporal dementia; MCI: mild cognitive impairment; MMSE: Mini-Mental State Examination

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>bvFTD</th>
<th>MCI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>17</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td><strong>Age (y)</strong></td>
<td>65.71 (5.11)</td>
<td>67.00 (7.94)</td>
<td>66.47 (8.62)</td>
</tr>
<tr>
<td><strong>Education (y)</strong></td>
<td>16.24 (2.74)</td>
<td>15.19 (2.27)</td>
<td>17.00 (2.74)</td>
</tr>
<tr>
<td><strong>Gender (N female)</strong></td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td><strong>MMSE (/30)</strong></td>
<td>29.29 (1.05)</td>
<td>26.38 (3.26)</td>
<td>26.71 (2.17)</td>
</tr>
<tr>
<td><strong>Disease Duration (y)</strong></td>
<td>N/A</td>
<td>5.85 (3.75)</td>
<td>3.71 (2.54)</td>
</tr>
</tbody>
</table>

Table 12. Sample Stimulus Materials for Experiment 3.
Operation definitions of each condition are as follows:

1. **direct reply**: The reply is a syntactic rearrangement of the question into statement form, with some minor variation in order to sound natural and negation possible
2. **indirect reply**: The reply is one sentence of elaborative information relevant to the question (e.g. answering a question such as why or how), without giving the direct reply
3. **direct filler**: The reply is composed of the direct reply, followed by the indirect reply
4. **indirect filler**: The reply is composed of indirect reply, followed by the direct reply
Neuropsychological Battery

In order to assess the potential contribution of linguistic and non-linguistic cognitive processes to speech act comprehension, both bvFTD and MCI patient groups were also administered a comprehensive neuropsychological battery. Language was assessed with 3 measures, each representing a different level of language processing. Phonological awareness was assessed with the Repetition score from the Philadelphia Brief Assessment of Cognition (PBAC) (Libon et al., 2011), and semantic knowledge with the Multi-Lingual Naming Test (MINT) (Gollan et al., 2012). Finally, grammatical comprehension was assessed using a two-alternative forced-choice sentence-picture matching task, which yields a ratio score comparing comprehension of object-relative sentences to subject-relative sentences (Charles et al., 2014).

Next, executive function was assessed with backward digit span (BDS) (Wechsler, 1997), a test of working memory which requires subjects to repeat an orally presented sequence of numbers in reverse order, and Trailmaking Test B (TMT) (Reitan, 1958), a test of mental flexibility in which subjects must connect a series of dots in ascending order, alternating between letters (A-K) and numbers (1-12). The time to complete Trailmaking Test B (in seconds) was normalized to each subject's time to complete Trailmaking Test A (in which only numbers are presented and there is no switching involved), in order to control for any potential motor differences across subjects.

Social cognition was assessed with the Social Norms Questionnaire (SNQ), a 22-item questionnaire probing social knowledge and an individual's ability to use context to decide when a behavior is or is not socially appropriate (Panchal et al., 2015). A higher score on the SNQ indicates greater knowledge of social norms. Scoring of the SNQ also yields two subscores: an “Overadhere” score, which refers to the endorsement of
socially appropriate behavior as inappropriate (e.g. wearing the same shirt twice in 2 weeks), and a “Break” score, which refers to endorsement of a socially inappropriate behavior as appropriate (e.g. hugging a stranger without asking first). A caregiver informant also completed the Perception of Conversation Index (PCI). Section 1 of the questionnaire assesses caregiver perception of conversational difficulties in patients and includes questions such as “Has difficulty with telephone conversations,” and “Mixes-up the details while telling a story” (Orange et al., 2009; Savundranayagam and Orange, 2011).

We also collected measures in two unrelated cognitive domains to serve as negative controls: visuospatial functioning and memory. Both of these abilities should be relatively preserved in bvFTD. To assess visuospatial functioning, we used the “copy” measure of Rey-Osterreith Complex Figure Test (Libon et al., 2011), in which a subject must copy a complicated geometric line drawing freehand, and Judgment of Line Orientation (JOLO), in which subjects to match an angled line to one of 11 lines that are arranged in a semicircle (Benton et al., 1983). Finally, to assess memory, we used the “recall” measure of the Rey-Osterreith Complex Figure Test (Libon et al., 2011), where a subject must draw the same complicated line drawing from memory, after a delay. We also assessed episodic memory with Philadelphia Verbal Learning Test (Libon et al., 1996), which is a 9-item list-learning task modeled after the California Verbal Learning Test. The number of correct items recalled on Trial 7 was used as the dependent variable here.
Structural Imaging: Methods and Analysis

**Image Acquisition**

High-resolution volumetric T1-weighted structural magnetic resonance imaging (MRI) were collected for 19 bvFTD patients and an independent cohort of 25 healthy age and education-matched controls from the surrounding community (mean age = 67.23 (7.46), p = 0.37; mean education = 15.88 (2.19) p=0.22). These controls were used to define an average template brain of comparable age that can be used to identify regions of significant gray matter disease in patients, on a voxel by voxel basis. A T1 image was not available for two patients with bvFTD due to contraindications and safety concerns, including claustrophobia and metal in the body (i.e pacemaker). MRI volumes were acquired using a magnetization prepared rapid acquisition with gradient echo (MPRAGE) sequence from a SIEMENS 3.0T Tim Trio scanner using an axially acquired protocol with the following acquisition parameters: repetition time (TR)=1620 ms; echo time (TE)=3.87 ms; slice thickness=1.0 mm; flip angle=15°; matrix=192×256, 160 slices, and in-plane resolution= 0.9766×0.9766 mm². Whole-brain MRI volumes were preprocessed using Advanced Normalization Tools (https://github.com/ANTsX/ANTs) using the state-of-the-art antsCorticalThickness pipeline described previously (Avants et al., 2008; Klein et al., 2010; Tustison et al., 2014)(Avants et al., 2008; Klein et al., 2010; Tustison et al., 2014). Briefly, processing begins by deforming each individual dataset into a standard local template space that uses a canonical stereotactic coordinate system, generated using a subset of images from the open access series of imaging studies dataset (OASIS) (Marcus et al., 2010). ANTs then applies a highly accurate registration algorithm using symmetric and topology-preserving diffeomorphic deformations, which minimize bias to the reference space while still capturing the
deformation necessary to aggregate images in common space. The ANTs Atropos tool uses template-based priors to segment images into six tissue classes (cortex, white matter, CSF, subcortical gray structures, brainstem, and cerebellum) and generate corresponding probability maps. Voxelwise cortical thickness is finally measured in millimeters (mm). Resulting images are warped into Montreal Neurological Institute (MNI) space, smoothed using a 2 sigma smoothing kernel, and downsampled to 2mm isotropic voxels.

**Voxel-wise Analyses**

To define areas of significant cortical thinning in bvFTD, non-parametric, permutation-based imaging analyses were performed with threshold-free cluster enhancement (Smith and Nichols, 2009) and the randomise tool in FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki). Briefly, permutation-based t-tests evaluate a true assignment of cortical thickness values across groups (signal) relative to many (e.g. 10,000) random assignments (noise). Accordingly, permutation-based statistical testing is robust to concerns regarding multiple comparisons and preferred over traditional methods using parametric-based t-tests as permutation testing effectively controls for false positives (Winkler et al., 2014). Cortical thickness was compared in patients relative to the independent cohort of 25 healthy controls described above and restricted to an explicit mask of high probability cortex (>0.4). We report clusters that survived a statistical threshold of p<0.01, correcting for multiple comparisons using the family wise error rate relative to 10,000 random permutations. Results were projected onto the Conte69 surface-based atlas using Connectome Workbench (http://www.humanconnectome.org/software/connectome-workbench.html).
To relate behavioral performance to regions of significant cortical thinning, we fit linear regression models with the randomise tool of FSL and the impairment score as a covariate. Permutations were run exhaustively up to a maximum of 10,000 for each analysis. To constrain our interpretation to areas of known disease, we restricted our regression analyses to an explicit mask containing voxels of significant cortical thinning, as defined by the group comparison described above. Results outside these regions of known disease would be difficult to interpret since they could be attributed to a variety of individual differences unrelated to disease per se (e.g. healthy aging, genetic variation, etc.). For the regression analyses, we report clusters with a minimum of 20 adjacent voxels and surviving a height threshold of $p<0.005$, which is recommended for optimal balance of Type I and Type II error rates (Lieberman and Cunningham, 2009). Results were projected onto slices using MRICron software (Rorden and Brett, 2000).

ROI Analyses

Next, we conducted a series of whole-brain region-of-interest (ROI) analyses in order to specifically test our hypothesis that indirect reply comprehension involves the interaction of multiple brain networks: the core language network, the theory-of-mind/social network, and the multiple-demand network/executive network. Using publicly available software (https://github.com/ftdc-picsl/QuANTS/tree/master/R), we extracted mean cortical thickness values for each of the 3 networks for each subject. Each network ROI (see below for network ROI definitions) was warped from MNI space to the subject’s native T1 space prior to extracting the estimates of cortical thickness (mm). To demonstrate specificity of our predicted relationship, we similarly extracted cortical thickness estimates from the sensorimotor network to use as a negative control.
The language network ROI was constructed by summing 4 language ROIs identified by (Fedorenko et al., 2010, 2013), who used a language localizer contrasting reading sentences to reading lists of unconnected, but pronounceable words. The final ROIs, which included left IFG, IFG (pars orbitalis), anterior temporal lobe, and posterior temporal lobe, were created from a probabilistic overlap map from 220 healthy participants.

The social network was the sum of 7 ROIs, which were originally constructed by Dufour et al., (2013) and included: dorsomedial prefrontal cortex (dmPFC), middle medial prefrontal cortex (mmPFC), ventromedial prefrontal cortex (vmPFC), precuneus (PC), right superior temporal sulcus (RSTS), right temporoparietal junction (RTPJ), and left temporoparietal junction (LTPJ). The ROIs were developed by contrasting the false belief and false photograph conditions of a standard story-based theory-of-mind task across 462 healthy participants.

The executive ROIs were also adopted from Fedorenko et al. (2013), who contrasted hard and easy versions of a spatial working memory task in 197 healthy participants. For our purposes, we summed only those MDN ROIs overlapping the so-called “fronto-parietal attention network.” The ROIs we selected thus included bilateral superior parietal lobe, inferior parietal sulcus, inferior parietal lobule, dorsolateral prefrontal cortex, and orbital middle frontal gyrus.

Finally, our control sensorimotor network was taken from Shirer et al. (2012), who defined ninety functional ROIs across 14 large-scale resting state brain networks using a classifier with leave-one-out cross-validation. Please see Figure 17 for the anatomic distribution of these brain networks.
Diffusion Tensor Imaging: Procedure and Analysis

White matter tracts play a critical role in network activity by transmitting electrical signals across spatially separate gray matter regions, both within and across hemispheres. Therefore, even when gray matter regions are intact, synchronized network activity can be disrupted if there is damage to the white matter projections connecting gray matter nodes to each other. Because of this possibility, we use diffusion tensor imaging to examine patterns of structural connectivity in bvFTD and build a large-scale, multimodal network underlying speech act comprehension.

Diffusion weighted imaging (DWI) was available for the same 19 bvFTD patients with T1 imaging. A 30-directional DWI sequence was collected using single-shot, spin-echo, diffusion-weighted echo planar imaging (FOV=240 mm; matrix size =128x128; number of slices = 70; voxel size = 1.875x1.875x2.2 mm3, TR = 8100 ms; TE = 83 ms; fat saturation). Thirty volumes with diffusion weight (b=1000 s/mm2) were collected along 30 non-collinear directions, and either one or five volumes without diffusion weight (b=0 s/mm2) were collected per subject. A chi-square test demonstrated that the distribution of subjects with either one of five volumes without diffusion weight did not differ significantly across our groups (X2=5.4412, p=0.08). We also include a nuisance covariate for sequence in our subsequent analyses.

The diffusion images were processed using ANTs (Tustison et al., 2014) and Camino (Cook et al., 2006). Motion and distortion artifacts were removed using affine coregistration of each diffusion-weighted image to the average of the unweighted (b= 0) images. Diffusion tensors were calculated using a weighted linear least-squares algorithm (Salvador et al., 2005) implemented in Camino. Fractional anisotropy (FA) was computed in each voxel from the DT image, and distortion between the subject’s T1 and DT image was corrected by registering the FA to the T1 image. DTs were then relocated
to the local template for statistical analysis by applying the FA-to-T1, T1-to-local template, and local template-to-MNI warps, and tensors were reoriented using the preservation of principal direction algorithm (Alexander et al., 2002). Each participant’s FA image was recomputed from the DT image in MNI152 template space and smoothed using a 2-sigma smoothing kernel.

Like the pipeline for GM analysis, we used the randomise tool in FSL to compare FA in patients relative to the same cohort healthy age-matched controls. The two-sample t-test of patients vs. controls was run with 10,000 permutations and restricted to voxels containing WM based on an explicit mask of high probability WM (minimum FA considered WM = 0.20). We also include a nuisance covariate of no interest for sequence difference (sequences with one versus five volumes without diffusion weight). We report clusters that survived a statistical threshold of p<0.005 and a minimum cluster extent of 200 voxels. Regression analyses then related patient impairment to reduced FA, using a covariate for the indirect impairment score and a nuisance covariate for sequence. These regressions were restricted to the results of the previous analysis—that is, only voxels showing a significant effect of group. As above, we report clusters surviving a height threshold of p<0.005 and a minimum of 20 contiguous voxels.

RESULTS

Analysis of Task Performance

Our first objective was to test the hypothesis that inferential demand (i.e. whether a reply was communicated directly versus indirectly) modulates response accuracy in bvFTD. Results (summarized in Figure 14) indicate that healthy control subjects performed at ceiling in both direct and indirect conditions, with no significant difference

109
between conditions (W=23.5, p=0.10). Patients with bvFTD, on the other hand, performed significantly worse in the indirect condition than the direct condition (W=132.5, p=0.0008). bvFTD patients were also significantly impaired relative to healthy controls in the indirect condition (W=276.5, p=0.003), but not the direct condition (U=237.5, p=0.07). The null result in the direct condition suggests that segmental language ability, such as the comprehension of single words and sentences, is not responsible for the decrement in indirect performance. To confirm the group-level results in bvFTD, we also calculated an “impairment score” by subtracting accuracy in the direct condition from accuracy in the indirect condition within each individual subject (impairment score = indirect accuracy – direct accuracy). Accordingly, more negative scores represent a greater degree of impairment. Here, results again indicated that bvFTD patients (mean impairment = -0.08 (±0.09)) were significantly more impaired than healthy controls (mean impairment = -0.01 (±0.02), U=273.00, p=0.004). Sixteen of 21 (76.20%) bvFTD patients showed a negative impairment score.

Patients with MCI show some cognitive decline for their age but remain largely capable of independent day-to-day functioning (Gauthier et al., 2006) and thus represent an appropriate brain-damaged control group to test the specificity of the effect observed in bvFTD. Results in MCI showed that, unlike bvFTD patients, MCI patients are not significantly impaired relative to healthy controls in either the direct (U=165.50, p=0.43) or indirect condition (U=170.00, p=0.36). Similarly, their mean impairment score (-0.006 ±0.06), calculated within each individual, does not differ than that of healthy controls, (U=171.00, p=0.35), but does differ from bvFTD (U=110.00, p=0.04) (please see Figure 1). Because bvFTD and MCI patients are matched in terms of global cognition as assessed by the MMSE (U=107.5, p=0.93), it seems likely that the effect observed in bvFTD is not simply an effect of overall cognitive impairment but rather is specific to the
deficits characteristic of bvFTD. We’ll return to this later when we examine
neuropsychological associations.

The reaction time data offer converging evidence for our claim that patients with
bvFTD are selectively impaired in indirect reply comprehension, relative to both healthy
controls and patients with MCI. Here, a Kruskal-Wallis test indicated that there are
significant differences across our three groups for reaction time in both the direct
condition ($\chi^2(2)= 10.97, p=0.001$) and indirect condition ($\chi^2(2)=13.75, p=0.001$). Upon
further analysis, we found that patients with bvFTD are significantly slower to respond to
direct replies than healthy controls ($U=81.5, p=0.004$), but not MCI ($U=155.00, p=0.5$).
More importantly, in the indirect condition, bvFTD were slower to respond than both
groups (controls: $U=67.5, p=0.001$; MCI: $U=108.00, p=0.038$). These data, however, do
not address whether bvFTD patients have slower, non-specific motor reaction times or
are more affected by the increased inferential demand characteristic of the indirect
condition relative to the two other subject groups. To answer this question, we computed
an individualized “slowing score” (slowing score = indirect RT - direct RT), analogous to
the impairment score calculated for accuracy. In this case, a positive slowing score
means a subject is relatively slower in the indirect condition. A significant difference in
slowing scores was observed across our three groups ($\chi^2 =9.30, p=0.001$). Post-hoc
testing indicated that patients with bvFTD have significantly larger slowing scores than
healthy controls ($U=81.5, p=0.005$) and MCI ($U=99.00, p=0.019$) (please see Figure 15).
Therefore, the disproportionate slowing for indirect compared to direct stimuli in bvFTD
suggests that our observations cannot be easily attributed to simple motor slowing.
Moreover, this finding demonstrates that patients with bvFTD do not slow their
performance in a strategic effort to improve accuracy. Taken together, our data confirm
that patients with bvFTD struggle to process indirect replies during conversation both quickly and accurately.
Figure 14. Response Accuracy Results for Experiment 3. Response accuracy in controls, patients with behavioral variant frontotemporal dementia, and patients with mild cognitive impairment in the experimental (short) conditions. A. Mean (±SEM) accuracy in the direct and indirect conditions. Controls are shown in dark gray (left-most bar), bvFTD patients in medium gray (middle bar), and MCI patients in light gray (right bar). B: Mean (±SEM) impairment score in the short condition across groups. A more negative impairment score indicates more difficulty with the indirect condition relative to a patient’s individual baseline performance on the direct condition.

* indicates significance at p<0.05, ** indicates significance at p<0.01, *** indicates significance at p<0.001.
Figure 15. Response latency Results for Experiment 3. Response latency in controls, patients with behavioral variant frontotemporal dementia, and patients with mild cognitive impairment. A. Mean (±SE) reaction time in the direct and indirect conditions. Controls are shown in dark gray (leftmost bar), bvFTD patients in medium gray (middle bar), and MCI patients in light gray (right bar). B: Mean (±SE) slowing score in the short condition across groups. A higher slowing score indicates longer reaction times in the indirect condition relative to a patient’s individual baseline performance in the direct condition.

* indicates significance at p<0.05, ** indicates significance at p<0.01, *** indicates significance at p<0.001
Correlational Analyses with Neuropsychological Measures

Next, to examine the cognitive mechanism(s) associated with the observed deficits in bvFTD patients, we administered a broad neuropsychological battery targeting core language skills, executive function, and social cognition that may contribute to inferential comprehension, as well as negative control measures of visuospatial functioning and memory. We used Spearman correlations to relate these independent measures to the impairment score. Our first aim was to demonstrate that impairment in bvFTD was independent of segmental language ability. Consistent with our earlier finding of intact performance in the direct condition, correlation analyses indicated that language ability at both the phonological (i.e. repetition test) and single word levels (i.e. MINT) is not related to impairment (please see Table 13). A measure of grammatical comprehension, however, comparing comprehension of object-relative sentences to subject-relative sentence, was significantly correlated with impairment (rho= 0.52, p=0.04). Next, although patients with bvFTD are known to have deficits in working memory capacity (Kramer et al., 2003; Libon et al., 2007; Baez et al., 2016), we found no relationship between backward digit span and indirect impairment. Other domains of executive function, however, did demonstrate an effect: poor task-switching ability (as indicated by Trailmaking) was correlated with impairment (Trailmaking: rho=-0.63, p=0.006), suggesting a role for mental flexibility in the interpretation of indirect replies. In the social domain, the impairment score was also positively associated with total score of the SNQ (rho=0.47, p=0.04). Upon further examination, we found that most patients performed worse on the SNQ had a higher Overadhere score than Break score [Overadhere: mean=1.95(1.47); Break: mean=1.05(1.35)] suggesting that patients who are more rigid in their application of rules to behavior, may be similarly rigid in their interpretation of language. Finally, we also confirm the construct validity of our indirect
speech task by demonstrating that impairment on the task is correlated with real-world conversational difficulties, as assessed by caregivers in the PCI-DAT (rho=0.49, p=0.02). bvFTD performance in the indirect condition was not related to visuospatial or memory functioning. The same correlation analyses were also performed in patients with MCI in order to test the specificity of the results in bvFTD, and no results in MCI were significant. In sum, we conclude that indirect impairment is specific to bvFTD and related to the social and executive deficits that characterize the disease. More specifically, we implicate the ability to adapt behavior to changing rules and/or contexts in the interpretation of indirect speech.

Based on these initial correlation results, we then used multiple linear regression to predict the impairment score based on 3 significant and possibly interacting variables, one from each domain: grammatical comprehension, Trailmaking (B-A), and SNQ. A total of 5 different models were tested: all variables as independent (Model 1); all variables interacting (Model 2); and each of the pairwise interactions (the remaining predictor as independent, Models 3-5). Only one model yielded a significant regression equation [(Impairment Score ~ Grammatical Comprehension + Trailmaking * SNQ); F(4,13)=9.346, p=0.006]. Both Trailmaking (β=0.009, p=0.004) and SNQ (β =0.067, p=0.002) were significant predictors of the impairment score, along with their interaction (β =-0.005, p=0.004), while grammatical comprehension was no longer a significant predictor (β =0.11, p=0.19). The overall model fit was strong, with R²=0.84. The results of this analysis demonstrate conclusively that social cognition and executive functioning interact with one another and play a large role in the interpretation of indirect speech in bvFTD.
Table 13. Correlation Results for Experiment 3. Mean (±SD) scores and correlations between neuropsychological measures and impairment score (indirect-direct) in bvFTD and MCI patients.

*indicates significance at p<0.05, ** indicates significance at p<0.01, *** indicates significance at p<0.001
Neuroimaging Analyses

We also sought to determine the neuroanatomic basis of indirect speech act comprehension. More specifically, we examined regions of gray and white matter disease that may be causally related to impaired performance in patients with bvFTD. We note here that we focus solely on bvFTD patients in the following analyses because patients were MCI showed no impairment in the indirect condition, which is our experimental condition of interest.

We first contrasted cortical thickness in patients with bvFTD relative to an independent cohort of age-matched healthy controls. As expected, this revealed significantly reduced cortical thickness throughout the frontal and anterior temporal lobes bilaterally in bvFTD, with a peak in orbitofrontal cortex, consistent with disease diagnosis and previous structural imaging studies (Rascovsky et al., 2011; Möller et al., 2016). The anatomic distribution of significant atrophy illustrated in Figure 16. Table 14 summarizes peak and subpeak coordinates.

Next, to relate patient deficits in indirect speech act comprehension to gray matter disease, we performed a regression analyses, using the impairment score (indirect - direct) as a covariate. Greater relative impairment in the indirect condition was related to reduced cortical thickness in a largely left-lateralized cortical network, spanning frontal, temporal, and parietal regions. Significant clusters were observed within the classic peri-Sylvian language network, including left inferior frontal gyrus and posterior middle to superior temporal gyri, as well as right inferior frontal gyrus (pars opercularis). Additional effects were seen in regions that are more traditionally associated with social cognition, including medial prefrontal cortex, orbitofrontal cortex, and precuneus; or with executive function, including dorsolateral prefrontal cortex. Although unpredicted, we also saw significant associations with premotor cortex,
precentral gyrus, and supplementary motor areas, which have been previously implicated as part of the multiple-demand network and thought to play a role in broad domain-general functions (Fedorenko et al., 2013).

Our next set of analyses tested our hypothesis that three primary networks (language, social, and executive) are related to indirect speech comprehension by computing linear models using the mean cortical thickness score for each network as predictors for the impairment score. We did this by using a ROI-based approach across the whole-brain, rather than a voxel-wise approach. Using the network ROIs associated with language, social, and executive function defined in the Methods section, we found significant effects for each of our three networks, as shown in Figure 18. This effect was specific to these 3 networks and was not observed in the sensorimotor network.

Finally, while the majority of previous work on language comprehension has focused primarily on gray matter contributions to processing, we adopt a more connectionist approach here. Using a voxel-wise approach, we observe a significant change in FA in the following tracts within bvFTD: uncinate fasciculus, superior and inferior longitudinal fasciculus, and inferior fronto-occipital fasciculus. These are all long-range association tracts. We also observed disease in the corpus callosum, as well as white matter of the middle frontal and temporal gyri. We next examined which of these tracts were associated to the impairment score in bvFTD, finding significant effects for the superior longitudinal fasciculus (typically implicated in language processing), as well as the uncinate fasciculus (typically implicated in social-behavioral functioning), and inferior fronto-occipital fasciculus and frontal aslant. Please see Figure 19 and Table 15 for more information.
Figure 16. Structural Neuroimaging Results for Experiment 3. A: Surface renderings depicting regions of significant cortical thinning in bvFTD patients related to age-matched healthy controls. Heat map intensity refers to t-stat values. B: Regions of significant cortical thinning in bvFTD patients relative to age-matched healthy controls (red and blue regions) and regions of significant cortical thinning associated with indirect impairment in bvFTD (red areas, only). C: Surface renderings depicting regions across the whole-brain associated with indirect impairment in bvFTD (red areas).
### Table 14. MNI Coordinates for Experiment 3 Imaging Results.

A: Peaks and subpeaks for regions of cortical thinning in patients with behavioral variant frontotemporal dementia relative to age-matched healthy controls. B: Regions of cortical thinning in patients with bvFTD related to indirect impairment in the short condition. BA, Brodmann Area; MNI, Montreal Neurological Institute; sub, subpeak.
Figure 17. Network Key for Experiment 3. Surface renderings of the brain showing each of the 4 network ROIs tested for their relationship with indirect speech processing: the language network (green), social network (blue), executive network (yellow), and sensorimotor network (red). See text for a description of how each network was defined.
Figure 18. Experiment 3 Network Associations with Indirect Impairment. Graphs plot the relationship between network cortical thickness and indirect impairment score for language, executive, social, and sensorimotor networks. Note that the sensorimotor network is included as a control network to demonstrate specificity. See bottom right corner of each plot for R² values. See Supplementary Materials for plots of individual nodes within each network.
Figure 19. White Matter Imaging Results for Experiment 3. A: Axial slices showing regions of significantly reduced fractional anisotropy in bvFTD patients relative to age-matched healthy controls (blue), regions of significantly reduced fractional anisotropy related to indirect impairment (red), and ancillary white matter regions (outside of blue regions of disease) also related to indirect impairment (violet). See key in upper right hand corner.
Table 15. MNI Coordinates for Experiment 2 Diffusion Tensor Imaging Results. A: Anatomic locations of white matter disease in patients with bvFTD relative to age-matched healthy controls. B: White matter regions related to indirect impairment in bvFTD. Results are considered significant at p<0.005 and a cluster extent threshold of k=20 contiguous voxels. MNI, Montreal Neurological Institute. ** indicates white matter region related to indirect impairment is contained within region of significantly reduced FA.

**DISCUSSION**
Most listeners are exceedingly adept at decoding a speaker’s intended meaning, despite the ambiguity inherent to conversational speech. An unresolved question in neuroscience is how the brain accomplishes this feat. To address this issue, we study speech act processing in non-aphasic patients with bvFTD, and demonstrate that their comprehension is impaired only when a speaker’s intended meaning is communicated indirectly. The observed patient impairment is related to disease not only in the traditional language network (including IFG and pMTG/STG), but also in two additional networks: the social brain network (including medial prefrontal cortex, orbitofrontal cortex, and precuneus) and the executive network (including dorsolateral prefrontal cortex, premotor cortex, and supplementary motor area), as well as the long-tract white matter projections that integrate these networks. Therefore, while traditional models of language highlight a left peri-Sylvian network, we conclude that the highly common but oft overlooked inferential component of conversational speech is supported in part an extended language network that also incorporates frontal and parietal cortices well beyond traditional language regions. We discuss these findings and their implications below.

**Inferential Demand Modulates Language Comprehension**

Our primary objective was to examine how inferential demand—whether a speaker’s message is communicated directly or indirectly—modulates comprehension. Analyses of patient performance based on accuracy and reaction time metrics suggests a selective deficit in indirect reply comprehension exists in bvFTD. We are unaware of other studies of indirect reply comprehension in bvFTD, although clinical observations of schizophrenia, autism, and traumatic brain injury suggest difficulties with indirect speech exist in these populations (Champagne-Lavau and Stip, 2010; Johnson and Turkstra,
2012; Pastor-Cerezuela et al., 2018). Consistent with our findings, previous studies have also reported that reaction time increases along with higher inferential demand (Ferstl and von Cramon, 2002; Kuperberg et al., 2006; Siebörger et al., 2007). Slowed processing can have considerable effects on real-world communication, as the gap between “turns at talk” is typically on the order of 200-250ms (Stivers et al., 2009; Levinson, 2016). In our data, bvFTD patients show a slowing effect of ~600ms: such a processing lag would obviously impede the rapid switching that characterizes human conversation.

We further demonstrate that our effects are specific to bvFTD and not observable in brain-damaged controls with MCI. While evidence suggests that pragmatic deficits, including in proverb interpretation, exist in MCI (Leyhe et al., 2011; Cardoso et al., 2014), such findings may be a consequence of experimental confounds related to stimulus length or “frozen” meanings—making any findings the consequence of impaired episodic memory retrieval rather than impaired inferential processing. More work is needed to investigate this possibility.

Next, we examined the cognitive mechanisms that mediate indirect speech comprehension by collecting a comprehensive neuropsychological battery. Results indicate that the observed patient deficit is likely multifactorial in nature, as the indirect speech impairment score is related to language, social, and executive functioning, but not episodic memory or visuospatial functioning.

Consider first executive function, which was assessed by Trailmaking. This finding aligns well with previous research showing a relationship between mental flexibility and pragmatic competence (Eslinger et al., 2007; Torralva et al., 2015). For example, Torralva et al. (2015) demonstrated that cognitive theory of mind and the ability to infer a speaker’s intention in a faux pas task is related to Trailmaking performance. In
the context of our experiment, we similarly suggest that bvFTD patients struggle to infer a speaker's intention and to switch from a literal to a pragmatic interpretation of utterance meaning accordingly. Although working memory is decreased in bvFTD (Kramer et al., 2003), we found no relationship between indirect impairment and digit span. This null result contradicts some evidence that working memory capacity predicts inference revision ability (Tompkins et al., 1994; Wright and Newhoff, 2002; Pérez et al., 2014). We may not observe any effect here due to our experimental design: we minimized off-target task demands by using written text that remained visible on the screen throughout the response window. Future work using auditory stimuli should further investigate working memory contributions to language.

We also report a positive association between the indirect speech impairment score and performance on SNQ—a questionnaire assessing an individual's ability to apply socially-dictated rules given different constraints (e.g. a conversation with a stranger versus a friend). One important social norm for conversational exchanges is Grice’s “Maxim of Relevance,” which states that an individual’s contribution to an ongoing exchange should always be pertinent and on-topic. If bvFTD subjects fail to appreciate this maxim due to degraded social knowledge, they may judge indirect speech as irrelevant to the ongoing exchange and disregard it accordingly—ultimately resulting in impaired comprehension, as observed here.

Multiple regression analysis confirms the role that executive function and social cognition play in impairment. The final model (Impairment Score ~ Grammatical Comprehension + Trailmaking * SNQ) also demonstrates that social and executive deficits are not independent, but rather interact. This result has implications for an ongoing debate in the bvFTD literature concerning the relationship between social
cognition and executive function (Lough et al., 2001; Eslinger et al., 2007; Le Bouc et al., 2012; Bertoux et al., 2016).

Although patients with bvFTD are non-aphasic according to clinician assessments of speech, their indirect impairment is associated in part with a language measure—grammatical comprehension. In this case, grammatical comprehension was assessed by comparing sentence-picture matching for object-relative compared to subject-relative sentences. (Note: the comprehension of object-relative phrases is known to be more difficult than subject-relative phrases, in both healthy adults and patients with bvFTD (Charles et al., 2014; Demberg and Sayeed, 2016)). This positive association may thus be related in part to the mental manipulation of linguistic materials that plays a role in both comprehension of object-related phrases and indirect speech acts. We also note here that the relationship between grammatical comprehension and impairment is lessened when concomitant deficits in social cognition and executive function are taken into account in our three-factor regression model. This suggests that the deficits in grammatical comprehension seen in our patients are likely secondary to other cognitive deficits.

An Extra-Sylvian Network for Speech Act Comprehension

Although neurobiological models of language centered on left peri-Sylvian regions have been foundational in studies of human brain functioning, these models remain limited in their external validity and generalizability to real-world contexts (Hasson et al., 2018). Here, we examine cortical thinning and fractional anisotropy in patients with bvFTD and build a large-scale, multimodal language network associated that can account for indirect speech act comprehension.
To date, only a limited number of studies have examined the neural basis of indirect reply comprehension (Shibata et al., 2011; Basnáková et al., 2013; Jang et al., 2013; Feng et al., 2017). While these fMRI studies offer preliminary evidence for the role of non-language regions including mPFC, TPJ, and precuneus in discourse processing, there are some caveats to keep in mind. For example, several studies used experimental tasks that involved reading a brief narrative followed by an exchange between speakers. Using narratives to establish context can increase executive demands and introduce carry-over effects that make it difficult to dissociate inferential processing from other task-related components of narrative processing—including tracking a character over time, processing event structure, maintaining narrative elements in working memory, and more. In response, we designed a novel question-answer paradigm that manipulated inferential demand while simultaneously minimizing task-related resource demands and controlling for linguistic variation across stimuli.

As our paradigm was language-based, we did observe significant effects in the IFG and the posterior MTG/STG. These areas, initially proposed by the WLG model and later confirmed, constitute the primary nodes of the classic language network (Binder et al., 1997; Price CJ, 2000). We point out, however, that these peri-Sylvian regions were related to patient impairment in the indirect condition over and above the direct condition. Therefore, our results support a role for left peri-Sylvian regions not only in lexical, semantic, and syntactic processing, but also in high-level selection and global integration, as suggested previously (Hagoort, 2005). Previous fMRI studies of indirect speech and causal inferencing make similar arguments (Mason and Just, 2004; Eviatar and Just, 2006). We also observe an effect in the right IFG, which is consistent with the dynamic spillover hypothesis described by Prat and colleagues (Prat et al., 2011).
According to this model, activity in the right hemisphere is more likely to be invoked 1) when readers are less skilled and 2) when passage difficulty is harder.

We now know that language processing also extends beyond peri-Sylvian regions (Ferstl et al., 2008; Fedorenko and Thompson-Schill, 2014; Hagoort, 2014). We report here that extra-Sylvian regions, including the orbitofrontal, medial prefrontal, dorsolateral prefrontal cortices, as well as precuneus and premotor and supplementary motor regions, are related to indirect speech processing in bvFTD. These are regions that belong to social and executive networks of the brain. Importantly, these findings are relatively selective, as we find no evidence of other network involvement (e.g. sensorimotor network).

Consider first mPFC and precuneus, which both belong to a social brain network commonly associated with “theory of mind” (Saxe and Kanwisher, 2003; Frith and Frith, 2012; Dufour et al., 2013; Healey and Grossman, 2018). While mPFC is traditionally associated with perspective-taking and the ability to make inferences about conspecifics, recent research also suggests that a ventral portion of mPFC, similar to the cluster observed here, plays a role in scene construction and situational processing (Lieberman et al., 2019). In the case of indirect speech acts, mPFC may help generate a “schema” or “situation model” that guides interpretation of ambiguous stimuli and events. The precuneus may play a similar role. One of the brain’s most globally connected areas, the precuneus is traditionally associated with a diverse set of cognitive functions including visuospatial processing, episodic memory (Shallice et al., 1994), and mental imagery (Hassabis et al., 2007; Johnson et al., 2007). Newer work, however, has demonstrated that the precuneus also plays a role in self-referential processing and first-person perspective-taking, as well as situation model building and the retrieval of contextual associations from internal stores (Lundstrom et al., 2005; Cavanna and Trimble, 2006;
Taken together, the relationship of mPFC and precuneus to indirect speech impairment suggests that indirect reply comprehension requires listeners to 1) adopt the speaker’s perspective and 2) integrate contextual information into some kind of mental model. Finally, we also observed an effect in orbitofrontal cortex, which is sometimes included in the social brain network. Like mPFC and precuneus, some studies implicate OFC in theory of mind, in addition to tasks involving reversal learning, set-shifting, and affective decision-making (Rolls, 2004; Sabbagh, 2004; Badre and Wagner, 2006).

DLPFC, on the other hand, is part of the “multiple-demand” network commonly linked to the domain-general, executive control processes involved in language and other behaviors (Novais-Santos et al., 2007; Duncan, 2010; Fedorenko et al., 2013) (Duncan, 2010; Fedorenko et al., 2013). These regions are often defined by contrasting two task conditions that vary in difficulty (e.g. verbal working memory tasks with 4 versus 8 digits), mirroring our indirect-direct contrast. It is important to note these “harder” tasks might not only require more computational resources, but could also invoke strategic reasoning processes mediated by DLPFC (Yoshida et al., 2010; Yamagishi et al., 2016). Finally, with well-documented roles in working memory and selection (Petrides, 2005; Badre, 2008) (Petrides, 2005; Badre, 2008), DLPFC is also implicated in the Memory-Unification-Control model of language (Hagoort, 2013), serving as the “control” component and mediating processes such as turn-taking and the selection of contextually-appropriate meanings. The motor-associated regions we observed, including premotor cortex, precentral gyrus, and supplementary motor area, have also been said to belong to this same network as DLPFC (Fedorenko et al., 2013). Our extended neurobiological model of language also proposes incorporating these executive brain regions.
Other materials have been used to study inferential demands in language, but are associated with several confounds that limit interpretation. For example, recent work using fMRI (Paunov et al., 2019) has demonstrated that story comprehension elicits synchronized network activity not only in traditional language-associated regions, but also in social regions, including medial prefrontal cortex, temporoparietal junction, and precuneus. Similar results have been reported elsewhere (Xu et al., 2005; Mar, 2011; AbdulSabur et al., 2014). A third, fronto-parietal network associated with executive control has also been implicated in story comprehension (Raposo and Marques, 2013; Smirnov et al., 2014; Mineroff et al., 2018; Aboud et al., 2019; Paunov et al., 2019). Although these results are promising, narratives are inherently long, which makes them difficult to control experimentally and overly dependent on task-related executive resources.

Another common approach to discourse has been the study of non-literal or figurative language, including sarcasm, irony, metaphors, idioms, and proverbs (see Rapp et al., 2012 for a comprehensive review). This body of work also implicates social and executive components in the comprehension of pragmatic language (Wakusawa et al., 2007; Bohrn et al., 2012; Uchiyama et al., 2012; Iskandar and Baird, 2014; Obert et al., 2016; Filik et al., 2019), but unfortunately is subject to confounds related to familiarity, valence, and concreteness among others (Nippold and Haq, 1996; Schmidt and Seger, 2009; Ziv et al., 2011; Kaiser et al., 2013).

White Matter Correlates of Speech Act Comprehension

Recent work has paid increasing attention to white matter connectivity. While the traditional WLG model of language focuses primarily on the arcuate fasciculus—a component of the superior longitudinal fasciculus connecting IFG and STG, newer work
has identified pathways that not only interconnect peri-Sylvian regions, but also connect these regions to extra-Sylvian regions (Catani et al., 2005; Dick and Tremblay, 2012). Analogous to the visual system, these pathways may be divided into dorsal and ventral streams. One characterization implicates the dorsal stream as broadly involved in auditory-motor integration and the ventral stream in mapping form to meaning (Hickok and Poeppel, 2004; Saur et al., 2008). Using voxel-based fractional anisotropy analyses, we find evidence implicating tracts in both dorsal and ventral streams in indirect reply comprehension. This includes the uncinate and inferior fronto-occipital fasciculi in the ventral stream and the superior longitudinal fasciculus and frontal aslant in the dorsal stream. The frontal aslant, in particular, is a newly discovered tract implicated in both speech and language (on the left) and executive function (on the right) (Varriano et al., 2018; Dick et al., 2019). The frontal aslant, which is thought to project from the IFG to the supplementary motor areas, has previously been implicated in verbal fluency deficits in other forms of frontotemporal dementia, including logopenic, non-fluent/agrammatic, and semantic variants of primary progressive aphasia (Catani et al., 2013). The uncinate fasciculus, which connects the orbitofrontal cortex to anterior temporal regions, has also gained more attention recently as a white matter tract mediating the interaction of social and language networks. For example, damage to the uncinate fasciculus is bvFTD not only predictive of a bvFTD diagnosis, but is also associated with deficits in non-literal language comprehension including sarcasm and irony (Agosta et al., 2012; Downey et al., 2015). Thus, we propose that cortical components of our extended language network are integrated by white matter projections in both dorsal and ventral projection streams.
Conclusions

Strengths of our study include the novel task design with carefully matched direct and indirect conditions, observation of a significant indirect language impairment in a non-aphasic brain-damaged cohort with selective social and executive deficits, and robust association of these deficits with an anatomic network implicating language, social, and executive networks. Nevertheless, several caveats should be kept in mind when interpreting our results. Although we tested a relatively large bvFTD cohort and demonstrated specificity with a brain-damaged control group, patients were not pathologically confirmed and generalizability is limited to the mild-moderate disease stage. Second, while we confirmed an indirect speech impairment with reaction time data, we report ceiling effects for accuracy in our control subjects, thereby limiting examination of individual differences associated with aging. Finally, to differentiate the functions of nodes within the extended language network, future studies should contrast different types of indirect speech, including indirect requests (which have a motor component) and “face-saving” replies (which have an affective component).

The findings discussed here also have meaningful clinical implications. Communication difficulties can compromise social interactions, and in turn, diminish interpersonal relationships and overall well-being. We found that impaired indirect speech is related to communicative efficacy, which is a crucial element of patient safety and quality of life. Accordingly, language deficits may be a target for intervention in bvFTD. Our data also have implications for “best-practice” communication strategies used by patient caregivers: to optimize successful communication, language should be as direct as possible.

With these caveats in mind, we conclude that patients with bvFTD struggle to make the pragmatic inferences necessary to support indirect reply comprehension, a
common but understudied example of conversational discourse. This is due in part to social-executive deficits and degradation of a multimodal, extra-Sylvian network supporting natural, daily language use. More specifically, our findings emphasize the extension of the brain’s traditional language network beyond left peri-Sylvian regions and into additional frontal and parietal regions. We conclude by emphasizing the importance of studying language in context—the way in which we use it in everyday life. Indeed, it is only when we study language in this way—as a means of communication—that we can begin to characterize the full extent of its neurobiology.
CHAPTER 5: A call to action: Indirect request comprehension in behavioral variant frontotemporal dementia


ABSTRACT

Indirect requests—statements like “it’s cold in here” that can be interpreted as “calls to action” when given adequate context (e.g. an open window adjacent to the listener) — are frequently used in daily communication. Like other forms of indirect or non-literal language, recipients of an indirect request must not only decode the phonetic, lexical, and syntactic components of the spoken utterance, but also make a pragmatic inference regarding the speaker’s true intended meaning. In the case of indirect requests, the speaker uses indirect speech as a polite means to ask someone else to initiate a certain behavior or perform a motor command— in the above example, perhaps, to close the open window in the room. We study indirect requests here as a means to investigate how the brain integrates information across linguistic and non-linguistic domains during everyday discourse. Building upon previous work on indirect speech, we use a novel dialogue-based paradigm to compare and contrast direct and indirect request comprehension in non-aphasic patients with behavioral variant frontotemporal dementia versus healthy age-matched controls. Results demonstrate that bvFTD patients are impaired in indirect but not direct request comprehension. High-resolution structural neuroimaging demonstrates that indirect request impairment is related to cortical thinning in prefrontal regions, including orbitofrontal cortex, medial prefrontal cortex, and dorsolateral prefrontal cortex. Complementary white matter analyses implicate uncinate fasciculus in the ventral stream, as well as frontal aslant
tract in the dorsal stream. Together, our results yield new insights into the processing of pragmatic language and its neural substrate.
INTRODUCTION

Indirect requests—verbal statements like “it’s cold in here” that can be interpreted as “calls to action” when given adequate context — are commonly used in natural conversation. Like other forms of indirect or non-literal language, recipients of an indirect request must not only parse the lexico-semantic content of the given utterance, but also make a pragmatic inference regarding the speaker’s intention. In the specific case of indirect requests, the speaker uses indirect speech as a polite means to ask someone else to engage in a certain behavior or initiate a specific motor command—in the above example, perhaps the speaker is asking the listener to close a window in the room or turn up the thermostat that is adjacent to the listener. As indirect requests are also conceptualized as “negative state remarks,” either of these inferred actions would eliminate, or at least ameliorate, the environmental conditions objected to by the speaker (i.e. the cold temperature). The preferred action, closing the window or adjusting the thermostat, would then likely be indicated in the surrounding discourse context, often by referring to shared information or using a nonverbal indicator like eye gaze or gesture (Kelly et al., 1999; Evans and Hux, 2011). We study indirect requests here as a means to examine how the brain integrates information from context with the speaker’s utterance during pragmatic language processing. More specifically, we test the hypothesis that the canonical peri-Sylvian language regions interact with social and executive regions in prefrontal cortex in order to facilitate inferential processing during indirect request comprehension.

Despite its ubiquity in daily conversation, surprisingly little research has examined the cognitive and neuroanatomic correlates of indirect request comprehension. Furthermore, a large proportion of the previous research on this topic
has focused on so-called “conventionalized” indirect requests, which are relatively subtle manipulations that typically involve questioning whether or not someone has the ability or felicity to perform an action, rather than the willingness to perform an action. For example, “Can you pass the milk?” is a conventional indirect request, with the direct meaning “Are you able to pass the milk” and indirect meaning “Pass the milk.” Previous research has demonstrated that these conventional indirect requests are processed quickly and automatically, perhaps without even recognizing that they are indirect at all (Gibbs, 1981, 1983; Holtgraves, 1994). Accordingly, conventionalized indirect requests are not an appropriate means to study the increased processing demands that may be associated with pragmatic language.

Non-conventional (or “particularized”) indirect requests, on the other hand, are situational- or context-dependent. Like the above example (“It’s cold in here”), this class of indirect request requires that recipients go beyond the directly coded meaning of the speaker utterance and make a pragmatic inference. The motivation of a speaker to use a non-conventional indirect request often depends on a variety of factors, including, but not limited to, plausible deniability, politeness, degree of imposition on the receiver, social relationship between speaker and receiver, and more (Holtgraves, 1994; Pinker et al., 2008; Stewart et al., 2018).

Another common theme in the early indirect request literature has been its developmental trajectory: when do children acquire the ability to interpret and respond to indirect requests for action? Generally speaking, these studies have demonstrated that children are able to interpret indirect requests at a young age, potentially as early as 18 months but more likely around 4-7 years (Leonard et al., 1978; Carrell, 1981; Elrod, 1983; Ledbetter and Dent, 1988; Bernicot et al., 2007; Schulze et al., 2013; Schulze and Tomasello, 2015). Importantly, children’s ability to interpret indirect speech acts and
other types of pragmatic language has been shown to depend not only on their chronological age, but also on their linguistic competence and “theory of mind” (Ledbetter and Dent, 1988; Sullivan et al., 1995; Hancock et al., 2000; Whyte and Nelson, 2015; Bosco and Gabbatore, 2017; Trott and Bergen, 2018). Such evidence supports our working hypothesis that pragmatic language processing, including that of indirect requests, involves language regions of the brain as well as non-language brain regions typically associated with social cognition and mentalizing.

Importantly, over the last few years, cognitive neuroscientists have begun to examine the neural basis of indirect request comprehension using fMRI. In two complementary studies, Van Ackeren and colleagues (2012, 2016) demonstrated that indirect requests activate social/mentalizing regions including medial prefrontal cortex (mPFC), temporoparietal junction (TPJ), and precuneus, as well as regions activated in an action localizer including precentral gyrus and inferior parietal lobule (IPL). While promising, these results were limited in their ecological and face validity. For example, in van Ackeren et al. (2012), the indirect request stimuli, which paired simple oral sentences (e.g. “It is very hot here”) with static visual stimuli (e.g. a room with a closed door versus a desert) were correctly identified as requests only ~70% of the time (Van Ackeren et al., 2012). Stimuli were similarly non-traditional in the follow-up experiment. We typically classify indirect requests as speaker-initiated: the speaker will make an indirect statement in order to prompt a thought or behavior in the listener. In this experiment, the speaker asked a direct question (e.g. “Shall I move the television closer to the sofa?”) and the listener replied with indirect speech indicating either agreement or disagreement with the proposed action (e.g. “It is quite far away”) (Van Ackeren et al., 2016).
Accordingly, in the current paper, we use a novel and carefully controlled
dialogue-based paradigm to study indirect request comprehension during natural
communication. Furthermore, rather than study healthy young adults using functional
neuroimaging techniques, a correlational approach that is commonly used but subject to
various confounds, we adopt a lesion model approach and study patients with behavioral
variant frontotemporal dementia (bvFTD). A rare young-onset neurodegenerative
disease, bvFTD is characterized by poor executive function and changes in social
comportment and personality due to progressive atrophy in frontal and anterior temporal
regions (Rascovsky et al., 2011). Importantly, while some discourse deficits have been
reported in bvFTD, including problems with non-literal and figurative language (Lough et
al., 2006; Kipps et al., 2009; Rankin et al., 2009; Shany-Ur et al., 2011; Kaiser et al.,
2013), patients are largely non-aphasic and consequently, represent an appropriate
lesion model for studying the contribution of non-linguistic cognition to everyday spoken
discourse (Kumfor et al., 2017; Grossman, 2018). To our knowledge, no studies to date
have examined indirect request comprehension in bvFTD, although deficits have been
reported in other populations also known to have pragmatic language deficits, including
post-stroke aphasia, traumatic brain injury, autism, and schizophrenia (Weylman et al.,
1989; Corcoran et al., 1995; Ozonoff and Miller, 1996; Levey and Goldfarb, 2003;
Champagne-Lavau and Stip, 2010; Evans and Hux, 2011). Importantly, extending upon
the work of these prior studies, which were all behavioral in nature, here we use high-
resolution T1 structural magnetic resonance imaging to examine the brain basis of
indirect request processing. Finally, as patients with bvFTD are also known to have
significant yet focal white matter disease (Agosta et al., 2012), we further examine the
patterns of structural connectivity related to performance in order to build a large-scale,
multimodal network for real-world, pragmatic communication.
MATERIALS AND METHODS

Participants

Participants included 16 patients with bvFTD and 16 age- and education-matched healthy controls. See Table 16 for a summary of demographic and clinical characteristics. All patients were diagnosed by board-certified neurologists (M.G. and D.J.I) using published criteria and a multidisciplinary consensus procedure (Rascovsky et al., 2011). As some bvFTD patients may develop language deficits associated with semantic variant primary progressive aphasia (svPPA) or motor deficits associated with amyotrophic lateral sclerosis (ALS), any patients with symptomatic evidence of a secondary diagnosis were excluded from the sample population. All alternative causes of cognitive difficulty (e.g. vascular dementia, Alzheimer's disease, hydrocephalus, stroke, head trauma) were also excluded by clinical exam, neuroimaging, CSF, and blood tests. Patients were not taking any medications that could interfere with cognition. As summarized in Table 16, severity of overall cognitive impairment was assessed in patients using the Mini-Mental State Examination (MMSE), a brief 30-point assessment of overall cognitive functioning in the elderly. On average, patient scores all fell in the mild range. Healthy control subjects were verified through negative self-report of neurological or psychiatric history, a score greater than or equal to 28 on MMSE, and a brief neurological exam by a physician. All subjects were recruited from the Penn Frontotemporal Degeneration Center and gave informed consent according to a protocol approved by the Institutional Review Board at the University of Pennsylvania and in accordance with the Declaration of Helsinki.
Experimental Design and Statistical Analysis

Stimulus materials consisted of 72 two-sentence narratives (48 matched experimental items and 24 filler items of similar structure). All narratives were formulated such that the first sentence provided situational context, and the second sentence contained a remark from Person A (“the speaker”) to Person B (“the listener”). Because non-verbal cues are known to improve comprehension of indirect requests (Kelly et al., 1999), the second sentence always included a present participial phrase as well, with the speaker either “gesturing” or “pointing at” an object in the environment.

Each narrative was constructed in a triad of stimuli, such that the first sentence was identical across each item in the triad and the second sentence differed. It was thus the second sentence that determined the item’s classification as direct, indirect, or filler. Please see Table 17 for more information on these 3 conditions, and note that only the direct and indirect trials will be analyzed in the current paper. Since both of these items required a “yes” response, we minimized response bias by including filler items that had a correct “no” response (see Table 2 for example). Filler items were not considered further.

Stimuli were carefully constructed to minimize linguistic variation within and across conditions. The direct and indirect items were matched within each items for number of syllables, mean word frequency (Brysbaert and New, 2009), and mean concreteness (Brysbaert et al., 2014). For word frequency and concreteness, a mean score was generated for each sentence by averaging across the individual scores of each content word. This careful matching procedure is meant to ensure that any differences in processing direct and indirect items are due to the manipulation of inferential demand, and not to any unintentional surface level differences in linguistic
properties. Finally, all stimuli were presented as printed text in order to avoid any confounds introduced by prosodic cues inherent in the speech stream.

Stimulus presentation, timing, and responses were controlled via E-Prime presentation software. On each trial, a fixation cross was presented (3 seconds), followed by Sentence 1 (3 seconds), and Sentence 2 (3 seconds). All sentences remained on screen as subsequent text was presented, in order to account for different reading speeds and to reduce any working memory demands. Following each trial, subjects were presented with the following probe: “Did [name of speaker] ask [name of listener] to do something?” and given 10 seconds to respond via button press. Response accuracy were recorded for each item. Items were counterbalanced so that half of the narratives had a female speaker and male listener, and half of the narratives had a male speaker and female listener. The gender balance in each narrative was intended to make character tracking easier for participants. Stimulus items were randomly ordered. All participants were trained prior to testing and completed 6 practice trials. In total, task administration took approximately one hour.

Prior to data collection, stimulus validity was confirmed via pre-testing. In a norming study, healthy, young adult subjects (n=8) were asked to read each dialogue and respond to a series of questions via button press. As in the main experiment, subjects were first asked to indicate if the speaker asked the listener to do something (yes or no). Overall, subjects performed at ceiling, with a mean accuracy of 97.59% across all items. Furthermore, there was no significant difference for accuracy [direct=99.43% (±3.10) correct, indirect=97.20(±12.50); t=0.95, p=0.35] between the direct and indirect conditions.

We assessed performance according to response accuracy, as well as a compound score we refer to as the “relative impairment score.” that incorporates both
direct and indirect accuracy into one measurement. The relative impairment score, which was intended to normalize a patient’s impairment in the indirect condition to their baseline performance in the direct condition, was calculated in each individual subject by subtracting accuracy in the direct condition from accuracy in the indirect condition and dividing by accuracy in the direct condition (impairment score per subject = [indirect accuracy – direct accuracy] / direct accuracy). All analyses of task performance used non-parametric statistics as the data were not normally distributed according to Shapiro-Wilks tests. Between-group comparisons were thus performed with Mann-Whitney tests, and within group-comparisons with Wilcoxon tests. Correlations were calculated using the Spearman method. All statistical analyses were performed in R (https://cran.r-project.org/).
Table 16. Demographics for Experiment 4. Mean (±SD) of group demographic characteristics. *bvFTD: behavioral variant frontotemporal dementia; MMSE: Mini-Mental State Examination

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>bvFTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Age (y)</td>
<td>62.06 (9.22)</td>
<td>63.88 (6.94)</td>
</tr>
<tr>
<td>Education (y)</td>
<td>16.00 (2.48)</td>
<td>16.75 (2.82)</td>
</tr>
<tr>
<td>Gender (N female)</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>MMSE (/30)</td>
<td>29.19 (0.98)</td>
<td>27.00 (2.55)</td>
</tr>
<tr>
<td>Disease Duration (y)</td>
<td>N/A</td>
<td>2.56 (2.03)</td>
</tr>
</tbody>
</table>

Table 17. Sample Stimulus Materials for Experiment 4.

Operational definitions of each condition are as follows:

1 direct request: The speaker explicitly asks the second actor to initiate a certain behavior using the imperative form. The answer to the prompt should be yes for all trials.

2 indirect request: The speaker makes a negative state remark (i.e. something that the environment or speaker is lacking/in need of), followed by a deictic gesture, in order to hint at the second actor to initiate a certain behavior. The answer to the prompt should be yes for all trials.

3 filler: The action is completed by the speaker him/herself. No request is made. This condition is included so that there are some trials in which “no” is the correct response to the given prompt. It will not be analyzed as part of this manuscript.
Neuropsychological Battery

In order to assess the potential contribution of linguistic and non-linguistic cognitive processes to indirect request comprehension, bvFTD patients were also administered a brief neuropsychological battery. Language was assessed with two measures, the Multi-Lingual Naming Test (Gollan et al., 2012) and a grammatical comprehension sentence-picture matching task (TROG) (Charles et al., 2014); executive function with the backward digit span (BDS) (Wechsler, 1997) and Trailmaking Test B (TMT) (Reitan, 1958); and social cognition with the Social Behavior Observer Checklist (SBOC, part of the National Alzheimer’s Coordinating Center Uniform Data Set).

Structural Image Acquisition

High-resolution volumetric T1-weighted structural magnetic resonance imaging (MRI) were collected for 14 bvFTD patients and an independent cohort of 25 healthy age and education-matched controls from the surrounding community (mean age = 67.23 (7.46), p = 0.37; mean education = 15.88 (2.19) p=0.22). These controls were used to define an average template brain of comparable age that can be used to identify regions of significant gray matter disease in patients, on a voxel by voxel basis. A T1 image was not available for two patients with bvFTD due to safety concerns (i.e. pacemaker, claustrophobia). MRI volumes were acquired using a magnetization prepared rapid acquisition with gradient echo (MPRAGE) sequence from a SIEMENS 3.0T Tim Trio scanner using an axially acquired protocol with the following acquisition parameters: repetition time (TR)=1620 ms; echo time (TE)=3.87 ms; slice thickness=1.0 mm; flip angle=15°; matrix=192×256, 160 slices, and in-plane resolution= 0.9766×0.9766 mm2. Whole-brain MRI volumes were preprocessed using Advanced Normalization Tools (https://github.com/ANTsX/ANTs) using the state-of-the-art antsCorticalThickness
pipeline described previously (Avants et al., 2008; Klein et al., 2010; Tustison et al., 2014). Briefly, processing begins by deforming each individual dataset into a standard local template space that uses a canonical stereotactic coordinate system, generated using a subset of images from the open access series of imaging studies dataset (OASIS) (Marcus et al., 2010). ANTs then applies a highly accurate registration algorithm using symmetric and topology-preserving diffeomorphic deformations, which minimize bias to the reference space while still capturing the deformation necessary to aggregate images in common space. The ANTs Atropos tool uses template-based priors to segment images into six tissue classes (cortex, white matter, CSF, subcortical gray structures, brainstem, and cerebellum) and generate corresponding probability maps. Voxelwise cortical thickness is finally measured in millimeters (mm). Resulting images are warped into Montreal Neurological Institute (MNI) space, smoothed using a 2 sigma smoothing kernel, and downsampled to 2mm isotropic voxels.

Voxel-wise Analyses

To define areas of significant cortical thinning in bvFTD, non-parametric, permutation-based imaging analyses were performed with threshold-free cluster enhancement (Smith and Nichols, 2009) and the randomise tool in FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki). Briefly, permutation-based t-tests evaluate a true assignment of cortical thickness values across groups (signal) relative to many (e.g. 10,000) random assignments (noise). Accordingly, permutation-based statistical testing is robust to concerns regarding multiple comparisons and preferred over traditional methods using parametric-based t-tests as permutation testing effectively controls for false positives (Winkler et al., 2014). Cortical thickness was compared in patients relative to the independent cohort of 25 healthy controls described above and restricted
to an explicit mask of high probability cortex (>0.4). We report clusters that survived a statistical threshold of p<0.01, correcting for multiple comparisons using the family wise error (FWE) rate relative to 10,000 random permutations. Results were projected onto the Conte69 surface-based atlas using Connectome Workbench (http://www.humanconnectome.org/software/connectome-workbench.html).

To relate behavioral performance to regions of significant cortical thinning, we fit linear regression models with the randomise tool of FSL and the relative impairment score as a covariate. Permutations were run exhaustively up to a maximum of 10,000 for each analysis. To constrain our interpretation to areas of known disease, we restricted our regression analyses to an explicit mask containing voxels of significant cortical thinning, as defined by the group comparison described above. Results outside these regions of known disease would be difficult to interpret since they could be attributed to a variety of individual differences unrelated to disease per se (e.g. healthy aging, genetic variation, etc.). For the regression analyses, we report clusters surviving a height threshold of p<0.005 and 10 contiguous voxels, a threshold selected a priori for optimal balance of Type I and Type II error rates (Lieberman and Cunningham, 2009). Results were projected onto slices using MRItcron software (Rorden and Brett, 2000).

**ROI Analyses**

Next, we conducted a series of region-of-interest (ROI) analyses in order to specifically test our hypothesis that the canonical peri-Sylvian language regions interact with social and executive regions in prefrontal cortex during indirect request comprehension. We defined prefrontal regions of interest using pre-existing and publicly available probabilistic group maps created from functional localizers—a theory of mind localizer (Dufour et al., 2013) for social brain regions and a working memory localizer...
(Fedorenko et al., 2013) for executive brain regions. Accordingly, the prefrontal social
ROIs included: dorsomedial prefrontal cortex (dmPFC), middle medial prefrontal cortex
(mmPFC), and ventromedial prefrontal cortex (vmPFC). The executive ROIs included
dorsolateral prefrontal cortex (DLPFC) and orbital middle frontal gyrus (oMFG).

Using customizable and open-source QuANTs software originally developed in
conjunction with our laboratory (https://github.com/ftdc-picsl/QuANTs/tree/master/R), we
extracted mean cortical thickness values for each of the 5 network ROIs for each
subject. Each ROI was warped from MNI space to the subject's native T1 space prior to
extracting the estimates of cortical thickness (mm).

Diffusion Tensor Imaging: Procedure and Analysis

White matter tracts play a critical role in network activity by transmitting neuronal
activity across spatially separate gray matter regions, both within and across
hemispheres. Therefore, even when gray matter regions are intact, synchronized
network activity can be disrupted if there is damage to the white matter projections
connecting gray matter nodes to each other. Because of this possibility, we used
diffusion tensor imaging to examine patterns of structural connectivity in bvFTD and
build a large-scale, multimodal network underlying speech act comprehension.

Diffusion weighted imaging (DWI) was available for the same 14 bvFTD patients
with T1 imaging. A 30-directional DWI sequence was collected using single-shot, spin-
echo, diffusion-weighted echo planar imaging (FOV=240 mm; matrix size =128x128;
number of slices = 70; voxel size = 1.875x1.875x2.2 mm3, TR = 8100 ms; TE = 83 ms;
fat saturation). Thirty volumes with diffusion weight (b=1000 s/mm2) were collected
along 30 non-collinear directions, and five volumes without diffusion weight (b=0 s/mm2)
were collected per subject.
The diffusion images were processed using ANTs (Tustison et al., 2014) and Camino (Cook et al., 2006). Motion and distortion artifacts were removed using affine coregistration of each diffusion-weighted image to the average of the unweighted (b= 0) images. Diffusion tensors were calculated using a weighted linear least-squares algorithm (Salvador et al., 2005) implemented in Camino. Fractional anisotropy (FA) was computed in each voxel from the DT image, and distortion between the subject’s T1 and DT image was corrected by registering the FA to the T1 image. DTs were then relocated to the local template for statistical analysis by applying the FA-to-T1, T1-to-local template, and local template-to-MNI warps, and tensors were reoriented using the preservation of principal direction algorithm (Alexander et al., 2002). Each participant’s FA image was recomputed from the DT image in MNI152 template space and smoothed using a 2-sigma smoothing kernel.

Like the pipeline for GM analysis, we used the randomise tool in FSL to compare FA in patients relative to the same cohort healthy age-matched controls. The two-sample t-test of patients vs. controls was run with 10,000 permutations and restricted to voxels containing WM based on an explicit mask of high probability WM (minimum FA considered WM = 0.20). We report clusters that survived a statistical threshold of p<0.005 and a minimum cluster extent of 200 voxels. Regression analyses then related patient impairment to reduced FA, using a covariate for the relative impairment score. These regressions were restricted to the results of the previous analysis—that is, only voxels showing a significant effect of group. As above, we report clusters surviving a height threshold of p<0.005 and a minimum of 10 contiguous voxels.

**Tract-based Analysis**
Analogous to the ROI analyses above, we next adopted a tract-based (rather than voxel-wise) approach to identify which white matter projections in the brain are related to indirect request comprehension. We defined our tracts of interest based on the Johns Hopkins’ ICBM-DTI-81 white matter labels atlas, a set of 48 white matter tract labels expertly created by hand segmentation of a standard-space average of DTI imaging maps from 81 healthy adult subjects (https://identifiers.org/neurovault.collection:264). We selected those white matter tracts with portions coursing through the frontal lobes, including: uncinate fasciculus, corpus callosum, superior longitudinal fasciculus, superior fronto-occipital fasciculus, and sagittal stratum (Note: per the atlas: the sagittal stratum includes both inferior longitudinal fasciculus and inferior fronto-occipital fasciculus). Using the same QuANTS software as above, we extracted mean fractional anisotropy values for each of the 5 white matter tracts for each subject. Each tract was warped from MNI space to the subject’s native space prior to extracting the estimates of fractional anisotropy.

RESULTS

Analysis of Task Performance

The critical contrast in the current experiment concerns the difference in performance between stimuli containing an indirect request compared to stimuli containing a direct request. Accordingly, our first objective was to test the hypothesis that inferential demand (i.e. whether a request is conveyed directly or indirectly) modulates response accuracy in bvFTD. Results (summarized in Figure 20) demonstrate that healthy controls subjects performed at ceiling in both direct and indirect conditions, with no significant difference between conditions ($W=34.5$, $p=0.50$). By
comparison, patients with bvFTD performed significantly worse in the indirect condition than the direct condition (W=91.50, p=0.01). Patients with bvFTD were also significantly impaired relative to healthy controls in the indirect condition (U=181.50, p=0.039), but did not differ in the direct condition (U=175.00, p=0.07). These findings underline a selective deficit in indirect comprehension in bvFTD, and the null result in the group comparison in the direct condition suggests that segmental language ability—the ability to parse single words and sentences—is difficult to implicate in bvFTD patients’ indirect performance deficit.

To confirm these group-level results on an individual basis, we also calculated a relative impairment score by dividing the difference between direct and indirect performance by direct performance. This procedure (relative impairment = [indirect accuracy – direct accuracy]/ direct accuracy) yields a normalized measure representing how much better or worse a subject performs in the indirect condition than the baseline direct condition, with more negative scores representing a greater degree of impairment. Here, results again indicated that bvFTD patients (mean relative impairment = -0.11(±0.19)) were significantly more impaired in indirect request comprehension than their healthy control counterparts (mean impairment = -0.002 (±0.05), U=189.50, p=0.01). 12 (75%) of 16 bvFTD patients showed a negative relative impairment score.

Correlational Analyses with Neuropsychological Measures

Next, to examine the cognitive associate(s) of the observed deficit in bvFTD patients, we administered a brief neuropsychological battery, including language, executive, and social measures that may contribute to inferential processing. We used Spearman correlations to relate these independent measures to the relative impairment score, defined above. Our first aim was to demonstrate that impairment in bvFTD is
independent of language ability. In line with the earlier behavioral findings (i.e. no patient impairment in the baseline, direct condition), results indicated that language ability, assessed by both a naming task and a grammatical comprehension task, was not associated with the relative impairment score. A null result was also observed for backwards digit span: even though patients with bvFTD consistently show decreased working memory capacity (Kramer et al., 2003; Libon et al., 2007; Baez et al., 2016), we found no relationship between working memory and impairment in indirect comprehension in this experiment. An independent component of executive function, however, did show a significant effect: mental flexibility, as assessed by Trailmaking Test B, was highly correlated with the impairment score ($\rho =-0.60$, $p=0.04$). Finally, in the social domain, the impairment score was also positively associated with the Descriptor score of the Social Behavior Observer Checklist—a measure reflecting the number of abnormal social behaviors (e.g. telling inappropriate jokes, disclosing overly personal information, violating personal space boundaries, etc.) demonstrated by a subject in an uncontrolled, naturalistic setting. This positive relationship ($\rho =0.60$, $p=0.03$) has at least two possible explanations: 1) a patient’s inability to infer a speaker’s true intended meaning from speech leads to abnormal social behavior (i.e. misdirect or lack of response/apathy to another’s request) and/or 2) a patient’s reduced social competence or insight leads to their inability to infer another’s intention during a request. Our data do not allow us to distinguish between these possibilities to determine the basis for the observed effect. See Table 18 for results.
Figure 20. Behavioral Results for Experiment 4. A. Mean (±SEM) response accuracy in the direct and indirect conditions for controls (black) and patients with behavioral variant frontotemporal dementia (gray). B. Mean (±SEM) relative impairment score for controls (right) and patients with behavioral variant frontotemporal dementia (left).

Table 18. Correlation Results for Experiment 4. Mean (±SD) scores and Spearman’s correlations between neuropsychological measures and relative impairment score in bvFTD patients only.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Measure</th>
<th>Mean (±SD)</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language</td>
<td>Semantic Word Picture Matching(^1)</td>
<td>19.88 (0.34)</td>
<td>(\rho = -0.12, p = 0.65)</td>
</tr>
<tr>
<td></td>
<td>Grammatical Comprehension (/1)</td>
<td>0.94 (0.11)</td>
<td>(\rho = 0.26, p = 0.42)</td>
</tr>
<tr>
<td>Executive</td>
<td>Backward Digit Span</td>
<td>4.88 (1.15)</td>
<td>(\rho = 0.08, p = 0.75)</td>
</tr>
<tr>
<td></td>
<td>Trailmaking Test [B-A] (s)</td>
<td>84.29 (63.75)</td>
<td>(\rho = -0.60, p = 0.04)</td>
</tr>
<tr>
<td>Social</td>
<td>Descriptor Total, SBOC</td>
<td>3.54 (2.73)</td>
<td>(\rho = 0.60, p = 0.03)</td>
</tr>
</tbody>
</table>

* indicates significance at \(p < 0.05\), ** indicates significance at \(p < 0.01\), \(^1\)indicates measure had a maximum score of 20. \(^2\)Trailmaking test reflects the difference in time to complete Trailmaking Test A and Trailmaking Test B (B-A).
Neuroimaging Analyses

Our next objective was to determine the neuroanatomic basis of indirect request comprehension using high-resolution structural T1 MRI imaging. First, we contrasted cortical thickness in bvFTD patients relative to an independent cohort of healthy controls. This analysis revealed significantly reduced cortical thickness throughout prefrontal cortex in bvFTD patients, consistent with clinical diagnosis and a mild stage of disease. The anatomic distribution of significant gray matter disease is illustrated in Figure 21A. Table 19 summarizes peak and subpeak coordinates.

To relate patient deficits in indirect request comprehension to cortical thickness, we performed a regression analysis with the relative impairment score as a covariate. Greater relative impairment in the indirect condition was related to reduced cortical thickness in a prefrontal network including medial prefrontal cortex and bilateral orbitofrontal cortex—both regions that are traditionally associated with perspective-taking and social cognition in bvFTD (Healey and Grossman, 2018). See Figure 21B for the voxel-wise results. Next, to directly test our hypothesis that prefrontal regions implicated in social cognition and executive function are involved in indirect request comprehension, we conducted a series of ROI analyses. Consistent with our voxel-wise analyses, we found a significant relationship between cortical thickness and impairment within two social ROIs: vmPFC and mmPFC. Importantly, we also observed a positive association between cortical thickness and relative impairment within the left DLPFC—a region typically associated with executive function and the multiple-demand network. We did not observe DLPFC in our previous voxel-wise analyses because it not included in the explicit mask of reduced cortical thickness that was used to constrain our regression. Together, the voxel-wise and ROI analyses offer strong support for our model of indirect request comprehension that posits critical roles of non-language brain regions in
prefrontal cortex, including those traditionally associated with social cognition and/or executive function. See Figure 22 for plots depicting the relationship between each ROI and relative impairment.

Finally, following much the same procedures as the gray matter analyses, we also conducted a series of white matter analyses. While the majority of previous work in language science has focused primarily on cortical contributions to processing, we adopt a network approach here and consider the structural connectivity necessary for intact performance. First using a voxel-wise approach, we observe a significant change in FA in the following tracts within bvFTD: superior longitudinal fasciculus (which interconnects peri-Sylvian regions) and frontal aslant (connecting inferior frontal gyrus to motor-associated regions). We then examined if either of these tracts were associated with the relative impairment score in bvFTD, finding a significant effect only for the frontal aslant. Please see Figure 23A and Table 20 for more information. Finally, in a follow-up series of tract-based analyses analogous to our ROI-based gray matter analyses, we found a significant relationship between FA in uncinate fasciculus and relative impairment in indirect request comprehension. Please see Figure 23B for the tract-based results.
Figure 21. Neural correlates of relative impairment in patients with behavioral variant frontotemporal dementia. A: Surface renderings depicting regions of significant cortical thinning in bvFTD patients related to age-matched healthy controls. Heat map intensity refers to t-stat values. B: Regions of significant cortical thinning in bvFTD patients relative to age-matched healthy controls (red and blue regions) and regions of significant cortical thinning associated with relative impairment in bvFTD (red areas, only).
Table 19. MNI Coordinates for Experiment 4 Imaging Results

A: Peaks and subpeaks for regions of cortical thinning in patients with behavioral variant frontotemporal dementia relative to age-matched healthy controls. B: Regions of cortical thinning in patients with bvFTD related to relative impairment in the short condition. BA, Brodmann Area; MNI, Montreal Neurological Institute; sub, subpeak.

<table>
<thead>
<tr>
<th>Neuroanatomic Region (BA)</th>
<th>L/R</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>t-stat</th>
<th>voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>lateral orbitofrontal cortex (47)</td>
<td>R</td>
<td>44</td>
<td>26</td>
<td>-16</td>
<td>5.95</td>
<td>5,215</td>
</tr>
<tr>
<td>medial prefrontal cortex (10)</td>
<td>R</td>
<td>16</td>
<td>46</td>
<td>10</td>
<td>5.70</td>
<td>sub</td>
</tr>
<tr>
<td>insula (13)</td>
<td>R</td>
<td>36</td>
<td>14</td>
<td>-16</td>
<td>5.64</td>
<td>sub</td>
</tr>
<tr>
<td>medial prefrontal cortex (10)</td>
<td>L</td>
<td>-4</td>
<td>50</td>
<td>12</td>
<td>5.21</td>
<td>sub</td>
</tr>
<tr>
<td>prefrontal cortex (9)</td>
<td>R</td>
<td>18</td>
<td>44</td>
<td>36</td>
<td>6.40</td>
<td>890</td>
</tr>
<tr>
<td>cingulate cortex (32)</td>
<td>L</td>
<td>-4</td>
<td>12</td>
<td>36</td>
<td>3.78</td>
<td>38</td>
</tr>
</tbody>
</table>

| lateral orbitofrontal cortex (11)         | L   | -26  | 38   | -18  | 3.91   | 20     |
| medial prefrontal cortex (10)             | R   | 6    | 50   | 12   | 2.57   | 19     |
| medial orbitofrontal cortex (11)          | R   | 26   | 30   | -14  | 2.90   | 16     |
| medial prefrontal cortex (9)              | R   | 10   | 40   | 18   | 2.42   | 10     |

Figure 22. Experiment 4 ROI Associations with Indirect Impairment. Graphs plot the relationship between network cortical thickness and relative impairment score. See bottom right corner of each plot for $R^2$ values.
Figure 23. White Matter Imaging Results for Experiment 4. A: Results of voxel-wise analysis show regions of reduced fractional anisotropy (blue) in bvFTD relative to healthy controls and regions of reduced fractional anisotropy (red) related to impairment in bvFTD. B: Results of tract-based analysis. Graph plots the relationship between fractional anisotropy and relative impairment score. See bottom right corner of plot for $R^2$ values.

Table 20. MNI Coordinates for Experiment 4 Diffusion Tensor Imaging Results. A: White matter tracts showing reduced fractional anisotropy in patients with behavioral variant frontotemporal dementia relative to age-matched healthy controls. B: Regions of fractional anisotropy in patients with bvFTD related to indirect impairment in the short condition. BA, Brodmann Area; MNI, Montreal Neurological Institute; sub, subpeak.
DISCUSSION

During natural conversation, people often state their needs or desires indirectly, rather than directly: they may hint at what they want or use innuendos and “doublespeak” (Pinker et al., 2008). Take, for instance, the following example: “It’s so loud in here.” Given adequate context, this statement can function as a request to turn down the music (or other noise source), rather than a passing factual comment on the volume with no intended consequence. While there has been some debate regarding the way in which we interpret indirect requests like this one, most contemporary theories agree that successful comprehension of indirect requests requires an inference process (Holtgraves, 1994). Accordingly, in the present work, we study indirect requests in non-aphasic patients with bvFTD as a means to investigate how the brain integrates information across traditional linguistic and non-linguistic domains. Using a novel dialogue-based task, we demonstrate that patient comprehension is impaired only when a speaker’s request is conveyed indirectly. Furthermore, patient impairment is largely due not to core linguistic function (i.e. the parsing of single words and sentences, dependent on left peri-Sylvian regions) but rather to social and executive functioning, dependent on a gray-and-white matter network network including medial, orbital, and dorsolateral prefrontal cortices. Our results and their implications for updated theories of language neurobiology are discussed below.

Indirect request comprehension is impaired in bvFTD

Overall, our behavioral results indicated that bvFTD patients are selectively impaired in indirect request comprehension: patients performed significantly worse than healthy controls in the indirect, but not direct, condition, and significantly worse in the
indirect condition than their own performance in the direct condition. These results parallel those found by our group previously for another type of indirect speech act—that is, indirect replies, which are replies that contain information relevant to the question posed but do not answer it directly (Healey et al., under review). While this is the first study of indirect requests in bvFTD to our knowledge, related deficits in pragmatic language, including sarcasm, irony, and humor, have also been observed in this population (Lough et al., 2006; Kipps et al., 2009; Rankin et al., 2009; Shany-Ur et al., 2011; Kaiser et al., 2013). Similarly, other clinical populations with known pragmatic deficits, including schizophrenia, autism, traumatic brain injury, and post-stroke aphasia, have also been shown to have difficulty responding to indirect requests (Weylman et al., 1989; Corcoran et al., 1995; S. and J.N., 1996; Levey and Goldfarb, 2003; Champagne-Lavaud and Stip, 2010; Evans and Hux, 2011).

We do note one important methodological detail here, relevant to the interpretation of our results. According to our data, healthy adults perform at ceiling in both the direct and indirect request conditions. This is inconsistent with previous studies (Van Ackeren et al., 2012, 2016; Tromp et al., 2016), which instead suggested that healthy adults correctly classified indirect requests as such only ~75% of the time. All of these studies used sparse pictorial stimuli (no human interlocutors present) accompanied by orally presented sentences. Therefore, we believe this discrepancy can be reconciled if differences in stimulus construction are taken into account. In the current experiment, we used written stimuli that included a participial phrase, each with a verb such as “pointing,” “gesturing,” or “motioning.” We included this element intentionally, as previous research has demonstrated that people are more likely to interpret an utterance as an indirect request when the speech is accompanied by a relevant gesture, versus when speech or gesture is presented alone (Kelly et al., 1999). Because we wanted to
ensure patients performed above chance on our forced-choice task, we chose to add
this non-verbal cue to facilitate processing. Future research should directly compare
stimulus materials without and without these cues to examine how both patients with
bvFTD and healthy adults use paralinguistic information to enhance comprehension.

We also examined the cognitive factors that may mediate indirect request
comprehension in bvFTD. Previous research, while unresolved, has suggested that
discourse deficits in bvFTD are largely attributable to executive dysfunction (Harciarek
and Cosentino, 2013; Grossman, 2018). Here, we find evidence that mental flexibility, as
assessed by Trailmaking, is associated with the relative impairment score. As the
Trailmaking test probes an individual’s ability to switch from one task to another, this
finding suggests that patients with bvFTD also have difficulty switching from the literal
interpretation of an indirect request (i.e. the request as a neutral statement of fact, with
no desired outcome vis a vis the speaker) to its pragmatic one. Similar arguments have
been made in previous studies examining indirect replies, scalar implicatures, and
cognitive theory of mind in bvFTD (Healey et al., under review, Spotorno et al., 2015;
Torralva et al., 2015).

Working memory, also referred to as information updating and monitoring, is
another component of executive function that is known to be impaired in bvFTD (Miyake
et al., 2000; Kramer et al., 2003). Interestingly, although some evidence suggests that
an individual’s working memory capacity predicts inference revision ability (Tompkins et
al., 1994; Wright and Newhoff, 2002; Pérez et al., 2014), we found little evidence for a
relationship between relative impairment and the backward digit span in this population.
This null result may be due in part to the visual, rather than auditory, nature of our
stimuli: we used written text that remained visible on the screen throughout the response
window, thus separating inferential processes from other off-target processes (e.g.
working memory, prosodic pitch processing, etc.) Future work should use live interlocutors or naturally recorded speech samples to increase the ecological validity of our task and further investigate the potential role of working memory in discourse.

We note here that we were not able to collect a measure of inhibitory control, which is a third hypothesized domain of executive function (Miyake et al., 2000). Originally based on figurative language understanding, the “standard pragmatic view” of language (also known as the indirect access view) suggests that listeners/readers must first appreciate the literal meaning of an utterance before they can inhibit this interpretation and use pragmatic information to derive what a speaker truly intends (Cacciari and Glucksberg, 1994). The “direct access view,” on the other hand, suggests that listeners/readers are able to recognize the non-literal meaning of an utterance immediately, as long as they are given sufficient context (Gibbs, 2002). While recent reading-time and phrase classification studies have garnered favor in terms of the direct access view (Holtgraves, 1994; McElree and Nordlie, 1999), exploring the relationship between inhibition and indirect impairment in the context of the current experiment would also help to evaluate these two models. Future work should use assessments of inhibitory control, such as the Stroop, Go/No-Go, or Hayling Sentence Tests, to help settle this debate.

Finally, we also report an association between the indirect request impairment score and performance on the Social Behavior Observation Checklist—that is, a checklist assessing an individual’s ability to behave appropriately in a social context. While this examiner-based evaluation provides a relatively global assessment of an individual’s social cognition, this result does support previous findings suggesting an independent role for social cognition in indirect speech act processing (Healey et al., under review). Additional work using more specific measures of theory of mind,
perspective-taking, and/or self-monitoring would also be informative. For example, previous research in healthy adults has shown that individual differences in mentalizing can predict indirect request comprehension (Trott and Bergen, 2018), but it is unknown if this pattern holds true in bvFTD.

Importantly, patients with bvFTD are non-aphasic according to both clinician assessments of speech, and their performance on segmental language measures (i.e. MINT, TROG) are unrelated to indirect impairment. This confirms our observation that patients are unimpaired in the baseline, direct condition and again suggests that impairment in the indirect condition is due in part to the inability to compute the inference correctly, rather than a covert or unspecified linguistic deficit. We do point out, however, that previous work examining indirect replies in bvFTD did find a relationship between complex grammatical comprehension and impairment (Healey et al., under review). This may reflect the difference between indirect reply and indirect requestion, and direct comparison of both of these indirect modalities in the same patients would be informative. Moreover, the patients participating are relatively mild in disease severity (as evidenced by MMSE scores comparable to the healthy control cohort, cortical thinning restricted to frontal cortex only, and short disease durations). Indeed, core language deficits are not typically associated with bvFTD, and are only thought to emerge later on in disease course (Harciarek and Cosentino, 2013). Future research using either a longitudinal approach or a larger, more diverse sample of patients could better test this hypothesis.

These observations have important implications for interpreting the social disorders central to bvFTD. While most interpretations of the social disorder in bvFTD are attributed solely to the inappropriate behaviors observed in these patients, our findings suggest that another component may also contribute to patient impairment.
Specifically, we suggest here that it may be the interpretation of the linguistic information often mediating social interactions that is compromised in these patients. Ancillary evidence consistent with this proposal comes from the observation that bvFTD patients are often able to indicate an appropriate interpretation of a social situation when explicitly asked, but nevertheless fail to act appropriately in their performance in a comparable, real-world context. Thus, the patients’ social knowledge per se may be relatively preserved, and it is instead their interpretation of the situation that is compromised.

A multi-modal, prefrontal network supports indirect request comprehension

Models of language neurobiology emphasizing left peri-Sylvian regions, including inferior frontal gyrus and superior temporal gyrus, have been foundational in language science. These models, however, are based on the view that the human brain is modular and functionally specific. More recently, as cognitive neuroscientists have developed more advanced neuroimaging techniques and shifted more towards thinking about large-scale brain networks, evidence has been gather that is consistent with an extended language network that also encompass non-linguistic brain regions in frontal, temporal, and parietal cortices (Ferstl et al., 2008). Accordingly, to examine the neuroanatomic basis for impaired indirect request comprehension in bvFTD, we conducted a series of structural neuroimaging analyses. Using a whole-brain, voxel-wise approach, we first demonstrated that patients with bvFTD show focal cortical thinning restricted to frontal regions, including mPFC, OFC, insula, and cingulate cortex. This is consistent with a study of mild bvFTD demonstrating that early atrophy is restricted to fronto-insular regions (Seeley et al., 2008). Subsequent voxel-wise analyses examined the potential role that these prefrontal regions may play in indirect request comprehension more
specifically, finding roles for both mPFC and bilateral OFC—two regions traditionally associated with social cognition and/or theory of mind (Van Overwalle, 2009).

Take first mPFC. A recent meta-analysis contrasting pragmatic versus literal language (Reyes-Aguilar et al., 2018) suggested that mPFC, which is reliably activated for a range of stimulus forms (e.g. metaphor, idiom, irony, speech acts, etc.), represents the universal neural substrate for pragmatic language comprehension. Citing previous studies on speech act comprehension specifically, the authors suggested that mPFC is involved in both mentalizing and establishing a coherent discourse representation (Shibata et al., 2011; Van Ackeren et al., 2012; Basnáková et al., 2013; Egorova et al., 2016). This view is compatible with the work of Lieberman and colleagues (2019), who suggested that ventral mPFC plays a role in situation model building, and Bögels et al. (2014), who suggested that the same region is recruited on-demand during conversation to resolve pragmatic anomalies. mPFC has also been consistently implicated in studies of social communication in bvFTD (Healey et al., 2015, 2019, under review).

Next, consider OFC, which is sometimes implicated in the social brain network along with mPFC. In addition to playing a role in theory of mind and mentalizing, OFC is also thought to mediate a range of social behaviors including everyday decision-making, emotion and reward processing, and response inhibition (Sabbagh, 2004; Viskontas et al., 2007; Wallis, 2007; Hornberger et al., 2011; Goodkind et al., 2012). Here, disease in OFC may diminish the patients’ ability to reject the literal reading of an indirect request. Finally, an ROI analysis also suggested a role for DLPFC in indirect request comprehension. DLPFC is one component of the so-called “multiple-demand” network (Duncan, 2010; Fedorenko et al., 2013), serving to mediate high-order cognitive control including self-monitoring, task-switching, suppression of irrelevant stimuli, and selection among competing responses (Petrides, 2005; Suzuki and Gottlieb, 2013; Lemire-Rodger
et al., 2019). In the specific case of indirect requests, DLPFC may perform a selection and/or switching function, suppressing the direct, literal interpretation while simultaneously initiating the desired action response (i.e. in the “It’s cold in here” example, selecting between shutting the window versus turning up the thermostat versus no action). In addition to confirming our neuropsychological findings regarding mental flexibility, this interpretation is also consistent with the Memory-Unification-Control (MUC) model of language (Hagoort, 2005, 2013). According to MUC, the DLPFC functions as the brain’s “control” component and is invoked when language is used for social interaction. Accordingly, it facilitates complex processes including (but not limited to): selecting contextually-appropriate meanings, turn-taking, and more. Numerous fMRI studies are also consistent with this view, reporting activation of DLPFC for a range of language phenomena, including non-local syntactic dependencies, anaphora resolution, and semantic ambiguities, and more (Novais-Santos et al., 2007; Peelle et al., 2010; McMillan et al., 2012, 2013). Regardless of the specific roles that these brain regions support, our findings are consistent with the hypothesis that a neural network supporting pragmatic discourse incorporates both language and non-language components.

White Matter Correlates in Indirect Request Comprehension

As scientists have begun acknowledging that language is processed within a distributed, large-scale cortical network, there has also been increasing recognition of the importance of studying the structural connectivity that mediates functional interactions between brain regions. Accordingly, we examined the role that white matter tracts may play in indirect request comprehension. Together, our analyses suggest that both left uncinate fasciculus, connecting orbitofrontal cortex to portions of the anterior temporal lobe, and frontal aslant tract, connecting inferior frontal gyrus to supplementary
motor areas, may be critically involved. While the frontal aslant is a newly discovered white matter tract that still requires investigation, the uncinate fasciculus is thought to be broadly involved in social-emotional processing (Von Der Heide et al., 2013). For example, the uncinate fasciculus has been implicated in studies of sarcasm identification, which is a form of non-literal language similar to the indirect requests discussed here (Downey et al., 2015). Several studies have also suggested that the uncinate fasciculus may play a role in the abnormal social behaviors characteristic of a variety of developmental and psychiatric disorders, including schizophrenia, autism, and social anxiety disorder, among others (Phan et al., 2009; Jalbrzikowski et al., 2014; Samson et al., 2016; Waller et al., 2017; Lemaitre et al., 2018). Finally, although consensus has yet to be reached in regards to the functionality of the frontal aslant tract, early proposals suggest that it may be characterized as a pathway involved in the planning, timing, and coordination of motor movements, as well as resolving conflict among competing motor programs (Dick et al., 2019). Given that indirect request comprehension involves the generation of a motor or action-based response, our data seem to support this preliminary hypothesis.

Conclusions and Future Directions

While the findings described here are statistically robust, several caveats should be kept in mind when interpreting our results. First, although we tested a rare disease group, our sample size was relatively small and limited to the early, mild disease stage. As suggested above, future studies of a larger, more diverse group of subjects may reveal additional brain-behavior relationships that we did not observe here (i.e. any brain-behavior relationships outside of the frontal lobe). Relatedly, longitudinal studies would helpful in investigating the cognitive and neural basis for indirect comprehension.
Second, we report ceiling effects in our control subjects, thereby limiting examination of the individual differences associated with aging. Future work using fMRI and the same stimulus materials may help characterize the cognitive and neural correlates of pragmatic language in more detail. Similarly, while our stimuli were as naturalistic as possible given the constraints of a well-controlled studies, we used written text rather than auditory stimuli in order to maintain strict experimental control. Future studies should consider using spoken language stimuli in order to test how we integrate prosodic information from the voice and maintain indirect requests in working memory during language processing. Finally, while we focus here on indirect requests themselves, it is also possible to use this paradigm as a means to study other social factors that influence language processing, such as politeness and social hierarchy.

With these caveats in mind, we conclude that patients with bvFTD have difficulty making the pragmatic inferences necessary to support indirect request comprehension during everyday conversational exchanges. This communicative impairment appears to be due in part to limitations in both social and executive functioning, as well as degradation of a prefrontal gray and white matter networks that extends beyond the traditional, left peri-Sylvian language network.
CHAPTER 6: Longitudinal trajectories of conversational ability in behavioral variant frontotemporal dementia and Alzheimer’s dementia


ABSTRACT

Background: Difficulties with language and everyday communication often present in dementia. Good communication skills are necessary for maintaining a person’s sense of social connectedness and quality of life, as well as navigating conversations about care decisions.

Objective: To examine the longitudinal trajectories of conversation difficulties in two forms of dementia: behavioral variant frontotemporal dementia (bvFTD) and Alzheimer’s dementia (AD), and relate the observed rates of change to cognitive and neuroanatomic markers of disease.

Methods: All patients (21 bvFTD, 21 AD) underwent evaluation at the University of Pennsylvania Frontotemporal Degeneration Center. Patient communication was assessed at two timepoints at least one year apart using the Perception of Conversation Index (PCI), an informant-based measure probing several aspects of language use. Patients also underwent neuropsychological testing and high-resolution structural MRI T1 volumetric neuroimaging.

Results: Linear mixed effects models predicting the annualized change in PCI indicate a significant interaction of disease duration and clinical phenotype. While conversation difficulties in AD remain relatively stable over time, conversation difficulties increase in bvFTD as a function of disease duration. Subsequent regression analyses demonstrate
that the annualized change in PCI in bvFTD is best predicted by baseline category naming fluency, a language-mediated measure of executive functioning. Faster rates of longitudinal decline on PCI in bvFTD are also associated with more severe baseline cortical thinning in prefrontal cortices.

**Conclusions**: Our results demonstrate a functional deficit in conversational ability exists in bvFTD but not AD. Follow-up analyses have strong prognostic value: bvFTD patients with either poor executive function or focal disease in prefrontal cortex are more likely to experience conversational problems later in the course of disease. Using this prognostic information, at-risk individuals and their caregivers may be able to initiate effective strategies prior to symptom onset and thereby preserve a higher degree of functional status and quality of life.
INTRODUCTION

Humans are inherently social creatures: in fact, as much as 70% of our working hours spent in communication with one another (Klemmer and Snyder, 1972). Not coincidentally, previous research has demonstrated that the happiest individuals are those who maximize this communicative time: an individual’s well-being is strongly associated with more time spent in groups, as well as having more “substantive” conversations compared to “small talk” (Mehl et al., 2010; Milek et al., 2018). Other work reaches similar conclusions: the people who are most satisfied with their lives are highly social and have strong family and peer relationships (Diener and Seligman, 2002; Diener et al., 2018).

Unfortunately, many neurodegenerative diseases can result in both language and communication deficits. This is indeed the case with the two most common forms of dementia: Alzheimer’s disease (AD) and behavioral variant frontotemporal dementia (bvFTD). While the language deficits observed in these dementias may be secondary to other symptoms, such as episodic memory impairment in AD and dysexecutive syndrome in bvFTD, they are nevertheless impactful. For example, language deficits in AD, which often exist even early on in the disease course, include a decline in lexico-semantic abilities, evidenced by anomias and semantic paraprasias during speech production, as well as impaired word comprehension during picture naming tasks and decreased output during verbal fluency and word generation tasks (Weiner et al., 2008; Fraser et al., 2015; Kavé and Goral, 2016; Boschi et al., 2017). While pragmatic deficits can also exist (e.g. proverb interpretation, sarcasm detection, etc.), these are less common (Rapp and Wild, 2011; Maki et al., 2013). Indeed, some researchers have suggested that language in AD follows a pattern of “hierarchical decline,” such that the
smallest and simplest units of language (i.e. morphology, lexico-semantics, etc.) are affected first, while the larger and more complex units of language (i.e. discourse pragmatics) are affected only later on and in more severe cases (Emery, 2000).

The inverse pattern may be applicable in bvFTD patients, who are grossly non-aphasic but display subtle language and communication deficits that are most observable at the suprasegmental discourse level— that is, with the everyday language of stories, narratives, and conversations (Grossman, 2018). Indeed, patients with bvFTD tend to show poor narrative organization that is often impoverished in global meaning and incorporates meandering comments and other tangential speech (Ash et al., 2006, 2019; Farag et al., 2010; Mendez et al., 2017). They may speak with abnormal prosody, simplified grammatical structures, and a relative reliance on concrete (rather than abstract) concepts (Charles et al., 2014; Cousins et al., 2017, 2018; Nevler et al., 2017). Most notably perhaps, patients with bvFTD struggle with the comprehension of non-literal and pragmatic language (e.g. sarcasm, irony, humor, proverbs) that requires perspective-taking or theory of mind (Kipps et al., 2009; Shany-Ur et al., 2011; Kaiser et al., 2013; Healey et al., 2019). In opposition to findings in AD, deficits at the segmental levels, including semantic impairment at the single word level, tends to be a more secondary and/or delayed phenomenon (Harciarek and Cosentino, 2013; Hardy et al., 2016).

Importantly, while there are numerous cross-sectional studies documenting language difficulties in both of these populations, longitudinal studies examining disease spread and progressive decline in language are extremely rare. Indeed, to our knowledge, only three longitudinal studies to date have directly compared progressive decline in bvFTD and AD in any cognitive domain (Kumfor et al., 2014; Schubert et al., 2016; Ramanan et al., 2017). For example, Kumfor et al. tracked longitudinal decline in
social cognition, including emotion recognition and sarcasm detection, in bvFTD and AD, demonstrating that both measures can identify clinical bvFTD at baseline, as well as predict those patients likely to show a faster rate of decline. Schubert et al. (2016), on the other hand, examined longitudinal executive, memory, and functional profiles in bvFTD and AD. These authors reported that baseline performance was equivalent in the two groups, thereby hindering clinical diagnosis, but decline was more rapid in bvFTD than AD. Ramananan et al (2017) generally replicate these findings, describing similar clinical presentation at disease onset but increased discriminability over time as disinhibition becomes more prominent in bvFTD. None of these studies examined the neuronatomic basis for these advancing deficits.

In an attempt to address this gap in the literature and further investigate a functional domain with great impact on both patient quality of life and caregiver well-being, we study here the longitudinal trajectories of conversational ability in bvFTD and AD. To this end, we use the Perception of Conversation Index (PCI), which is a psychometrically-validated measure of conversation difficulties designed for use in non-aphasic patients and completed annually by a caregiver or other informant (Orange et al., 2009; Savundranayagam and Orange, 2011). In order to develop cognitive and neuroanatomic markers that may be important for advanced disease planning, we also collect high-resolution structural MRI imaging and a comprehensive neuropsychological battery at the initial timepoint. Indeed, early and accurate prognostic information based on testing shortly after disease onset is crucial, as it may allow for appropriate treatments aimed at preserving functional communication skills to be initiated early and families to have clear expectations regarding symptom progression.
MATERIALS AND METHODS

Subjects

The current study compared longitudinal cohorts of patients with behavioral variant frontotemporal dementia (bvFTD) and Alzheimer’s disease (AD) recruited from the Penn Frontotemporal Degeneration Center at the University of Pennsylvania. Patients were selected who 1) met published diagnostic criteria for bvFTD or AD according to board-certified neurologists and consensus procedure and 2) had at least two annual visits with the required cognitive tests. Medical and psychiatric causes of cognitive impairment were excluded by clinical exam, blood tests, and clinical neuroimaging. Patients with a diagnosis of bvFTD who had clinical evidence of a secondary phenotype, such as semantic difficulties indicative of primary progressive aphasia, were excluded. Similarly, Alzheimer’s patients with a clinical history consistent with a non-amnestic form of Alzheimer’s disease (e.g. logopenic variant primary progressive aphasia, posterior cortical atrophy) were also excluded. In total, we tested 21 patients with bvFTD and 21 patients with AD.

We selected the first two timepoints available for all subjects, with the criterion that they were separated by at least one year (bvFTD: M=1.68 years apart, SD=1.03; AD: M=1.36 years apart, SD=0.86; t=1.11, p=0.27). Disease duration was measured from onset of first reported symptom until time of test at baseline (Time 1) and follow-up (Time 2). Patients were native speakers of English, and matched for education, disease duration (at both Time 1 and Time 2) and global cognition as assessed by the Mini Mental State Exam (MMSE; Folstein, Folstein, and McHugh, 1975). Patient groups differed significantly in terms of age at onset and caregiver burden (as assessed by the Zarit Burden Interview, see below), with bvFTD patients showing an earlier age of onset.
and greater degree of caregiver burden. Accordingly, all subsequent analyses control for these metrics. For a summary of demographic and clinical variables, please see Table 21. All subjects completed a written informed consent procedure in accordance with the Institutional Review Board at the University of Pennsylvania.

<table>
<thead>
<tr>
<th></th>
<th>bvFTD</th>
<th>AD</th>
<th>t-stat</th>
<th>p-val</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>21</td>
<td>21</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td><strong>Age at Onset</strong></td>
<td>55.8 (8.3)</td>
<td>62.8 (8.2)</td>
<td>-2.72</td>
<td>0.01*</td>
</tr>
<tr>
<td><strong>Education (y)</strong></td>
<td>16.7 (2.0)</td>
<td>16.7 (2.5)</td>
<td>-0.09</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>Disease Duration (y)</strong></td>
<td>T1: 4.6 (2.1)</td>
<td>T1: 4.9 (2.5)</td>
<td>-0.37</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>T2: 6.4 (2.4)</td>
<td>T2: 6.3 (2.6)</td>
<td>0.06</td>
<td>0.95</td>
</tr>
<tr>
<td><strong>MMSE (out of 30)</strong></td>
<td>T1: 25.2 (4.9)</td>
<td>T1: 24.0 (2.7)</td>
<td>1.00</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>T2: 22.7 (7.4)</td>
<td>T2: 22.3 (4.6)</td>
<td>0.20</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Conversation Difficulties</strong></td>
<td>T1: 57.8 (31.5)</td>
<td>T1: 49.6 (27.0)</td>
<td>0.90</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>(PCI-DAT, Section 1)</strong></td>
<td>T2: 79.2 (38.4)</td>
<td>T2: 57.5 (31.6)</td>
<td>2.10</td>
<td>0.05*</td>
</tr>
<tr>
<td><strong>Caregiver Burden (ZBI)</strong></td>
<td>T1: 43.1 (15.9)</td>
<td>T1: 30.7 (12.4)</td>
<td>2.82</td>
<td>0.01*</td>
</tr>
<tr>
<td></td>
<td>T2: 43.9 (13.7)</td>
<td>T2: 33.6 (12.8)</td>
<td>2.52</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

**Table 21.** Demographics for Experiment 5. Mean (±SD) demographic and clinical variables for bvFTD and early-onset AD patients. T-tests are used to compare groups at each timepoint (T1 and T2). MMSE: Mini-Mental Status Exam; PCI-DAT: Perception of Conversation Index, Dementia of Alzheimer's Type; ZBI: Zarit Burden Interview.
The Perception of Conversation Index – Dementia of the Alzheimer Type (PCI-DAT) is an empirically derived questionnaire used to assess the nature of communication problems experienced by family caregivers of patients with AD (Orange et al., 2009; Savundranayagam and Orange, 2011). Caregiver informants complete the 74-item questionnaire, which is divided into 5 sub-sections: 1) conversation difficulties of individuals with AD; 2) conversation repair strategies used by family caregivers; 3) conversation repair strategies used by individuals with AD; 4) family caregivers’ feelings related to conversational difficulties; 5) social challenges faced by AD-caregiver dyads as a result of their communication problems. We focus here on Section 1 (“Conversation Difficulties”), which has 22 items rated on 7-point Likert Scale (maximum score: 154 points). Sample items include: “has difficulty with telephone conversations,” “only talks about a few topics,” “pauses or hesitates while searching for the right word(s),” and “has difficulty following directions.” We computed Section 1 totals for Time 1 and Time 2 for each subject, as well as a measure of annualized conversation change. The annualized change metric was calculated taking the difference in PCI-DAT scores and dividing by the interval between testing sessions. A positive annualized change score indicates the patient demonstrated increased conversation difficulties over time. In a subsequent item analysis, we also computed annualized change scores for each individual item in Section 1 of the PCI-DAT.

After completion of the PCI-DAT, caregiver informants were also given the Zarit Burden Interview (ZBI), a widely-used self-report questionnaire assessing the level and type of burden experienced by the principal carer(s) of persons with dementia (Zarit et al., 1980). Sample questions include “Do you feel embarrassed when you are around relative?” “Do you feel your social life has suffered because of your relative?” and “Do
you feel that you will be unable to take care of your relative much longer?” There are 22 items, each ranked on a Likert scale from 0-4 (maximum score 68).

Neuropsychological Assessment

All subjects selected for the current study also completed a comprehensive battery of neuropsychological testing as part of the National Alzheimer's Coordinating Center Uniform Data Set (NACC UDS) and associated FTLD Module. To assess language function, the Boston Naming Test and/or the Multi-Lingual Naming Test (MINT) was used as a measure of confrontation naming. If the MINT was used, scores were converted to the BNT scale according to the established conversion algorithm (Gollan et al., 2012). For executive function, the following tests were administered: phonemic verbal fluency (i.e. words beginning with the letter F), category fluency (i.e. animals, vegetables), backward digit span (Wechsler, 1997), and Trailmaking Test B (Reitan, 1958). For social cognition, patient caregivers completed the Interpersonal Reactivity Index, which yields subscores for Perspective-Taking and Empathic Concern, in addition to the Revised Self-Monitoring Scale, which yields subscores for “Sensitivity to Socio-emotional Expressiveness” and “Ability to Modify Self-Presentation.”

Statistical Modeling

To examine how conversation difficulties change over time, linear mixed effects models were performed using the package lmerTest in R Studio. A linear mixed effects model assessed change in PCI-DAT (Section 1, Conversation Difficulties) as a function of disease duration at timepoints 1 and 2 and clinical phenotype (bvFTD, AD). Fixed effects thus included disease duration and patient phenotype, as well as age at onset and caregiver burden, while random effects included the variability across individuals. By
including disease duration as a factor, we were able to account for differences in the timing of testing sessions across patients. Age at onset and caregiver burden were included due to the observed differences across groups (see Table 1). Furthermore, as the PCI-DAT is an informant-based measure, ratings could be skewed by the degree of burden experienced by the caregiver informant. In sum, to test for an interaction between patient phenotype and longitudinal change in conversation ability, we used the following formula: lmer(Conversation Difficulties ~ Disease Duration * Phenotype + Age at Onset + Caregiver Burden + (1|Individual). We also computed the same model in each patient group, separately.

To identify which neuropsychological measures were associated with subsequent decline, we performed a series of simple correlations, each relating the annualized rate of change in PCI within a group to each of the neuropsychological measures tested at baseline (see above for list of tests). For any significant associations, we also computed a linear regression model controlling for age of onset and caregiver burden (for the sake of consistency with previous analyses).

**Structural Imaging: Data Collection and Analysis**

MRI imaging was available at Time 1 in all patients (N=42) and an independent cohort of demographically-matched healthy controls (N=40) who self-report no psychiatric or neurological history (mean age = 61.2 years, mean education =16.0 years). All participants underwent a structural T1-weighted MPRAGE MRI acquired from a SIEMENS 3.0T Trio scanner with an 8-channel coil using the following acquisition parameters: repetition time = 1620ms, echo time = 3ms; slice thickness=10.mm, flip angle=15, matrix=192x256; 160 slices, and in-plane resolution = 0.9766 x 0.9766 mm. T1 image preprocessing was performed using Advanced Normalization Tools (ANTs)
using the state-of-the-art antsCorticalThickness pipeline described previously (Avants et al., 2008; Klein et al., 2010; Tustison et al., 2014). Briefly, processing begins by deforming each individual dataset into a standard local template space that uses a canonical stereotactic coordinate system, generated using a subset of images from the Open Access Series of Imaging Studies (OASIS) dataset (Marcus et al., 2010). ANTs then applies a highly accurate registration algorithm using symmetric and topology-preserving diffeomorphic deformations, which minimize bias to the reference space while still capturing the deformation necessary to aggregate images in common space. The ANTs Atropos tool uses template-based priors to segment images into six tissue classes (cortex, deep grey, brainstem, cerebellum, white matter, and cerebrospinal fluid/other) and generates corresponding probability maps. Voxelwise cortical thickness is finally measured in millimeters (mm). Resulting images are warped into Montreal Neurological Institute (MNI) space, smoothed using a 2 sigma smoothing kernel, and downsampled to 2mm isotropic voxels.

Voxelwise analyses of cortical thickness were performed via non-parametric permutation testing using threshold-free cluster enhancement (Smith and Nichols, 2009) and the randomise tool in FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki). Briefly, permutation-based t-test evaluate a true assignment of cortical thickness values across groups (signal) relative to many (e.g. 10,000) random assignments (noise). Accordingly, permutation-based statistical testing is robust to concerns regarding multiple comparisons and preferred over traditional methods using parametric-based t-tests, which are more susceptible to false positives (Winkler et al., 2014). Cortical thickness was compared in each patient group relative to the independent cohort of 40 healthy controls described above and restricted to an explicit mask of high probability cortex.
(>0.4). We report clusters that survived a statistical threshold of p<0.05, correcting for multiple comparisons using the family wise error (FWE) rate. Results were projected onto the Conte69 surface-based atlas using Connectome Workbench (http://www.humanconnectome.org/software/connectome-workbench.html)

To relate the longitudinal decline to regions of significant cortical thinning at Time 1, we fit linear regression models with the randomise tool of FSL and the annualized change in conversation metric as a covariate. Permutations were run exhaustively with threshold-free cluster enhancement and up to a maximum of 10,000. To constrain our interpretation to areas of known disease and minimize confounds due to simultaneously-occurring age-associated changes, we restricted our regression analyses to an explicit mask containing vowels of significant cortical thinning, as defined by the group comparison described above. For the regression analyses, we report clusters surviving a statistical threshold of p<0.05, FWE-corrected.

RESULTS

Longitudinal Changes in Conversational Ability

Both AD and bvFTD patients experience clinically significant conversation difficulties at baseline according to PCI-DAT Section 1, with 73.81% of patients scoring above the cutoff score of 35 (bvFTD = 76.19%, AD = 71.43%). This cutoff score represents one standard deviation above mean control performance, as determined by the PCI’s initial validation study (Orange et al., 2011). A one-way ANOVA shows that AD and bvFTD patients were matched for degree of conversational difficulties at baseline (Time 1) (F(1,40)=0.818, p=0.37). To examine how conversation ability changes with time, Figure 1 plots longitudinal change in PCI-DAT Section 1 scores at Times 1 and 2 in
bvFTD and AD. We then tested the relationship between conversational difficulties and disease duration at Times 1 and 2 in each patient group using a linear-mixed effects model that included age at onset and caregiver burden as fixed effects and individual as a random effect. Age at onset and caregiver burden were included as fixed effects because they were significantly different across groups (see Table 21). In the bvFTD group, results indicated that disease duration ($\beta_{\text{DiseaseDuration}} = 9.42, t=5.17, p<0.0001$; Table 22A) significantly predicted increase in conversation difficulties with time. The same mixed effects model in AD revealed no longitudinal change in conversational difficulties with time ($\beta_{\text{DiseaseDuration}} = 2.30, t=1.27, p=0.21$; Table 22B).

We next tested if the change in conversation difficulties was in fact significantly different across bvFTD and AD patients (Table 22C; Interaction Model). A mixed-effects model revealed a significant interaction between disease duration and patient group ($\beta_{\text{Duration}\text{*Group}} = 6.45, t=2.46, p=0.01$). An ANOVA comparing the null model (no Duration*Group term) and the interaction model showed that including the DiseaseDuration*Group interaction term significantly improved model fit ($X^2(1)= 5.82, p=0.015$), indicating that the increase in conversation difficulties over time in bvFTD was significantly greater than in AD. We also note here that all models were run without the inclusion of age at onset and caregiver burden as fixed effects, and results remained consistent. Furthermore, in all models, no individuals had high leverage according to Cook’s Distance (all Cook’s D<0.2).

Then, to create an index of change for each individual patient, we calculated an annualized change in conversation metric: conversation difficulties at Time 1 was subtracted from conversation difficulties at Time 2, and normalized by the interval in years between testing sessions. The annualized change in conversation was significantly greater for bvFTD (M=14.72, SD=12.78) than AD patients (M=5.85, ...
Furthermore, the annualized change in conversation metric was significantly greater than 0 in bvFTD ($t(20)=5.28$, $p<0.0001$), but not in AD ($t(20)=1.86$, $p=0.08$). A one-way ANCOVA controlling for baseline conversation difficulties (PCI at Time 1) also confirms that the annualized conversation change metric is significantly greater in bvFTD than AD ($F(1,39)=4.41$, $p=0.04$).

Finally, having observed a significant effect of disease duration in bvFTD only, we used a linear model to determine the mechanism of longitudinal decline seen in this cohort. Correlation analyses using measures from baseline neuropsychological testing revealed that only verbal fluency (either category fluency or phonemic fluency) is significantly associated with the annualized change in conversation metric ($r=-0.51$, $p=0.019$ for category fluency; $r=-0.51$, $p=0.021$ for phonemic fluency). A linear model (Table 24) suggests that annualized change in conversation can be predicted by baseline category fluency ($\beta=-1.14$, $p=0.02$) while controlling for age at onset ($\beta=-0.46$, $p=0.14$) and caregiver burden ($\beta=-0.14$, $p=0.39$). The overall model fit was good ($R^2=0.40$, Adjusted $R^2=0.30$, $p=0.03$).
Figure 24. A. Longitudinal change in conversation difficulties in bvFTD and AD. Total conversational difficulties (Section 1, PCI-DAT) for each individual with bvFTD (red) and AD (blue) at Time 1 (circle) and Time 2 (triangle) by disease duration (years from symptom onset) at each timepoint. Testing sessions for each individual are connected by dashed lines. A higher score on the PCI-DAT (maximum 154) indicates greater difficulty with day-to-day conversational exchanges, as perceived by a caregiver informant. Bold trend lines plot the linear model between Conversation Difficulties and Disease Duration separately for each patient group.
### Table 22. Linear Mixed Effects Models for Experiment 5

All models describe Conversation Difficulties as a function of disease duration. A: bvFTD only. B: AD only. C: All patients. * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>t-stat</th>
<th>p-val</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Linear Mixed Effects Model in bvFTD only</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-20.50</td>
<td>62.60</td>
<td>-0.33</td>
<td>0.15</td>
</tr>
<tr>
<td>Disease Duration</td>
<td>9.42</td>
<td>1.82</td>
<td>5.17</td>
<td>&lt;0.0001***</td>
</tr>
<tr>
<td>Age at Onset</td>
<td>0.49</td>
<td>1.02</td>
<td>0.49</td>
<td>0.63</td>
</tr>
<tr>
<td>Caregiver Burden (ZBI)</td>
<td>0.22</td>
<td>0.30</td>
<td>0.73</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>B. Linear Mixed Effects Model in AD only</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>117.18</td>
<td>49.87</td>
<td>2.35</td>
<td>0.029*</td>
</tr>
<tr>
<td>Disease Duration</td>
<td>2.30</td>
<td>1.81</td>
<td>1.27</td>
<td>0.21</td>
</tr>
<tr>
<td>Age at Onset</td>
<td>-1.42</td>
<td>20.51</td>
<td>-1.77</td>
<td>0.09</td>
</tr>
<tr>
<td>Caregiver Burden (ZBI)</td>
<td>0.378</td>
<td>40.50</td>
<td>1.12</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>C. Linear Mixed Effects Model in all patients (AD, bvFTD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>61.75</td>
<td>42.23</td>
<td>1.46</td>
<td>0.15</td>
</tr>
<tr>
<td>Disease Duration</td>
<td>2.38</td>
<td>1.93</td>
<td>1.23</td>
<td>0.22</td>
</tr>
<tr>
<td>Group (bvFTD)</td>
<td>-26.50</td>
<td>17.87</td>
<td>-1.48</td>
<td>0.14</td>
</tr>
<tr>
<td>Age at Onset</td>
<td>-0.47</td>
<td>0.66</td>
<td>-0.72</td>
<td>0.48</td>
</tr>
<tr>
<td>Caregiver Burden (ZBI)</td>
<td>0.25</td>
<td>0.23</td>
<td>1.12</td>
<td>0.27</td>
</tr>
<tr>
<td>Duration*Group</td>
<td>6.45</td>
<td>2.62</td>
<td>2.46</td>
<td>0.01*</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Mean (±SD)</td>
<td>Pearson’s r</td>
<td>p-val</td>
</tr>
<tr>
<td>----------------------</td>
<td>----</td>
<td>----------------</td>
<td>-------------</td>
<td>-------</td>
</tr>
<tr>
<td>Confrontation Naming</td>
<td>19</td>
<td>25.9 (2.90)</td>
<td>-0.20</td>
<td>0.39</td>
</tr>
<tr>
<td>Phonemic Fluency</td>
<td>19</td>
<td>9.45 (5.41)</td>
<td>-0.51</td>
<td>0.021*</td>
</tr>
<tr>
<td>Category Fluency</td>
<td>19</td>
<td>11.69 (5.41)</td>
<td>-0.51</td>
<td>0.019*</td>
</tr>
<tr>
<td>Backwards Digit Span</td>
<td>20</td>
<td>3.95 (1.66)</td>
<td>-0.02</td>
<td>0.90</td>
</tr>
<tr>
<td>Trailmaking Test B</td>
<td>15</td>
<td>172.13 (98.98)</td>
<td>0.32</td>
<td>0.22</td>
</tr>
<tr>
<td>Apathy (NPI)</td>
<td>17</td>
<td>1.94 (0.64)</td>
<td>-0.11</td>
<td>0.65</td>
</tr>
<tr>
<td>Disinhibition (NPI)</td>
<td>17</td>
<td>1.50 (1.15)</td>
<td>0.36</td>
<td>0.14</td>
</tr>
<tr>
<td>Perspective-Taking (IRI)</td>
<td>14</td>
<td>12.33 (5.05)</td>
<td>0.11</td>
<td>0.69</td>
</tr>
<tr>
<td>Empathic Concern (IRI)</td>
<td>14</td>
<td>17.4 (4.81)</td>
<td>-0.23</td>
<td>0.39</td>
</tr>
<tr>
<td>Revised Self-Monitoring Scale</td>
<td>14</td>
<td>17.53 (10.50)</td>
<td>-0.39</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Table 23. Correlation Analyses for Experiment 5. Baseline neuropsychological performance in bvFTD patients and correlations with Annualized Change in Conversation metric. NPI: Neuropsychological Interview; IRI: Interpersonal Reactivity Index. * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001.
Figure 25. Behavioral Results for Experiment 5. Annualized change in Conversation Difficulties differs across groups (A) and is related to baseline Category Fluency (B).

Table 24. Predictive Model in bvFTD for Experiment 5. Model predicts Annualized Change in Conversation metric based on baseline category fluency.
**Item Analysis**

Having demonstrated that conversation difficulties increase significantly over time in bvFTD but remain stable over time in AD, we next wanted to confirm 1) that these patterns were consistent in regards to individual features of conversation and 2) are well-aligned with the known properties of discourse impairment in each population. In other words, did the individual items showing an effect in bvFTD align with their clinical diagnosis, and were these items different from the items showing a significant change in AD? To do this, we calculated an annualized change metric for each individual item and used t-tests to determine if there is a significant change in item ratings from Time 1 to Time 2. See Supplementary Table S1 for all results in bvFTD, and Supplementary Table S2 for all results in AD. Items are ranked from highest amplitude of annualized change to lowest, and subsequently summarized in Table 25 of the main Chapter. Here, we show that the subset of items showing the most significant increase over time in bvFTD includes: only talks about a few topics, has difficulty understanding questions, needs sentences to be repeated, has difficulty keeping a conversation going, has difficulty with telephone conversations. Interestingly, these same items show no significant change in AD. We also identify some items showing no change in bvFTD over time: makes harsh or critical comments, becomes anxious or frustrated when spoken to in a loud voice, pauses or hesitates while searching for the right words, repeats the same ideas or words, forgets the details after hearing a story. While not the exact same, these items do overlap with the five individual items showing a small but significant increase in AD over time: forgets the details after hearing a story, forgets what he/she wants to say, has difficulty finding words, becomes confused, does not finish sentences, has orientation difficulties. We therefore suggest that the patterns of impairment seen in bvFTD and AD are largely dissociable.
Table 25. Summary of Item Analysis in bvFTD versus AD. An item analysis was conducted in both groups (independently) to determine the specific behaviors or features of conversation showed a significant increase over time, compared to those that remained stable over time (no significant change). Note that the bvFTD and AD groups are characterized by change in different items, and that, generally speaking, items showing a significant increase in bvFTD showed no change in AD. For more detailed information about each of the 22 items included in Section 1, please see the Supplementary Materials (Tables S1 and S2).
Structural Imaging Results in bvFTD

A two-sample t-test was conducted to identify regions of significant cortical thinning in bvFTD at Time 1 compared to healthy controls. This analysis revealed extensive atrophy throughout the frontal and temporal lobes (consistent with disease diagnosis). Next, a regression analysis relating each individual's annualized change in conversation metric to baseline cortical thickness showed that more rapid decline in conversation ability (i.e. rapid increase in PCI-assessed conversation difficulties) was associated with cortical thinning in prefrontal cortex, including portions of orbitofrontal cortex (OFC), medial prefrontal cortex (mPFC), and lateral/dorsolateral prefrontal cortex (DLPFC). See Figure 26 and Table 26 for more information.

Figure 26. Structural Neuroimaging Results for Experiment 5. Baseline cortical thinning predicts subsequent rate of annualized change in Conversation Difficulties in bvFTD. Regions of significant cortical thinning in bvFTD at baseline relative to age and education-matched healthy controls are shown in blue. Regions of significant cortical thinning associated with the Annualized Change in Conversation metric are shown in red/yellow. Heat map intensity refers to t-values.
### MNI Coordinates

<table>
<thead>
<tr>
<th>Neuroanatomic Region (BA)</th>
<th>L/R</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>t-stat</th>
<th>voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Regions of cortical thinning in bvFTD at Time 1 relative to healthy controls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>anterior insula (13)</td>
<td>L</td>
<td>-36</td>
<td>22</td>
<td>-2</td>
<td>7.25</td>
<td>39,668</td>
</tr>
<tr>
<td>anterior insula (13)</td>
<td>R</td>
<td>38</td>
<td>18</td>
<td>2</td>
<td>7.10</td>
<td>sub</td>
</tr>
<tr>
<td>orbitofrontal cortex (47)</td>
<td>R</td>
<td>30</td>
<td>36</td>
<td>-16</td>
<td>7.07</td>
<td>sub</td>
</tr>
<tr>
<td>middle temporal gyrus (20)</td>
<td>R</td>
<td>56</td>
<td>-6</td>
<td>-34</td>
<td>6.84</td>
<td>sub</td>
</tr>
<tr>
<td>medial prefrontal cortex (9)</td>
<td>L</td>
<td>-4</td>
<td>52</td>
<td>22</td>
<td>6.50</td>
<td>sub</td>
</tr>
<tr>
<td>inferior frontal gyrus (47)</td>
<td>R</td>
<td>42</td>
<td>20</td>
<td>-12</td>
<td>6.31</td>
<td>sub</td>
</tr>
<tr>
<td>inferior parietal lobule (40)</td>
<td>R</td>
<td>56</td>
<td>-38</td>
<td>44</td>
<td>4.59</td>
<td>536</td>
</tr>
<tr>
<td><strong>B. Regions of cortical thinning at Time 1 that predict subsequent decline in PCI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>medial orbitofrontal cortex (11)</td>
<td>L</td>
<td>-8</td>
<td>64</td>
<td>-14</td>
<td>5.13</td>
<td>1,725</td>
</tr>
<tr>
<td>medial prefrontal cortex (10)</td>
<td>R</td>
<td>2</td>
<td>64</td>
<td>8</td>
<td>4.75</td>
<td>sub</td>
</tr>
<tr>
<td>dorsolateral prefrontal cortex (8)</td>
<td>L</td>
<td>-22</td>
<td>34</td>
<td>48</td>
<td>5.15</td>
<td>254</td>
</tr>
<tr>
<td>lateral prefrontal cortex (10)</td>
<td>L</td>
<td>-42</td>
<td>42</td>
<td>18</td>
<td>4.41</td>
<td>116</td>
</tr>
<tr>
<td>medial prefrontal cortex (10)</td>
<td>L</td>
<td>-2</td>
<td>60</td>
<td>10</td>
<td>4.68</td>
<td>89</td>
</tr>
<tr>
<td>lateral prefrontal cortex (10)</td>
<td>L</td>
<td>-50</td>
<td>42</td>
<td>18</td>
<td>3.83</td>
<td>47</td>
</tr>
<tr>
<td>dorsomedial prefrontal cortex (9)</td>
<td>L</td>
<td>-6</td>
<td>48</td>
<td>30</td>
<td>4.57</td>
<td>33</td>
</tr>
<tr>
<td>dorsal premotor cortex (8)</td>
<td>L</td>
<td>-8</td>
<td>26</td>
<td>58</td>
<td>4.48</td>
<td>28</td>
</tr>
<tr>
<td>medial prefrontal cortex (9)</td>
<td>R</td>
<td>12</td>
<td>50</td>
<td>44</td>
<td>3.75</td>
<td>16</td>
</tr>
</tbody>
</table>

Table 26. MNI Coordinates for Experiment 5 Imaging Results. A: Regions of significant cortical thinning at baseline. Results are thresholded at p<0.01, corrected for multiple comparisons using the family-wise error rate and threshold-free cluster enhancement. B: Regions of significant cortical thinning related to Annualized Change in Conversation in bvFTD. Results are thresholded at p<0.05, corrected for multiple comparisons using the family-wise error rate and threshold-free cluster enhancement. BA: Brodmann Area; MNI: Montreal Neurological Institute; sub: subpeak.
DISCUSSION

In this study, we describe the longitudinal trajectories of conversational ability in two forms of dementia: bvFTD and AD. We first demonstrate that conversation difficulties get progressively worse over time in bvFTD, while conversation difficulties remain stable over time in AD. This confirms previous research showing that patients with bvFTD, who are clinically non-aphasic and assumed to be free of language difficulties, actually have significant impairments at the discourse level—that is, with the language of everyday life and social interactions (Ash et al., 2006; Kipps et al., 2009; Gola et al., 2015; Healey et al., 2015, 2019; Spotorno et al., 2015). We then examine the cognitive and neuroanatomic basis for this progressive decline and find that a faster rate of decline in conversational ability in bvFTD is associated with worse executive function (i.e. verbal fluency) at baseline, as well as greater cortical thinning in prefrontal cortices at baseline. Based on this information, individuals with bvFTD and their caregivers may be able to anticipate communication difficulties before they arise, initiate effective compensatory strategies, and thereby achieve a higher degree of functional status. In the sections below, we discuss the potential mechanisms underlying the decline in conversational ability that we observe in bvFTD and potential implications for treatment.

Our first analysis demonstrated that conversational difficulties increase significantly over time in bvFTD, but not in AD. While we are unaware of previous work directly examining conversation difficulties in daily life in bvFTD, this is largely consistent with the previous literature, which has found that patients with bvFTD, although non-aphasic, nonetheless struggle with communication at the discourse level. For example, patients with bvFTD have difficulties with narrative organization, referential communication, non-literal language comprehension, and indirect speech (Ash et al.,
2006; Kipps et al., 2009; Gola et al., 2015; Healey et al., 2015, 2019, submitted; Spotorno et al., 2015). All of these are components of daily conversation. Patients with AD, on the other hand, may have difficulties with language, but they tend to present more at the single word level— with word finding difficulties, substitutions, or paraphasias, for instance (Weiner et al., 2008; Fraser et al., 2015; Kavé and Goral, 2016; Boschi et al., 2017). This pattern is also confirmed by our item analysis. Here, demonstrate that items showing the most change in bvFTD are those at the discourse level (e.g. has trouble with telephone conversations, only talks about a few topics, etc.), while those items showing the most change in AD are either at the single word/sentence level (e.g. has difficulty finding words, does not finish sentences) or directly related to their primary memory impairment (e.g. forgets the details after hearing a story, forgets what he/she wants to say).

It is important to note here that the majority of previous studies showing impaired discourse communication in bvFTD were all cross-sectional in nature, with one main exception: using a sarcasm detection task, Kumfor et al. (2014) were able to demonstrate that social communication declines over time in bvFTD— a result that is well-aligned with our own results here. Although these authors observe that sarcasm detection also declines over time in AD, it is the bvFTD group that shows a greater rate of decline when the groups are directly contrasted. Sarcasm comprehension in AD (as well as bvFTD) may also show some evidence of decline due to the emotional demands of the task; emotion identification and regulation can be compromised in both groups (Bayard et al., 2014; Kumfor et al., 2014; Guzmán-Vélez et al., 2016). Future work using a variety of different social communication tasks and measures is still needed to confirm these findings.
It is also important to point out that, while the diagnostic criteria and patterns of pathological burden differ in AD and bvFTD, the two diseases can be difficult to differentiate early on in disease course—due to heterogeneity across patients, overlapping neuropsychological profiles, and the absence of definitive in vivo biomarkers for FTD (Harciarek and Jodzio, 2005; Hutchinson and Mathias, 2007). For example, a subset of bvFTD patients has been shown to have episodic memory impairment equally as severe as those seen in typical AD (Hornberger and Piguet, 2012; Irish et al., 2014; Schubert et al., 2016; Ramanan et al., 2017; Fernandez-Matarrubia et al., 2017). Recent work, however, has demonstrated some utility for social-behavioral evaluation both in the differential diagnosis of AD and bvFTD, as well as the separation of the two diseases over time (Dodich et al., 2018; Kumfor et al., 2014). For example, Dodich and colleagues (2018) demonstrated that evaluation of social behavior (including the Interpersonal Reactivity Index and Revised Self Monitoring Scale) improves the diagnostic accuracy of bvFTD relative to AD during the first two years of symptom onset. Several other groups also report significant group differences between AD and bvFTD on social and sociolinguistic measures, including theory of mind, deception and sarcasm, social decision-making, the appreciation of social norms, and more (Dodich et al., 2016; Synn et al., 2018; Bertoux and Hornberger, 2015; Shany-Ur et al., 2012; Panchal et al., 2016; Possin et al., 2013; Mendez et al., 2014). Accordingly, we suggest here that a history of progressive decline in conversational ability, either assessed objectively through experimental means or subjectively through a caregiver informant (as in the current report), represents a potential diagnostic marker to be used in differentiating these two forms of dementia.

Our next goal was to identify a cognitive marker that would help identify patients who are at risk for experiencing a faster rate of decline in their conversational abilities.
We focused this analysis solely on bvFTD patients, since this was the population at-risk for decline according to our previous analyses. We tested measures in three domains (language, executive, and social) for their association with the annualized change in conversation metric, and found that only verbal fluency (either category fluency or phonemic fluency) was significantly related to the rate of conversational decline. More specifically, individuals with poor executive function at Time 1 were shown to have a faster rate of decline in PCI from Time 1 to Time 2. This finding is consistent with previous research showing that 1) executive function, including verbal fluency, is decreased in bvFTD (van den Berg et al., 2017; Rascovsky et al., 2007; Libon et al., 2009) and 2) discourse impairment in bvFTD is due in part to executive dysfunction (Eslinger et al., 2011; Torralva et al., 2015; Healey et al., 2015, 2019, submitted).

Finally, we also sought to identify a neuroanatomic marker that would identify patients likely to experience subsequent decline in conversational abilities. Structural neuroimaging analyses indicated that more severe disease in prefrontal cortex at Time 1, including portions of medial prefrontal, orbitofrontal, and lateral prefrontal cortices, is associated with a greater rate of decline in conversation in bvFTD. Importantly, we did not observe a relationship between disease in classic language-associated brain regions (i.e. left peri-Sylvian cortex) and subsequent decline, which is consistent with the fact that patients with bvFTD are considered non-aphasic, and that baseline measures of core linguistic function, including naming, were not related to decline according to regression analyses. Instead, our results suggest that a decline in conversation in bvFTD is due to disease in extra-Sylvian regions typically associated with executive function (i.e. DLPFC) and social cognition (i.e. mPFC and OFC) (Jonker et al., 2015; Rolls, 2004; van Overwalle, 2009; Schurz et al, 2014; Kipps and Hodges, 2006; Yuan and Raz, 2014; Badre and Wagner, 2004; Badre, 2008)—the two hallmark
characteristics of bvFTD. Findings such as these are consistent with the hypothesis that effective conversation depends on a large-scale neural network involving cortical regions important not only for segmental language, but also for social-executive functioning, and that disease in any portion of this network can disrupt conversational abilities.

Our results have important implications for clinical diagnosis and intervention, as we demonstrate 1) it is possible to distinguish bvFTD and AD based on decline in communicative behaviors and 2) it is possible to identify bvFTD patients at risk for faster decline based on baseline neuropsychological functioning and structural neuroimaging. We hope that these early prognostic markers can be used to prompt important conversations about care decisions early on in disease course, so that patients can participate in their own treatment and medical decisions in a way that may not be possible as symptoms progress. Clinicians can also use these prognostic markers to initiate new treatment strategies aimed at preserving language function in an individual. For example, recent studies in other forms of FTD (namely semantic variant primary progressive aphasia and non-fluent agrammatic primary progressive aphasia) have demonstrated that neuromodulatory techniques including transcranial direct current stimulation are effective in improving linguistic outcomes, including naming, grammatical comprehension, and overall speech output (Cotelli et al., 2014; Gervits et al., 2016; Trebbastoni et al. 2013). In bvFTD specifically, one study has also demonstrated that tDCS over medial prefrontal cortex (a region also implicated here) can improve theory of mind and the ability to represent another’s communicative intent—two abilities key to daily discourse and conversation. Beyond brain-based interventions, past research has also suggested that caregivers can be trained to use conversational repair strategies (e.g. use co-speech gesture, give options, etc.) to help improve communication outcomes with their loved one (Savundranayagam and Orange, 2014; Samuelsson and
Hyden, 2017; Taylor-Rubin et al., 2017; Olthof-Nefkens et al., 2018; Nguyen et al., 2019). Our results may help identify couples who would most benefit from this type of intervention.

Strengths of our study include the multidimensional assessment of patients with an uncommon neurodegenerative condition—bvFTD—relative to patients with AD. We report a novel investigation of a functional domain that is important for quality of life, and our longitudinal assessment emphasizes the validity of our observed changes over time. Nevertheless, our findings should be interpreted in light of several limitations. First, although FTD is a relatively rare disorder and the size of our cohort is reasonably powered, results are based on a small sample of patients who are not pathologically confirmed. We also examined patients only at two timepoints that were approximately one year apart, and all patients were recruited from a single-site subspecialty clinic—two factors that may further limit the generalizability of our findings. Finally, we did not collect data in an age-matched healthy control group because of the likelihood of floor effects and limited expectation of age-associated change over a relatively brief, one-year follow-up, but this would have provided an additional reference group for comparison with bvFTD and AD.

With these considerations in mind, our findings suggest that patients with bvFTD, but not AD, show significant decline in conversation ability over time, due in part to both executive dysfunction and disease in prefrontal cortices.

<table>
<thead>
<tr>
<th>Item (Number)</th>
<th>T1</th>
<th>T2</th>
<th>Annual Δ</th>
<th>t-stat</th>
<th>p-val</th>
</tr>
</thead>
</table>

199
<table>
<thead>
<tr>
<th>Items showing significant increase over time in bvFTD</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>t-statistic</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has difficulty understanding questions (21)</td>
<td>2.3 (1.9)</td>
<td>4.1 (2.6)</td>
<td>1.3 (1.5)</td>
<td>3.92</td>
</tr>
<tr>
<td>Has difficulty understanding what is said to him/her (22)</td>
<td>2.2 (1.9)</td>
<td>4.0 (2.5)</td>
<td>1.2 (1.5)</td>
<td>3.73</td>
</tr>
<tr>
<td>Needs sentences to be repeated (19)</td>
<td>2.6 (1.9)</td>
<td>3.9 (2.7)</td>
<td>0.93 (1.7)</td>
<td>2.43</td>
</tr>
<tr>
<td>Has difficulty keeping a conversation going (3)</td>
<td>3.0 (2.5)</td>
<td>4.3 (2.3)</td>
<td>0.92 (1.6)</td>
<td>2.67</td>
</tr>
<tr>
<td>Has difficulty with telephone conversations (5)</td>
<td>2.6 (2.4)</td>
<td>4.0 (2.6)</td>
<td>0.92 (2.2)</td>
<td>1.91</td>
</tr>
<tr>
<td>Has orientation difficulties (18)</td>
<td>2.0 (2.0)</td>
<td>3.3 (2.5)</td>
<td>0.91 (2.1)</td>
<td>2.03</td>
</tr>
<tr>
<td>Becomes confused (15)</td>
<td>2.2 (1.9)</td>
<td>3.6 (2.3)</td>
<td>0.88 (1.1)</td>
<td>3.60</td>
</tr>
<tr>
<td>Does not finish sentences (11)</td>
<td>2.2 (2.4)</td>
<td>3.5 (2.9)</td>
<td>0.86 (1.4)</td>
<td>2.71</td>
</tr>
<tr>
<td>Forgets the details when telling a story (6)</td>
<td>2.4 (2.2)</td>
<td>3.8 (2.4)</td>
<td>0.85 (1.1)</td>
<td>3.64</td>
</tr>
<tr>
<td>Only talks about a few topics (4)</td>
<td>3.0 (2.0)</td>
<td>4.0 (2.3)</td>
<td>0.84 (1.5)</td>
<td>2.60</td>
</tr>
<tr>
<td>Says nothing (1)</td>
<td>2.2 (1.9)</td>
<td>3.2 (2.4)</td>
<td>0.74 (1.4)</td>
<td>2.44</td>
</tr>
<tr>
<td>Has difficulty following directions (20)</td>
<td>3.7 (1.9)</td>
<td>4.7 (2.0)</td>
<td>0.72 (1.0)</td>
<td>3.20</td>
</tr>
<tr>
<td>Has a short attention span (17)</td>
<td>3.4 (1.9)</td>
<td>4.5 (2.2)</td>
<td>0.72 (1.7)</td>
<td>1.97</td>
</tr>
<tr>
<td>Forgets what he/she wants to say (14)</td>
<td>2.6 (2.1)</td>
<td>3.7 (2.4)</td>
<td>0.60 (1.0)</td>
<td>2.79</td>
</tr>
<tr>
<td>Has difficulty finding words (9)</td>
<td>3.2 (2.1)</td>
<td>3.0 (2.5)</td>
<td>0.55 (1.0)</td>
<td>2.51</td>
</tr>
<tr>
<td>Mixes-up the details while telling a story (8)</td>
<td>2.8 (2.0)</td>
<td>3.6 (2.3)</td>
<td>0.47 (0.94)</td>
<td>2.28</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Items showing no significant change over time in bvFTD</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>t-statistic</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forgets the details after hearing a story (7)</td>
<td>3.4 (2.1)</td>
<td>3.9 (2.4)</td>
<td>0.38 (1.1)</td>
<td>1.57</td>
</tr>
<tr>
<td>Repeats the same ideas or words (13)</td>
<td>3.1 (2.4)</td>
<td>3.3 (2.6)</td>
<td>0.38 (1.5)</td>
<td>1.17</td>
</tr>
<tr>
<td>Pauses or hesitates while searching for the right words (10)</td>
<td>3.3 (2.4)</td>
<td>3.8 (2.4)</td>
<td>0.31 (1.1)</td>
<td>1.29</td>
</tr>
</tbody>
</table>
### Supplementary Table S1. Item Analysis in bvFTD

For each item (number denoted in parentheses), the mean caregiver rating (from 1-7) at timepoints 1 and 2. The maximum score of 7 indicates the caregiver informant endorsed high frequency of that behavior. Annual Δ is the change in rating from Time 1 to Time 2, divided by the years between timepoints to create an annualized measure. T-tests are used to determine if there significant change in item ratings from Time 1 to Time 2. Items are ranked from highest amplitude of annualized change to lowest. * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001.

<table>
<thead>
<tr>
<th>Item</th>
<th>Timepoint 1</th>
<th>Timepoint 2</th>
<th>Δ</th>
<th>T-test 1</th>
<th>T-test 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uses words that do not go together to form a clear idea (2)</td>
<td>1.5 (1.7)</td>
<td>2.0 (2.4)</td>
<td>0.19 (1.9)</td>
<td>0.44</td>
<td>0.33</td>
</tr>
<tr>
<td>Becomes anxious or frustrated when spoken to in a loud voice (16)</td>
<td>2.1 (2.5)</td>
<td>2.3 (2.2)</td>
<td>0.10 (2.2)</td>
<td>0.20</td>
<td>0.42</td>
</tr>
<tr>
<td>Makes harsh or critical comments (12)</td>
<td>2.0 (2.0)</td>
<td>1.8 (1.6)</td>
<td>0.04 (1.0)</td>
<td>0.18</td>
<td>0.43</td>
</tr>
<tr>
<td>Item (Number)</td>
<td>T1</td>
<td>T2</td>
<td>Annual Δ</td>
<td>t-stat</td>
<td>p-val</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------</td>
<td>-----</td>
<td>-----</td>
<td>----------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td><strong>Items showing significant increase over time in AD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has orientation difficulties (18)</td>
<td>2.00 (1.91)</td>
<td>3.00 (2.17)</td>
<td>0.75 (2.28)</td>
<td>3.05</td>
<td>0.003**</td>
</tr>
<tr>
<td>Mixes-up the details when telling a story (8)</td>
<td>2.57 (1.96)</td>
<td>3.57 (1.83)</td>
<td>0.64 (0.96)</td>
<td>3.05</td>
<td>0.003**</td>
</tr>
<tr>
<td>Forgets what he/she wants to say (14)</td>
<td>2.14 (1.53)</td>
<td>2.81 (1.94)</td>
<td>0.58 (1.02)</td>
<td>2.60</td>
<td>0.008**</td>
</tr>
<tr>
<td>Forgets the details when telling a story (6)</td>
<td>2.48 (1.89)</td>
<td>3.19 (1.89)</td>
<td>0.57 (0.99)</td>
<td>2.62</td>
<td>0.008**</td>
</tr>
<tr>
<td>Makes harsh or critical comments (12)</td>
<td>0.25 (0.92)</td>
<td>1.05 (1.93)</td>
<td>0.52 (1.41)</td>
<td>1.71</td>
<td>0.05*</td>
</tr>
<tr>
<td>Becomes confused (15)</td>
<td>2.19 (1.72)</td>
<td>2.90 (2.17)</td>
<td>0.48 (1.15)</td>
<td>1.92</td>
<td>0.035*</td>
</tr>
<tr>
<td>Forgets the details after hearing a story (7)</td>
<td>3.24 (1.76)</td>
<td>3.86 (1.80)</td>
<td>0.46 (1.02)</td>
<td>2.04</td>
<td>0.027*</td>
</tr>
<tr>
<td>Does not finish sentences (11)</td>
<td>1.90 (1.87)</td>
<td>2.43 (2.11)</td>
<td>0.45 (1.09)</td>
<td>1.89</td>
<td>0.036*</td>
</tr>
<tr>
<td>Has difficulty finding words (9)</td>
<td>3.29 (1.84)</td>
<td>3.71 (1.67)</td>
<td>0.43 (1.11)</td>
<td>1.75</td>
<td>0.047*</td>
</tr>
<tr>
<td><strong>Items showing no significant change over time in AD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has difficulty following directions (20)</td>
<td>3.28 (1.98)</td>
<td>3.81 (1.99)</td>
<td>0.45 (1.34)</td>
<td>1.53</td>
<td>0.07</td>
</tr>
<tr>
<td>Needs sentences to be repeated (19)</td>
<td>2.19 (1.63)</td>
<td>2.48 (1.99)</td>
<td>0.38 (1.82)</td>
<td>0.96</td>
<td>0.17</td>
</tr>
<tr>
<td>Repeats the same ideas or words (13)</td>
<td>2.71 (1.90)</td>
<td>3.05 (2.42)</td>
<td>0.28 (1.70)</td>
<td>0.76</td>
<td>0.22</td>
</tr>
<tr>
<td>Has difficulty understanding questions (21)</td>
<td>2.62 (1.69)</td>
<td>2.90 (1.81)</td>
<td>0.26 (1.26)</td>
<td>0.93</td>
<td>0.18</td>
</tr>
<tr>
<td>Pauses or hesitates while searching for the right words (10)</td>
<td>3.10 (2.07)</td>
<td>3.43 (2.06)</td>
<td>0.25 (1.16)</td>
<td>0.98</td>
<td>0.17</td>
</tr>
<tr>
<td>Has a short attention span (17)</td>
<td>2.67 (1.68)</td>
<td>3.10 (1.89)</td>
<td>0.23 (1.72)</td>
<td>0.62</td>
<td>0.27</td>
</tr>
</tbody>
</table>

202
<table>
<thead>
<tr>
<th>Item Description</th>
<th>Timepoint 1 Mean (SD)</th>
<th>Timepoint 2 Mean (SD)</th>
<th>Annual Δ Mean (SD)</th>
<th>p-value</th>
<th>p-value corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has difficulty understanding what is said to him/her (22)</td>
<td>2.14 (1.71)</td>
<td>2.38 (1.88)</td>
<td>0.19 (1.43)</td>
<td>0.60</td>
<td>0.28</td>
</tr>
<tr>
<td>Becomes anxious or frustrated when spoken to in a loud voice (16)</td>
<td>2.10 (1.89)</td>
<td>2.47 (2.42)</td>
<td>0.19 (1.73)</td>
<td>0.50</td>
<td>0.31</td>
</tr>
<tr>
<td>Has difficulty with telephone conversations (5)</td>
<td>1.57 (1.66)</td>
<td>1.90 (1.48)</td>
<td>0.08 (1.70)</td>
<td>0.23</td>
<td>0.41</td>
</tr>
<tr>
<td>Only talks about a few topics (4)</td>
<td>2.0 (1.58)</td>
<td>1.86 (1.68)</td>
<td>-0.13 (1.70)</td>
<td>-0.36</td>
<td>0.64</td>
</tr>
<tr>
<td>Says nothing (1)</td>
<td>1.38 (1.53)</td>
<td>1.29 (1.55)</td>
<td>-0.2 (1.39)</td>
<td>-0.40</td>
<td>0.66</td>
</tr>
<tr>
<td>Uses words that do not go together to form a clear idea (2)</td>
<td>1.52 (1.63)</td>
<td>1.10 (1.61)</td>
<td>-0.44 (1.35)</td>
<td>-1.50</td>
<td>0.93</td>
</tr>
<tr>
<td>Has difficulty keeping a conversation going (3)</td>
<td>1.85 (1.49)</td>
<td>1.29 (1.00)</td>
<td>-0.52 (1.24)</td>
<td>-1.91</td>
<td>0.97</td>
</tr>
</tbody>
</table>

**Supplementary Table S2. Item Analysis in AD.** For each item (item number denoted in parentheses), the mean caregiver rating (from 1-7) at timepoints 1 and 2. The maximum score of 7 indicates the caregiver informant endorsed high frequency of that behavior. Annual Δ is the change in rating from Time 1 to Time 2, divided by the years between timepoints to create an annualized measure. T-tests are used to determine if there significant change in item ratings from Time 1 to Time 2. Items are ranked from highest amplitude of annualized change to lowest. * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001.
CHAPTER 7: DISCUSSION

Longstanding views of the human language system suggest a functionally specific network, with two primary hubs in left peri-Sylvian cortex: the inferior frontal gyrus, commonly known as Broca’s Area, and posterior superior temporal gyrus, commonly known as Wernicke’s area. In recent years, however, cognitive neuroscientists have come to agree that this classic model is undeniably limited and in need of revision— it is not only based on imprecise and outdated neuroanatomy, but it cannot account for the full spectrum of language phenomena we experience in everyday life.

In this dissertation, we use behavioral variant frontotemporal dementia, a rare, young-onset neurodegenerative disease characterized by dysexecutive syndrome as well as changes to behavior and personality, to test the hypothesis that language processing in a real-world context is dependent on regions beyond left peri-Sylvian cortex. In Chapters 2 and 3, we describe two experiments in the production domain probing referential communication—that is, the ability to describe an object in such a way that a conversational partner can identify that same object. In Chapter 2, we examine continuous speech production, and find that non-language brain regions in medial, orbital, and dorsolateral prefrontal cortices are critically involved in a speaker’s ability to design an utterance for a listener. In Chapter 3, we extend upon this work by examining the cognitive factors that mediate referential communication and modifying the paradigm to minimize the task-related demands associated with overt speech. In addition to confirming our previous results regarding the role of prefrontal cortices in pragmatic discourse, we also implicate an individual’s mental flexibility (one of three subdomains of executive function) in their ability to communicate successfully.
In the following section, Chapters 4 and 5, we turn from language production to language comprehension. Do the same mechanisms apply when a listener interprets the utterance of a given speaker, as when a speaker designs an utterance for a given listener? In Chapter 4, we examine the comprehension of indirect replies in patients with bvFTD compared to healthy controls, as well as brain-damaged controls with amnestic mild cognitive impairment. Here, we demonstrate that patients with bvFTD struggle to make the pragmatic, bridging inferences necessary to comprehend indirect speech acts during conversational discourse. Furhtermore, we suggest a tripartite model of language neurobiology, such that comprehension is mediated by three interacting networks: the core language network, the executive control (or “multiple demand”) network, and the social brain network. In Chapter 5, we find converging evidence for the results we obtain in Chapter 4, by examining a different type of speech act known as indirect requests.

We finally conclude with a real-world, clinical application—a longitudinal study investigating the progressive decline of conversational abilities in bvFTD patients compared to brain-damaged controls with Alzheimer’s disease. In line with our previous results, we find that the decline in conversation ability in an individual bvFTD patient can be predicted by either a) their executive function at Time 1 or b) the degree of cortical thinning in prefrontal cortex at Time 1, again including medial, orbital, and dorsolateral portions.

Considered together, this body of work emphasizes that a neurobiological model of language must extend beyond the core peri-Sylvian language regions initially described by Broca and Wernicke. Instead, when a speaker uses language with a particular listener in mind, or conversely, when a listener interprets language with a particular speaker in mind, additional cognitive resources—namely executive resources including mental flexibility and social resources including perspective-taking or theory of
mind—are critically required. From a neuroanatomic perspective, this means that the core language regions do not operate in isolation, but rather in concert with extra-Sylvian regions of the brain. Indeed, our updated model of language neurobiology posits functional interactions between 3 primary networks: the core language network (mediating single word and sentence comprehension), the social brain network (mediating perspective-taking and theory of mind), and the executive/multiple-demand network (mediating mental flexibility and task-switching). See Figure 27 for a visual depiction of this model.

In regards to bvFTD, our findings mean that damage to any one of these cortical networks can result in impaired communication skills, even if core language skills are still in tact. Accordingly, even though bvFTD is not typically considered a language disorder, it is important to recognize that these patients can still struggle with language use in everyday life and require appropriately-targeted interventions.
Figure 27. Proposed three-part model for processing language in context. Based on the results of Experiments 1-5, we suggest that the core language network (green) interacts with the social network (blue) and executive network (yellow) to facilitate language and communication in a real-world context.

THEORETICAL AND METHODOLOGICAL CONSIDERATIONS

While remarkably consistent and statistically robust, there are several issues—both theoretical and methodological—to discuss when interpreting our results. The primary shortcoming of our work is its somewhat artificial nature—while our stimuli are naturalistic, we do not examine truly interactive exchanges between two or more human partners in real-time. Future work using hyperscanning—a relatively new and innovative approach that allows brain activity to be measured in two people in two scanners, simultaneously—could be used to study the neural basis of effective communication and the role of inter-brain synchrony in establishing mutual understanding (Koike et al., 2015). As a more incremental approach, future work may also consider using auditory or auditory-visual (i.e. video-based) stimuli to investigate how paralinguistic information from the face, voice, and body (for instance) may interact with linguistic input during
communicative exchanges. Such manipulations may reveal additional brain-behavior and cognitive-behavior relationships that we did not observe in our studies (for example, see Chapter 4 for a discussion of stimulus modality and working memory effects).

Next, while we were able to collect data from relatively large numbers of rare patients and healthy age-matched controls, we did not examine comparative performance in healthy young adults, which would have allowed us to form a comprehensive model of social communication in health, aging, and disease. In failing to study younger adults, we are unable to fully disentangle the effects of aging from the effects of neurodegenerative disease, and some of our observations may have been due to an interaction between the two. On a similar note, we also observed ceiling effects in our control subjects, which prevented the further study of individual differences associated with normal aging. Such an individual differences approach was also made impossible due to the lack of neuropsychological data available in this healthy control cohort. In the future, it would help inform our interpretation of the results observed in bvFTD (e.g. the role of mental flexibility but not working memory in indirect speech act comprehension) if we better understood how these same constructs operated in healthy individuals. A final critique of the neuropsychological batteries used pertains to the particular measures included— which were not consistent across studies due to data availability, and often lacked desirable measures of inhibitory control and mentalizing/theory of mind. As a result, we were largely unable to comment on the potential roles these constructs may play in pragmatic language processing, which is a topic of significant interest for future work. Our cognitive model, which focused primarily on social cognitive and executive function, could also be incomplete as it did not address the potential role of other domains, including but not limited to: attentional control, affective processing, motor function, episodic memory, and more.

208
Finally, we must consider the shortcomings of our general methodology—studying neurodegenerative disease patients using structural imaging techniques. Although we believe bvFTD to be an appropriate lesion-model for real-world communication (see Introduction for motivation), bvFTD is a rare and relatively heterogeneous disorder. While our sample sizes were in line with previous work and generally reasonable given considering the overall prevalence of bvFTD, our studies may have been underpowered. Consequently, we may have failed to observe some significant brain-behavior relationships that would have added to our neuroanatomical model. Further contributing to this problem, atrophy in bvFTD is most prominent in the frontal and anterior temporal lobes of the brain and accordingly, it can be difficult to observe any significant effects in posterior regions, where variance in cortical thickness across subjects is more restricted. Therefore, to confirm or even extend upon our existing results, it would be useful to conduct fMRI studies in healthy adults using the same stimulus materials. While fMRI is admittedly a correlative technique, this whole-brain approach may be better suited to the identification of previously unidentified or unpredicted brain-behavior relationships and could help provide converging evidence for the results obtained here.

FUTURE DIRECTIONS

Not only does the body of work described here 1) make a compelling argument regarding the importance of studying language in a real-world, communicative context and 2) culminate in an updated model of language neurobiology, but it has 3) also sparked several directions for future inquiry. First and foremost, we know that deficits in communication and social interaction impact overall morbidity, mortality, and qualify of life (Berkman and Syme, 1979; Achat et al., 1998; Holt-Lunstad et al., 2015). Accordingly, attention need be paid to the possibility of intervening in communication
disorders using neuromodulatory techniques such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS). Previous research from our laboratory has already demonstrated that tDCS to the left fronto-temporal region can improve linguistic performance (e.g. speech production, grammatical comprehension) in patients with non-fluent forms of primary progressive aphasia (PPA) (Gervits et al., 2016). Similarly, a recent case study using TMS over the left dorsolateral prefrontal cortex found significant improvements in both oral and written language tasks in a patient with the logopenic variant of PPA (Trebbastoni et al., 2013). Finally, a meta-analysis examining the effects of single-session anodal tDCS on language has also demonstrated that the positive effects of brain stimulation are not limited to patients with neurodegenerative conditions, but also extend to healthy adults. Indeed, there was a significant effect of tDCS in healthy adults compared to sham across all language measures studied, ranging from artificial language learning to verbal fluency (Price et al., 2015). Surprisingly, we are only aware of one study using tDCS in bvFTD to date. Using a randomized, double-blind, and sham-controlled design, Cotelli et al. (2018) demonstrated that tDCS over the medial prefrontal cortex enhances theory of mind and the specific ability to represent another’s communicative intent. Based on these findings, we suggest that brain stimulation techniques like TMS and tDCS could hold significant promise for ameliorating the language deficits we typically observe in bvFTD, including those in referential communication and indirect speech processing described in this dissertation.

Future work should also investigate behavioral methods to improve communication in impaired populations. Ongoing work in our laboratory has suggested that the degree of conversation difficulties in a patient (measured by PCI, as in Chapter 6) modulate the degree of burden experienced by caregivers. As the PCI also assesses
the different repair strategies (e.g. use co-speech gesture, use repetition, give choices, etc.) that patients and caregivers use, our next analyses will examine what the most effective techniques are for improving communication outcomes “in the moment.”

Finally, while the three-part model we describe here is both more nuanced and more comprehensive than previous models, there are still some refinements to be made. We believe the three networks we identified—the core language network, the social brain network, and the executive control (or multiple demand) network—to be fundamentally involved in discourse processing. However, this does not exclude the possibility that other networks are flexibly recruited given the specific demands of the stimuli. For example, sarcasm and irony have an intrinsic affective component, and accordingly, may require limbic regions like the amygdala to come online. We have begun to develop experiments to explore this possibility of “fundamental” versus “on demand” networks. For example, we are in the process of pilot testing a follow-up study on “face saving” indirect replies (e.g. Did you like my presentation? / It’s hard to give a good presentation). In the specific case of face-saving replies, a speaker uses indirect speech to reduce the impact of a critical comment (e.g. “I did not like your presentation”) and thereby preserve the other’s ego or reputation. Accordingly, they may involve high-order affective perspective-taking and empathy above and beyond that required by the neutral indirect replies studied here. We also propose a follow-up study on indirect requests examining how the social status of the communicators (e.g. who has higher status according to culturally-defined social hierarchies) may modify how an indirect request is interpreted and processed.

CONCLUDING THOUGHTS
The capacity for complex language is a hallmark of the human species and culture. Despite much scientific inquiry on the subject, however, central questions still remain about how the human brain supports this fundamental ability. While previous research has focused primarily on the representation of single words and sentences in isolation, this does not represent how we communicate in everyday life. Accordingly, the research described in this thesis attempts to define an updated model of language neurobiology – one that can account for the complexities of real-world communication from the perspective of both speakers and listeners. Across all experiments, I aimed to use carefully-controlled, but ecologically valid stimuli. Accordingly, I believe our results provide convincing evidence that using language in a real-world, communicative context involves non-language brain regions extending beyond the traditional peri-Sylvian language regions described by Broca and Wernicke. More specifically, I implicate the core language network, the social brain network, and the executive control (“multiple demand”) network in naturalistic communication, and demonstrate that disease in relevant brain regions can interfere with daily discourse by compromising this extended network. Considered together, these findings not only help to define a more comprehensive neurobiological model of language, but also have significant implications for treatment studies in patients with neurodegenerative disease.

REFERENCES


223


Lieberman MD, Cunningham WA (2009) Type I and Type II error concerns in fMRI research: Re-balancing the scale. Soc Cogn Affect Neurosci 4:423–428.


Wernicke C (1874) Der Aphasiische symptomencomplex. Breslau: Cohn and Weigert.


